Wilms' Tumor

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Dedicated to my patients and my mentors.

Foreword

There can be little doubt that the management of children with Wilms' tumor represents one of the great medical advances of the last 50 years. This achievement rests on the twin pillars of cooperative clinical trials and basic science research around the world, and pediatric surgeons and oncologists have been pivotal in driving this progress and can be justly proud of their contributions.

Childhood cancer remains uncommon but effective treatment is now available and access to such treatment should be every child's legitimate expectation.

However the benefits of the new management paradigms have not been available to everybody, and progress has exposed the inequities of healthcare provision around the globe. In high-income countries with well-resourced and robust healthcare systems, Wilms' tumor is no longer a diagnosis to be feared, but most children with cancer do not live in high-income countries! There is still much work to be done to make these advances accessible to the overwhelming majority of children with cancer who live in middle- or low-income countries in Africa, Asia, or South America where comorbidities impact on treatment options and where fragile healthcare systems and lack of resources make compliance with current management protocols difficult or impossible.

From time to time in periods of rapid change it is essential to pause and take stock of developments and to assess their relevance to the extant situation on the ground. This is what Director Professor Sarin has achieved with this authoritative book. He has assembled a formidable team of contributors, continuing the tradition of teamwork among pediatric colleagues, to present the current state of play so that treating physicians and surgeons have up-to-date guidelines to aid patient management. He has addressed current controversies and included advice on nephron-sparing surgery and minimally invasive techniques, thereby allowing the treatment team to design management plans commensurate with their skills and resources and discuss options available to physicians where facilities are lacking. It will be an invaluable resource to trainees and practicing physicians in oncology and surgery alike.

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Past President of the International Society of
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Preface

Children are the light of the world. When such pristine innocence and joy get cloaked by a dark veil of any ailment, which sometimes unfortunately turns out to be a malignancy, there can not be anything more satisfying than sailing the child through his/her illness thereby restoring the lost colors of the early years. As physicians, it is our utmost duty to give children diagnosed with Wilms' tumors a pain-free and unperturbed ride through their treatment journey.

Wilms' tumor is an embryonal malignancy of infancy and early childhood, the management of which is often quoted as an *epitome of success* in pediatric oncology. Although the overall survival rates for Wilms' tumor were only about 33% in the 1960s, they jumped to more than 90% in the next three decades. This improvement resulted from better diagnostics and the multimodal treatment that evolved because of the efforts of clinical trials conducted by the cooperative consortia, of which the National Wilms Tumor Study Group/Children's Oncology Group in the USA and the International Society of Pediatric Oncology (SIOP) are noteworthy.

In the twenty-first century, the focus shifted from improved survivals to avoidance of treatment-associated toxicity and long-term effects in the survivors. Minimalism is the buzz word with efforts being made to minimize all three limbs of multimodality treatment—the surgery (extension of scope of nephron-sparing surgery to even unilateral nonsyndromic Wilms' tumors), the chemotherapeutic drugs (avoidance of doxorubicin in pretreated stage III intermediate risk tumors), and the radiotherapy (avoidance of whole lung irradiation to rapid complete responders of pulmonary-alone metastases).

Non-contrast computerized tomography of the chest to rule out pulmonary metastases has more or less replaced the chest roentgenograms done earlier. Abdominal magnetic resonance imaging (MRI) would soon be preferentially recommended for cross-sectional imaging of the abdomen in high-income countries. SIOP is attempting to correlate apparent diffusion coefficient mapping with histopathology prediction after preoperative chemotherapy. However, any attempts to stage tumors on preoperative imaging are fallacious as the perirenal extension and lymph node involvement predicted on imaging have poor correlation to histologic staging; 75% of stage I or II tumors are overstaged and 40% of stage III tumors are understaged by the imaging modalities.

The present century also witnessed a steep rise in the knowledge of the genetics and epigenetics in the development of Wilms' tumor. In 2005, the

biological markers (chromosomal abnormalities) were incorporated in the treatment stratification for the first time. The recent advances in liquid biopsy techniques for diagnostics, monitoring of therapy, and detection of minimal residual disease are another value addition in the management of Wilms' tumor.

However, the progress cited above has not been duplicated in the low- and middle-income countries. The factors responsible for the poor outcomes have been detailed in one of the chapters. They mandate prioritization in resource utilization in such settings so as to successfully treat those who have better prognosis and the use of adapted regimens that could give comparable outcomes.

I hope that this book with 39 chapters would serve as an authoritative source for the intended readership (students, basic scientists, and clinicians) who want a comprehensive understanding of the basics and management of Wilms' tumor. I am not aware of any other book that covers the different clinical scenarios that we witness while treating these tumors.

I am indebted to my colleagues and collaborators who have contributed their ideas, time, and knowledge to this project. In particular, I would like to thank Drs. Bhaskar N Rao, GP Hadley, and Sushmita Bhatnagar for their friendship, mentorship, and wisdom. Their teachings will continue to be an endless source of passion and inspiration.

New Delhi, India Yogesh Kumar Sarin

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Editor and Contributors

About the Editor

Yogesh Kumar Sarin, MS,DNB,MCh,MBA,FAMS,FIAP,FNNF is certified in General Surgery, Pediatric Surgery, and Health Care Administration (FMS, DU) and trained in Traumatology (Australia), Pediatric Laparoscopic Surgery (UK), and Pediatric Surgical Oncology (St. Jude's, USA). He is Director Professor and Head of Department of Pediatric Surgery at the 105-year-old Lady Hardinge Medical College, New Delhi. He has over 300 publications in national and international scientific journals with ~1300 citations, many chapters in textbooks, and has participated in/supervised 43 research projects/thesis. He had been editor-in-chief of an e-journal *Journal of Neonatal Surgery* (2012–2019); he is Emeritus Editor-in-Chief now. He is a member of editorial boards of two dozen more scientific journals. He is President of the Indian Association of Pediatric Surgeons. Government and nongovernmental organizations have awarded him many times, notably the Delhi State Award for Doctors (2012). Besides being an accomplished academician and astute administrator, he is a skilled pediatric surgeon. His special areas of clinical interest include reconstructive Pediatric Urology and Pediatric Surgical Oncology.

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The History of Renal Tumors in Children

1

V. Raveenthiran

1.1 Introduction

Giulio D'Angio rightly said that oncology should be seen through the prism of Wilms' tumor (WT) [1]. Obviously the prism is displaying a colorful spectrum, which is unusual for other tumors. It is one of the few first tumors that achieved near perfect survival despite starting the journey with near total failure [1]. How this dramatic transformation occurred is a fascinating story. Contrary to the belief of many pediatric surgeons, the story of renal tumor in children did not begin with Marx Wilms but extends to great antiquity. Although the historical events are discontinuous, for descriptive convenience they are divided four distinct but overlapping eras, namely prehistoric, pathological understanding, therapeutic discoveries, and cooperative groups.

1.2 Prehistoric Era

There are two parallel systems of medicine that originated at incalculable antiquity: One was Egyptian, and the other was Indian. The Arabic and Greek medicine largely borrowed from these two systems. Among them, the Egyptian system is well documented in the form of Papyrus scrolls which were excavated by Edwin Smith. Therefore, its archeological authenticity is robust and dates back to 3000 BCE. On the contrary, Hindus of ancient India considered it a sin to scribe *Vedas*, of which *Ayurveda* (the Indian medical system) is a part [2]. Medical knowledge was then transmitted orally from one generation to the other. This not only resulted in lack of archeological material evidence but also introduced unwitting errors during oral transmission [2]. Fortunately, the arrival of Buddhism around the 400 BCE changed the scenario. Buddhists who defied all meaningless Hindu rituals began to document Hindu *Vedas* by writing them on palmyra leaves and copper plates. One such Buddhist monk, Nagarjuna (circa 200 CE) documented and wrote commentaries on the *Sushruta Samhita*, the ancient *Ayurvedic* text of Hindu surgery. Even Nagarjuna's original manuscript got lost in due course and a redaction of its many redactions survived to reach the hands of Sir Hamilton Bower, the British General and antique collector. The Bower manuscript was deciphered, translated, and published by Rudolf Hoernle in 1897, 2 years before Marx Wilms would publish his monumental monograph on mixed renal tumors of childhood. The Bower manuscript, which is now preserved in Bodleian Library, Oxford, is dated circa 500 CE (Fig. 1.1). But the *Sushruta Samhita* is much more ancient than the Bower manuscript, which is just a copy of the original text. The *Samhita* (book) is believed to have been written by *Acharya* (Professor) Sushruta between 8000 BCE and 600 BCE [2]. Although Edwin

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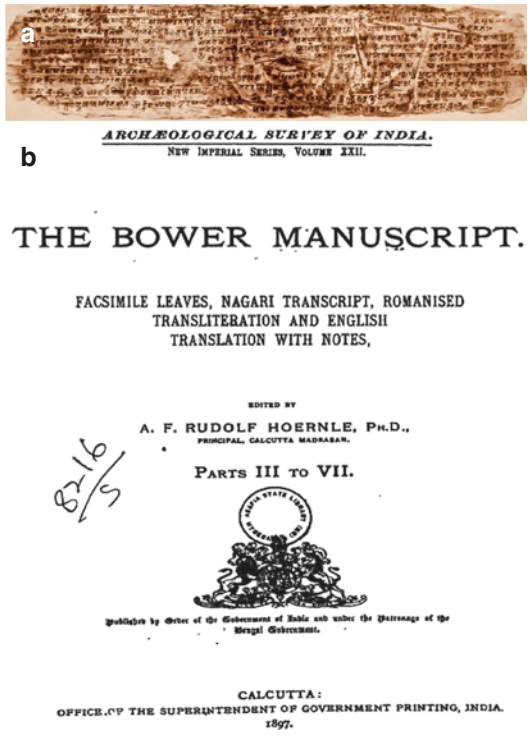

Fig. 1.1 (**a**) Bower manuscript preserved in Bodleian Library, Oxford, showing Gupta era Brahmi script on birch bark leaf (Photocredit to Ms Sarah Welch; Reproduced under CC BY-SA 4.0). (**b**) Frontispiece of the English translation of Bower manuscript published by Rudolf Hoernle

Smith *papyrus* contains descriptions of a single case of breast cancer and an osteosarcoma, there is no mention of renal tumors in it. Contrastingly, *Sushruta Samhita* devotes a full chapter on abdominal tumors called *Gulma* [3, 4].

1.2.1 The Parshve Gulma of Sushruta

Sushruta described *Gulma* as a smooth ball-like mass inside the abdomen. He elaborated its differential diagnosis from *Vidradhi* (intra-abdominal abscess). According to him, *Gulma*, unlike *Vidradhi*, will seldom suppurate and will usually be painless. These are typical features common to any abdominal tumor or organomegaly. He then classified *Gulma* into five types according to its location: *Parshve Gulma* in both loins, *Hrinna Gulma* in epigastrium, *Nruna Gulma* of central periumbilical zone, and *Vasti Gulma* in suprapubic area [4]. Among these the *Parshve Gulma* could either be hepatosplenomegaly or renal tumor. Sushruta further subdivided each of these, five *Gulmas* into *Sanchari* (mobile) and *Yadhi* (fixed) types. Thus, the fixed type of *Parshve Gulma* is more likely to be a renal tumor, while mobile *Parshve Gulma* is probably hepatosplenomegaly. Making an exception to his generalization that *Gulmas* would not usually suppurate, Sushruta had noted that fixed *Gulmas* may rarely suppurate. This probably refers to spontaneous tumor necrosis that is seen not infrequently in huge WT. *Charaka* and *Vagbatha* too attested this phenomenon in their *samhitas* (books). From these, it can be safely concluded that *Acharya* Sushruta might have had seen and treated some WT in ancient India.

While discussing the etiology of *Gulmas*, Sushruta shrewdly reminded the readers of its etymology [3]. *Gulma* actually referred to shrubby plants whose many branches directly sprout from soil without a trunk connecting them to roots. By this simile, Sushruta cryptically indicated that it would be difficult to identify a connecting link between *Gulma* and any of the known causative factors. Sushruta's wisdom remained unchallenged as late as the eighteenth century. For example, George Walker from Johns Hopkins Hospital, in his 1897 review of pediatric renal tumors, enlisted blunt abdominal trauma (21%), hereditary (6%), and infectious exanthemata (4%) as probable etiologies but concluded that it was difficult to identify a causal link [5]. In ancient times when microscopes and cellular pathology were completely unknown, Sushruta believed that *Gulma* was formed by the accumulation of *Dosha* (bodily humor) in *Koshtha* (abdomen). Consequently, *Gulma* of each organ was classified as *Vataja*, *Pittaja*, *Kaphaja*, or *Rakthaja* types [4]. Which of these types among the *Parshve Yadhi Gulmas* would be the modern equivalent of WT needs to be established by further research.

Sushruta mentioned that *Gulmas* were typically painless, smooth, ball-like, and slow growing tumors. They were said to cause constipation, poor appetite, vomiting, fever, lassitude, indigestion, and suppression of urine. Sushruta mentioned *Sula* (colicky pain) as a complication of *Gulma*. It is unclear as to what he meant was ureteric colic due to clot hematuria or intestinal colic due to bowel obstruction from contiguous tumor invasion. Such advanced clinical presentation is nothing unexpected in primitive days because as late as in 1897, Walker found 23% of "renal sarcomas" presenting with abdominal pain and one of them had the tumor fungating through the anterior abdominal wall [5].

1.2.2 Ayurvedic Treatment of Gulma

Irrespective of the underlying causative *Doshas*, all the *Gulmas* were treated with purgatives, liniments, and *Ghrita* (oily extracts of medicines). Sushruta has elaborately described the recipes of these medications. Interestingly, even at the turn of nineteenth century, 12–20% of WT children required laxatives for relief of constipation [5]. Even as late as in 1814, the prescriptions for a pediatric renal tumor by Thomas Rance included only a long list of syrups, liniments, and tinctures [6] (Table 1.1).

Sushruta was ahead of his times that he alluded to the use of cauterization in the treatment of *Gulmas* [3]. Probably, he applied hot iron to partially debulk the tumor. However, in the absence of detailed descriptions, one cannot be sure as to how exactly the cautery was then applied. The biggest drawback of *Sushruta Samhita* is its stoic silence on the final outcome of any treatment. It is not known as to how many of the *Parshve Yadhi Gulma* patients survived or temporarily improved with treatment. But we can easily presume that mortality must have been 100%. Hindu custom of cremating the dead has left no opportunity of pursuing paleopathological studies.

Table 1.1 The first known prescription of nephroblastoma (fungus haematodes) by Thomas Rance in 1814

Latin prescription[a]	English translation
Aqua cinnamom	Cinnamon extract (juice)
Aqua purae	Pure water
Confectio aromata	Aromatic confection
Cremum tartarus	Cream of potassium bitartrate
Emplastrum hydrargyrum	Bandage of mercury (amalgam)
Fructus tamarindus	Tamarind fruit
Hydrargyricus submurias	Mercuric precipitate
Infusionem rosae	Infusion of rose extract
Infusionem sennae	Senna infusion (enema)
Kalium praecipitat	Potassium salt
Lactis amygdala	Almond cream
Linimum hydrargyrum	Mercuric liniment
Magnesiae sulphata	Magnesium sulphate
Pulvis conii	Hemlock powder
Pulvis cretae compositis	Compound powder of chalk
Pulvis radix jalap	Powdered root of jalap
Pulvis scammon compositis	Compound powder of scammony
Saccharum alba	White sugar
Sodae subcarbon	Sodium bicarbonate
Succi limon	Lemon juice
Syrup croci	Syrup of saffron
Syrup papaver alba	Syrup of white poppy
Syrup simpleton	Simple syrup
Tinctur opii	Tincture of opium

[a]Compiled from Rance [6]. Combinations of these drugs were prescribed on several occasions over a period of 1 year

1.3 Era of Pathological Understanding

Following the dark ages (from fifth to fifteenth century CE), the era of renaissance brought in great enthusiasm to systematically study diseases and their treatments. John Hunter (1728–1793), the father of modern surgery, procured and preserved a set of bilateral renal tumor from an infant in 1792, the year before his untimely death from ruptured aortic aneurysm [7]. Hunter did not have time to examine the specimen in detail and hence was unaware of handling the first known

specimen of nephroblastoma in modern history. Almost 200 years later in 1986, the specimen, which is still preserved in the Hunterian Museum of the Royal College of Surgeons of England, was histologically examined by Bruce Beckwith and found to be classical WT [8].

1.3.1 Phase of Morphological Descriptions

The credit of first detailed description of pediatric nephroblastoma goes to Thomas Rance. In 1814, he described a 17-month-old girl infant with left renal mass [6]. At that time neither the name "Wilms' tumor" nor the term "nephroblastoma" had been coined. Rance called this tumor as "*fungus haematodes of the kidnies*" (Fig. 1.2). He borrowed the term from William Hey of Leeds who coined it to mean fleshy tumors of any organ. As we now attribute cancers etymologically to crab, surgeons of yore named them after fungus. Rance explained that the tumor was named as "fungus hematodes" because of its fungated (mushroom-like) appearance and frequent hemorrhages seen within it. Interestingly we still use the description "fungating tumor" to describe ulcerated cancers. Aiming a cure, Rance applied four leeches to suck out vitiated blood from the affected side. When this failed, the child was treated symptomatically with various herbal preparations, laxatives, and liniments. Bandages were applied to support the weight of the tumor (Table 1.1). As expectedly, the tumor expanded steadily, and in 6 months it spread to the contralateral kidney (the first historical description of metachronous bilateral WT). After 12 months of diagnosis, the child died of huge tumor, and the autopsy specimens of both kidneys were sent to Sir Astley Cooper for detailed examination [6]. It is not known whether Cooper undertook any histological studies, but Rance's autopsy description of the tumor morphology is unmistakably that of a WT.

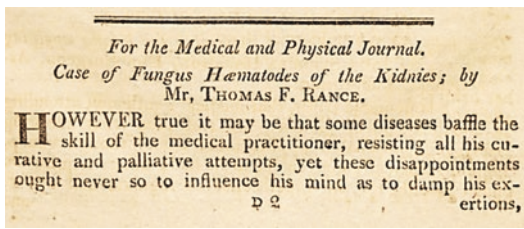
For the Medical and Physical Journal.
Case of Fungus Hæmatodes of the Kidnies; by Mr, THOMAS F. RANCE.
HOWEVER true it may be that some diseases baffle the skill of the medical practitioner, resisting all his curative and palliative attempts, yet these disappointments ought never so to influence his mind as to damp his ex-
ertions,

Fig. 1.2 Title page of the first description of nephroblastoma by Thomas Rance in 1814

Almost a decade later, in 1828, Ebenezer Gairdner described the second patient, a 3-year-old girl with huge (25 × 41 cm; 2.35 kg) bilateral tumors of 2-year duration [9]. This is probably the first description of synchronous bilateral tumor. This is soon followed by a plethora of reports so that in 1891, Chevalier Czerny [10] collected 150 cases from literature, and in 1897 George Walker collected another 145 cases [5]. The largest ever reported tumor measuring 50 × 40 × 30 cm and weighing 17 kg was described by Day in 1881 [11]. Contrarily, Israel (1893) recorded the smallest tumor of 3 × 3 × 2 cm, weighing that of a hazelnut (28 g) in a 6-year-old girl who was operated for hematuria [12].

1.3.2 Interest in Histological Studies

Although Robert Hook in 1665 and Antonie van Leeuwenhoek in 1674 perfected the modern microscope, histological study of tumors was not routine until 1858 when Rudolph Virchow, the father of modern pathology, mooted interest in cellular pathology. Interestingly, as early as in 1856, two years before Virchow's seminal publication on cellular origin of diseases, Van der Byl described the first histological appearance of "fungus hematodes" in a 7-year-old boy which was a rapidly growing gelatinous renal tumor of 14 kg [13]. In his presentation at the Pathological Society of London, Byl declared that "fungus hematodes" was indeed a form of cancer, which was until then thought to be a non-cancerous fleshy mass. It is to be noted that until 1884, there was no distinction between sarcoma and carcinoma; both the terms were often used interchangeably despite being shown to be different entities as early as in 1870 by Cattanni [5]. A review of Byl's description in the light of

modern understanding suggests that it could be the first description of cystic partially differentiated nephroblastoma (CPDN) [14].

In 1872, Eberth of Zurich was the first to recognize the mixed nature of cells [15]. He was baffled to see the presence of spindle-shaped cells resembling striated muscles and rounded undifferentiated cells. This made Eberth to believe that it was actually a skeletal muscle tumor arising in the vicinity of kidneys. So, he renamed the tumor as "myoma sarcomatodes renum." The confusion introduced by Eberth persisted for several decades even after the publication of Wilms' monograph. For example, Alfred Friedlander's paper on the first usage of radiotherapy (XRT) published in 1916 was still entitled as "Sarcoma of the Kidney Treated by the Roentgen Ray" [16].

1.3.3 American Scenario

While the European centers were curiously discussing this perplexing tumor of childhood, North Americans did not report it until 1880 when Sir William Osler, the father of modern medicine, described two cases of "oncological curiosities" from McGill University [17]. One of them was indeed much more curious because the 3-year-old girl, a patient of Dr. Finnie, had suddenly died due to tumor embolus causing occlusion of the tricuspid and pulmonary valves. This is the first recorded case tumor extension into IVC and right heart.

Surgeons, enthusiastic of reporting the new found tumor, sometimes mistook several other lesions for "renal sarcoma." For example, in 1884, Jacobi reported a cystic renal tumor that contained more than 4 liters of uriniferous fluid [5]. It is not clear as to whether it was a cystic WT, or hydronephrosis caused by ureteric obstruction by a tumor.

1.3.4 Unified Nomenclature

In the late nineteenth century, international scientific communications were very primitive. Consequently, surgeons of different countries, probably unaware of the work done by others, introduced multitude of terms to denote the same kind of tumor (Table 1.2). In 1894, Felix Victor Birch-Hirschfeld, a renowned German pathologist (Fig. 1.3), published a comprehensive monograph on pediatric renal tumors [18]. He collected pediatric renal tumors described with as many as 20 different names and concluded that they all represented the same pathology. Thus Birch-Hirschfeld's contribution is seminal in unifying several confusing terminologies of the same disease, and Wilms appreciated this in his work. No wonder, nephroblastoma was called as "*Birch-Hirschfeld tumor*" in German literature for a short period [7]. Interestingly, Birch-Hirschfeld called the tumor as "*embryonal adenosarcoma*" (Fig. 1.4) [19].

1.3.5 Etiologic Theories

Obviously, Birch-Hirschfeld was not the first to suspect the embryonic origin of nephroblastoma. Landsberger and Geddings reported fetal nephroblastoma at the seventh month of gestation [5]. In 1875, Cohnheim remarked "*avitium primae formationes*" [20, 21]. He observed that frequent bilateralism of the tumor could possibly be an indication of error in renal embryogenesis [20]. He suggested that the fragments of mesenchymal myotome could have accidentally got incorporated into the capsule of primitive kidneys developing nearby. This *theory of misplaced embryonic tissues* neatly explained the presence of striated muscles but failed to explain the epithelial component. Eberth thought that the striated cells were probably derived from metaplasia of smooth muscles that are usually present in renal capsule [15]. In 1886, Ribbert suggested that the epithelial cells could be aberrant derivatives of the Wolffian body, while Grawitz attributed them to adrenals and Waldeyer to tubular cells of nephrons [5].

Birch-Hirschfeld rejected these misplaced-tissue theories and suggested that tumorigenesis could be due to abnormal differentiation of metanephric blastema [18, 19]. In 1899, Busse considered that the metaplasia of blastemal cells

Table 1.2 List of terms used to denote nephroblastoma

Year	Synonyms of nephroblastoma	Author of first known usage
1814	Fungus haematodes of the kidnies	Thomas Rance[a]
1850	Kidney tumors of childhood	Charles West
1856	Cancerous grought of the kidney	Van der Byl
1872	Nephrogenous dysembryoma	Rudolph Virchow
1872	Renal teratomata	Rudolph Virchow
1872	Myoma strio-cellulare	Rudolph Virchow
1872	Myoma sarcomatodes renum	Eberth
1873	Kidney cancer	Hansen
1875	Striated muscle sarcoma of kidney	Cohnheim and Freundt
1877	Encephaloid sarcoma	Jessop
1877	Malignant tumor of kidney	Thomas Richard Jessop
1878	Renal sarcoma (Sarkome renum)	Kocher and Langhans
1879	Rhabdomyosarcoma of the kidney	Huber Bostrom
1880	Striated myo-sarcoma of kidneys	William Osler
1884	Congenital renal tumor	Paul
1884	Sarcomatous glandular tumor	Birch-Hirschfeld
1891	Liposarcoma of kidney	Steele
1894	Adenoma myosarcomaosum[b]	–
1894	Adenoma renum[b]	–
1894	Adenosarkome renum[b]	–
1894	Adenomyosarcoma[b]	–
1894	Carcinoma of kidney[b]	–
1894	Cerebriform tumor of kidney	–
1894	Embryonal sarcoma	–
1894	Hypernephroma[b]	–
1894	Malignant embryoma[b]	–
1894	Malignant nephroma[b]	–
1894	Medullary tumor of kidney[b]	–
1894	Mesoblastic sarcoma[b]	–
1894	Myosarcoma[b]	–
1894	Myosarcomatodes renum[b]	–
1894	Myxosarcoma[b]	–
1894	Rhabdomyoma of kidney[b]	Zenker
1894	Round cell sarcoma of kidney[b]	–
1894	Sarkome musculare renum[b]	–
1894	Spindle cell sarcoma of kidney[b]	–
1894	Teratoid mixed tumor[b]	–
1894	*Birch-Hirschfeld's tumor*	Doderlein
1894	Embryonal adenosarcoma	Birch-Hirschfeld
1899	Mixed tumor of kidney	Max Wilms
1900	*Wilms' mixed tumor*	Hugo Ribbert
1907	Nephroma embryonale malignum	Trappe
1923	Embryoma of the kidney	Homer Gage and Donald Adams
1923	Malignant mixed tumor of kidney	Hood and Henry Albert
1924	Mixed cell sarcoma of kidney	Fry
1927	Renal neoplasms of children	Wollstein
1938	Wilms embryomata	Ruby Stern and Newns
1941	Wilms' tumor	William Ladd

Table 1.2 (continued)

Year	Synonyms of nephroblastoma	Author of first known usage
1950	Nephroblastoma	Charles Olcott/Rupert Willis[c]

[a]Rance borrowed this term from Mr. William Hey of Leeds who coined it to mean any fleshy vascular tumor
[b]These names were collected by Birch-Hirschfeld in his 1894 monograph. The original manuscripts cited by him could not be accessed now. Hence the first usage of these terms was prior to 1894
[c]Both Olcott and Willis used this term for the first time in 1950. Olcott's paper was submitted in May and got published in October, while Willis used the term in his Middleton-Goldsmith Lecture in July. From this it appears that both of them independently coined the term

Fig. 1.3 Felix Victor Birch-Hirschfeld (1842–1899) who unified diverse terminologies used to mean nephroblastoma. Prior to Max Wilms, the tumor was known as Birch-Hirschfeld tumor in German literature (public domain photograph from the History of Medicine archives of US National Library of Medicine)

could have taken place at a late stage of fetal life. Occasional presence of cartilaginous tissue and frequent occurrence of striated cells could not be explained by *Busse's metaplasia theory*. Evan offered quick solution by suggesting that these tumors are something similar to teratoma containing cells of all three germinal layers. Evan's *teratoid theory* was endorsed by none other than Rudolph Virchow, the father of modern pathology. In fact, Virchow referred to this tumor as "*renal teratomata*" [5].

It is the nature of science to go astray before returning to the correct path. Etiological expositions of nephroblastoma are no exception to this rule. Surgeons frequently elicited a history of blunt trauma shortly before the tumor was diagnosed. Injury probably drew attention to a preexisting silent tumor. But Rindfleisch hypothesized that injury could have caused tumor formation by damaging a regulatory nerve that controls renal growth [5]. Weigert proposed that foreign tissue lying dormant within kidneys could have got activated by exanthematous fevers [22]. What Weigert referred to as dormant cells could be the modern equivalent of "*nephrogenic rests*." Perivewseff mistook tumor angiogenesis for the main pathology and suggested that it was a form of vascular endothelioma [5]. Pathologists of the nineteenth century were preoccupied with local irritation as a cause of neoplasia. Accordingly, Dickinson incriminated renal calculus [5]. Strumpell reported nephroblastoma in two brothers and deduced it could be hereditary [5].

1.3.6 Arrival of Max Wilms

By the late 1890s, almost every pathological fact of pediatric renal tumors had been well understood, yet confusion persisted for want of a connecting link between them. Carolus Maximilianus Wilhelmus Wilms arrived at this scene [7, 21–24]. He was born in Hunshoven on November 5, 1867 as the seventh child of Peter Mathias Wilms and Emilie Wilms (Fig. 1.5). It is to be noted that his family name ends with a

XIV.

Beiträge zur pathologischen Anatomie der Nierengeschwülste.

Aus dem pathologischen Institut der Universität Leipzig.

Hierzu Tafel VI und VII.

I.

Sarkomatöse Drüsengeschwulst der Niere im Kindesalter (Embryonales Adenosarkom).

Von

Professor Dr. F. V. Birch-Hirschfeld.

Die primären, nach ihrem klinischen Verlauf bösartigen Nierengeschwülste bilden keine einheitliche Gruppe im onkologischen System. Auch mit der Gegenüberstellung des aus dem Drüsenepithel hergeleiteten Carcinoms einerseits und des auf Wucherung der Zellen des bindegewebigen Stromas zurückgeführten Sarkoms andrerseits ist keineswegs eine brauchbare Grundlinie für die klare Unterscheidung der Hauptgruppen maligner Nierentumoren gegeben. Die Hauptschwierigkeit ergiebt sich aus der Thatsache, dass ein Theil der hier zu berücksichtigenden Neubildungen zwar innerhalb der Niere sich entwickelt, aber dabei aus einem Gewebe hervorgeht, das von vornherein in Anordnung und Form seiner Elemente fremdartig gegen die normale Nierenstructur absticht. Das gilt bekanntlich in erster Linie für die Neubildungen, die nach dem Vorgange von Grawitz (1) auf geschwulstförmige Weiterentwicklung von versprengten in das Nierengewebe eingeschlossenen Theilen der Nebenniere zurückgeführt werden. Unzweifelhaft sind hierhergehörige primäre Nierengeschwülste in der Casuistik theils als Carcinome, theils als Sarkome aufgeführt worden. Auch jetzt noch ist über

DIE MISCHGESCHWÜLSTE

Von

Dr. M. WILMS

HEFT 1:

DIE MISCHGESCHWÜLSTE DER NIERE

LEIPZIG

VERLAG VON ARTHUR GEORGI

1899.

Fig. 1.4 Frontispiece of two highly influential monographs on pediatric renal tumors. Birch-Hirschfeld's book is obviously more comprehensive and antedated than that of Wilms

"s" and hence it is wrong to insert an apostrophe after "Wilm." Like his father and elder brother, young Wilms too initially perused a career in law. After spending one semester at Law College, for reasons unknown, Wilms switched over to medical school. As per the tradition of those days, he rotated his training in Munich, Marburg, Berlin, and Bonn. In 1890, he graduated from Rheinischen Friedrich-Wilhelm University of Bonn by submitting a 40-page doctoral thesis on esophageal resections. Two years later, he joined the Institute of Pathology at Geissen, where his mentor was Eugen Bostroem. It is worth noting that Bostroem was interested in pediatric tumors and he had already published a case of "*Rhabdomyoms der Kindlichen Niere*" in 1879, a tumor which was later going to be named after his mentee [25]. The 4 years that Wilms spent in Geissen sufficiently kindled his interest in pediatric renal tumors, and he started working on that under the able tutelage of Bostroem. Eight years later, in 1899, his work culminated in the publication of the much celebrated 91-page monograph "*Die Mischgeschwulste der Niere*" (Fig. 1.4) [26].

Of course, the book on "*Mixed Renal Tumors*" was not considered the magnum opus of Marx Wilms during his lifetime. It was one of the trilogies and the other two being "*mixed tumors of the uterus and vagina*" and "*tumors of head and neck*." In fact, Wilms obituary did not even mention his work on renal tumors. Wilms was well known for his textbook "*Lehrbuch der Chirurgie*" which he co-edited with Dr. Wullstein. The book saw six editions in German and was translated into five foreign languages [7]. Perhaps his monumental contribution was the textbook on intestinal obstruction entitled "*Der Ileus Pathologie*

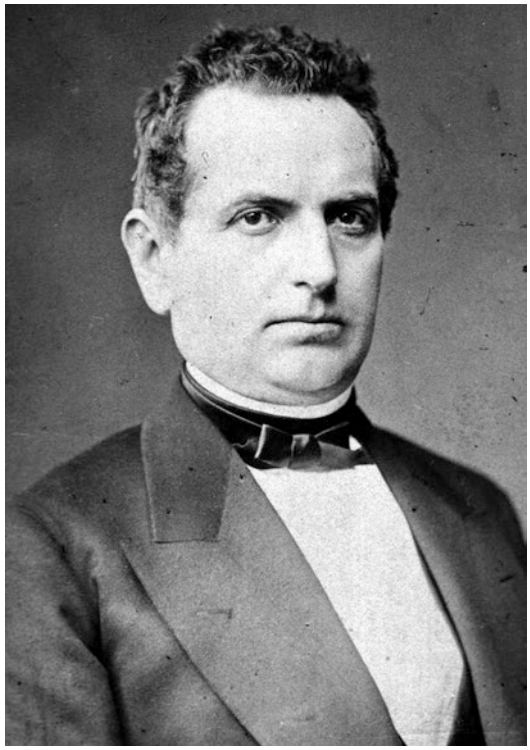

Fig. 1.5 Carolus Maximilianus Wilhelmus Wilms (1867–1918) whose name is indelibly attached to nephroblastoma (Public domain photograph from the History of Medicine archives of US National Library of Medicine)

und Klinik des Darmverschlusses." Until the publication of this seminal work in 1906, ileus (intestinal obstruction) was considered to be a medical disorder. It was Wilms who rightly insisted it a surgical problem and encouraged operative cure. It was he who told that pyloric stenosis is better treated by surgeons rather than by physicians. He was also well known for a technique of tendon suturing called "*Wilms–Sieverischen technique*." The manometer, which he designed to measure cerebrospinal fluid pressure, was widely used during World War I. Wilms' innovation list included designing of a roentgen examination table to prevent superimposition of spine over the esophagus, description of borborygmus as a sign of intestinal obstruction, use of antitoxin in the treatment of tetanus, documentation of bone development from birth to adulthood, and recommendation of endocarditis prophylaxis [7].

1.3.7 The Erroneous Eponym

It was Cohnheim, not Wilms, who attributed pediatric renal tumors to embryogenic error. It was Busse, not Wilms, who proposed that all the diverse cells of the tumor are derived from metaplasia of primitive nephritogenic cells. Wilms simply made a humble contribution by modifying Busse's metaplasia theory. Busse thought that tumor cells de-differentiate at a very late stage of fetal life, while Wilms suggested it to occur early in embryogenesis. He reached this conclusion based on four cases he had collected from literature and three cases of his own. Contrary to the practice of his days, Wilms insisted multiple sections of the tumor must be examined before concluding its nature. It is acclaimed that Wilms used a special stain for elastic fibers that enabled him to identify that the round cells, previously mistaken for sarcoma, were in fact primitive epithelium of glandular alveoli. However, epithelial nature of these cells was not previously unknown. For example, Kocher and Langhans as early as in 1878 described the classical triphasic nature of these tumors. Wilms introduced the term "*mixed renal tumor*," which hardly reflects anything on its pathogenesis. Mixed nature of cells was well known to several authors before Wilms. His analysis of seven cases was very humble as compared to the awesome analysis of his predecessors Birch-Hirschfeld, Czerny, and Walker, who had reviewed more than 100 cases each. Therefore, Rupert Willis rightly disagreed with the eponym "*Wilms' tumor*" [27]. He insisted to call it as nephroblastoma—a term coined by Charles Olcott in 1950 [28]. However, voices of dissent were drowned by the overwhelming enthusiasm of eponyms in early twentieth century. Hugo Ribbert was the first to use the term **"***Wilms' mixed tumor*" [7]. It was William Ladd who popularized the eponym, "*Wilms' tumor*," in 1941, although he himself used it in parenthesis supporting the main name "*embryoma of the kidney*" [29].

How a disease was eponymously named after a trivial (perhaps misleading) contribution is surprising. Wilms was a sincere, intelligent, honest,

and diligent physician but lacked diplomacy. In May 1918, Wilms was called to see a French prisoner of war suffering from diphtheria. The patient was gasping for breath, and it was obvious that he required life-saving tracheostomy. Wilms always considered his professional callings sacred. Thus, ignoring his own safety, he performed the operation. Unfortunately, he got infected with *Corynebacterium diphtheria* from his patient and died of diphtheria in May 1918 [7, 20]. Wilms would have felt happy to know the survival of his last patient. Wilms was survived by his wife Else Sefferth. The fact that these couple did not have children may partly explain the keen interest of Wilms in childhood cancers. The tumor was named after Wilms probably not because of the merits of his scientific contribution, but as ex gratia to honor his professional commitment.

1.4 Era of Therapeutic Discoveries

The history of humanity has repeatedly proved that man usually do not wait for understanding certain thing before acting upon it. This was evident from the writings of Sushruta and Rance who prescribed herbs for symptom relief. But the first real attempt of cure by nephrectomy was made by Hueter in 1876 [23]. His bold attempt was facilitated by two important discoveries made earlier—the discovery of ether anesthesia and chloroform anesthesia by Thomas Morton and James Simpson, respectively, and the demonstration by Gustave Simon of Heidelberg in 1860 that unilateral nephrectomy was compatible with life [23]. Unfortunately Hueter's well-conceived plan failed as his 4-year-old patient died of excessive intraoperative bleeding [5]. A year later, in 1877, Kocher attempted the second nephrectomy in a 2-year-old child under chloroform anesthesia; the patient survived the procedure only to die 2 days later of wound infection [30]. In the same year, Thomas Richard Jessop from Leeds General Infirmary performed the world's first successful pediatric nephrectomy of a tumor, which was yet to be named after Wilms [31].

1.4.1 Surgical Remedy

Jessop was born at Brighouse, Yorkshire, on November 11, 1837. It is a strange coincidence that his father, like that of Wilms, was a solicitor. Jessop, despite being the vice president of the Royal College of Surgeons maintained a general practice of both surgery and medicine. He was the first surgeon to successfully operate upon a pregnant woman with intraperitoneal rupture of pregnancy. No wonder he did the first successful tumor nephrectomy in a 2-year-old child under chloroform anesthesia. The operation lasted for 55 min, and a 450 g tumor was removed [31]. Jessop partly attributed the success to his regimen of postoperative analgesia in the form of 40 drops of whiskey every two hourly. Jessop's patient died 9 months later of recurrent disease. This did not dissuade surgeons from enthusiastically adopt nephrectomy as the treatment of renal tumors because they thought it was the only hope of survival and at worst it simply accelerated the death, thereby avoiding prolonged agony [5].

In early days of surgical treatment, intraoperative and perioperative deaths were very common. Surgeons trying to decipher the cause of such deaths stumbled upon the nature of incision. A variety of incisions had been used that included Czerny's extraperitoneal lumbar incision, Koenig's extended lumbar incision, Scmidt's midline incision, Abbe's oblique transperitoneal lumbar incision extending to umbilicus, and Kelly's incision extending from costovertebral angle to iliac spine [5]. Those who favored lumbar approach insisted that peritoneal cavity should not be contaminated by tumor spills and those who advocated transperitoneal approach complained of inadequate access in lumbar approach. It was William Ladd who popularized transperitoneal incision across the abdomen as the standard approach [29].

Table 1.3 Long-term survival of nephroblastoma prior to Max Wilms

Author	Year	Patient details	Long-term survival[a]
Clementi	<1890	(Cited by Czerny)	Alive at 5 years
Schede	<1890	(Cited by Czerny)	Alive at 5 years
Kronlein	<1890	(Cited by Czerny)	Alive at 4 years 9 months
Czerny	1891	Out of 12 nephrectomies, one survived	Alive at 5 years
Schmidt	1892	6-months-old girl; Huge left renal mass excised by 1 and half hour surgery	Living 4 years
Malcolm	1892	2-years-old girl; right renal tumor	Alive at 30 years
Israel	1894	14-years-old boy with right side tumor of 7 months duration	Alive at 5 years 4 months
Israel	1894	(Cited by Czerny)	Alive at 6 years 9 months
Abbe	1894	2 and half-years-old girl; 1.25 kg right renal tumor excised in 45 min operation	Developed metachronous tumor on contralateral kidney after 5 years
Abbe	1894	14-months-old girl; huge right renal tumor; tumor weight was 3.5 kg while child's weight was 7 kg; partial nephrectomy	Alive at 34 years

[a]Probably considering the life expectancy of the nineteenth century Thomas Walker defined long-term survival as disease-free survival of 3 years or more

Walker noted that none of the children survived if the surgical procedure was extended more than 2 h duration [5].

Prior to the 1940s, success with surgery was anecdotal. Operative mortality was 45–70%, and recurrences were invariably the rule. Until the end of the nineteenth century, out of 150 operations, only half-a-dozen patients had survived beyond 3 years of nephrectomy (Table 1.3). However, there were some exceptions to this generalization. For example, Robert Abbe, in 1892, operated upon a 14-month-old girl with right renal tumor. The tumor weighed 3.5 kg, while the child herself weighed only 7 kg. Despite the huge size of the mass, the lower pole of the kidney was found to be well preserved. Hence Abbe did partial nephrectomy and closed stump with catgut. This is arguably the first case of nephron preserving surgery of WT. She survived for more than 34 years and Abbe presented her at the 1912 meeting of the New York Surgical Society! [32, 33]. Another 2-year-old child operated by Malcolm in 1892 survived more than 30 years [34]. Tumors of these exceptional survivors could probably be a benign variant of WT. For example, the tumor removed by Malcolm then was diagnosed as "malignant adenoma" by Targett, but when Shattock re-examined the specimen after 30 years, he found no evidence of malignancy in it [34]. Malcolm's patient could probably be the first reported case of mesoblastic nephroma.

1.4.2 Radiotherapy

From the foregoing account, it is clear that surgery alone was not sufficient to achieve a long-lasting cure [35]. Barely within 1 year of Roentgen's discovery of X-rays in 1895, Emil Grubbe, a third-year medical student at Hahnemann Medical College of Chicago, discovered the cytotoxic effect of X-rays by observing blisters on hands exposed to the rays [14]. He suggested that this adverse effect can be used to the advantage of treating carcinoma breast and lupus. Even Marx Wilms was aware of XRT. He was in fact a champion of testicular and pelvic XRT for prostatic cancer [7]. Strangely, he did not consider it an option for the tumor that now bears his name. Wilms' reluctance to use XRT for renal tumors could have been due to two different reasons. First of all, his surgical training under the internationally famous Professor Trendelenburg could have left a strong positive impression about the efficacy of surgical treatment. Secondly, Wilms

classified tumors into operable and inoperable and considered XRT only, when it was inoperable. As the pediatric renal tumors were most often easily enucleated, Wilms did not recommend XRT for them.

In 1915, Anna Heimann of Freiburg was the first to explore the role of XRT in WT [14]. Within a year, Alfred Friedlander of Cincinnati used XRT to treat a 4-year-old child with inoperable nephroblastoma of 3 months duration [16]. He administered seven sittings of irradiation, and the child survived only to die later of measles. In the late 1930s, radiosensitivity of WT was attested by Gage, Prather and Friedman, Kretschmer, and Kerr [36–38]. They even proposed it preoperatively to reduce tumor size and to prevent intraoperative tumor spillage. It took another 30 years to accept their intuitively wise recommendation through the findings of SIOP studies! Unpopularity of XRT was partly due to radiation-induced vertebral damage and scoliosis among survivors. When Wittenborg included whole vertebral column in radiation field to avoid this complication straight spine was achieved at the cost of stunted height. The greatest setback to XRT came when William Ladd showed excellent results with nephrectomy in 1940 and Sydney Farber demonstrated the miracle of chemotherapy (ChT) in 1955 [39]. Strangely, it was Farber himself who later revived XRT. On seeing histological evidences of necrosis in irradiated tumors, he quickly recognized the usefulness of XRT and advocated intraoperative radiotherapy to tumor bed.

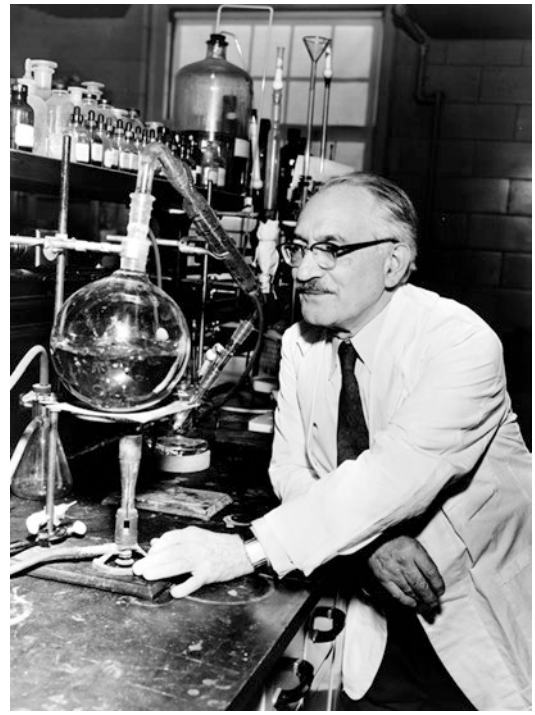

Fig. 1.6 Selman Abraham Waksman (1888–1973), the discoverer of actinomycin and Nobel Laureate (1952) (Public domain photograph from Sun Newspaper Photograph collection)

1.4.3 Chemotherapy

In 1930, totally unconcerned with the progress made in the treatment of Wilms' tumor, a Ukrainian-born Jewish-American microbiologist, Selman A. Waksman (Fig. 1.6) at Rutgers University, was experimenting with soil fungus with an aim to discover antibiotics. By then, the discovery of penicillin by Alexander Fleming in 1928 had created great fervor of discovering newer antibiotics from soil fungi. Unlike Fleming who discovered penicillin by serendipity, Waksman worked methodically and painfully that he discovered as many as 15 antibiotics [40]. The most notable among them are Streptomycin from *Streptomyces griseus* and actinomycin and neomycin from actinomycetes. Although Waksman and Woodruff discovered actinomycin in the 1930s, they reported it only in 1940 [41]. Various structural derivatives of actinomycin are designated as A, B, C, D, I, J, and X [42]. Actinomycin C prepared by Hackmann and actinomycin D (AMD) (sometimes called as Dactinomycin by transposing the "D" to the beginning) prepared by Manaker was found suitable for human usage. They were originally introduced as antibacterial drugs. Robinson and Waksman in 1942 and Hackmann in 1954 became aware of the lymphopenic side effect of the drug. Sydney Farber was quick in recognizing its therapeutic implication in leukemia (Fig. 1.7). Its dramatic effect in killing cancer cells encouraged Farber to apply it for WT as well. In 1966,

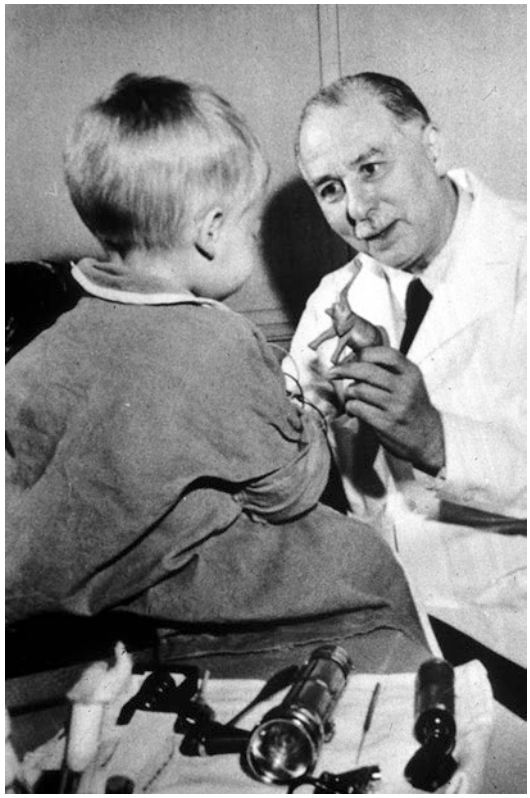

Fig. 1.7 Sydney Farber (1903–1973), the father of pediatric chemotherapy who introduced AMD in the treatment of Wilms' tumor in 1955 (Public domain photograph from US National Cancer Institute)

Faber published his groundbreaking research, from there upon AMD became inseparable component of WT treatment [43]. Farber, a clinical pathologist, developed lifelong preoccupation with cancer management and went on to create the iconic Diana-Farber Cancer Institute. While Farber was yet to publish his study results on the role of AMD on WT, John Raffensperger at Cook County Hospital, Chicago, began to use it regularly in his patients since 1959 [7]. Interestingly, he used it both before and after surgery thus pioneering neoadjuvant therapy.

A decade after the discovery of penicillin, physicians became aware of the phenomenon of drug resistance in bacteria. When these antibiotics were used for cancer treatment, they drew analogy and predicted similar phenomenon of drug resistance with cancer cells also. Consequently, there was an increasing trend to use combination

Fig. 1.8 Madagascar Periwinkle flowers (*Vinca rosea*) from which vincristine is extracted. This flower known as Nithyakalyani in Tamil had been used in the treatment of "*Puttru Noi*" (cancer) in the ancient Siddha system of medicine

of drugs to avoid emergence of resistant clones of the tumor cells. A search for companion drug of actinomycin materialized when Sutow, Thurman, and Windmiller reported the usefulness of vincristine (VCR) in 1963 [44]. It is a plant alkaloid derived from Madagascar periwinkle (*Vinca rosea*) flowers (Fig. 1.8). It is interesting to note that ancient Tamil physicians of *Siddha* medical system used periwinkle flowers (called *Nithyakalyani Poo* in Tamil) to treat "*Puttru Noi*" (cancers) [45]. Although Doxorubicin (DOX) and cyclophosphamide (CTX) were introduced much later, they did not attain the prominence of AMD and VCR.

1.5 Era of Cooperative Groups

By the turn of 1960, three major therapeutic approaches, namely surgery, ChT, XRT, and their combination permutation, had been well established [35]. However, this introduced a new problem of deciding as to which of these

regimens is the best. Particularly, when ChT load was reduced, the disease relapsed, and when it was increased, children died of toxicity. This classic dilemma of pediatric oncology was formidable. Simple remission was no longer deemed sufficient; sustainable cure with fewer side effects was targeted. In fact, "*cure is not enough*" became the motto of *National Wilms' Tumor Study* (NWTS) Group.

Cancer research is generally cumbersome because a cure can be ascertained only by prolonged follow-up over decades but by the time newer agents might have been introduced, thus making the conclusions of decades-long study invalid. Compounding this, the annual incidence of WT is extremely small that fewer than 400 new patients are diagnosed each year in the United States. Thus, enrolling adequate number of patients for properly designed randomized controlled trails is extremely difficult. This prompted doctors from various hospitals to pool up patients and form cooperative groups.

1.5.1 The North American Cooperative Groups and NWTSG

In 1955, the first North American cooperative group formed was the *Acute Leukemia Cooperative Chemotherapy Study Group-A* [46]. It was predominantly concerned with adult leukemia but also included a small number of pediatric leukemia and other solid tumors. Soon it was clear that mixing up of adult and pediatric data was not good enough and hence the pediatric wing of the co-operative group split off to form the *Children's Cancer Study Group A* (CCSG-A) in 1967. Its name was subsequently shortened as the *Children's Cancer Group* (CCG). Giulio D'Angio, a radiotherapist, thought that instead of mixing up all pediatric tumors under CCG, it would be better to have focused research on WT separately. So, in 1968, he founded the North American cooperative group, the *National Wilms' Tumor Study Group* (NWTSG). Founding members of the group include Giulio D'Angio (radiotherapist), Daniel Green and Audrey Evans (hemato-oncologists), Bruce Beckwith (pathologist), Norman Breslow (statistician), Harry Bishop (pediatric surgeon), and Willard Goodwin (urologist). The NWTS has so far conducted five studies, as a result of which overall survival has improved from 50% to 95% (Table 1.4) [47].

Simultaneous to the formation of CCSG-A, another parallel cooperative group called *Southwest Cancer Chemotherapy Study Group* (SWCCSG) was formed in 1956, with its pediatric base at the MD Anderson Cancer Hospital. Its original aim was to study leukemia in children. In 1958, National Cancer Institute directed SWCCSG to include adult tumors as well, and hence the group was rechristened as *Southwest Oncology Group* (SWOG). In 1973, the SWOG was merged with the *Cancer and Acute Leukemia Group-B* (CALG-B). In 1979, a faction of oncologists headed by Teresa Vietti of St. Louis split off from CALG-B and formed the *Pediatric Oncology Group* (POG).

At the turn of this millennium, the futility of several parallel groups conducting studies on the same tumor was realized. Therefore, in 2000, NWTSG, CCG, and POG were merged with yet another group—the *Intergroup Rhabdomyosarcoma Study group* (IRSG)—to form a single comprehensive pediatric cancer study group called the *Children's Oncology Group* (COG). COG is obviously a formidable association of 200 member institutions and 8000 cancer specialists. At any given time more than 100 concurrent trails are being conducted by COG [46].

Although therapeutic improvements were the hallmark of NWTS, pathological understandings of the bygone century were complemented by Bruce Beckwith, the chief pathologist of the group. He established two important principles that became the foundation of improved outcome. Firstly, he introduced the concept of risk stratification, which allowed dose reduction and lesser therapy toxicity in a subset of patients. Secondly, he considered clear cell sarcoma of kidney and rhabdoid tumor of kidney as separate entities from WT. Interestingly, Manasse's description of a 3-year-old girl was probably the first case of

Table 1.4 Chronology of NWTS Group trials

Study	Registration	*n*	Key conclusions
NWTS 1	Oct 1969–Feb 1975	741	• XRT is not essential for low risk patients of group I[a] • AMD + VCR is more effective than either alone • Histological subtypes (FH and UH) recognized
NWTS 2	Jan 1975–Apr 1979	950	• 6 months of ChT is sufficient for group I[a] • Addition of DOX improves survival of groups II–IV[a] • 50% ChT dose reduction is appropriate for infants • Prognosis of FH is better than that of UH • New staging system introduced (LN involvement is shifted from group II to stage III)[a]
NWTS 3	May 1979–Sep 1986	2496	• Histology and stage-specific treatment proposed • Focal or diffuse anaplasia, clear cell sarcoma, and rhabdoid tumor are classified as UH • XRT not essential for Stage I (both FH or UH) • Stage III FH requires three drugs (AMD + VCR + DOX) plus XRT • Stage II-IV UH requires four drugs (AMD + VCR + DOX + CTX)
NWTS 4	Aug 1986–Aug 1995	3335	• Pulse-intensive ChT gives good results with less toxicity • pulse intensive ChT of FH of all stages significantly reduces the cost of care
NWTS 5	Aug 1995–May 2002	3031	• Among FH, LOH-1p or LOH-16q has poor prognosis • Among UH, LOH-1p has poor prognosis in stages I and II but not for stages III and IV • LOH-1p plus LOH-16q has the worst prognosis • Surgery alone is enough for stage I FH tumors of <550 g in children below 2 years of age • Lung secondaries detected by only CT but not by chest X-ray benefit by adding DOX to VCR and AMD. They do not require XRT • High telomerase expression in FH has poor prognosis • Pathobiology of bilateral Wilms' tumor was documented • Biological sample bank was established • ET and CTX improves OS and EFS of UH • Increased DNA content of FH has poor prognosis

XRT radiotherapy, *AMD* actinomycin D, *VCR* vincristine, *ChT* chemotherapy, *CT* computerized tomography, *DOX* doxorubicin, *FH* favorable histology, *UH* unfavorable histology, *LN* regional lymph node, *CTX* cyclophosphamide, *ET* etoposide, *LOH* loss of heterogeneity of chromosome, *OS* overall survival, *EFS* event-free survival
[a]In the first two NWTS the concept of 'study grouping' was used instead of 'staging'

clear cell sarcoma. He mistook the giant oblong cells with clear cytoplasm and glassy debris of glycogen, for signs of degeneration [5].

1.5.2 Societe International d'Oncologie Pediatrique (SIOP)

Ideas and preferences often differ significantly across the Atlantic. What the Europeans call as adrenal and paracetamol will be called respectively as suprarenal and acetaminophen by the Americans. This Americanism of linguistics is also true of oncology. Americans usually pursue tumors more aggressively, while the British prefer gentle approach. When Americans considered surgery as the principal treatment of WT, Europeans proposed ChT as the first-line treatment. European doctors believed that preliminary treatment with anticancer drugs would downsize the tumor thereby making its excision safe. For decades, Americans knew the importance of adjuvant ChT that was given even after complete excision of tumor. Therefore, Europeans called their approach as neoadjuvant therapy (upfront ChT). Similarly, Americans did not favor tumor biopsy prior to nephrectomy, while Europeans

preferred to have a tissue diagnosis in selected patients before starting treatment. Had William Ladd been alive today, he would never have approved the European approach of upfront ChT [29].

These differences in the way of thinking between Americans and Europeans necessitated a separate cooperative study group in Europe [48]. Odile Schweisguth, the first pediatric oncologist at the Institute Gustave Roussy, took the lead in organizing the "International Society of Pediatric Oncology" (known by its French acronym SIOP). On July 3, 1967, a small group of experts interested in pediatric tumors met at the *Institut Gustav Roussy* in Villejuif to form the *Club d'Oncologie Pediatriquie* (Paediatric Oncology Club). The inaugural meeting of the club was held in 1969 at the *Institut Gustave Roussy*. During the second meeting held in Madrid on the 6 November 1969, the club was formally renamed as the *Societe International d'Oncologie Pediatrique* (SIOP). Its registered office is located at Zurich and central secretariat in the Netherlands. SIOP was originally a bilingual society with French and English as official languages, but now it is predominantly English. In 1991, during the SIOP meeting at Rhodes, surgeons of SIOP formed a separate subgroup known as the *International Society of Paediatric Surgical Oncology* (IPSO). [49–51] SIOP has so far concluded six trials (Table 1.5) [49]. In December 2007, Renal Tumor Study Group (RTSG) was formed as a collaborative subgroup of SIOP intending to study all renal tumors of childhood as well as adolescence and young adults.

In 1972, Medical Research Council of United Kingdom set up a *Working Party on Childhood Leukemia* (UK-MRC-WPCL). In 1977 *UK Children's Cancer Study Group* (UKCCSG) was founded to study other pediatric malignancies. In August 2006, both these organizations were merged to form *UK Children's Cancer and Leukemia Group* (UKCCLG). UKCCLG is a large body of 600 members and 21 centers of England and Ireland. Over the last 5 decades, these cooperative groups have done more than eight trials.

Monumental contributions of SIOP include neoadjuvant ChT to downsize tumors thereby making surgery safer, use of imaging studies to avoid routine contralateral explorations, preconfirmation of pathological subtype before commencing treatment, and nephron sparing surgery in low-risk groups [49].

1.6 A Century of Wilms' Tumor

It is appropriate to call the period between 1899 and 1999 as the century of WT. Its outlook has changed dramatically in these hundred years (Table 1.6). Bizarre presentations such as duodenal erosion, paraplegia due to spinal invasion, and trans-abdominal fungating tumor mass are no longer seen. Advanced anesthesia techniques and neoadjuvant ChT have made operations safer. As a result, operative mortality, which was 70% in 1889, has now been brought below 1% [50, 51]. Overall long-term survival, which was anecdotal, has now become routine. Yet, all the puzzles are not yet fully solved. For example, with modern diagnostic and screening tools, one would anticipate the tumor to be diagnosed much early in life. Contrary to this expectation, its age distribution has remained almost the same over 100 years (Fig. 1.9). This indicates that we should learn more about the biological nature of the tumor. Success of science has raised the bar of public expectations. A simple cure is no longer considered enough. We are certainly stepping into the next century with higher and different goals.

Table 1.5 Chronology of SIOP trials

Study[a]	Registration	*n*	Key conclusions
SIOP 1	Sep 1971–Oct 1974	338	• Pre-op XRT reduces intra-op tumor rupture/spillage • Post-op AMD of 1 *vs* 6 cycles have comparable EFS/OS
SIOP 2	Oct 1974–Dec 1976	138	• Non-RCT reconfirm the findings of SIOP 1 • VCR + AMD for 9 *vs* 15 m has equal EFS/OS • Pre-op XRT is beneficial even in small size tumors
SIOP 5	Jan 1977–July 1979	397	• Tumor rupture rate is equal in 4 weeks of pre-op VCR + AMD *vs* pre-op XRT + 1 cycle of AMD • For pre-op preparation ChT is preferable over XRT due to fewer side effects
SIOP 6	July 1980–Oct 1987	1095	• Post-op VCR+AMD for 17 weeks *vs* 38 weeks are comparable in stage I • No difference in EFS /OS in XRT vs no XRT for stage II, but no XRT group had more relapse • 2 years-EFS better when DOX added to VCR for stage IIN and IIIR but 5years OS was equal
SIOP 9	Nov 1987–Nov 1991	852	• Pre-op ChT for 4 weeks *vs* 8 weeks are comparable for stages I-III • In node negative stage 2 epirubicin without XRT reduces tumor relapse
SIOP 93-01	July 1993–2001	2162	• Post-op ChT for intermediate risk and anaplastic tumors can be reduced to fours doses of VCR+1 dose of AMD without compromising the outcome
SIOP WT 2001	2001 - 2015	5728	• DOX not required in Stages II and III intermediate risk • (Ongoing data capturing and analysis)
Umbrella Protocol[b]	June 2019	–	(Ongoing enrollment)

Pre-op preoperative, *Intra-op* intraoperative, *Post-op* postoperative, *EFS* event-free survival, *OS* overall survival, *AMD* actinomycin D, *VCR* vincristine, *XRT* radiotherapy, *ChT* chemotherapy, *DOX* doxorubicin, *int.* intensive dosage, *RCT* randomized controlled trial

[a]As SIOP trials are concerned with all childhood tumors, they interspersed with Wilms' tumor studies. Hence the SIOP trials on Wilms' tumor are numerically discontinuous

[b]UK IMPORT study which enrolled 692 patients between Oct 2012 and Feb 2020 is now merged with Umbrella Protocol trial

Table 1.6 Timeline of nephroblastoma

Year	Events pertinent to Wilms' tumor	Parallel events that indirectly influenced the treatment of nephroblastoma
1200 BCE	Sushruta treated *Parshve Yadhi Gulma,* the description of which resembles nephroblastoma	
1665 CE		Discovery of cell (Robert Hook)
1674		Construction of modern microscope (Leeuwenhoek)
1792	First specimen of bilateral tumor procured and preserved by John Hunter	
1814	First ever detailed description of metachronous bilateral tumor by Thomas Rance	
1828	Second case (first case of synchronous bilateral tumor) described by Ebenezer Gairdner	
1846		Discovery of ether anesthesia (Morton)
1847		Discovery of chloroform anesthesia (Simpson)
1856	First histological description of tumor (?CPDN) by Van der Byl	

(continued)

Table 1.6 (continued)

Year	Events pertinent to Wilms' tumor	Parallel events that indirectly influenced the treatment of nephroblastoma
1858		Development of cellular pathology (Virchow)
1860		Feasibility of nephrectomy shown by Simon
1865–1867		Discovery of antiseptic surgery (Lister)
1872	Mixed nature of cells (presence of striated cells) noted by Eberth	
1875	Embryogenic error proposed by Cohnheim	
1876	First unsuccessful attempt of nephrectomy by Hueter	
1877	Second unsuccessful attempt of tumor nephrectomy by Kocher	
1877	First successful tumor nephrectomy by Jessop	
1880	First case of IVC invasion (William Osler)	
1886	Ribbert proposed sex cord aberration theory	
1892	First known long-term (34 years) survivor operated upon by Abbe	
1894	Birch-Hirschfeld unified diverse terminologies	Discovery of X-ray (Roentgen)
1895	–	First radiotherapy for breast cancer (Grubbe)
1899	Busse proposed metaplasia theory	
1899	Marx Wilms published monumental monograph on mixed renal tumors	
1915	Suggestion of radiotherapy by Heimann	
1916	First report of radiotherapy by Friedlander	
1928	–	Discovery of penicillin (Fleming)
1940	Discovery of actinomycin by Waksman	
1960	First use of actinomycin D by Faber	
1963	Introduction of vincristine	
1967	Formation of Pediatric Oncology Club, the forerunner of SIOP	
1967	Formation of Children's Cancer Group	
1968	Formation of NWTS group	
1969	Formation of SIOP	
1971–1975	–	Invention of CT scan (Hounsfield)
1978	Prognostic subtyping of histology (Beckwith)	
1979	Formation of Pediatric Oncology Group	
1991	Formation of IPSO	
2000	Merging of various cooperative groups under Children's Oncology Group	

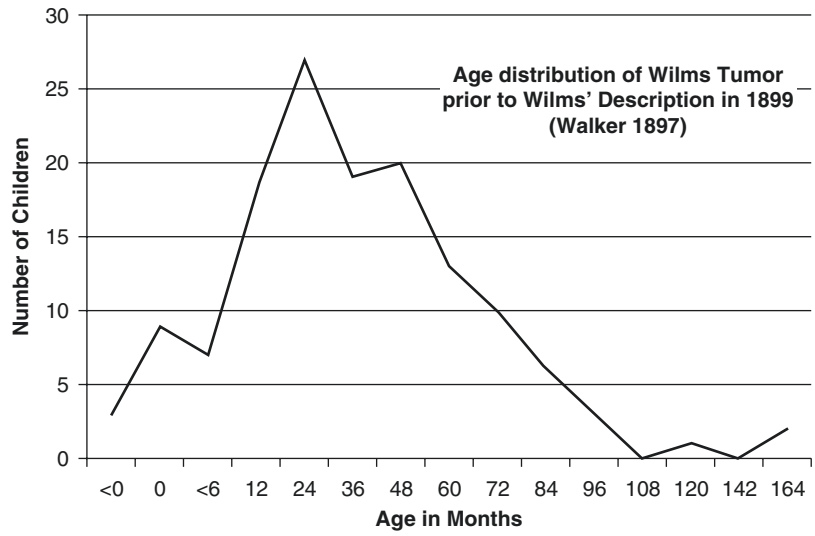

Fig. 1.9 The nineteenth century age distribution of Wilms' tumor (graph is constructed from the data of 150 patients reviewed by Thomas Walker in 1897)

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Epidemiology

2

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2.1 Introduction

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of the health problems. Epidemiology plays an important role in identifying the etiology and pathogenesis of various diseases including malignancies.

2.2 Incidence and Geographical Variation

Wilms' tumor (WT) is the most common renal tumor of childhood, affecting seven to eight per million person years in children. It accounts for 95% of all pediatric renal cancers and 6% of all cancers below 15 years of age [1–3]. More than 77% of children are diagnosed before 5 years of age [4]. Most of the tumors are unilateral with the incidence of bilateral WT ranges from 5 to 7% [1, 4, 5].

The gender-specific incidence is almost similar with slight female preponderance in most of the regions except in Eastern Asia [3, 6]. Initially the WT was thought to be an "index tumor" of childhood with little variation in tumor incidence between the different countries and ethnic groups [7]. However, the recent data has revealed the difference in incidence between different geographic regions and ethnic groups within that geographic region [8]. Cunningham et al. analyzed World Health Organization (WHO) International Incidence of Childhood Cancer (IICC) Volume III dataset and found that the median global incidence of WT was 7.7 (IQR 5.5–9.1) age-specified rate per million (ASR/million) [8].

Though the low-income countries (LIC) had the highest median incidence of WT at 9.8 (6.2–16.4) ASR/million, but the difference was not found to be statistically significant. The limited data from the LIC was one of the limitations of that analysis [8].

Steliarova-Foucher et al. did the study of the population-based registry of childhood cancer of the decade 2001–2010 [9]. World standard age-standardized rate (WSR) of 4.1 per million person years for the renal tumors was found to be lowest for India. The incidence varied in various geographic regions. The Eastern and Western Europe had WSR of 9.8, while Sub-Saharan Africa had the WSR of 6.7. The WSR in Native Americans in the USA was 9.3 in comparison to the highest WSR of 10.9 in American Blacks. Interestingly, the Asians and pacific islanders residing in the USA had the low WSR of 4.2, similar to that in Eastern and Southern Asia. This

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indicates that ethnicity plays a major role on incidence of WT than the geographic residence [9].

2.3 Age and Sex Predisposition

There is slight female preponderance of the tumor with male-to-female ratio of 0.92:1.00 for those with unilateral disease and 0.68:1.00 for bilateral disease in the USA [10]. The mean age at diagnosis is about 6 months earlier in boys than girls. The mean age of diagnosis is 41.6 months in boys and 46.9 months in girls for unilateral disease [10]. It has been noted that patients of either gender with bilateral disease present approximately 1 year before those with unilateral disease. The unilateral multifocal tumor was found to be intermediate between unilateral and bilateral disease. The mean age at diagnosis for those who present with bilateral disease is 29.5 months for boys and 32.6 months for girls [10].

Pastore et al. extracted the data from the datasets of the Automated Childhood Cancer Information System (ACCIS) during the period 1988–1997 and analyzed the malignant renal tumors incidence and survival in European children. In their report male-to-female ratio was 0.9. There were bimodal peaks at age 1 and 3 years. The median age at diagnosis was 2 years for males and 3 years for females [4].

The median age at diagnosis of WT in South Africa has been reported to be 39 months, while the French African Pediatric Oncology Group found it to be 36 months [11, 12].

The NWTS data shows that WT occurs earlier in persons with Asian descent. The age at diagnosis was late in Blacks than Whites [10]. Similar trend was seen in international data and in Britain [6, 13]. All WT associated with congenital malformations except hemihypertrophy have younger age at diagnosis [10].

2.4 Causative Hypothesis and Role of Environmental Factors

The normal kidney develops from mesenchymal stem cells, under the inductive influence of ureteric bud on metanephric blastema. These metanephric blastemal cells completely disappear 4–6 weeks prior to birth. The abnormal persistence of these cells is labelled nephrogenic rest (NR), and multiple rests are called nephroblastomatosis [14, 15].

Most of these nephrogenic rests remain either dormant or regress, but some undergo hyperplastic or neoplastic proliferation. The neoplastic proliferation can either be benign (adenomatous rests) or malignant (WT) [14]. It has been hypothesized that mutational events in utero may be responsible for this abnormal presence of NR [15]. Higher incidence of WT in association with some congenital malformations and syndromes also suggest the role of mutation in its causation. The genetics and molecular biology of the WT has been discussed in detail separately, so we will not elaborate it further in this chapter.

The molecular and genetic studies may explain the inherited abnormalities and demonstrate the type and exact site of mutations. To identify the cause of new mutations and other acquired changes in the genome is still a challenge. The epidemiologic studies try to fill this gap by trying to identify the environmental causes of these acquired changes and determine the interaction between carcinogen and the genome [15]. WT being a rare disease, the case control studies are the most feasible studies to determine the causative factors leading to WT. The difficulty of conducting etiologic epidemiologic studies due to the rarity of WT has been circumvented by coupling the etiologic studies to the studies of the results of the Wilms tumor [15]. Various case control studies have been conducted to study the role of paternal occupational exposure and maternal occupational and hormonal exposure during pregnancy [16–22]. The various maternal exposure studies included radiation exposure, oral contraceptives, pesticides, tea, coffee, alcohol, hair dye, vaginal infection, etc. The paternal occupational exposure studies included exposure to hydrocarbon, lead, boron, paper mills, and farming with pesticides use before birth.

There have been inconsistencies in the pattern of exposure, and most of the studies had small number of cases. Based on this it seems unlikely that environmental exposure has any significant role to play in the pathogenesis of WT [15].

2.5 Syndromic and Non-syndromic Associations

WT is known to be associated with some predisposition syndromes, genetic abnormalities, and clinical malformations. Several overgrowth syndromes such as Beckwith-Weidman syndrome (BWS), Perlman syndrome, and Simpson-Golabi-Behmel syndrome have been associated with WT [23, 24]. BWS is the most common overgrowth syndrome with estimated prevalence of 1 in 14,000 [24]. It is linked with genetic or epigenetic abnormalities in WT2 gene at 11p15 region. Mutations of WT1 gene at 11p 13 is associated with other predisposition syndromes like Denys-Drash Syndrome (DDS), Frasier syndrome, WAGR syndrome, and bilateral WT [25]. Approximately 90% of the patients with DDS, 30% with WAGR syndrome, and 20–30% with BWS develop WT [24, 26, 27].

The non-syndromic malformations associated with WT include hemihypertrophy and genitourinary malformations. Hemihypertrophy may be isolated or can be associated with other predisposition syndrome like BWS. The risk of WT in patients with hemihypertrophy is 3–5% [24, 25]. Similarly, genitourinary malformations can be associated with other syndromes like DDS or WAGR. Isolated genitourinary malformations associated with WT include undescended testis, hypospadias, or kidney abnormalities. About 5% of the patients with WT have been found to have associated genitourinary malformations [24, 25].

2.6 WT in Low-Income Countries

The cooperative group clinical trials have demonstrated excellent results with more than 90% 5-year overall survival (OS) rate in WT [28, 29]. However, the OS of WT is still poor in developing countries and countries with lower socioeconomic development [30–35]. Several studies have been conducted to find out the causes of the sub-optimal results in LIC. It has been noted that Sub-Saharan African region has the high incidence of WT, delayed presentation, advanced stage at the time of diagnosis, and dismal outcome [35]. Rabeh et al. retrospectively reviewed the clinical records of 35 children with WT at a cancer institute in Lebanon. Half of their patients presented with advanced stage disease (III and IV), and a similar trend has been noted in most of the low- and middle-income countries (LMIC) [36]. The rate of bilateral tumors was also higher in their series (11%) than that observed in high-income countries.

This inferior outcome in developing countries may be due to socioeconomic factors like malnutrition, delayed and advanced stage of presentation, limited healthcare facilities, abandonment of the treatment, etc. However, there are some pointers like high incidence, higher proportion of bilateral tumors, and advanced stage at presentation suggesting that these tumors are biological different leading to the poor outcome. Murphy et al. did the molecular characterization of the WT patients of Kenyan origin (Sub-Saharan Africa) [35]. Based on the clinical features, DNA sequencing, immunohistochemistry, and imaging mass spectrometry (IMS), they suggested that these tumors have molecular features of aggressive phenotype. Thus, this unique tumor phenotype may be responsible for the disease aggressiveness and resistance to chemotherapy in this ethnic group [35].

2.7 Role of Tumor Registries

Tumor registries receive and collect data about cancer patients. These registries provide an important epidemiological data to the health professionals, researchers, administrators, and health policy makers. Tumor registries can be either population-based or hospital-based. The population-based registries collect data about the cancer from the general population. In comparison, the hospital-based registries maintain and collect the data about all the cancer patients managed in that hospital. There are special cancer registries also that maintain and collect data about a particular cancer type. International Association of Cancer Registries has members from most of the countries in the world. The percentage of population covered in these registries

varies widely among different countries. The countries with higher socioeconomic level of development and better treatment facilities have advanced tumor registration system and better reporting than those with LIC with poor socioeconomic system [9].

Benefits and role of the tumor registries include the following:

1. To know the current status of the disease in the population and determining the trends over time
2. To determine the cancer pattern among various populations and subpopulations
3. To identify the etiology and risk factors
4. To help in health policy decision-making by guiding the health resource allocation and determining the impact of various health interventions and cancer control efforts done at population level
5. To help in clinical and epidemiological research

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Genetics and Molecular Biology

3

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3.1 Introduction

Wilms' tumor (WT) is the commonest renal tumor of infancy and childhood. Abnormal molecular signaling during the normal nephrogenesis is known to cause WT. Several genes some known and other few unknown are believed to be associated with the etiopathogenetic of this tumor [1, 2]. The complex molecular pathways in the pathogenesis of WT are being elucidated in the recent years. The genetics and molecular biology of the tumor has opened several avenues ranging from molecular diagnosis, prognostication tools, and personalized approach to syndromic patients. Recent advances such as WT stem cells and newer animal models have opened up interesting research areas.

3.2 Genetic Events in Normal and Abnormal Nephrogenesis

It is interesting to note that normal embryogenesis and the growth of a tumor are very similar, in terms of differentiation, proliferation, and migration of various cellular elements. This is a principle which may hold true for several pediatric solid tumors and is most apt in the formation of WT.

3.2.1 Nephrogenesis Pathways

The normal nephrogenesis that starts around the fifth week of gestation is a complex process. There are three following basic cell lines in the renal development, and their interplay is an intricate process:

1. Epithelial nephric or Wolffian duct
2. Mesenchymal cells, which go on to form the nephrons and
3. Foxd 1 positive cells that is the progenitor line to stromal cells [2]

To understand the nephrogenesis, we need to understand the Wnts, the factors that regulate cell growth, motility, and differentiation during embryonic development [3–6]. Wnt stands for "wingless-related integration site." Wnts act in a paracrine fashion by activating diverse signaling cascades or pathways inside the target cells. Wnt pathways facilitate the induction of nephrogenesis in metanephric mesenchyme by the ureteric bud and mesenchyme-to-epithelial transition (MET) [7]. Wnt pathways are regulated by various genes such as *WT1* and *WT2*

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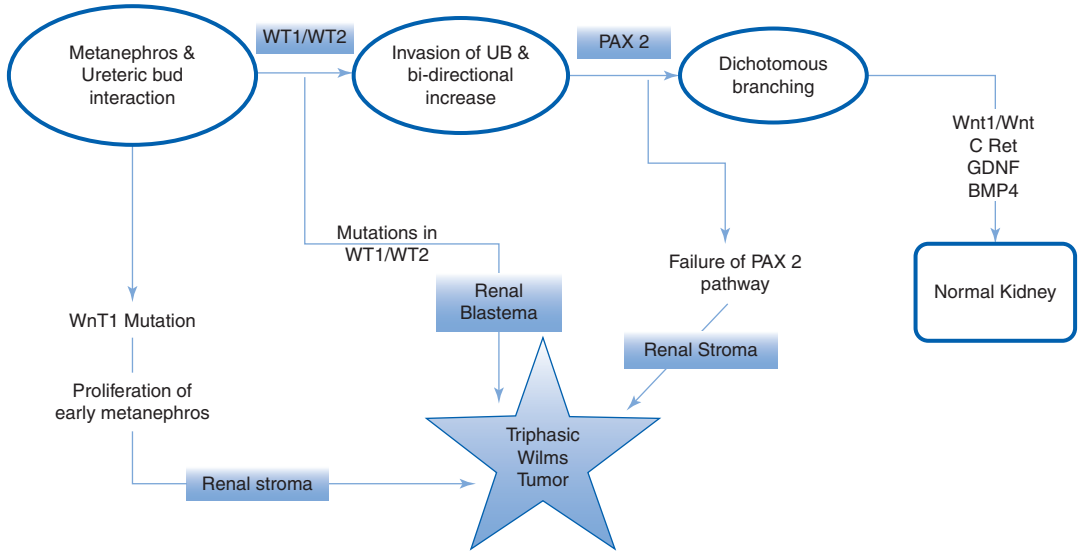

Fig. 3.1 Embryogenesis of WT

and other transcriptional factor/proteins such as β-catenin (which is encoded by CTNNβ1) and SIX2 [4, 8–10].

Under normal circumstances metanephric blastemal cells that are not differentiated will undergo apoptosis [4–6]. But some of these metanephric blastemal cells that failed differentiation would persist as nephrogenic rests (NRs). Though NRs are present even in ~1% of normal kidneys, they are known as precursors of WT [7]. Their presence is noted in up to 40% in sporadic WT and up to 100% in bilateral WT, suggesting that WT is an embryopathy [11].

The persisting NRs may either be hyperplastic, dormant or regressing. Both regressive NRs cells and to some extent hyperplastic NR cells undergo malignant differentiation into WT [6, 7]. NRs are also classified the perilobar (PLNR) or intralobar (ILNR) as per different locations within the kidney, which are placed at. The ILNR are found toward the medulla and are thought to arrive early in the renal development, and PLNR are in the periphery and retain nephrogenic activity up to late in gestation. The possibility of malignant transformation is much higher in the ILNRs as compared with the PLNRs. PLNRs show a strong association with synchronous bilateral WT, whereas ILNRs tend to be associated with metachronous tumors [12].

Mutations in WT1/WT2 and PAX 2 pathways at different steps cause proliferation rather than differentiation into the three cell lines and result in the development of WT (Fig. 3.1).

3.3 Multistep Model for Sporadic WT Development

In 1971, Knudson proposed a two-event hypothesis with a double-hit model [13]. He proposed that there will be a genetic factor and then a second mutation is required for final phenotypic expression of WT. The second mutation can be spontaneous or acquired. This theory supports renal NR cells forming WT at one end and the benign metanephric adenoma on the other (Fig. 3.2). The first hit on the NR cells is either germline, or a somatic genetic change that either promotes oncogenes or causes loss of imprinting in PLNR. Around 36 weeks of gestation, the second hit occurs either by way of p53 mutation, or 16q mutation. These mutations add malignant potential to NRs that are already primed by either *WT1* or *WT2* gene [14].

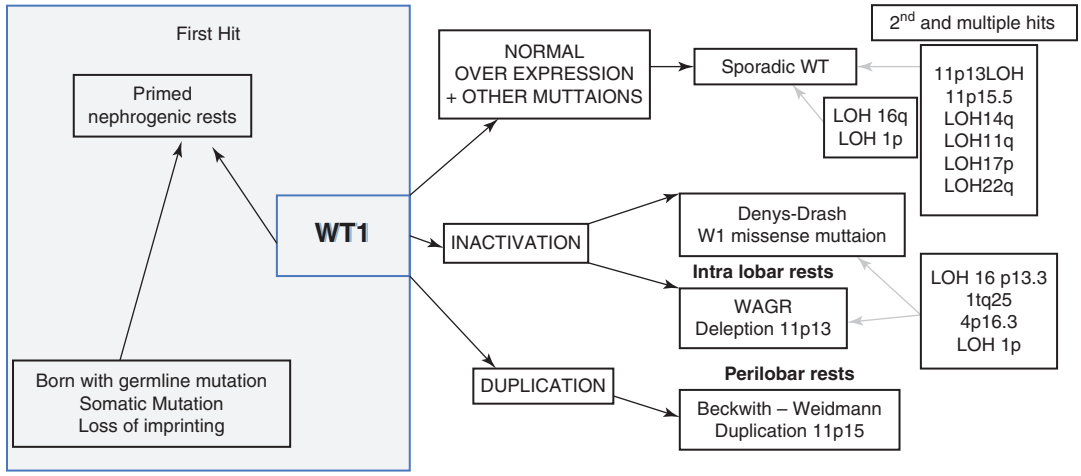

Fig. 3.2 Illustration showing first hit as WT 1 primed NRs and other mutations as second and other hits

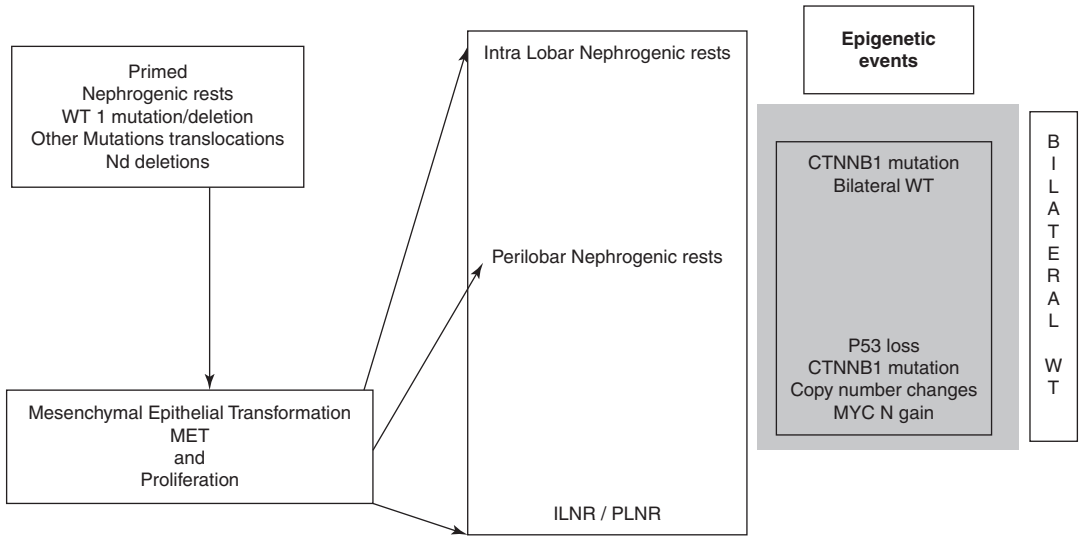

Fig. 3.3 Multiple events involved in bilateral WT

There are multiple genetic and epigenetic changes that are considered to result in WT (Fig. 3.3). Genetic changes denote genetic mutations, deletions, and insertions. Epigenetics literally means "above" or "on top of" genetics [15]. It refers to external modifications to DNA that turn genes "on" or "off." These modifications do not change the DNA sequence, but instead, they affect how cells "read" genes. So, they can affect the ways the genes work. For example, DNA methylation—the addition of a methyl group, or a "chemical cap," to part of the DNA molecule, prevents certain genes from being expressed [15]. The genetic and epigenetics changes associated with WT are detailed below.

3.4 Genetic Changes and WT

Numerous genetic changes have been found associated with tumorigenesis of WT. The first gene to be identified was WT1 at 11p13 [8, 9].

As mentioned earlier most cases of WT are sporadic and non-syndromic, and approximately

5% of these children have mutations at WT1 or WT2 (11p15.5). The known syndromic conditions like Wilms' tumor, aniridia, genitourinary malformations(s) and intellectual disability (previously termed as mental retardation) (WAGR), Denys-Drash syndrome (DDS), and Beckwith-Wiedemann syndrome (BWS) have mutations of *WT1* or *WT2* in about 10–15% cases [16].

Familial disease is known to be associated with *FWT1* and *FWT2* genes; these are localized at 17q12-21 [10] and 19q13.33-13.41 [17]. Another associated gene is the CTNNB1 at 3p22.1 which is commonly mutated in most tumors with WT1 mutations [18]. This gene encodes β-catenin and is present in approximately 15% of WT patients [19]. *WTX* and *TP53* are other genes implicated in WT formation in children [20]. Various other somatic genes with prevalence of more than 5% include *AMER1* (Xq11) [21], *MYCN* (2p24) [22], micro RNA processing genes (miRNAGs) [23, 24], *SIX1* (14q23), and *SIX2* (2p21) [25, 26]. The mutations may be somatic or germline, the latter being more predominant in the syndromic WT patients.

In a large cohort of 125 patients, analysis of five crucial genes (*WT1*, *WT2*, *WTX*, *CTNN*β1, and *TP53*) was studied. Tumorigenesis-associated aberrations were noted in 12% WT1 and 69% *WT2* genes. These changes were also seen in the nephrogenic rests. The remaining three genes *WTX* (32%), *CTNN*β1 (15%), and *TP53* (5%) are thought to contribute to tumor progression instead of tumor initiation [27].

3.4.1 WT1 and WT2

The *WT1* is essential for the normal embryogenesis of the kidney and is responsible for the maintenance of the ureteric bud and the differentiation of the renal blastema into the nephrons [28, 29]. *WT1* encodes a zinc finger transcription factor and consists of a C-terminal zinc finger DNA-binding domain and an N-terminal transactivation domain and occurs in multiple alternatively spliced isoforms [30].

The *WT2* mutations are the commonest genetic defect in sporadic WT. It occurs in the region of 11p15.5. Out of this cluster of genes insulin-like growth factor II (*ILG2*) and *H19* are the most extensively studied. Satoh et al. in their study showed more than 80% loss of heterozygosity (LOH) or loss of imprinting (LOI) at 11p15.5 in a series of 35 patients [31]. In most of the cases of WT, the underlying molecular aberrations may determine the type of histologic features of WT and the type of accompanying NRs (ILNR vs PLNR).

3.4.2 CTNNβ1

This gene present at 3p22.1 encodes β catenin, which plays an important role in cell-to-cell adhesions and gene transcription. Mutations of *CTNN*β1 have been studied in cancers of the breast, ovary, colon-rectum, and endometrium. In WT, the Wnt pathway has a strong association with *WT1* mutations. These mutations and overexpressions may be required in the later stages of the WT development as the overexpression is not seen in the normal kidney and nephrogenesis [29, 32, 33].

3.4.3 WTX

Another gene known to play a role in kidney development is the *WTX*. It is situated on the X chromosome, near the centromere, and encodes a protein with no specifically known function [34]. Somatic mutations in the *WTX* may be as high as 30% in patients of WT. Germline mutations in the *WTX* cause a rare syndrome (sclerosing skeletal dysplasia, osteopathia striata congenita with cranial sclerosis) and are not associated with WT [35]. Downregulation of this gene is known to cause signal defects in the Wnt pathway, possibly causing tumorigenesis in WT [36].

3.4.4 MYCN, 16q and 1P, and TP53

MYCN amplification and its impact on the outcome of neuroblastoma and various other adult malignancies are well established. This proto-

oncogene encodes *MYCN*, which plays a crucial role in cell growth, proliferation, differentiation, and apoptosis [37]. Recently, amplification of this oncogene has been reported in WT with low penetrance. It is associated with the poorer prognostic diffuse anaplastic WT [38]. There are interesting research prospects using gene therapy to alleviate the outcome in the poor prognostic tumors.

LOH at 1p36 and 16q21-24 have been reported with approximately 10–17% of WT. These patients had a significantly worse overall survival and relapse-free survival. The exact mechanisms of these gene loci alterations and their effect on tumorigenesis are not clearly defined as yet [39].

TP53 is a tumor suppressor p53 gene located on the 17p13.1 locus. It is the commonest mutated gene in human malignancies. In WT it is a marker of anaplasia and poorer outcome and seen in almost 75% of these tumors. TP53 in WT indicates tumor progression [40].

3.5 Newer Genes

DROSHA and *DGCR8* are two new genes discovered recently. If these are defective, they disrupt the molecular machinery responsible for creating mRNAs. mRNAs are able to regulate the function of a large number of messenger RNA molecules and thus completely reprogram cells. Identification of these genes along with other transcription factors might lead to development of personalized treatment in WT [26].

3.6 Other Forms of WT and Associated Genetic Changes

Bilateral WT is more frequently associated with germline genetic and epigenetic aberrations. During embryonal development, MET and proliferation (Prol) are influenced by mutation in *CPNNB* gene on ILNR and PLNR. Primed ILNR/PLNR leads to formation of bilateral WT [41]. Additional factors include p53 loss, large copy number changes, and MYCN domain. These p53 loss, β catenin 1 (CTNNβ1) mutation, DNA copy number change, and MYCN number change are usually late events.

3.7 Syndromes Associated with WT

Syndromes associated with WT include WAGR (11p13), Denys-Drash (11p 13/Point mutation), Frasier (11p13, Beckwith-Wiedemann (11p15/IGH.H19), Simpson Golaib-Behmel (Xp26/cpg point mutation), Familial WT (17 q12-21) and Familial WT2 (19q13.3).

Additional manifestations of WAGR syndrome such as aniridia are due to continuously deleted autosomal gene like *PAS6*. They are both located on 11p13 with w15.

3.8 Epigenetic Changes and WT

All the above genetic loci follow either classic mutational or cytogenetic mechanism. Recent investigations reveal changes particularly DNA methylation occurring on chromosome 11 at 11p13 and 11p15 [42].

3.8.1 Epigenetic Changes at 11p15

An observation made regarding LOH at 11p was loss of maternal allele, thus indicating involvement of *WT2* genes. These imprinted genes can behave like clusters at 11p15 containing IGF-11 growth factor on paternal allele and maternal allele. Inhibitory gene like H19 and CDKinase (p57) loss of imprinting also has been shown biallelic expression of IGF-2 expression. This is associated with hypermethylation on a normally methylated maternal allele [43, 44]. Imprinting gene may be playing a role in early stages of tumorigenesis. Allelic imprinting of11p15 was also observed in fetal overgrowth syndrome, Beckwith-Wiedemann syndrome, and some familial WT.

3.8.2 Epigenetic Changes at 11p13

11p13 locus was observed to be abnormally hypermethylated in some adult malignancies. Maternal allele gets methylated, while paternal allele remains non-methylated in normal nephrogenesis. Therefore, two hypomethylated alleles of 11p13 may be involved in some WT and non-Wilms' renal tumors, but common observation is hypermethylated as a tumor-specific epigenetic variation at 11p locus [31].

Genomic and biological characteristics of WT are increasingly being recognized to play an important role in tumor behavior and response to therapy and are now being incorporated more and more in treatment planning. The most important biomarkers currently being studied are loss of heterozygosity (LOH) at 1p and 16q and chromosome gain at 1q.

Gain of chromosome 1q is the most common cytogenetic abnormality found in 28% of patients in NWTS 5 [45, 46]. It is the single most powerful predictor of poor response, relapse, and poor outcome and overrides all other biomarkers being currently studied. In the presence of 1q gain, neither 1p nor 16q loss is significant [45, 46]. In patients with 1 q gain, there is significantly lower EFS and OS on stage by stage basis.

16q and 1p are believed to carry additional tumor suppressor or progression genes. LOH at 16q and 1p are present in 17% and 11% of WT, respectively, and carries worse prognosis [39]. However, they have an independent effect on tumor behavior only in the absence of 1q gain [46].

To conclude, several poor prognostic subgroups may benefit from novel therapies, targeted at these potential points during tumorigenesis. Whether these advances will improve the clinical outcome in these children remains to be seen as the genetic landscape of this complex tumor further unravels.

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4 Tumor Microenvironment and Inflammatory Markers

G. Raghavendra Prasad, Wafa Yasmeen, and Mohammed Ikram

4.1 Tumor Microenvironment

Although the concept of tumor microenvironment (TME) dates back to Virchow in the nineteenth century who had first described neutrophils and lymphocytes in tumors, it was only in the 1990s that the critical role of TME in the genesis, maintenance, and survival of the tumor cells was well understood. The second hit in Knudson's poly-hit model of tumorigenesis in Wilms' tumor (WT) is now believed to be due to environmental factors and local immune inflammatory changes in and around malignant tumor. The malignant tumor cells and the TME can be compared to the seeds and soil [1]; they are known to work in tandem.

TME was probably most beautifully elucidated by Karin in the year 2006 [2]. TME comprises of the peri-tumoral cellular components and the non-cellular components (extracellular matrix) (Fig. 4.1). The peri-tumoral cellular components include *the inflammatory and immune cells* such as adaptive immune cells (T and B lymphocytes) and innate tumor cells (tumor-associated macrophages (TAM), monocytes, and mast cells), and *nonimmune cells* like tumor-associated fibroblasts (TAF). *Noncellular components* include various matrix enzymes and proteinases, for example, matrix metalloproteinases [3].

The immune cells, working through both the innate and adaptive immune pathways, mediate through various cytokines, chemokines, growth factors, reactive oxidant species and nitrogen species proteases, and other bioactive molecules (Fig. 4.1). These cells and their cytokines function by both autocrine and paracrine effects. This assembly of inflammatory and immune cells along with their mediators is termed as tumor inflammatory immune microenvironment (TIIME) [2].

Malignancy is characterized by relentless growth, uncontrolled and dysregulated proliferation, metastasis, evasion of host's immune response, and neoangiogenic properties [1]. It is the TME that causes dynamic interplay between the different components and helps to resist host immune surveillance and bypasses the host immune suppression with self-perpetuating bidirectional dynamic interaction, thus initiating, promoting, preserving, and maintaining the survival and proliferation of malignant tumor cells (Fig. 4.2).

4.2 TME and Genesis of WT

Development of WT is known to follow Knudson's poly-hit model. The multiple hits are either inherited or acquired during the period of embryogenesis. Currently, surgery radiotherapy and chemotherapy in combination achieve high cure rates in most of the patients of WT. But the

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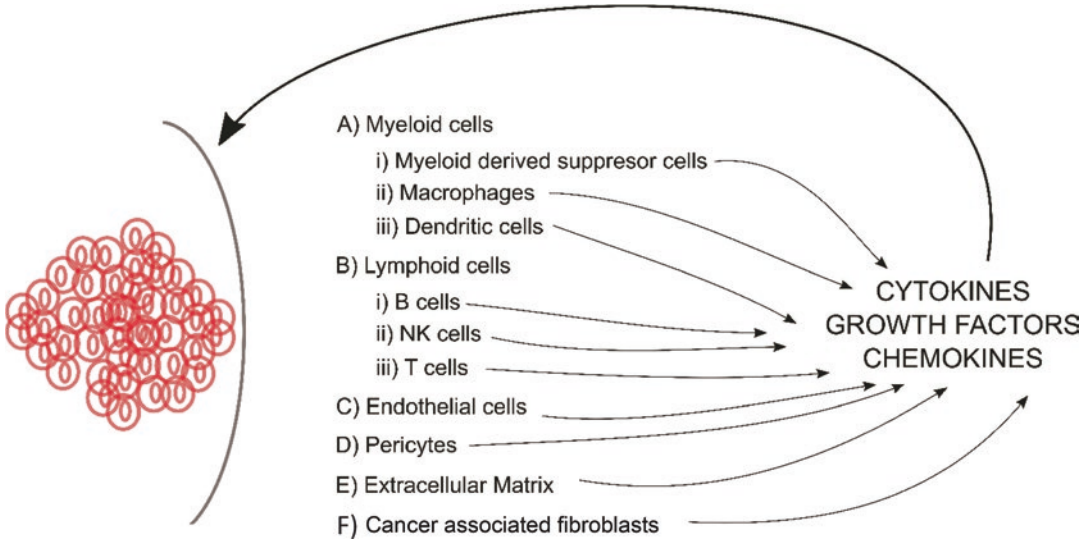

Fig. 4.1 Components of TME

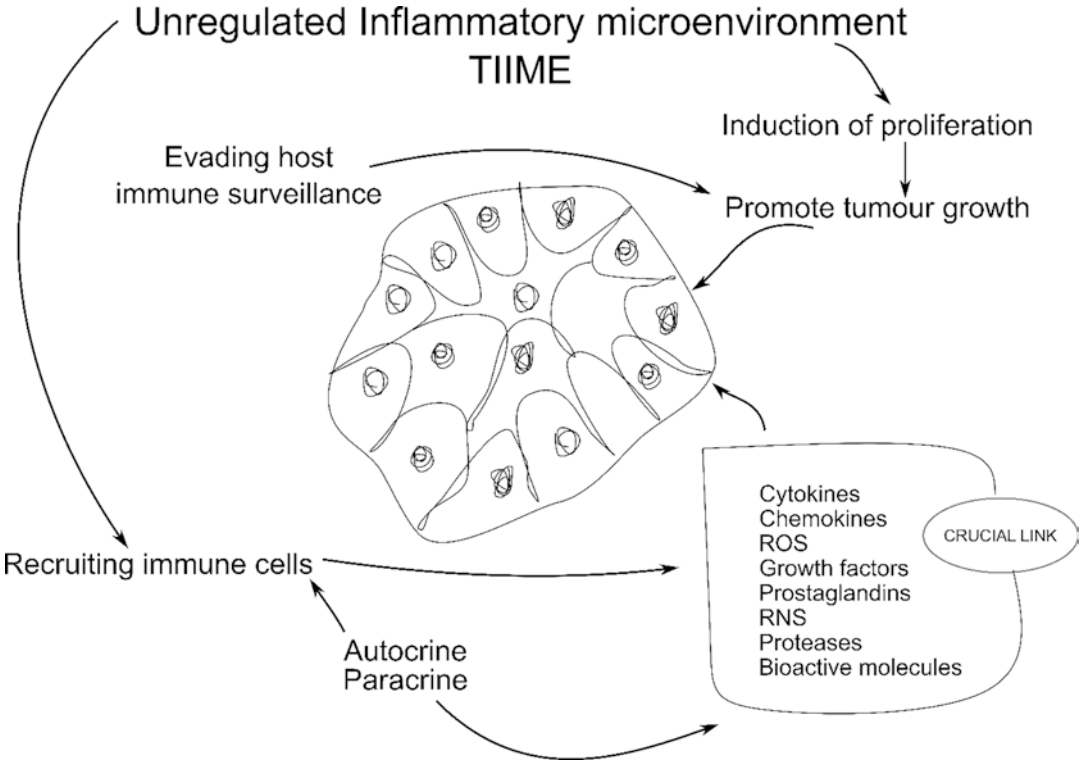

Fig. 4.2 TIIME promoting tumor creating tumor-friendly and tumor-protecting milieu

relapsing, chemoresistant, and metastatic WT continue to throw challenges. Understanding of TME and use of the inflammatory mediators may throw some answers to these difficult subsets of WT.

Not much has been studied about the role of TIIME in WT as compared to adult solid tumors like renal cell carcinoma. Vakkila first documented macrophages and T cells in human WT [4]; the study, however, was incomplete because

only two immune cell markers were used [5]. Others observed cyclooxygenase-2 expression ubiquitously in all WT [6, 7]. This phenomenon was observed in WT independent of stage and differentiation [7]. Karth et al. studied hypoxia-inducible factor-1α (HIF-1α) in WT and provided support to the fact that the TME plays an important role in WT genesis [8]. HIF-1α, produced by hypoxic tumor-associated immune cells, induces production of vascular endothelial growth factor (VEGF), and its effect on tumor neoangiogenesis, tumor growth, and tumor progression are well established. Further, Maturu et al. studied the inflammatory markers of immune cells in WT both quantitatively and qualitativels [9].

Genetics and epigenetic changes are critical in maintaining the cell homeostasis; any aberration leads to progression of cancer [1, 10–12]. The cytokines, chemokines, free radicals, growth factor enzymes, and prostaglandins like COX2 are involved in inducing genetics and epigenetic changes [6]. TME-mediated cytokines and chemokines are also known to influence a number of genes, *WT1* gene CTNND1 and *WTX1* gene (Fig. 4.3) [13, 14].

4.3 Immune cells, Inflammation, and Their Effect on Tumor Progression

Inflammation is tightly controlled, initiated, modulated, suppressed, and augmented by immune cells, and the immune cells could either promote or suppress the tumor (Fig. 4.4). The distribution of pro-tumor and anti-tumor immune cells that induce expression of various inflammatory markers (described below) confirms the existence of TIIME in WT.

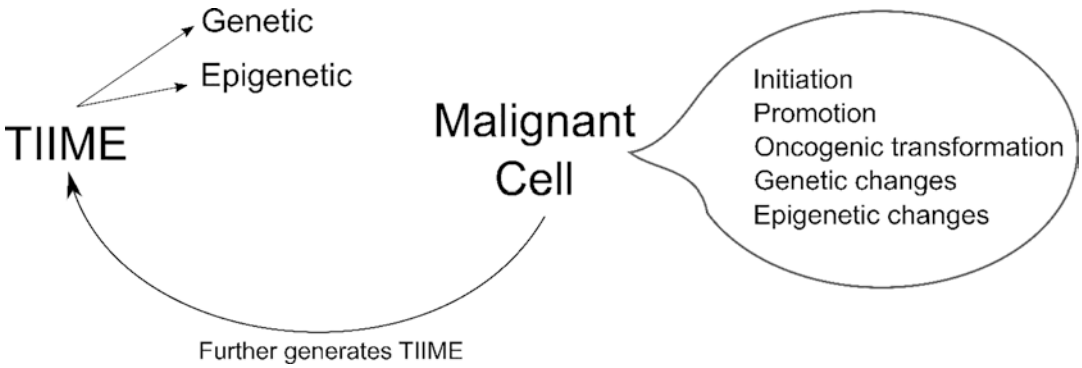

Fig. 4.3 TME-mediated genetic and epigenetic changes

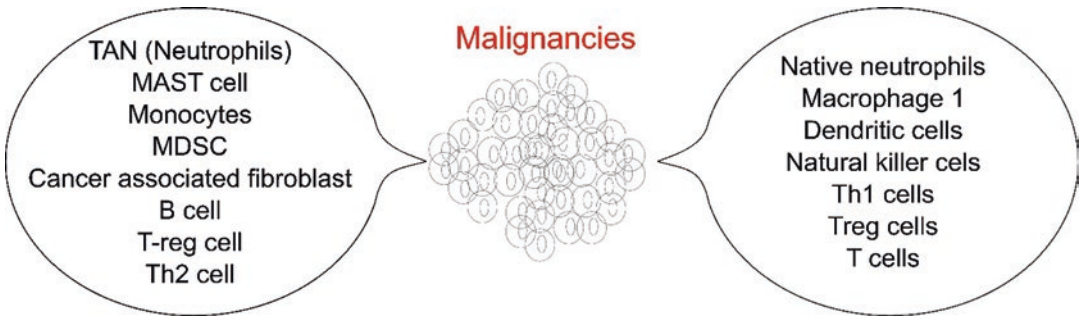

Fig. 4.4 Tumor promoting (left) and tumor suppressing (right) immune cells

4.3.1 WT and Immune Cells

WT is an undifferentiated mesodermal tumor constituting blastemal, epithelial, and stromal components [8, 9]. WT is now known to be infiltrated by both adaptive and innate immune cells [5]. Adaptive immune cells are confined to tumor stroma, whereas innate immune cells are predominantly found in the tumor stroma as well as in the other components of the tumor. This results in differential localization of chemokines and cytokines produced by the respective immune cells.

4.3.2 WT and B Lymphocytes

cd20+ B lymphocytes were seen scattered both within and outside the WT but were characteristically absent in normal kidney tissue in the excised specimens. The inflammatory cell patterns were much more prominent in the peri-tumoral area as compared to intra-tumoral area. This may have a role in evasion of host immune response [9].

4.3.3 WT and T Lymphocytes

Similarly, WT is heavily infiltrated with CD3+ T cells (adaptive immunity) as compared to normal renal tissue [9]. The T cells that are otherwise abundantly seen in tumor stroma are also observed in the epithelial and blastemal components. A huge number of T cells were seen in tumor islands in peri-tumoral zone. Far more T lymphocytes were seen in the peri-tumoral zone as compared to within the tumor [9].

4.3.4 WT and Macrophages

cd68+ macrophages were abundantly seen in tumor stroma, whereas T and B cell lymphocytes were found in the blastemal and epithelial elements [9]. The cd68+ macrophages are closely related to the advancing edge of tumor.

4.3.5 WT and Tumor-Infiltrating Neutrophils (TIN)

Tumor-infiltrating neutrophils (TIN) like TAM are predominantly present within epithelial and blastemal areas and to a lesser density in stromal regions of WT and show tumor-centric distribution. This feature is more clearly observed in WT with anaplastic histology [9].

4.3.6 WT and Mast Cells

Maturu observed mast cells in TME [9]. Mast cells were primarily distributed in invading areas of WT. Mast cells were found in small groups around neoplastic cells within the stroma and peri-tumoral area and were characteristically absent in intra-tumoral, epithelial, and blastemal zones.

4.3.7 Tumor Cell-Immune Cell Interaction and Expression of Inflammatory Mediators in WT

The distribution of pro-tumor and antitumor immune cells such as TAMs and the expression of the inflammatory markers that they induce in the tumor stroma confirm the existence of TIIME in WT (Table 4.1) [9, 15]. TAMs are known to be involved in the production of proangiogenic factors like transforming growth factor beta (TGF-beta), interleukin 10 (IL-10), and prostaglandin E2 (immunosuppressive chemokines).

TIIME in WT upregulates downstream pathway promoting tumor growth initiation, spread, metastases, and tumor immune resistance through upregulated expression of inflammatory markers such as phosphorylated extracellular signal regulated kinase 1 and 2 (p-ERK) and cyclo-oxygenase-2 (COX2) described below [7, 15, 16].

Table 4.1 WT and inflammatory markers

Marker	Epithelial	Blastemal	Stromal	Normal kidney	Assoc. immune cells	Function and relevance
COX2	0-+	0-+	++++	0-+	TINs, TAF	• COX2 inhibitor reduces metastasis
HIF alpha	++++	++++	++++	0-+	TINs, TAFs	• Similar to COX2 • No correlation with clinicopathological variables
p-ERK 1 & 2	0	++	+++	0-+	TINs	• Similar to COX2, VEGF, HIF-α
p-STAT 3	0	++++	++++	0-+	TINs, TAMs, CD3 + T cells, B cells	• Similar to COX2 • Correlates with progression • Unfavorable prognosis
i NOS	0	++++	++++	nil	TINs, TAMs	• Higher in tumoral and peri-tumoral area
NT	0	++++	++++	0-+	TINs, TAMs	• Localized to tumoral area • Absent in peri-tumoral area
VEGF	++	++	++++	PCT and DCT	TINs, TAMs, MCs, CD20, CD3	• Similar to COX2, HIF-1α
CITED-1	0	_+++	0	0		• Blocks MET • Indicates disseminated disease at presentation • Marker primitive blastema • Adverse effect on development of WT
B7-H1	-	-	-	-	TAMs	• Induces T cell apoptosis leading to reduction of host antitumoral response • Increased risk of recurrence in favorable histology • Indicates aggressive behavior • Helps to differentiate aggressive FH and low risk UH
CD 44	+++	+++	++++			• CD 44 v5 correlates with tumor stage, clinical progression, tumor related death • Prognostic marker for high risk of metastasis
CA 1X	+	++	+	nil		• Upregulated in untreated WT • No correlation with clinico-pathological variables, • Correlates with HIF-1α • Both in normoxic and hypoxic conditions

COX2 cyclo-oxygenases 2, *HIF-1α* hypoxia-inducible factor-1α, *p-ERK 1 and 2* phosphorylated extracellular signal-regulated kinases 1 and 2, *p STAT 3* phosphorylated STAT 3, *I NOS* inducible nitric oxide synthetase, *NT* nitrotyrosine, *VEGF* vascular endothelial growth factor, *CITED 1* CBP/p300–interacting transactivators with glutamic acid [E]/aspartic acid [D]-rich C-terminal domain, *B7 H1* B7 Homolog1, *CD 44* cluster of differentiation CD44, *CA 1X* carbonic anhydrase 1X, *FH* favorable histology, *UH* unfavorable histology

4.3.8 WT and COX2

Diffuse and strong cytoplasmic expression of COX2 immunoreactivity is observed both in intratumoral and stromal regions. COX2 expression, on the other hand, is almost absent in renal interstitial cells and glomeruli. TAF are also reactive for COX2 protein. The expression of COX2 is known to be ubiquitous and independent of type and stage of tumor [6, 17].

Lee et al. observed that when COX2 was inhibited, it led to prevention of neoangiogenesis and survival of the orthotopic xenograft model of WT [12]. COX2 inhibitors also inhibited tumor metastasis neoangiogenesis in pediatric WT model [6].

4.3.9 WT and Phosphorylated Extracellular Signal-Regulated Kinase 1 and 2

Inflammation leads to upregulation of insulin growth factors (IGF-2) that in turn induces pERK 1 and 2 pathways [18], and this results in proliferation and neoangiogenesis in WT [19]. p ERK 1 and 2 expression and signaling are expressed predominantly in stroma and blastemal cells and absent in epithelial cells [9].

4.3.10 WT and HIF-1α

Hypoxia-inducible factor 1 alpha (HIF-1α) is expressed in blastemal stroma and epithelial components and has a prominent nuclear localization [9]. HIF-1α expression resembles COX2 expression. The overexpression HIF-1α was reported by Dungwa [20]. This HIF-1α expression does not correlate well with clinicopathological variables.

4.3.11 WT and VEGF

The expression of VEGF and its receptors (VEGF-C, VEGFR 2) in stromal and epithelial components correlates with an unfavorable outcome and may suggest usefulness of antiangiogenic treatment strategy [9].

4.3.12 WT and Phosphorylated STAT 3

Phosphorylated STAT 3 (p stat 3) predominantly is confined in the nucleus and absent in the cytoplasm in WT. P STAT 3 expression was confined to tumor stroma and blastemal region and tumor islands near tumor and absent in epithelial cells. The expression of p STAT 3 correlated with TAM and Cd+ T cells and expressions of COX 2 and HIF-1α. Zhang et al. showed p STAT 3 expression predicts unfavorable prognosis and might act as novel therapeutic target [21].

4.3.13 WT and Inducible Nitric Oxide Synthase (iNOS)

iNOS expression in WT was seen in stroma in nucleus and cytoplasm of blastemal cells. The tumor-associated immune cells show high expression of iNOS. The neovascular adhesion around the tumor shows positive expression of iNOS [9].

4.3.14 WT and Nitrotyrosine (NT)

The tumor-associated immune cells in stroma and blastemal epithelial region show Nitrotyrosine (NT) expression in WT [9].

4.3.15 WT and Chemokines/ Cytokines

Metastatic WT predominantly shows excessive expression of chemokines. The chemokines family members like CHCL2 and CHCL7 along with their receptors are seen in metanephric development in animals, and there are required for survival and maintenance of nephrogenic rests [22].

4.3.16 WT and CBP/p300 Interacting Transactivators with Glutamic Acid [E]/Aspartic Acid [D]-rich Carboxy-Terminal Domain (CITED1)

WT arises from CITED1 + mesenchymal-epithelial transition (MET) and is expressed in blastema of developing kidney [23]. Increased expression of CITED1 in WT influences rapid proliferation in vitro [24]. Persistent expression of CITED1 might play an adverse role in pathogenesis of WT.

4.3.17 WT and B7 Homolog 1

B7 Homolog 1 (B7H1) is a T cell coregulatory ligand and an important regulator of T-cell-mediated immunity [25, 26]. The expression of B7H1 correlated with tumor biology and is associated with increase recurrence with favorable histology [26]. Thus, the B7H1 expression may be a future prognostic marker showing aggressive behavior in favorable histology WT. B7H1+ WT may require aggressive treatment.

4.3.18 WT and CD44

Epithelial, mesenchymal, and immune cells express CD44 [27]. cd44 is observed in all three components of WT. Increased expression of cd 44 genes is associated with metastatic disease CD44 Iso forms and may also indicate good prognosis [28–30].

4.3.19 WT and Carbonic Anhydrase 9

The growth and survival of tumor cells is controlled by carbonic anhydrate 9 (CA9) [9, 31, 32]. Untreated WT shows upregulated expression of CA9. CA9 expression doesn't correlate with clinicopathological variables and metastatic disease in WT following chemotherapy.

4.3.20 WT and PDGF

Platelet-derived growth factor (PDGF) is expressed by most immune cells and TAFs in stroma similar to COX2 and HIF-1α [33].

4.4 Future Directions

Blocking COX2 pathway might have a great therapeutic value in the treatment of WT. COX2 can be targeted to prevent and treat malignancies reference [9]. COX2 inhibitors along with VEGF inhibitors might form vascular basis of preventing pro-tumor inflammatory environment. Future therapeutic targets (Fig. 4.5) include ET-BR 3 inhibition, Fas ligand inhibition, VEGF inhibition, 1L-10 inhibition, Granulocyte-macrophage colony-stimulating factor (GM CSF) receptor inhibition, and inhibition of TAF by activating C-X-C receptor (CXCR) signalling pathway [34].

The host resistance to tumors is provided by T cells. But stroma protects the tumors by exclud-

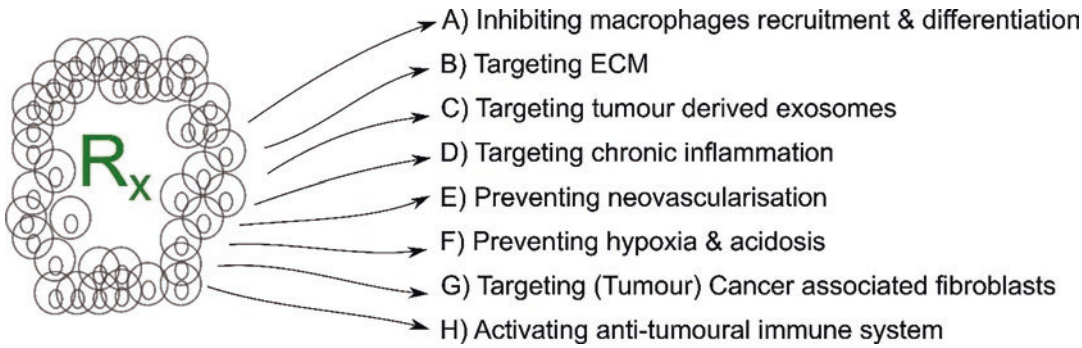

Fig. 4.5 Future therapeutic modalities

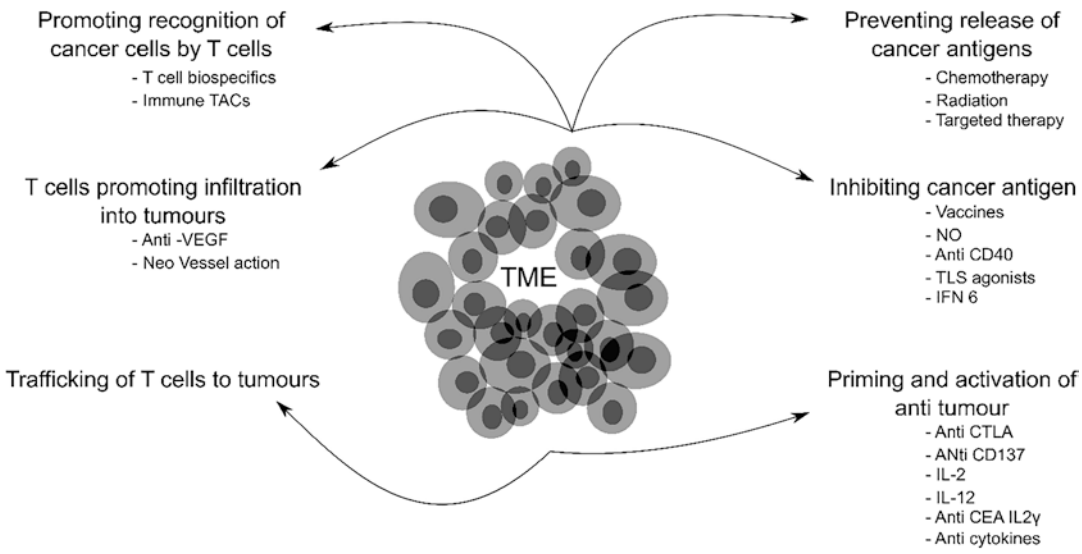

Fig. 4.6 Various available modalities of treatment targeting hallmarks of malignancy

ing T cells so that they cannot come in contact with immunogenic tumor cell. This is called tumor privilege. T cell exclusion check point manipulation may be another tool to overcome tumor immune privilege [35]. Echinomycin, a small-molecule inhibitor of HIF-1α DNA-binding activity, has been found promising as a targeted agent in preclinical WT mice model [36].

Figure 4.6 depicts some of the available therapeutic options targeting various hallmarks of malignancy.

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Syndromic Wilms' Tumor

5

Nitin James Peters and Ram Samujh

5.1 Introduction

Anomalies, either isolated or as part of a syndrome, occur in approximately 10% of children with Wilms' tumor (WT). WT1 and WT2 genes on chromosome bands 11p13 and 11p15.5 act as tumor suppressors and play multiple roles during kidney and gonad development. Several other genes include WTX (on chromosome X), CTNNB1 (chromosome 3), and TP53 (chromosome 17) among others. The genes with their mutations and epigenetic defects associated with tumorigenesis of WT have been described elsewhere.

Among the various syndromes, the moderate to high-risk conditions include WAGR syndrome, Denys-Drash syndrome (DDS), familial WT, Perlman syndrome, and Frasier syndrome. These syndromes may be causative for WT in up to 7–15% of children. There is at the best an anecdotal association between a variety of other clinical scenarios also in patients with WT; these include Li-Fraumeni syndrome, Down syndrome, Marfan syndrome, and the neurofibromatosis group of syndromes. For common urological conditions like horseshoe kidney, multicystic dysplastic kidney, cryptorchidism, and hypospadias. There is very little data to corroborate the increased risk of WT association with these conditions.

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5.2 Incidence and Genetic Penetrance

The median age of diagnosis of WT is 3–4 years, and it is extremely rare in patients about the age of 15 years [1]. Most cases of WT are unilateral and unifocal in nature, and only ~5% affect bilateral kidneys [2]. WT is essentially a sporadic disease, with familial cases contributing only 1–2% of the incidence [3].

There are several syndromes and clinical and genetic conditions which have been reported to be associated with WT and with varying frequency of ~ 9–17%. Either an epigenetic modification or a germline anomaly during the early development is hypothesized to be the cause of these associations [4, 5]. However, only a small number of conditions have any definitive evidence of an increased risk of developing WT. The association with several other conditions is serendipitous at best. Non-syndromic bilateral WT and familial cases are probably explained by low-penetrance predisposition alleles as seen in several other malignancies like neuroblastoma [6]. Most of these cases remain unexplained, suggesting predisposition variants at other genetic loci [7].

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5.3 Syndromes and Clinical Conditions

Several conditions with risk of developing WT have been reported, and these can be classified as low, moderate, and high risk (Table 5.1) [8].

These conditions with risk of developing WT can broadly be studied under five groups:

1. WT1-associated phenotypes
2. Overgrowth syndromes
3. Familial WT
4. Other tumor predisposition syndromes
5. Constitutional chromosomal disorders

Table 5.1 Conditions with an increased risk of WT [8]

High risk (>20%)
• WT1 deletions (including WAGR syndrome)
• Truncating and pathogenic missense WT1 mutations (including Denys-Drash syndrome)
• Familial WT
• Perlman syndrome
• Mosaic variegated aneuploidy
• Fanconi anemia D1/biallelic BRCA2 mutations
Moderate risk (5–20%)
• WT1 intron 9 splice mutations (Frasier syndrome)
• Beckwith-Wiedemann syndrome caused by 11p15 uniparental
• Disomy, isolated H19 hypermethylation, or of unknown cause
• Simpson-Golabi-Behmel syndrome caused by GPC3 mutations/deletions
Low risk (<5%)
• Isolated hemihypertrophy[a]
• Bloom syndrome
• Li-Fraumeni syndrome/Li-Fraumeni-like syndrome
• Hereditary hyperparathyroidism-jaw tumor syndrome
• Mulibrey nanism
• Trisomy 18
• Trisomy 13
• 2q37 deletions

[a]Individuals with hemihypertrophy caused by 11p15 uniparental disomy or isolated H19 hypermethylation are at moderate risk

5.4 WT1-Associated Phenotypes

WT1 is somatically inactivated in patients developing WT. Since WT1 is essential for the embryogenesis of the kidney, it may cause the lowering of the median age of diagnosis of WT in these children (median age 1 year) in comparison to the normal population (median age 3–4 years). These tumors are more likely to be bilateral and multifocal (up to 38% in associated syndromes). These tumors are commonly stromal rich and contain intralobar nephrogenic rests (ILNRs) [9]. WT1 defects have different phenotypes, which usually manifest as WT, genitourinary malformations, and renal dysfunction.

5.4.1 WAGR Syndrome

WAGR (WT, aniridia, genitourinary malformations, intellectual disability, previously mental retardation) syndrome was one of the first syndromes to be associated with WT (Fig. 5.1).

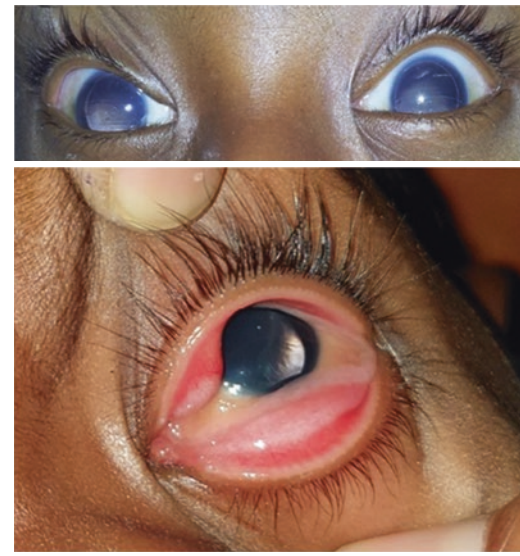

Fig. 5.1 Aniridia (a component of WAGR syndrome) (Picture courtesy Prof S. Kumaravel, JIPMER, Puducherry)

Deletion of PAX6 causes aniridia, and WT1 deletion causes genitourinary malformations and WT. Microdeletions encompassing WT1 are seen in 33% of patients with aniridia [10].

Risk stratification for individuals with WAGR syndrome ranges from 45 to 60%. These patients are diagnosed at an earlier age and have a greater preponderance of harboring bilateral disease in comparison to other syndromes. Ninety percent develop WT by the age of 4 years and 98% by the age of 7 years [11]. They have a favorable histology and are associated with a higher incidence of ILNR.

There is an increased risk of developing end-stage renal disease (ESRD) in this group, and almost 40% individuals develop renal failure before the age of 20 years. Patients developing WT reported to have a survival rate of 48% after the age of 27 years [12].

5.4.2 WAGRO Syndrome

WAGR associated with obesity comprises of the WAGRO syndrome [13]. It has a variable phenotype. Of all the components aniridia is the most consistent [14]. Intellectual impairment is associated with over 70% WAGRO patients along with several neurological and metabolic disorders like obesity. They are commonly noted to have genitourinary disorders such as cryptorchidism, hypospadias, uterine anomalies, and streak gonads.

Obesity ("O" for obesity) is the differentiating feature between WAGRO syndrome and WAGR. In WAGRO syndrome, the deletion of the short arm of chromosome 11 is to the larger extent, involving the brain-derived neurotrophic factor (BDNF) gene. Deletion of BDNF gene is associated with symptoms of polyphagia, developing by the second year of life leading to obesity in all children by 10 years of age [15].

5.4.3 Denys-Drash Syndrome

Denys-Drash syndrome (DDS) is defined as an association of diffuse mesangial sclerosis leading to proteinuria and renal failure along with ambiguous genitalia (Fig. 5.2), which in a male may be 46XY disorder of sexual development (DSD) and a high risk of developing WT [16, 17]. Children with this condition have a germline point mutation in WT1 exon eighth or ninth. These mutations target important residues in the zinc finger domains that are essential for DNA binding of the WT1 protein. There may be other variants of aberrations in cases without renal failure [9].

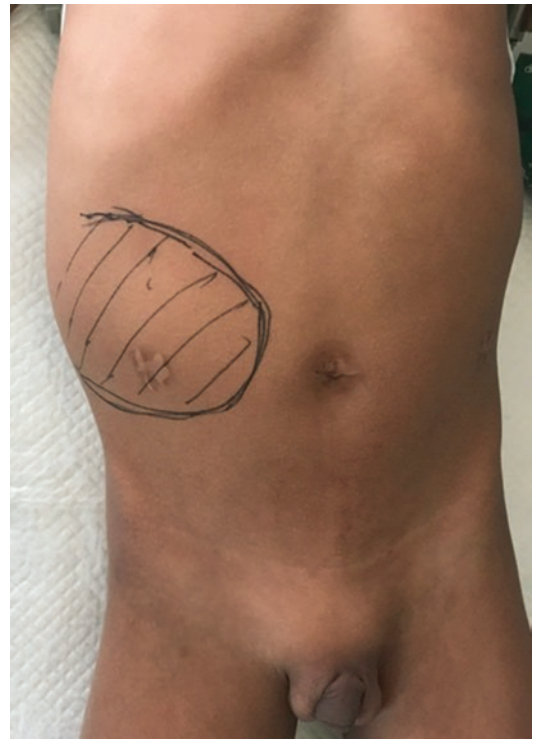

Fig. 5.2 Denys-Drash syndrome with ambiguous genitalia and WT

The incidence of children with DDS who go on to develop WT may be as high at 74%, but some workers believe that even this is underreported. Most of these children may die of ESRD before the potential development of WT [18].

5.4.4 Frasier Syndrome

Frasier syndrome (FS) characteristically has gonadal dysgenesis (476XY) DSD, gonadoblastoma, and nephropathy (focal segmental glomeru-

losclerosis) [19]. The genito-urinary malformations in males are usually severe. Initially thought to be a separate entity from DDS, more researchers believe that FS and DDS are two extremes of a phenotypic spectrum [20, 21]. Heterozygous single-nucleotide variants in the WT1 intron 9 donor splice site are the predominant type of alteration observed in individuals with FS. The risk stratification for these individuals to develop WT is moderate (5–20%).

5.4.5 Other WT1 Phenotypes

There may be clinical conditions with only one or two of the cardinal features of WT1 phenotypes, like WT and cryptorchidism and WT and nephropathy. Only about 2% of non-syndromic WT patients have germline WT1 gene mutations. The risk of developing WT in patients with microdeletions and missense mutations affecting zinc finger domains is significantly high—up to 50% in some series [9].

5.5 Overgrowth Syndromes

Overgrowth syndromes in children are a heterogeneous group of conditions which have antenatal or postnatal overgrowth usually associated with other abnormal clinical conditions. These syndromes were thought to have an association with an increased incidence of WT; however in view of recent understandings, it is now known that only a few specific syndromes predispose to WT. There should be a tailored approach instead of a generalization of WT association in overgrowth syndromes.

5.5.1 Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is a disorder, associated with pre- and post-natal overgrowth, anterior abdominal wall defects, macroglossia, earlobe creases, and hypoglycemia with hemihypertrophy (Fig. 5.3). There may be associated CAKUT, nephrolithiasis, and embryonal tumors (WT, hepatoblastoma, neuroblastoma, rhabdomyosarcoma) [22]. The incidence is 1 in 14,000 [23].

BWS is a result of mutations, epigenetic abnormalities, and aberrations at 11p15.5. Most patients with 11p15 defects may not fulfill the criteria of BWS even though they may have features like isolated hemihypertrophy [24].

The risk of developing WT in patients of BWS is difficult to ascertain because of the carried genotypical and phenotypical presentations in the

Fig. 5.3 Macroglossia and hemihyperplasia in Beckwith-Wiedemann syndrome in a case of WT (Picture courtesy Prof. S. Kumaravel, JIPMER, Puducherry)

entire spectrum of this disease. Approximately 7% of children with BWS develop WT. Defects that cause an increase in growth promoters are related with a higher risk of WT in BWS patients (Disomy of 11p15.5 or gain of methylation); about 25% of these individuals go on to harbor WT. In patients with BWS with WT, 81% will develop the tumor by five years and almost 93% by 8 years [25].

Isolated hemihypertrophy may have an association with various other syndromes such as Proteus, Klippel-Trenaunay-Weber, and Cutis marmorata telangiectatica congenita. The association of these with WT is around 3% [26].

5.5.2 Simpson-Golabi-Behmel Syndrome

It is an X-linked overgrowth syndrome in which patients may present with skeletal and cardiac malformations, coarse facial features, accessory nipples, and intellectual impairment. About one-third of patients may have associated renal dysplasia [27].

Mutations or deletions of glypican-3 (GPC3) at Xq26 are seen in 70% of individuals affected. The risk stratification for WT is moderate, with about 9–10% incidence. There is low penetrance for other embryonal tumors [28].

5.5.3 Perlman Syndrome

It is an autosomal recessive overgrowth disorder identified by antenatal overgrowth with polyhydramnios, visceromegaly, cryptorchidism, facial dysmorphism, developmental delay, renal dysplasia, and WT [29]. The genetic aberration is unclear; however, it may be similar to Simpson-Golabi-Behmel syndrome due to GPC3 mutation. Renal hamartomas or WT (33%) or both are seen in the majority of reported cases. Five of the eight patients who survived the neonatal period went on to develop WT [30].

5.5.4 Sotos Syndrome

It is an overgrowth syndrome associated with facial, extremity, and cognitive abnormalities [31].

5.6 Familial Wilms' Tumor

Sporadic WT running in families has an incidence of 1–2%. The genetic defects are not well identified; however, WT1 mutations, mosaic variegated aneuploidy, and biallelic BRCA2 mutations are seen in specific families [32].

FWT1, an autosomal dominant gene on chromosome 17q21 and another gene FWT2 at chromosome 19q13, have been identified. The exact loci have not been mapped as yet. It is interesting to note that the penetrance of FWT1 mutation is about 30%, and WT in these families are diagnosed at a delayed age (median: 6 years) [33]. Several families without linkages to WT1, FWT1, and FWT2 exist, suggesting that significant genetic heterogeneity and penetrance is a complex phenomenon.

5.7 Other Tumor Predisposition Syndromes

Mutations in more than 70 genes are associated with benign and malignant tumors, of which only a few have an increased risk of WT.

5.7.1 Bloom Syndrome

This is an autosomal recessive chromosomal illness characterized by short stature, hypo- and hyper-pigmented skin lesions which may be photosensitive, immunodeficiency, and a specific facial appearance. This syndrome has proven association with different malignancies, developing tumors in up to 50% of patients. Around 200 cases have been reported, and this condition has a low penetrance for WT (approximately 3%) [34, 35].

5.7.2 Mosaic Variegated Aneuploidy

Mosaic variegated aneuploidy is an autosomal recessive disorder associated with mosaicism for deletions and additions of whole chromosomes. Clinical features may include microcephaly, growth retardation, developmental delay, cataracts, and congenital heart defects. Biallelic mutations in BUB1B are thought to be the specific genetic defect in this disorder. This syndrome is associated with embryonal and hematological cancers. About one-fourth of cases have an associated WT [36].

5.7.3 Fanconi Anemia

Fanconi anemia is usually diagnosed in children with short stature, microcephaly, "radial-ray" defects, skin lesions, and bone marrow failure. These patients are prone to myelodysplastic syndrome and acute myeloid leukemia. There are several overlapping clinical and cellular phenotypes associated with recessive chromosomal breakage. More than 13 subtypes have been identified, and D1 and N subtypes have an increased association with WT.

Biallelic BRCA2 mutations cause Fanconi anemia subgroup D1 [37]. There is an associated risk of solid tumors and brain tumors in these patients. About 40% may have an associated WT.

5.7.4 Other Syndromes

Li-Fraumeni syndrome, Mulibrey nanism, and hereditary hyperparathyroidism-jaw tumor syndrome are other conditions with low penetrance. These are associated with less than 5% of WTs in these patients [38–40].

5.8 Constitutional Chromosomal Disorders

Trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and 2q37 deletion are other constitutional chromosomal disorders with preponderance for WT. Trisomy 18 and 13 are associated with early death in the neonatal period and infancy. Given the early mortality in both of these conditions, there will be a significant increase in association with WT in survivors.

5.9 Conditions with Uncertain Association with WT

There is a significantly large number of conditions associated with WT, where the increased risk of tumor is at best implausible. Various congenital abnormalities and syndromes such as Down syndrome, Marfan syndrome, tuberous sclerosis, and Turner syndrome have reported WT. There is little evidence to link these genetically [41].

Clinically relevant conditions like horseshoe kidney and multicystic dysplastic kidney have no or very little risk of developing WT. [42] Cardiac defects have an unknown risk association of developing WT, which remains most likely minuscule [43]. Cervical ribs are also reported to associate with WT; however, data from a case-control study suggests otherwise [44].

5.10 Evaluation and Surveillance in Predisposed Children

5.10.1 Evaluation

Evaluation of the predisposed child should begin with a detailed history and a detailed physical examination. Most syndromes will have characteristic clinical markers, which aid in narrowing down the syndromic associations. Adequate time must be spent on a family history to look for clues of genetic penetrance and aberrations in the family. Radiological features specific to conditions like nephrogenic rests must be taken into consideration while deciding the management algorithm in these patients.

Genetic testing even though not easily available in the developing world must be sought to narrow down the mutations and aberration. This may aid in emphatically diagnosing specific syndromes associated with WT.

5.10.2 Molecular Genetic Testing

Individuals who have physical, radiological, and histological features suggestive of a predisposition should undergo genetic testing. Any WT in a family member should be taken seriously, and genetic testing is recommended. A geneticist should be an integral part of the multidisciplinary team deciding the management strategies.

Molecular genetic testing includes various gene analyses like single-gene testing, gene-targeted deletion/duplication analysis, methylation studies, use of a multigene panel, and chromosomal microarray. Clinical features should guide the selection of test.

5.10.3 Surveillance

There are various strategies for surveillance; however, the efficacy of these is not well established. Surveillance of predisposed individuals is recommended even though it may not lead to a significant decrease in the mortality of WT. The basic premise of surveillance is to have early detection of WT so as to reduce the intensity of various adjuvant therapies.

Both in the United Kingdom and in the European Union, surveillance is offered to patients at a >5% risk of WT. Renal ultrasound is by far the easiest and commonest tool applied for screening. As WT can be a rapidly growing disease, an ultrasound abdomen is recommended to be performed every 3–4 months [45]. Screening should begin as soon as a syndrome is thought of and should cover the age range so as to cover at least up to 95% of tumors for the associated syndrome.

For the WT1-associated syndromes, Fanconi anemia types D1 and N, mosaic variegated aneuploidy, and Perlman syndrome, virtually all tumors occur before 5 years, and thus surveillance may be stopped after this age is achieved. For children with Simpson-Golabi-Behmel syndrome, familial WT families, and similar genotypic defects like 11p15, the tumors may occur even beyond 5 years. It is recommended to keep these individuals for 7–10 years of follow-up.

5.11 Surgical and Medical Management in Syndromic Patient

5.11.1 Oncological Management

Mutations in WT1 and associated genes influence the surgical and oncological treatment of patients. Chemotherapy regimens must be tailored to the renal function and the weight of the individual patient. There is a significantly high risk of chronic kidney disease (CKD) in syndromes associated with WT1 mutation. This can reach up to 80% for Denys-Drash and 50% for WAGR syndrome [46]. This future progression to ESRD with nephropathies must be kept in mind by the oncologist when deciding the types and dosages of chemotherapeutic drugs.

Perioperative management needs to be looked at carefully in the setting of conditions like hypertension and proteinuria, which may predispose to thrombotic events.

5.11.2 Nephron-Sparing Surgery (NSS) in Syndromic WT

It is believed that NSS is the logical step in managing syndromic patients of WT. This approach helps clinicians prevent or delay the development of chronic kidney disease, which can occur due to intrinsic renal dysfunction (associated with WT1 syndromes) or cumulative insults like hypertension, hyperfiltration, etc. that suffered over a long time.

A substantial number of patients with DDS and FS, tend to progress to ESRD as mentioned earlier. NSS is recommended in patients with bilateral tumors without ESRD to delay the onset of renal failure or the requirement of dialysis. Patients diagnosed with unilateral WT and have point mutations in exons 8-9/intron 9 are inherently at higher risk of progressing to ESRD. There may be some merit in performing an NSS in these patients; however, some workers recommend bilateral nephrectomy with a renal transplant cohort [47].

Patients with DDS who develop ESRD after undergoing NSS for WT should be counseled to undergo total nephrectomy before renal transplantation in order to prevent recurrences under immunosuppressive therapy. It is recommended to have an interval of about two years for renal transplantation after completing the treatment for WT.

It is imperative to strike a fine balance between conservative treatment, NSS, nephrectomy, and oncological safety in these patients.

5.12 Future Directions

There have been considerable advances in the molecular and genetic diagnosis of WT and associated syndromes over the past few decades. In spite of these advancements, several new genes and high penetrance alleles need to be identified and remain to be identified. Newer technology like next-generation sequencing may aid in detecting further genotypes and even low penetrance alleles.

Identifying newer therapeutics, especially in poor prognostic subgroups, is the need of the hour. Targeting epigenetic modifiers and the advent of promising monoclonal antibodies remains to be assessed for the management of WT in the future.

Children with syndromic WT carry a huge burden of disease in terms of cancer predisposition, renal failure, gonadal deficiency, and infertility. As the clinical and genetic associations are better established, experts may be able to offer prime quality and individually customized care to these patients with syndromic WT in the future.

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6 Familial Non-syndromic Wilms' Tumor

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6.1 Introduction

A patient with Wilms' tumor (WT) is considered to have a familial disease if at least one family member has confirmed diagnosis of WT. The familial cases of WT (FWT) are not associated with the syndromes or cancers and account for only 1–2% of all cases [1]. They generally present at an earlier age, and the frequency of bilateral disease is more than sporadic cases [1]. FWTs are found in twins, siblings, successive generations, and consanguinity which suggests the possibility of a monogenic determination [2–4].

6.2 Epidemiology of FWT

Most of the WT families are small affecting one or two family members. The disease often occurs in siblings, cousins, and other relatives, but only one-tenth of the kindreds involve affected parents [5, 6]. The siblings or cousins having WT are usually related to each other by an unaffected carrier [1, 5–7]. The age of onset in FWT is earlier than in sporadic cases (35 months vs 44.7 months in cases with unilateral tumors and 16 months vs 32 months in patients with bilateral tumors) and they have an equal male to female incidence [5, 6]. The frequency of bilateral disease in FWT increases to around 16% [5, 7], and the cases of bilateral and metastatic disease aggregate within specific families [5]. The age at onset, penetrance, and the frequency of bilateral tumors are heterogeneous in WT families. This is because the predisposition to WT is due to an autosomal dominant allele with incomplete penetrance which is estimated between 25 and 60% [1, 6, 8].

6.3 Risk of WT in Kindreds of WT Families

The risk of transmission of WT to children of individuals who survived the disease is estimated as follows [6]:

1. The risk of transmission of the tumor to offspring is 30% if one parent had unilateral WT [6].
2. The risk of transmission of the tumor to offspring is 40% if one parent is a known case of familial WT [6].
3. The risk of transmission of the tumor to offspring is 50% if one parent had bilateral WT [6].
4. If two or more children have WT without any affected parents, the parents are considered unaffected gene carriers, and the risk of transmission of tumor in prospective children is 30% [6].

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The risk of recurrence of WT is small among relatives. In siblings, it is estimated to be less than 0.4%, in uncles and aunts around 0.06%, and 0.04% in first cousins [9].

6.4 Pathology of Familial WT

The histopathology features of FWT are not remarkably different from those of nonfamilial cases, although some predisposition genes are associated with particular histology. Husong et al. reported the presence of neural elements in all four affected members of a WT family [10].

6.5 Genetics and Molecular Biology

Initially, WT was considered to occur due to the loss of function of a single gene as per Knudson's two-hit hypothesis [1], but now several genes are implicated in tumorigenesis of WT. There are several mutations of WT genes, areas of loss of genetic material, and allelic uniqueness (loss of heterozygosity (LOH)) which have been identified to be responsible for tumorigenesis. The mutations of the *WT1* gene located at 11p13 have been implicated as a predisposing factor in some families, but it was excluded in most of the WT families. The linkage analysis has ruled out the role of genes at 11p15, 16q, and 1q for most of the familial WT [11, 12].

Two other FWT genes are recognized: FWT1 at 17q12–q21 and *FWT2* at 19q13.4 [13, 14]. Nevertheless, the role of other unidentified familial WT genes is to be sought as many of the WT families are not attributed to either of these loci [12, 14–16].

6.5.1 WT1 Gene

This was the first gene to be found responsible for the WT occurrence. It regulates the transcription of growth factors, growth factor receptors, and other transcription factors that are responsible for cell growth, differentiation, and apoptosis. The *WT1* mutations, whether truncation, deletions, or missense mutation, are required on both the alleles for tumorigenesis [16]. However, the presence of germline *WT1* mutations has been noted in only 4–6% cases of FWT [16, 17]. The tumors being homozygous for paternally derived alleles indicate a paternal origin of the WT mutation [16].

The constitutional *WT1* mutations have been implicated for tumorigenesis in three other WT families: first, a male child with WT and urogenital malformations with the paternal inheritance of *WT1* mutation from the affected father [18]; second, the three sisters with a paternal inheritance from their unaffected father [19]; and third, three affected members with WT and aniridia due to translocation t(2;11)(q32;p13) [20]. However, the direct sequence analysis of *WT1* has excluded the *WT1* mutation in most WT families as a predisposing factor [11, 16].

6.5.2 Familial Predisposition Gene

The linkage analysis of two WT families revealed the role of a putative tumor gene at the 17q12-21 locus which was named *FWT1* [13]. Moreover, the LOH at 19q was noticed in individuals from two families, and their predisposition was not linked to 17q locus. This suggested that mutations at two different loci; a germline predisposing mutation and a somatic mutation at the second locus are responsible for tumorigenesis in FWT. The subsequent studies demonstrated the role of inherited WT gene *FWT2* at 19q13.3-q13.4 in five WT families [14].

In *FWT1*-linked families, the average age of presentation was 5 years (2–12 years) which is older than the average age of sporadic tumors [12, 13]. Also, these *FWT1*-linked patients present at a significantly *later stage than* sporadic WT [12]. The age of presentation and laterality were found to be variable in patients with the *FWT2* gene [14].

6.5.3 Novel Predisposition Genes for Familial WT

In the last decade, several novel predisposition genes have been implicated in the tumorigenesis of FWT. In a recent exome sequencing study involving FWT, one-third were found to have constitutional mutations in *WT1*, *CTR9*, *REST*, *TRIM28*, *H19* hypermethylation (IGF2 locus), *CDC73*, *BRCA2*, and *NYNRIN* [17]. The *REST* and *TRIM28* mutations were most common being present in 8% of families, followed by *WT1* in 6% of families. The *CTR9* mutations and *H19* hypermethylation were found in 5% and 3% of families, respectively. The *CDC73* mutation and biallelic mutations of *BRCA2* and *NYNRIN* genes were found in one family each [17].

The *CTR9* (Cln 3-requiring 9) gene is an important unit of the RNA polymerase-associated factor complex (PAF1c) which is paramount in the regulation of RNA polymerase II. It is identified as a predisposition gene for WT and functions as a tumor suppressor gene [21]. The *CTR9* gene is sited at 11p15.3 and encrypts a 1173 amino acid protein. It is demonstrated in fetal and adult kidneys and is responsible for embryonic organogenesis and maintenance of embryonic cell pluripotency [22].

The *REST* gene encoding RE1-silencing transcription factor was detected as a tumor suppressor gene in four familial and nine nonfamilial cases [23]. It is a zinc-finger transcription factor that helps in cellular differentiation and embryogenesis [24]. The age of presentation is earlier in familial cases than in sporadic cases. The inheritance of mutation is maternal in most cases, and the tumors are triphasic in histology [23].

The *TRIM28* gene or KAP1 (Krüppel-Associated Box (KRAB)-Associated Protein 1) or TIF1-β (transcriptional intermediary factor 1 β) situated at chromosome 19q13.43 has been identified as a predisposing gene in families of WT [17, 25, 26]. It is involved in maintaining the genome stability, repair of DNA, and embryogenesis [27]. The mutations are transmitted from the mother with incomplete penetrance. Most of the patients have epithelial histology which carries a favorable prognosis [17, 25, 26]. Thus, *TRIM28* expression is a possible marker to identify a group of tumors with an excellent prognosis [25]. It may lead to both unilateral and bilateral tumors, and most of the patients exhibit perilobar nephrogenic rests (PLNR) [26]. The immunohistochemistry of tumor tissue shows loss of TRIM28 protein and loss of heterozygosity (LOH) of *TRIM28* suggesting it to be a classical tumor suppressor gene [25, 26].

The truncating mutations of *FBXW7* (F-box and WD repeat domain containing 7) and *KDM3B* genes also predispose to WT [17]. Both of them are pleiotropic cancer predisposition genes; *FBWX7* is found to be associated with osteosarcoma, extra-renal rhabdoid, and multiple childhood and adult cancers, while *KDM3B* is associated with WT, hepatoblastoma, acute myeloid leukemia, and Hodgkin's lymphoma [17]. The *KDM3B* and *NYNRIN* (NYN Domain and Retroviral Integrase Containing) mutations may also cause nonmalignant conditions, particularly intellectual disability [17].

6.6 Genetic Counseling and Surveillance

The presence of a relative with WT is sufficient to implicate the genetic predisposition of WT. The molecular testing is indicated in such individuals and includes single gene analysis, gene-targeted deletion/duplication analysis, methylation studies, whole genome, and whole exon sequencing [28]. All patients with a genetic predisposition (bilateral or multifocal tumors, syndromic babies, with associated congenital anomalies and familial WT) and the offspring of affected parents with unilateral or bilateral disease and those with a carrier parent should receive genetic counseling and surveillance [6, 28]. The surveillance includes molecular genetic testing and a three-monthly abdominal ultrasound until the age of 8 years to detect the tumors at an early stage [28]. The aim is to detect tumors in the early stages when they have a better prognosis as compared to advanced-stage tumors.

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7 Pathology

Parul Tanwar

7.1 Introduction

Wilms' tumor (WT) or nephroblastoma is the most common pediatric renal tumor comprising 6–7% of all pediatric malignancies [1–4] and ~85% of all pediatric renal malignancies [1, 5, 6]. WT usually occurs in kidney, although extrarenal cases have also been described in retroperitoneum, uterus, cervix, testes, skin, and even in the thorax [7, 8].

WT is a malignant embryonal tumor taking origin from embryonic precursor cells of kidney, showing divergent differentiation recapitulating the developing renal tissue [9]. Though majority of cases are sporadic, 5–10% cases are associated with genetic syndromes, discussed elsewhere in this book [5, 10].

Other pediatric renal tumors include congenital mesoblastic nephroma (CMN) (4%), clear cell sarcoma of kidney (CCSK), (3–4%), malignant rhabdoid tumor of kidney (MRTK) (2%), renal cell carcinoma (RCC) (3–4%), and miscellaneous (1–2%) [6]. Historically, CCSK and MRTK were considered as unfavorable variants of WT but now are considered separate entities. Due to difference in their management and prognosis, precise diagnosis and accurate staging of childhood renal tumors are essential.

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The International Society of Paediatric Oncology (SIOP) and Children's Oncology Group (COG) are the two major groups working on management protocols of WT and other pediatric renal tumors. For WT, COG protocol recommends primary resection of tumor followed by adjuvant therapy, whereas nephrectomy is performed after neoadjuvant chemotherapy (ChT) as per the SIOP protocol [6, 11]. Due to the different therapeutic approaches between the two groups, there are further differences in histological subclassification and staging [6].

In case of WT, examination of the tumor specimen is not limited to just making a correct diagnosis. Evaluation of the tumor histologic subtype, its risk group assessment, and precise interpretation of the pathological stage are crucial, as they will govern the further course of therapy [6]. Post-ChT specimens show many secondary changes, making it difficult to assess the tumor morphology and stage accurately. The criteria for tumor subtyping and risk-group stratification are different for previously treated and untreated samples; therefore, it is of utmost importance to examine both type of specimens thoroughly [5, 12].

7.2 Gross Features

WT usually presents as a large, unifocal, rounded, multinodular renal mass having a fibrous pseudocapsule, sharply delineating it from adjacent renal parenchyma. Multifocal tumors in single kidney

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are observed in 5–10% cases and are more commonly associated with nephrogenic rests (NRs) [13, 14]. As many as 5% cases present with tumors in bilateral kidneys [5, 15]. The tumor originates from the renal parenchyma, arising from anywhere in medulla or cortex and compressing the adjacent normal renal tissue. Seldom, it can present as an exophytic mass, connected to the renal surface by a narrow pedicle, simulating extrarenal WT. Tumor can extend into renal pelvis or renal vein, forming a thrombus in the latter, which can extend to the inferior vena cava (IVC) and even the right atrium [15].

Botryoid WT is a less frequently encountered pattern of WT in which the tumor extends into the pelvicalyceal system of the kidney in a polypoidal fashion. It is not a separate entity, but merely a tumor growth pattern, which is subclassified as per the final histologic features [16].

Cut surface of the tumor is usually solid, pale gray to tan and soft in consistency, due to which there can be displacement artifact of capsule while handling the specimen [14, 15]. Tumors with predominant stromal components can have firm, myomatous consistency.

Post-ChT specimens show heterogeneous cut section with areas of viable tumor, hemorrhage, and necrosis. Some of these tumors can be completely necrotic without any residual viable area. Unusually, the tumor can be markedly cystic, requiring careful search for the presence of solid foci [5, 15].

7.3 Microscopy

WT derives its name from German surgeon Max Wilms, who defined it as a tumor comprising of three different tissues [2]. It is classically described as a triphasic tumor containing undifferentiated blastema, together with cells differentiating toward epithelial and stromal lineages in variable proportions (Fig. 7.1) [5, 15]. The tumor has myriad of morphologic patterns owing to unequitable distribution and varied degrees of differentiation of these components [14]. Biphasic and monophasic tumors are not uncommon, comprising of any two or one of these cell lineages [15]. The three components can show differentiation, usually corresponding to the stages in nephrogenesis, though occasionally heterologous nonrenal elements are also noted [5]. *Teratoid WT* is a rare subtype comprising of >50% heterologous components. Surgery is the preferred mode of therapy in cases of teratoid WT as they respond poorly to ChT, due to the presence of mature tissue elements [17].

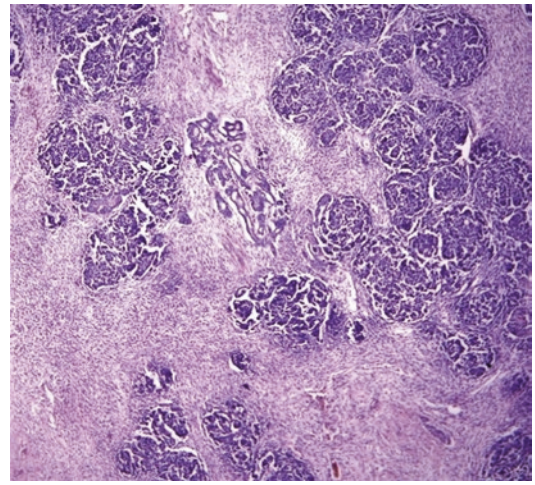

Fig. 7.1 Triphasic WT

7.3.1 Blastemal Component

The blastemal cells are densely packed small cells showing nuclear overlapping and molding. These cells have high nucleo-cytoplasmic ratio with round to oval nucleus, coarse chromatin, inconspicuous nucleolus, and scant cytoplasm. Blastemal cells are mitotically active and do not show any morphologic evidence of differentiation toward epithelial or stromal component (Fig. 7.2). Distinct morphologic arrangements have been distinguished.

Diffuse Blastemal Pattern The most aggressive blastemal pattern, defined by the presence of sheets of poorly cohesive monomorphic cells with widespread infiltration into adjacent connective tissue and blood vessels. Though most aggressive, it responds well to the therapeutic

regimens and thus categorized under "favorable histology" (FH) type in COG protocol [18].

Nested Blastemal Pattern Sharply delineated nests of blastemal cells in a background of myxoid matrix. These nests are more cohesive, having sharply defined margins and do not invade the surrounding parenchyma. Several organizational patterns have been described:

1. Serpentine blastema: Undulating anastomosing cords of blastemal cells in a loose myxoid stroma. Since this pattern is distinctively seen in WT, its presence helps to differentiate it from other small round cell tumors.
2. Nodular blastema: Similar to serpentine pattern, composed of round nests of blastemal cells, instead of cell cords [5, 15, 18].
3. Basaloid blastemal pattern: Nests of cells showing peripheral palisading of cuboidal or columnar cells, similar to cutaneous basal cell carcinoma [15].

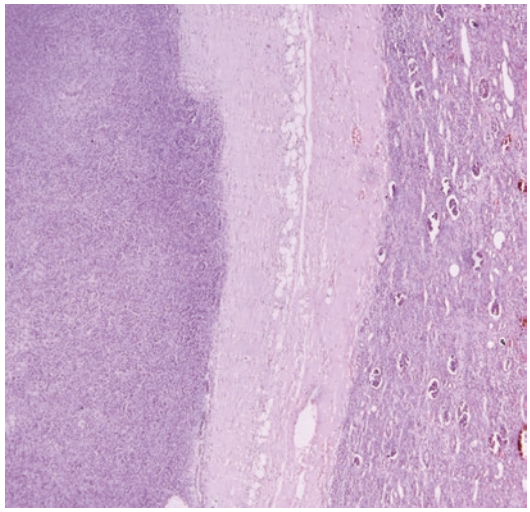

Fig. 7.2 Blastemal type WT showing pseudocapsule at junction with renal parenchyma

7.3.2 Epithelial Component

Epithelial components recapitulate different stages of normal nephrogenesis in the form of tubular or glomerular structures (Fig. 7.3a). Tubular structures are usually well defined with distinct lumens; however, primitive tubular structures mimicking rosettes can also be seen [10]. Tumors with predominant tubular pattern usually are less aggressive, presenting at lower stage [18]. Differentiation can range from ill-formed papillary formations, to well-formed glomeruloid structures (Fig. 7.3b). Heterologous epithelial components may be identified in the form of mucinous or squamous cells [5, 14].

7.3.3 Stromal Component

Varied stromal components can be identified including immature myxoid, spindled mesen-

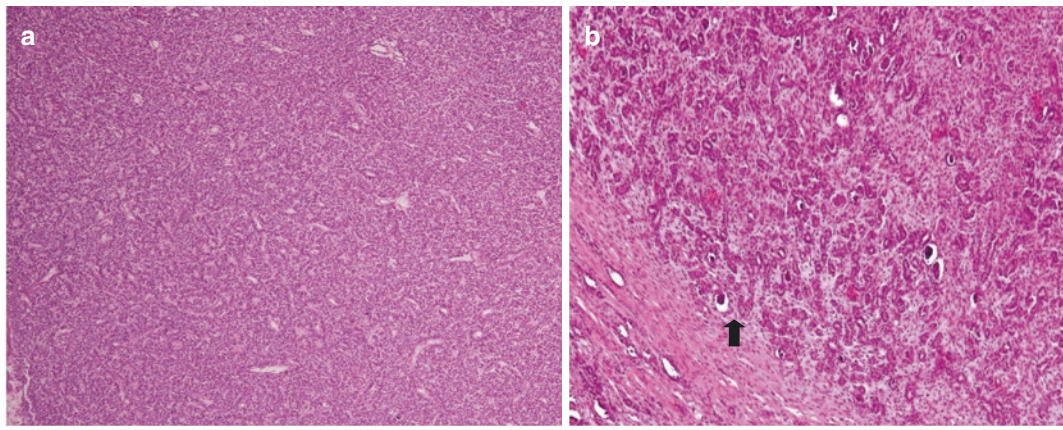

Fig. 7.3 (**a**) WT: Blastema with early epithelial differentiation and (**b**) epithelial predominant WT with tubular differentiation and glomeruloid structures (arrow)

chyme, smooth muscle differentiation, and fibroblastic differentiation. Heterologous differentiation can also be encountered in the stromal component. Skeletal muscle is the most common heterologous stromal cell type (rhabdomyoblastic differentiation) (Fig. 7.4a), and others like bone, cartilage (Fig. 7.4b), adipose tissue, and ganglion cells may also be seen, especially in post ChT tumors [5, 14].

7.4 Anaplasia

Beckwith and Palmer in 1978 first categorized WT histologically as anaplastic and non-anaplastic types [19]. Anaplasia was first described by the authors as presence of enlarged, hyperchromatic nuclei, associated with atypical multipolar mitotic figures. Affected nuclei are three times or larger than adjacent nuclei of similar cell type (Fig. 7.5a) [19]. Seen in 5–8% of all cases of WT, anaplasia is seldom encountered in children less than 2 years of age. The prevalence increases with age, with almost 13% cases showing features of anaplasia by 5 years of patient age [5, 10, 15]. In COG protocol, the presence of anaplasia in WT is the only criteria for "unfavorable histology" (UH), while all the other WT without anaplasia are called as FH [15]. Anaplastic histology is one of the most significant prognostic factors in WT associated with poor response to ChT and increased aggressiveness [5, 20, 21].

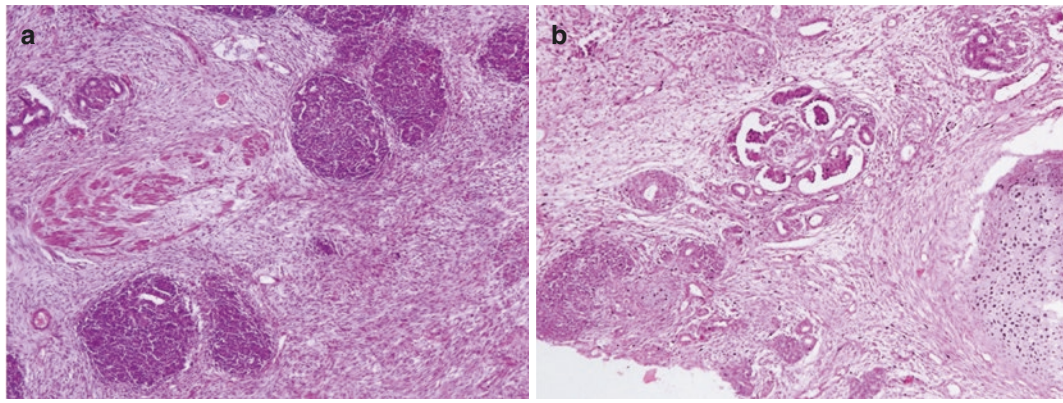

Fig. 7.4 Triphasic Wilms' tumor with (**a**) rhabdomyomatous differentiation and (**b**) cartilaginous differentiation of the stroma

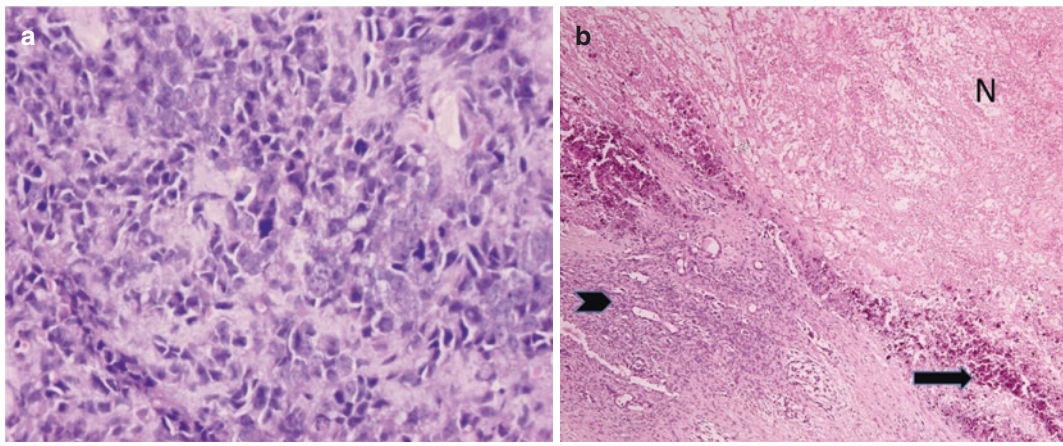

Fig. 7.5 (**a**) Anaplastic WT showing enlarged hyperchromatic nuclei with mitosis; (**b**) ChT-induced changes: large area of necrosis (N), focal calcification (arrow) along with viable tumor (arrowhead)

Table 7.1 Histologic criteria for anaplasia [22]

Focal anaplasia (FA)
• Well circumscribed, discrete foci of anaplasia within the primary tumor surrounded by non-anaplastic tumor on all sides • Anaplasia limited to intrarenal tumor • No anaplastic foci within vascular spaces • No severe nuclear unrest in "non-anaplastic" tumor areas
Diffuse anaplasia (DA)
• Non-localized anaplasia • Anaplastic focus outside tumor capsule • Anaplastic foci involving vascular spaces (intrarenal/extrarenal) or renal sinus • Metastatic sites or extracapsular invasive sites showing anaplastic cells • Anaplasia not well demarcated from non-anaplastic tumor • Focal anaplasia, but with presence of severe nuclear unrest in other areas of tumor • Biopsy or other incomplete tumor sample showing anaplasia • Not meeting the criteria of focal anaplasia.

Anaplasia can be either focal or diffuse. In their classical article, Beckwith and Palmer described <10% atypia as focal anaplasia (FA) and >10% as diffuse anaplasia (DA) [19]. This definition was modified later, defining focal anaplasia as discrete foci of anaplasia within the primary intrarenal tumor (Table 7.1) [22].

Assessment of anaplasia should not be done in cells showing rhabdomyoblastic (skeletal muscle) differentiation, as these cells may show nuclear pleomorphism, hyperchromasia, and karyomegaly, which may be spuriously labelled as anaplasia [23]. Post-ChT tumors may show cellular atypia or degenerative changes, worrisome enough to be misjudged as anaplasia [18, 24]. Since the presence of FA has therapeutic significance as per the current protocols, it includes only those cases of WT fulfilling all of the defined criteria [5]. Presence of even a single unambiguous giant tumor cell nucleus or a multipolar mitotic figure is acceptable to label DA in a small percutaneous needle biopsy. FA is not reported in small biopsy [23].

7.5 Nuclear Unrest

Presence of worrisome cellular atypia, nuclear enlargement, and histological disarray in a favorable histology WT, which is not severe enough to be labelled as anaplasia, is known as nuclear unrest [25, 26]. Such tumors contain enlarged hyperchromatic nuclei but lack atypical multipolar mitotic figures, as seen in anaplastic WT [25].

Zuppan et al. categorized nuclear unrest in three grades based on its severity. Grade 1 unrest shows minimal histologic disarray with nuclear diameter similar to RBC. Grade 3 is severe nuclear unrest showing marked nuclear atypia and pleomorphism, however, lacking multipolar mitotic figures. Grade 2 is intermediate between Grade 1 and 3 [27].

WT with nuclear unrest lies in-between the histologic spectrum of WT having FH and anaplastic histology on the two extreme ends. Hill et al. in their study found that patients having WT with nuclear unrest and those with FH had comparable overall survival and 5-year cumulative incidence of death. The authors also noted that tumors with nuclear unrest rarely showed p53 overexpression by immunohistochemistry (IHC), in contrast to anaplastic histology WT, which is associated with strong p53 positivity [25]. On the other hand, Salama et al. observed that WT with severe nuclear unrest showed p53 overexpression more than grade 1 and 2 nuclear unrest with significant statistical difference ($p = 0.014$) and therefore WT with severe nuclear unrest resemble anaplastic WT more than the FH type [26]. The discrepant results can be explained by the fact that the former study included all the three grades of nuclear unrest as a single category whereas in the later study all the three categories were studied separately.

It is still unclear if the presence of severe nuclear unrest will necessitate more aggressive therapy than the favorable histology WT.

7.6 Chemotherapy-Induced Changes

ChT is an efficient and essential modality of WT treatment. Subjects managed as per SIOP protocol undergo nephrectomy following ChT. ChT reduces the tumor burden, the chances of tumor rupture, and accidental spill during surgery. ChT-induced changes can be seen in the form of necrosis (Fig. 7.5b), fibrosis, and presence of xanthomatous or hemosiderin-laden histiocytes [28]. On occasions, therapy may also bring about maturation of the blastemal, epithelial, or stromal components [5]. Extensive necrosis of immature and mitotically active cell types (blastema) is usually noted post-ChT, whereas the more differentiated elements (epithelial and stromal) show poor response to therapy. As a result, in post therapy specimens, percentage of blastema decreases, whereas that of epithelial component increases [29]. Subsistence of large proportion of blastemal component post ChT signifies worse prognosis [5, 15]. Cells with anaplastic features are resistant to ChT and are preserved in post therapy specimens [29]. SIOP has characterized various risk groups based on post ChT histological tumor response (Table 7.2).

The *residual tumor volume* after preoperative ChT is a significant prognostic factor and therapeutic indicator, especially in the intermediate-risk group tumors. In stage II/III WT of the mixed type, regressive type, and focal anaplasia type, a postoperative *tumor volume of* >500 ml is associated with worse prognosis, and such patients should be treated aggressively [30–32].

Table 7.2 Revised SIOP working classification (2001) of renal tumors of childhood [12]

Low-risk tumors	• Cystic partially differentiated nephroblastoma (CPDN) • Completely necrotic nephroblastoma • Congenital Mesoblastic nephroma (CMN)
Intermediate-risk tumors	• Nephroblastoma, epithelial type • Nephroblastoma, stromal type • Nephroblastoma, mixed type • Nephroblastoma, regressive type • Nephroblastoma, focal anaplasia type
High-risk tumors	• Nephroblastoma, diffuse anaplasia type • Nephroblastoma- blastemal type • Clear cell sarcoma of the kidney • Malignant Rhabdoid tumor of kidney (MRTK)

In SIOP protocol, the pre-treated WT cases are subcategorized as follows (Table 7.3):

The COG/ NWTS protocol recommends primary surgery followed by ChT, but patients with *bilateral WT* are prescribed preoperative ChT and subsequent surgery. Further therapy is in accordance with histopathological evaluation of the post ChT sample. As per this protocol, the post therapy tumors are graded as given in Table 7.4.

Table 7.3 ChT-induced changes in WT histopathology (SIOP protocol) [22]

Completely necrotic type	• No viable tumor identified, even on extensive sampling
Regressive type WT	• Less than 1/3 of residual tumor, regardless of the viable component • Remaining area (>2/3) showing ChT induced changes
Epithelial type WT	• Viable tumor comprises more than 1/3 of total tumor volume • More than 2/3 of viable tumor is composed of epithelial component • Dispersed foci of blastema may comprise <10% of viable tumor
Stromal type WT	• Viable tumor comprises more than 1/3 of total tumor volume • More than 2/3 of viable tumor is composed of stromal component • Dispersed foci of blastema may comprise <10% of viable tumor
Mixed type WT	• Viable tumor comprises more than 1/3 of total tumor volume • More than 2/3 of viable tumor is composed of more than two components, none of them being more than 2/3 of the total viable tumor mass
Blastemal type WT	• Viable tumor comprises more than 1/3 of total tumor volume • More than 2/3 of viable tumor is composed of blastema • Other components may be present in variable amounts

Table 7.4 Pathological classification of post-ChT WT, COG/NWTS guidelines (for bilateral WT) [11]

Completely necrotic tumor	<1% residual viable tumor
Blastemal predominant tumors	>1/3 residual viable tumor, and ≥2/3 of viable tumor is composed of blastema
Intermediate tumors	Not applicable to any other category
Anaplastic tumors	Tumors showing focal or diffuse anaplasia

7.7 Role of Pre-Therapy Biopsy/ Fine Needle Aspiration Cytology

SIOP protocol recommends neoadjuvant ChT followed by nephrectomy as the treatment modality for WT. Classically, the diagnosis is based on only clinical and radiological parameters [33]. However, initiating therapy without histopathological confirmation can lead to erroneous treatment in some cases. A pre-therapy needle biopsy, however, can ensure correct histopathological diagnosis and instillation of appropriate therapy, especially in cases of non-Wilms' renal tumors (NWRT) [34]. Role of biopsy, its advantages, and pitfalls have been extensively dealt elsewhere in this book.

The sensitivity of FNAC in detection of pediatric renal tumors varies from 76% to 95% in various studies [33, 35–37]. FNAC is a less invasive modality with less morbidity and complications as compared to core needle biopsy [35]. Cytological diagnosis is unambiguous in triphasic tumors where all the three elements can be seen in variable proportions. Blastemal elements are most easily aspirated due to their dyscohesive nature, appearing as small round cells, twice the size of small lymphocyte, having dispersed chromatin and scant cytoplasm. Epithelial elements are more cohesive, seen as group of cells arranged as tubules, sheets, and rosette like structures. Stromal elements form fascicles of spindle-shaped cells with elongated nuclei. Anaplasia can also be identified in the smears by the same criteria as described for histopathology [33, 36]. The pitfall of FNAC is that extensive sampling of a large mass is usually not possible. Anaplasia, if sampled by FNAC, cannot be categorized as focal or diffuse [33, 36].

7.8 Immunohistochemistry (IHC)

Strong nuclear expression of WT1 is noted in blastema and primitive epithelial foci. Well differentiated epithelial elements and stroma, however, may not show nuclear WT1 expression. Strong and diffuse CD56 positivity is also observed in blastemal elements. P53 expression is associated with anaplastic WT [38]. There is a limited role of IHC in typical triphasic tumors. It may be of help in mono or biphasic tumors, especially for ruling out other differential diagnoses.

7.9 Differential Diagnosis

The classic triphasic WT, usually, do not pose any diagnostic challenge. However, the monophasic and biphasic variants can mimic other NWRT and cause diagnostic dilemma, more so, in trucut biopsy specimens. These NWRT are detailed in another chapter.

Blastemal component of WT can mimic other small round cell tumors like neuroblastoma (NB), primitive neuroendocrine tumor (PNET), desmoplastic small round cell tumor, MRTK, monophasic synovial sarcoma, and non-Hodgkin's lymphoma (NHL) [1, 36, 38–40]. In adults, possibility of metastatic small cell carcinoma should also be ruled out [41]. Early epithelial tubules of WT may resemble rosettes of NB (Fig. 7.6). Tubules in WT are lined by single layer of cells and devoid of neuropil; on the other hand NB rosettes show multilayering of cells around central neuropil [15, 36]. Both NB and WT may show expression of CD56, but strong nuclear expression of WT1 is characteristically seen in

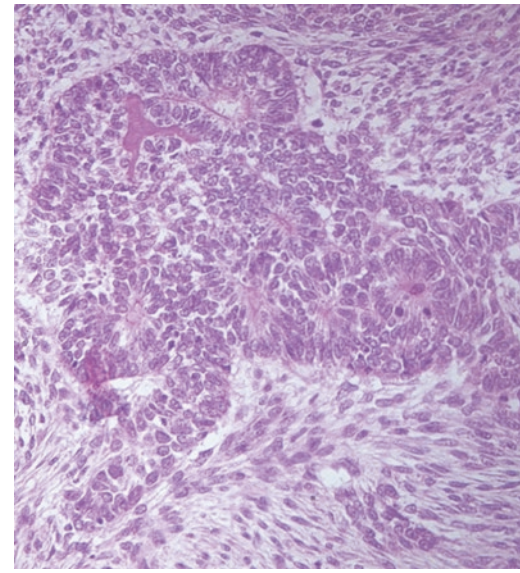

Fig. 7.6 Epithelial component of WT resembling rosettes of neuroblastoma

WT. NB also shows expression of other neuroendocrine markers like synaptophysin, neuron-specific enolase, and chromogranin which are negative in WT [42].

Strong membranous CD99 expression is characteristically seen in Ewing's sarcoma/primitive neuroectodermal tumor (PNET); however, rarely WT may also show focal expression of CD99. WT1 expression though distinctively seen in WT may also be sometimes expressed in PNET. Significant proportion of PNETs express FLI1 (friend leukemia virus integration 1), Leu7, and synaptophysin and show t(11;22)(q24;q12) in 85–95% of cases, which can confirm the diagnosis [43].

Rarely, MRTK can be confused with WT. On IHC, loss of nuclear INI 1 expression is specifically seen the former [44].

Desmoplastic small round cell tumor (DSRCT) and blastemal predominant WT have many overlapping IHC features including WT1 expression. However, no case should be labeled as DSRCT without detection of EWS-WT1 t(11;22) (p13;q12) translocation, the molecular hallmark of this tumor [45].

Synovial sarcomas show distinctive t(X;18) translocation and *SYT-SSX* gene fusion products, which is the gold standard for diagnosis. On IHC, synovial sarcoma expresses Bcl2, Vimentin, CD99, and CD56 [46].

NHL will show expression of leucocyte common antigen and presence of lymphoglandular bodies in the background [38].

Metanephric adenoma and RCC can cause confusion with pure epithelial type WT. Well-differentiated epithelial type WT can morphologically resemble the closely packed small tubules of metanephric adenoma. However, the virtual absence of mitotic activity and deficiency of tumor capsule favor metanephric adenoma over WT. IHC is not helpful in differentiation, as both the tumors show positivity for WT1 and other epithelial markers [1, 47]. Papillary renal cell carcinoma, a close morphologic mimic of epithelial type WT shows CK7+, EMA+, Vimentin+, and WT1− which helps in differentiating the two [48].

Stromal type WT should be differentiated from CCSK and CMN. CCSK shows vimentin+, CK+, Alpha 1 antitrypsin+, Bcl 2+, t(10;17), and deletion 14q [49].

WT with prominent cysts needs distinction from other pediatric cystic renal tumors, namely, cystic nephroma (CN) and cystic partially differentiated nephroblastoma (CPDN) [50].

7.10 Cystic Nephroma (CN) and Cystic Partially Differentiated Nephroblastoma (CPDN)

In children, the spectrum of multiloculated cystic tumors of kidney is composed of cystic nephroma (CN), cystic partially differentiated nephroblastoma (CPDN), and cystic WT (cWT). These entities have a proposed common origin from intralobar nephrogenic rests and probably show a continuum of maturation. CN is benign, WT is malignant, and CPDN lies in between these two extremes. Clinical and pathological features of CN, CPDN, and cWT overlap significantly [50].

On histopathology, CN show fibrous tissue septae lined by flattened or cuboidal epithelium. No blastemal element is seen [51]. CPDN, on the other hand, show presence of undifferentiated or differentiated mesenchyme, blastemal, and epithelial elements in the septae (Fig. 7.7) [51]. WT can coexist with CPDN and rarely with CN [50]. Presence of any solid nodule excludes the diagnosis of CN or CPDN.

7.11 Handling of Nephrectomy Specimen

WT, like other pediatric renal tumors, are friable bulky tumors with tense capsules causing distortion of normal anatomy of kidney. While cutting, such tumors are susceptible to capsular retraction and displacement artifact, leading to hindrance in exact tumor staging [15]. Therefore, proper handling of nephrectomy specimen is essential.

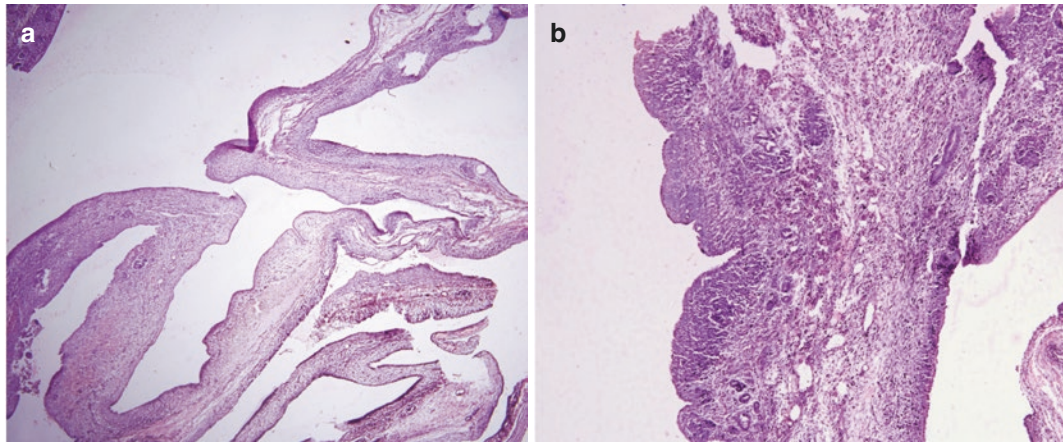

Fig. 7.7 Cystic partially differentiated nephroblastoma: (**a**) low-power view showing cystic spaces lined by septae. No solid area seen. (**b**) High-power view of the septae containing epithelial and blastemal components

7.11.1 Frozen Section

Intraoperative frozen section should be avoided, as much as possible, unless its result alters the course of the operative procedure [52]. However, recently frozen sections loco-regional lymph nodes and resection margin are being sent by the surgeons who believe in performing nephron-sparing surgery in unilateral non-syndromic WT. It is recommended to snap freeze and preserve viable tumor (1gm or more) in two or more vials and a part of non-tumorous renal parenchyma (at least one vial) for future molecular studies [23, 52].

7.11.2 Sample Handling

Intact nephrectomy specimen should be delivered to the pathology department for proper evaluation. Bivalving or cutting the unfixed specimen in operation theater leads to retraction of tumor capsule, displacement artifact, and tumor spillage on surface, altering the relationship of tumor and capsule thereby jeopardizing the precise staging.

Specimen should be measured and weighed, and external surface is cautiously evaluated for any capsular breach. Appropriate photographs should be clicked before inking the surface. Sections from renal vascular margin and ureteric margin should be taken before bivalving the specimen to avoid contamination by tumor. Capsule of the nephrectomy specimen should never be stripped as it can sabotage the evidence of capsular invasion by the tumor and obscure the presence of perilobar nephrogenic rests, located in the periphery of renal cortex. Bivalving of the specimen should be done taking the hilar structures as pointers. Subsequently parallel slices should be given in cases of large tumors, to facilitate adequate fixation. Specimen should be allowed to fix in formalin for 24–48 h.

Tumor should be sampled adequately, taking at least one microscopic section per centimeter of tumor size. These sections should be taken primarily from the tumor periphery, including the junction of tumor with renal capsule and with surrounding uninvolved kidney. Adequate sectioning of renal sinus and renal vessels should be done for staging. Unremarkable renal parenchyma is sampled for the presence of NRs. Hilar fat and lymph nodes are evaluated to look for metastasis. All the sections should be cautiously mapped using photographs or drawings, for precise staging and also

for assessment of focal vis-a-vis diffuse anaplasia. Each nodule of multicentric tumor should be sampled [23, 34, 52].

7.12 Nephrogenic Rests and Nephroblastomatosis

Defined as locus of abnormally persistent nephrogenic embryonal tissue beyond 36 weeks of gestation, NRs are potential precursors of WT [53]. They are detected in 25–44% of cases with unilateral WT, in more than 90% of cases with bilateral WT and in ~1% infant autopsies [54–57]. Microscopically NRs are identified as clusters of blastemal cells, tubules, and few glomeruli intermixed with fibrous stroma [58].

NRs are subtyped as perilobar (PLNR) and intralobar (ILNR) types. Both of these can be further categorized as dormant, sclerosing, adenomatous, or hyperplastic types [53]. Rarely NR can be identified in extrarenal sites like adrenal gland, inguinal canal, lumbosacral area, thorax, etc. [58]. ILNR results due to aberration early in the course of development, leading to the presence of nephrogenic tissue within the renal lobe. PLNRs, on the other hand, are due to anomalies later in the renal development and hence show nephrogenic tissue in the periphery of the renal lobe. PLNR and ILNR may occur synchronously in a patient, termed as combined NRs [59]. ILNRs are seen as foci of nephrogenic tissue, usually in the central areas of the renal lobe (Fig. 7.8). They are poorly circumscribed lesions, rich in stromal and epithelial components. PLNRs, on the other hand, are usually well-demarcated lesions located in the periphery of the lobe showing predominance of blastema along with epithelial tubules [60, 61]. Overgrowth syndromes like Beckwith-Wiedemann and hemihypertrophy are associated with PLNRs, while ILNRs are commonly seen with WAGR syndrome and Denys-Drash syndrome [8, 61].

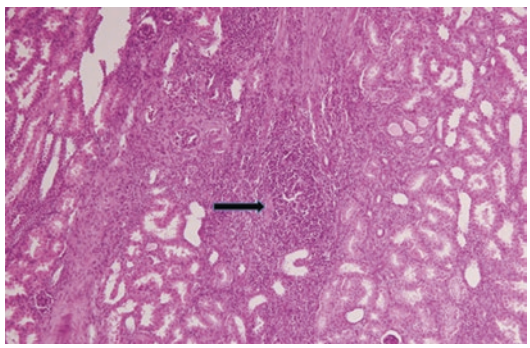

Fig. 7.8 Intralobular nephrogenic rest

The term nephroblastomatosis was first coined by Hou et al., and it is defined as the presence of diffuse or multifocal NRs [62]. *Diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB)* is a rare form of PLNR, in which one or both kidneys show thick crust of hyperplastic NRs, replacing the cortex and leading to massive renal enlargement. This condition is significantly associated with development of WT in both ipsilateral and contralateral sides [60, 63].

DHPLNB and WT may pose a diagnostic dilemma, and due to their varied therapeutic selection, distinguishing these two is of utmost importance [63, 64]. Ultrasonography can identify DHPLNB, but cannot differentiate it from WT. Computerized tomography scan and magnetic resonance imaging identify hyperplastic nephroblastomatosis as non-contrast enhancing homogenous lesions, whereas WT appears as a more heterogeneous lesion exhibiting contrast enhancement [65]. On histopathology, presence of fibrous pseudocapsule at the junction of lesion and adjacent renal parenchyma is the most distinguishing feature of WT [63, 64]. FNAC is of no diagnostic utility in differentiating the two [14, 65]. In small biopsy sections, it may be extremely difficult to distinguish the two, especially in cases where the lesion-surrounding parenchyma junction has not been sampled. For such instances, in small biopsy, the term "nephroblastic process, consistent with either WT or nephrogenic rest" is acceptable [63].

7.13 Adult Wilms' Tumor

Although it is the most common renal tumor of childhood, but rarely WT can be encountered in adults also. Adult WT accounts for less than 1%

of diagnosed renal tumors with an incidence of 0.2 per million per year [66]. Kilton et al. laid down the following criteria for the diagnosis of adult WT [65]:

1. The tumor should be primary renal in origin.
2. Tumor should comprise of primitive blastemal, spindle, or round cell component.
3. Presence of abortive/embryonal tubular or glomeruloid structures.
4. No area of tumor diagnostic of renal cell carcinoma.
5. Pictorial confirmation of histologic diagnosis.
6. More than 15 years of age.

7.14 Extrarenal Wilms' Tumor

Rare cases of WT have been identified in extrarenal sites including retroperitoneum, uterus, cervix, testes, skin, bladder, lumbosacral region, and thorax [7, 8, 10]. Extrarenal (ER) WT can be seen in children as well as in adults [7]. Before designating a tumor as ERWT, it is essential to rule out primary renal tumor. ERWT can either arise de novo, or in a background of teratoma [67].

7.15 Conclusions

Despite being the most common pediatric renal neoplasm, WT is rare. Owing to its diverse morphologic appearances, it is a diagnostic challenge to differentiate WT from its morphologic mimics. Accurate histopathological diagnosis, risk group assessment, and pathological staging are crucial in deciding the course of therapy. Preoperative ChT significantly alters the histomorphology, which the dealing pathologist should be acquainted with. Correct handling of nephrectomy specimen and adequate sampling are the keys to precise staging. Few prognostic molecular signatures have been identified, and many more are under research, but still the gold standard for diagnosis, subtyping, and staging is histopathological examination.

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Clinical Presentation

8

Parveen Kumar and Parthapratim Gupta

8.1 Clinical Presentation

The patients are usually asymptomatic during the early stages of development of Wilms' tumor (WT). An *asymptomatic abdominal mass* usually noted by a family member while bathing, dressing, or playing with the child is the commonest presentation (90%). The other symptoms may be due to the tumor itself, its mass effects/extensions, or metastasis. It may include abdominal pain, fever, hypertension, blood in urine, loss of appetite, unexplained weight loss, constipation, etc. Rarely, it may present with respiratory symptoms (cough, fast breathing, or distress) secondary to lung metastasis.

Hypertension occurs in 35–63% cases of WT, presenting with both raised systolic and diastolic pressure [1]. This is due to increased production of renin probably due to ischemic effects of the kidney by the expanding mass. The expanding mass (rapidly growing tumor or sudden hemorrhage into tumor) causes compression effect on kidney substance and its vasculature, leading to activation of renin angiotensin system and thus hypertension [2]. The hyperreninemia is mostly due to tumor secretion and possibly due to compression of the surrounding renal tissue. High renin levels induce aldosteronism causing electrolyte imbalances (hypokalemia), which in turn may cause polyuria and vasopressin resistance and polydipsia [3]. Hyperreninemia, hypertension, and secondary hyperaldosteronism has been associated with WT [4–6]. Hypertension may also be caused rarely by intrarenal arteriovenous fistula formation secondary to tumor [1]. It may not cause any symptoms at own, but very high blood pressure may cause headaches, vision, and consciousness issues.

Hematuria (microscopic and/or gross/macroscopic) occurs in 5–30% of patients [7]. Macroscopic hematuria is blood in urine as seen by naked eye. Microscopic hematuria is more common (20–30%) as compared to microscopic hematuria (5–18%). This may be due to extension of the tumor within the renal pelvis or rarely renal vein thrombosis. Tumor extension into ureter (2–4%) may present with hematuria, passage of clots/mass per urethra, or hydronephrosis [8]. Engel described three cases of gross hematuria with nonfunctioning kidney (NFK) on intravenous pyelography, which later proved to be WT [9]. Retrograde pyelography revealed collecting system mass causing nonfunctioning of kidney. In all the three patients, there was no invasion of venous drainage system, and the tumor was exclusively protruding into the collecting system rather than displacing the parenchyma itself.

Abdominal pain may be a presenting feature in 30–40% patients [8]. It occurs due to expand-

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ing mass, subcapsular hemorrhage, mass effects of tumor, or liver metastases.

Constitutional symptoms like loss of appetite, unexplained weight loss, constipation, etc. are due to mass effects, or malignant potential of tumor, or metastases. Low-grade fever occurs due to high metabolism secondary to fast growth of tumor. Loss of 5% of weight over past 6 months is considered significant.

Any history of easy bruisibility should be noted. WT may also cause *coagulopathy*. Acquired von Willebrand disease has been reported in 4–8% of children with WT [10, 11]. The exact etiology remains unknown, but von Willebrand factor (vWF) inhibitors and rapid abnormal vWF clearance have been the proposed mechanisms. Though the bleeding is usually clinically insignificant, it may present with epistaxis, hematuria, or gingival bleed. *Anemia* may occur secondary to hemorrhage in tumor. Though rare, *polycythemia* has also been reported in children with WT, and it has been ascribed to elevated erythropoietin levels [12].

Ramsay et al. in 1977 described three cases of acute hemorrhage in WT, which caused rapidly developing abdominal mass, hypertension, anemia, and fever [2]. It has been usually described as *Ramsay's triad* and is associated with poor prognosis; some mention Ramsay's *tetrad*, incorporating the fourth feature of egg-shell calcification that may be seen on imaging in such cases. Peng et al. also emphasized the need of paying attention of complains of abdominal pain and anemia, so as not to miss malignancy (WT) in children [13].

Occlusion of the left renal vein by tumor extension may obstruct the drainage of left spermatic vein, resulting in *left side varicocele* and a dragging pain in left scrotum. Hence, it is prudent to examine the abdomen thoroughly while evaluating a patient presenting with varicocele on left side and vice versa.

In rare cases, more so in right-sided WT, *cardiac manifestations* including arrhythmias may be the presenting symptoms at the time of diagnosis, and the prognosis of these patients is poor. This is due to the tumor extension through the inferior vena cava to the right atrium [14]. Thrombus embolization to pulmonary artery may be lethal.

The patient may also rarely present to emergency room with an *acute abdominal crisis* (acute abdominal pain, anemia, and hypotension) that can happen due to rupture of tumor secondary to trivial abdominal trauma [15]. The quoted incidence of such an event in WT patients is ~2% [16]. There have been occasional patients with WT cases who have been managed conservatively with a misdiagnosis of renal trauma [17, 18].

The *metastases* in WT are usually to regional lymph nodes, lungs, and liver. The patient may present with cough, tachypnea, or respiratory distress as a result of metastases in the lung. It may be associated with chest retractions, indrawings, and use of accessory muscles of respiration. Lung metastasis has been reported to cause pneumothorax [19, 20]. Liver metastasis may cause right hypochondriac pain, vomiting, loss of appetite, generalized weakness, jaundice, ascites, edema, or coagulation disorders.

Rare sites of metastases include bone, spine, mediastinum, brain, gonads, pancreas, etc. [21–24] The postmortem examination of WT patients had cerebral metastasis in 12.9% cases, but these are rarely diagnosed before death [25]. The intracranial metastasis may present with cerebral bleeding and hydrocephalous [26]. Brain and/or spinal compression may present with signs of irritability, seizures, projectile vomiting, radicular pain, muscular weakness, paraplegia, or loss of bowel or bladder control [27–30]. Bone pains or pathological fracture may be presenting feature of bone metastasis [28].

Any history of similar complains in other siblings, family members, or first cousins should be inquired about. Any history of other congenital anomalies and cause of death for deceased family members if any should also be elicited.

8.2 Examination

A meticulous head-to-toe examination should be carried out.

1. Temperature: Low-grade fever because of high metabolism secondary to fast-growing tumor.

2. Blood pressure (surveillance to rule out hypertension). It should be recorded when child is calm and with proper arm cuff size to avoid false readings.
3. Eye examination to rule out of aniridia (partially formed or not at all formed) and pallor (anemia).
4. Face: Dysmorphic features/bulldog facies (large protruding jaw, widened nasal bridge, upturned nasal tip, broad nose, wide mouth, thick lips) and macroglossia to be looked for.
5. Spine needs to be examined to rule out any gross abnormalities and bone pain.
6. Any evidence of easy bruisibility (acquired vWF deficiency).
7. Nutritional status should be assessed. Height, weight, mid-arm circumference, skin fold thickness, etc. need to be recorded.
8. Genitalia examination: Look for hypospadias, undescended testis, any evidence of varicocele (especially on the left side).
9. Isolated hemihypertrophy to be ruled out.
10. Developmental milestones to be assessed (rule out mental retardation or intellectual disabilities).

The physical examination should characterize the location and extent of the abdominal mass. The abdominal mass should be carefully examined. The mass should not be palpated too vigorously as it could lead to the rupture of a large tumor into the peritoneal cavity. Any other organomegaly or ascites to be ruled out. Renal angle fullness and tenderness to be noted.

WT needs to be clinically differentiated from abdominal neuroblastoma (NB) and other non-Wilms' renal tumors (NWRT) based on history and examination. A child with WT is usually well preserved, while it's ill-looking child with NB; more than half of the patients with NB with have metastases and malnutrition at presentation. On palpation, the abdominal NB mass almost always crosses the midline, whereas this presentation is uncommon with WT and seen only in those patients that present very late. Most of the patients with malignant rhabdoid tumor of kidney also present with a fast-growing tumor and fever and look sick, similar to NB. Clear cell sarcoma kidney usually presents with bone and/or brain metastasis. Renal cell carcinoma starts showing up from pre-adolescence. Congenital mesoblastic nephroma is most common tumor kidney in first 6 months of life, while WT commonly occurs in children of 1–3 years of age. The signs and symptoms of NWRT are detailed in another chapter.

8.3 Associated Syndromes

As associated abnormalities or syndromes may be present in patients with WT, the examination should include assessment of urological abnormalities like maldescended testis or hypospadias. These associated syndromes have been detailed elsewhere in the book.

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9 Laboratory Workup

Ayushi Vig and Kirtikumar J. Rathod

9.1 Panel of Biochemical Investigations

9.1.1 Complete Hemogram

The preliminary assessment of a child presenting with a suspected renal mass includes a full blood count, with chief importance to hematocrit and platelet count. Wilms' tumor (WT) is associated with high hematocrit, possibly due to elevated erythropoietin levels, which also correlates with the clinical and surgical course of the disease. Erythropoietin levels return to normal after successful tumor excision in the absence of metastasis. Increasing erythropoietin levels may also be useful in detecting recurrence of WT, in those cases in which the levels were high prior to surgical removal of the tumor [1].

9.1.2 Renal Function Tests

Although WT rarely presents with renal failure, however renal function should be routinely assessed in all patients as the mass effect of the tumor can cause ureteral compression, more often in patients with WT in single kidney or with bilateral WT. These patients at times also present with severe hypertension in 20–55% patients due to increased plasma prorenin and renin levels as a response to ischemia due to compression effect of tumor on intrarenal or hilar vessels [2]. Moreover, the tumor cells might also produce renin itself. Increased levels of glucocorticoids or catecholamines, treatment with steroid therapy, and cancer-related pain can also cause hypertension [3]. Hypertension resolves almost completely after successful tumor excision. Only in very few cases, hypertension may be persistent even after nephrectomy. The cause of which, according to Brenner Barker hypothesis, is significant reduction of nephrons post nephrectomy causing renal hypertension and progress to renal failure [2].

9.1.3 Serum Electrolyte Panel

Full panel of electrolytes are required including sodium, potassium, chlorides, magnesium, phosphorus, and calcium. Calcium levels are elevated primarily in congenital mesoblastic nephroma and malignant rhabdoid tumor of kidney.

9.1.4 Urine Examination

A complete urinalysis is warranted in all patients. Although hematuria is an uncommon symptom of WT, however if it appears, it may suggest that the tumor has invaded into the renal pelvis or rarely, into the ureter. Even an extremely small

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tumor can produce hematuria if it situated in close proximity to renal sinuses [2]. Proteinuria more than trace on routine urine analysis is an indicator of renal injury. Urinary tract infection (UTI) should be always be excluded if fever is the major complaint at the time of presentation. Urine microscopy and bacterial culture sensitivity is an important investigation in these children.

9.1.5 Clotting Screen

A complete coagulation profile should be routinely done in all the patients of WT. Rarely acquired von Willebrand syndrome (avWS) may be detected incidentally. The diagnosis may be further confirmed by a decrease of ristocetin cofactor activity, collagen binding activity, and by von Willebrand factor (vWF) multimeric analysis usually with selective loss of large multimers [4]. Various pathogenic mechanisms include formation of autoantibodies to vWF, increase of vWF proteolysis, adsorption of vWF onto tumor cells or activated platelets, and mechanical damage of vWF under shearing stress [5]. Identification of deranged coagulation profile is primarily important prior to any surgical procedure such as central venous line insertion or prechemotherapy (ChT) tumor biopsy. Desmopressin (DDAVP) is advocated as the first-line therapy in this condition. Factor VIII/vWF concentrates and high dose immunoglobulin infusions are kept reserved for patients not responding to this initial management. avWS always resolves after nephrectomy [6].

9.1.6 Novel Tumor Markers

Few recent papers have shown that urinary basic fibroblast growth factor (bFGF) to be preoperatively raised in children with WT. However, this test neither is specific nor a constant finding, so the test is clinically not useful till date [7]. Tissue polypeptide-specific antigen (TPS) which was a potential serum tumor marker in adult epithelial tumors is also found elevated in childhood solid tumors such as WT and neuroblastoma. TPS is a highly sensitive and specific for both of these conditions, and levels are also noted to decrease after successful management. Role of TPS in monitoring the therapy of pediatric solid tumors was first described by Rebhandl [8].

9.1.7 Investigations to Exclude Other Differentials

The level of serum neuron-specific enolase (NSE) and urinary catecholamine levels can be performed to eliminate neuroblastoma. Tumors markers like alpha feto-protein (AFP) and human chorionic gonadotrophin (HCG) can sometimes be used if there is radiological suspicion of teratoma of kidney [9].

9.1.8 Pre and Post Chemotherapy Investigations

Vincristine forms an important component of ChT for WT and is known to cause nonocclusive disease of the liver. This makes a baseline liver function panel an essential part of pre ChT workup [10].

Routine echocardiography is essential prior to starting doxorubicin as it is known to cause Doxorubicin-associated cardiomyopathy which causes heart failure and is known to be lethal in approximately 50% cases [11].

Auditory/Hearing Late Effects Task Force of Children's Oncology Group recommends comprehensive audiological evaluation (comprising of pure tone air and bone conduction, speech audiometry, and tympanometry for both the ears) of children who have received platinum-based ChT [12]. Frequency-specific auditory brain auditory brain stem response is done if the above tests are inconclusive [12].

According to the SIOP 2016 umbrella protocol, EDTA blood samples can be centrifuged and used to detect circulating tumor DNA and miRNA for initial tumor evaluation and for follow-up to detect relapse. Blood samples are collected at diagnosis, after two weeks of ChT,

before surgery, one week after the surgery, and at the completion of the management. Storage of serial samples of blood, urine, tumor, and germline material is done at standard national biobanks and is evaluated for international collaborative studies. This sample collection shall facilitate parallel and future translational research [13].

To conclude, a thorough evaluation is required prior to starting ChT or opting for surgical management of these patients. Also, few of these novel investigations such as urinary fibroblast growth factor and tissue polypeptide-specific antigen, and serum DNA and miRNA patterns are of both diagnostic and prognostic significance and may also be used to monitor response to therapy in future.

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Imaging Studies

10

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Imaging plays an important role in both, the International Society of Paediatric Oncology (SIOP) as well as in the Children's Oncology Group (COG) management strategies for Wilms' tumor (WT) [1–5]. Imaging is useful for the following:

1. Detect the mass lesion and identify its organ of origin
2. Establish the initial diagnosis of WT
3. Evaluate the post-chemotherapy (preoperative) tumor response in the SIOP regimen
4. Help in staging the tumor by determining its locoregional extent and distant metastases
5. Assess the requirement of a preoperative biopsy and localization of the site for biopsy
6. Guide the biopsy wherever required
7. Postoperative follow-up for tumor recurrence
8. Surveillance of children with high risk for WT development

10.1 Imaging Modalities

The various imaging modalities available are plain radiographs of the abdomen and chest, ultrasonography (USG) with Doppler, computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography (FDG PET-CT).

10.1.1 Conventional Radiography

A plain radiograph of the abdomen is usually not included in the essential workup in the imaging protocol of WT. However, when performed, it can show evidence of a large, flank mass with the displacement of bowel loops. Calcification may be seen in less than 10% of cases [4]. Intravenous urography (IVU), which was used for many years to assess the renal mass, does not have any role in the current workup and has been replaced by ultrasound and CT/MRI as contrast-enhanced CT (CECT)/MRI provides all the information of IVU.

10.1.2 Ultrasonography

USG is often used as the first imaging modality of choice for the evaluation of children with clinical suspicion of an abdominal mass [2, 5, 6]. It can help to define the renal or extrarenal origin of the mass lesion as well as demonstrate the solid or cystic nature of the lesion. On USG, WT is visualized as a large, intrarenal, predominantly solid mass with heterogeneous and variable echotexture (Fig. 10.1) [1]. The hypoechoic and anechoic areas within the mass usually represent central necrosis or cystic degeneration, whereas

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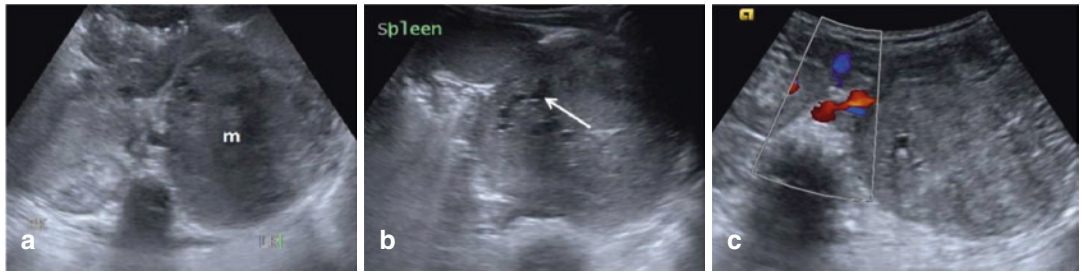

Fig. 10.1 WT in a 2-year-old girl child. Axial (**a**) and longitudinal (**b**) greyscale USG images show a large, well-defined solid heteroechoic mass lesion (m) in the left flank with small cystic areas within (arrow). Axial color Doppler USG image (**c**) shows normal color flow with patent appearing renal vein (blue)

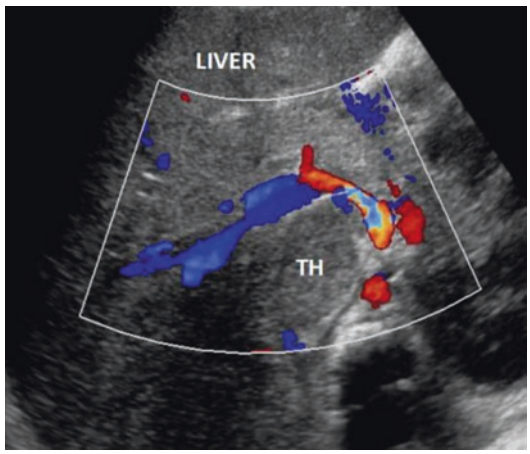

Fig. 10.2 Colour Doppler ultrasound image of a patient with WT showing intravascular extension with the thrombus (TH) in the distended IVC

echogenic areas within the mass are often due to hemorrhage and less frequently due to calcification [5, 7]. The residual renal parenchyma may be seen along the periphery of the lesion in cases presenting with large masses. A pseudocapsule can be detected on USG marginating the tumor from the rest of the renal parenchyma.

The tumor extension into the inferior vena cava (IVC) can be detected by the USG and Doppler evaluation (Fig. 10.2) [1, 5]. Intrahepatic IVC can be assessed relatively easily by Doppler; however, detection of thrombus confined only to the renal vein is relatively difficult on USG because of distortion by the tumor [7]. In cases with equivocal CT/MRI findings regarding intravascular tumor extension, Doppler sonography can act as a problem-solving tool [8]. Invasion into neighboring organs such as the liver can be evaluated by the real-time US. If the mass is seen to move freely from the organ, then invasion or adherence to the organ can be ruled out [9]. Metastases to the liver are well seen on USG. The presence, nature, and amount of fluid in the peritoneal cavity can be noted on ultrasound.

USG is good in detecting the tumor as well as the vascular extension of the lesion; however, it has a limited role in defining extra-capsular tumor spread and detecting nodal involvement and small tumors in contralateral kidneys [10]. Hence other cross-sectional imaging modalities are usually required for further characterization and determining the local tumor extent for optimal staging and operative planning [9–11].

10.1.3 Magnetic Resonance Imaging (MRI)

As per the latest UMBRELLA protocol by the Renal Tumor Study Group of the International Society of Pediatric Oncology (SIOP–RTSG), abdominal MRI is considered the preferred complementary imaging modality owing to the lack of ionizing radiation [5]. MRI is also the imaging study of choice in pediatric patients with bilateral WT or suspected bilateral tumor predisposition [2].

On MRI, WT is seen as a relatively well-defined heterogeneous lobulated mass appear-

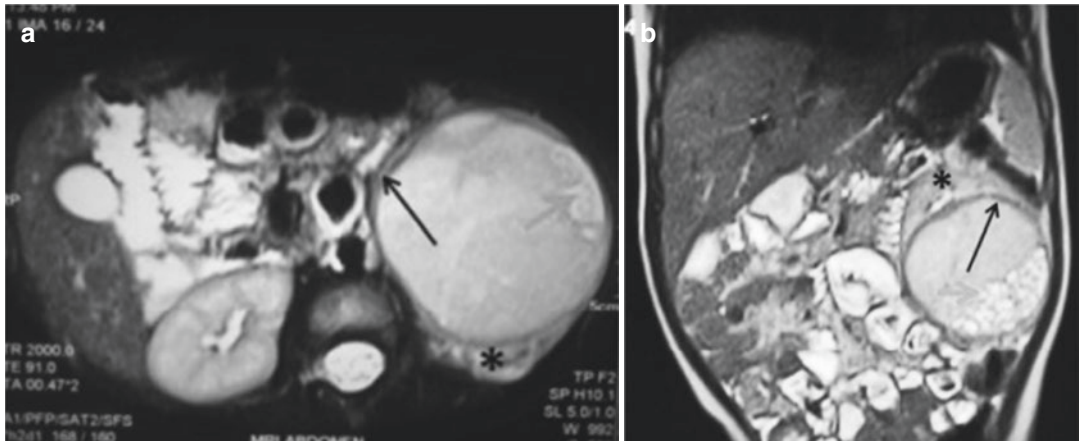

Fig. 10.3 MRI in WT in a 5-year-old male child. Axial (**a**) and coronal (**b**) T2W MR images show a well-defined hyperintense mass lesion arising from the left kidney with clawing of residual renal parenchyma (asterisk) with a hypointense pseudocapsule (black arrows). Note made of relatively more hyper-intense areas (grey arrows) within the tumor consistent with necrosis/cystic degeneration

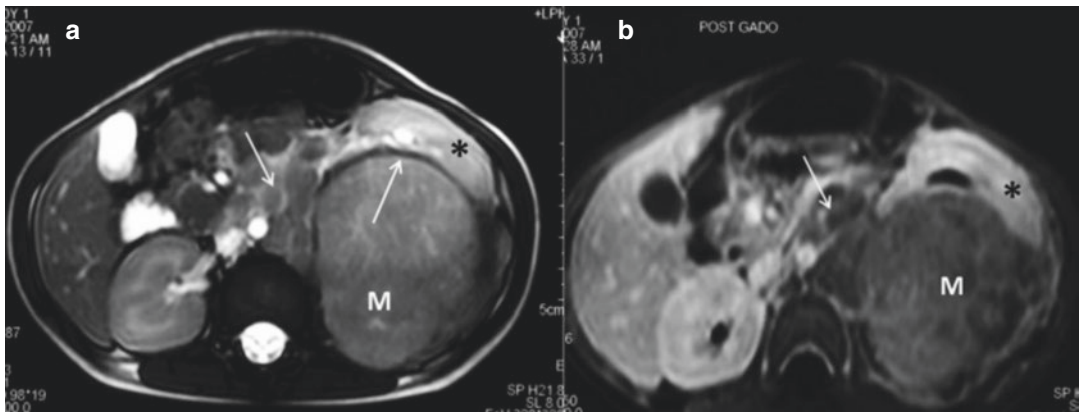

Fig. 10.4 MRI in WT in a 3-year-old girl. Axial T2W MR image (**a**) shows an iso- to hypointense mass with few focal hyperintense areas representing necrosis. The hypointense pseudocapsule (arrow in (**a**)) can be well seen separating the tumor mass (M) from the residual kidney (asterisk) which is displaced anteriorly. On the post-contrast image (**b**) the renal parenchyma (asterisk) is seen to enhance much more than the tumor mass (M). Multiple hypointense retroperitoneal lymph nodes (arrows in (**a**) and (**b**)) are seen anterior and to the left of the aorta

ing hypointense on T1W images and iso to slightly hyperintense on T2W images as compared to the normal renal cortex. Intra-tumoral necrosis and cystic changes show T2 hyperintense signal (Fig. 10.3). T1 hyperintense signal typically results from intra-tumoral hemorrhage. The pseudocapsule is seen as T1 and T2 hypointense peri-tumoral rim. The renal origin of the tumor is confirmed by the presence of a "positive beak sign" or "claw sign" which refers to the stretching and splaying of normal renal parenchyma at the periphery of the mass (Fig. 10.3). The tumors show heterogeneous postcontrast enhancement that is characteristically less as compared to normal renal parenchymal enhancement (Fig. 10.4). Gadolinium chelates in a dose of 0.1–0.2 ml/kg body weight are used as MR contrast agents.

Extension of tumor thrombus into the renal vein, IVC, and right atrium can be accurately evaluated by MRI with specific flow sequences [1, 9]. MR imaging accurately assesses the primary tumor, its size, regional extension, and relation to other organs. However, detection of subtle capsular invasion is still difficult on MRI similar to other imaging modalities. It can pick enlarged lymph nodes (LNs) (Fig. 10.4) and accurately detect focal hepatic metastatic lesions and other intra-abdominal sites of metastases [1, 9]. Small WT and nephrogenic rests (NRs) are also better detected and evaluated with gadolinium-enhanced MRI [2].

Diffusion-weighted (DW) MRI with apparent diffusion coefficient (ADC) mapping is a functional MR imaging technique that can provide additional information above conventional MRI sequences. Most malignant lesions have a high cellular density and show restricted diffusion. Hence, they show hyperintense signals on DW images. ADC is a quantitative value that decreases as the cellular density increases, and therefore, areas with diffusion restriction have low ADC values and appear hypointense on ADC maps. The DW images typically demonstrate restricted diffusion in the solid non-necrotic components of the WT [7]. DW images can differentiate viable and necrotic areas within the tumor, which is useful in selecting the optimal site for biopsy. It also helps in assessing the tumor response to neoadjuvant ChT with tumor shrinkage and increased ADC values seen in tumors responding to ChT, whereas persistently low ADC values indicate nonresponse to therapy [5]. ADC values of residual viable tumors obtained from DW images have also been found to be useful in post-ChT stratification of histological subtypes of WT (the high-risk blastemal type shows lower ADC values than various intermediate-risk subtypes) [12]. Besides this, DW imaging can be useful in detecting small synchronous tumors in the same or contralateral kidneys [2].

MR examination may sometimes become difficult to complete in children due to longer examination time with their inherent inability to lie still during the study. Sedation and in some cases general anesthesia may be necessary, which have associated risk of adverse events [5].

10.1.4 Computed Tomography

According to the SIOP-RTSG UMBRELLA protocol, CT of the abdomen for evaluation of WT should only be performed if MRI is not available [5]. However, because of its ready availability, short imaging time, and reduced need for sedation, CT is often used as the second-line imaging modality after USG.

CT examination mandates the administration of intravenous iodinated contrast for the evaluation of renal mass lesions [5]. The nonionic iodinated contrast is injected at a dose of 2 ml/kg of patient body weight. Usually, a single portal venous phase image is obtained after 65–70 s of contrast injection, which enables the opacification of venous structures including portal vein, IVC, and renal veins [13]. This single phase can provide all the information sufficient for diagnosis and staging [2, 5]. Oral contrast should be avoided as it unnecessarily prolongs the examination without providing any additional information. An extra phase—the delayed excretory phase—can be obtained in case of a small renal mass being considered for nephron-sparing surgery as this can provide information regarding the tumor's relationship with the collecting system [2].

On CT, WT appears as a large, well-defined heterogeneous mass, with a lesser degree of enhancement as compared to normal renal parenchyma. The "positive beak or claw sign" suggesting a renal origin of the mass is often well demonstrated on CECT images (Fig. 10.5). CT usually demonstrates intra-tumoral hypoattenuating areas resulting from necrosis, cystic changes, and/or fat deposition. Calcification, when present, is best seen on CT (Fig. 10.6). Exophytic growth pattern with contour irregularity may suggest capsular invasion. The renal

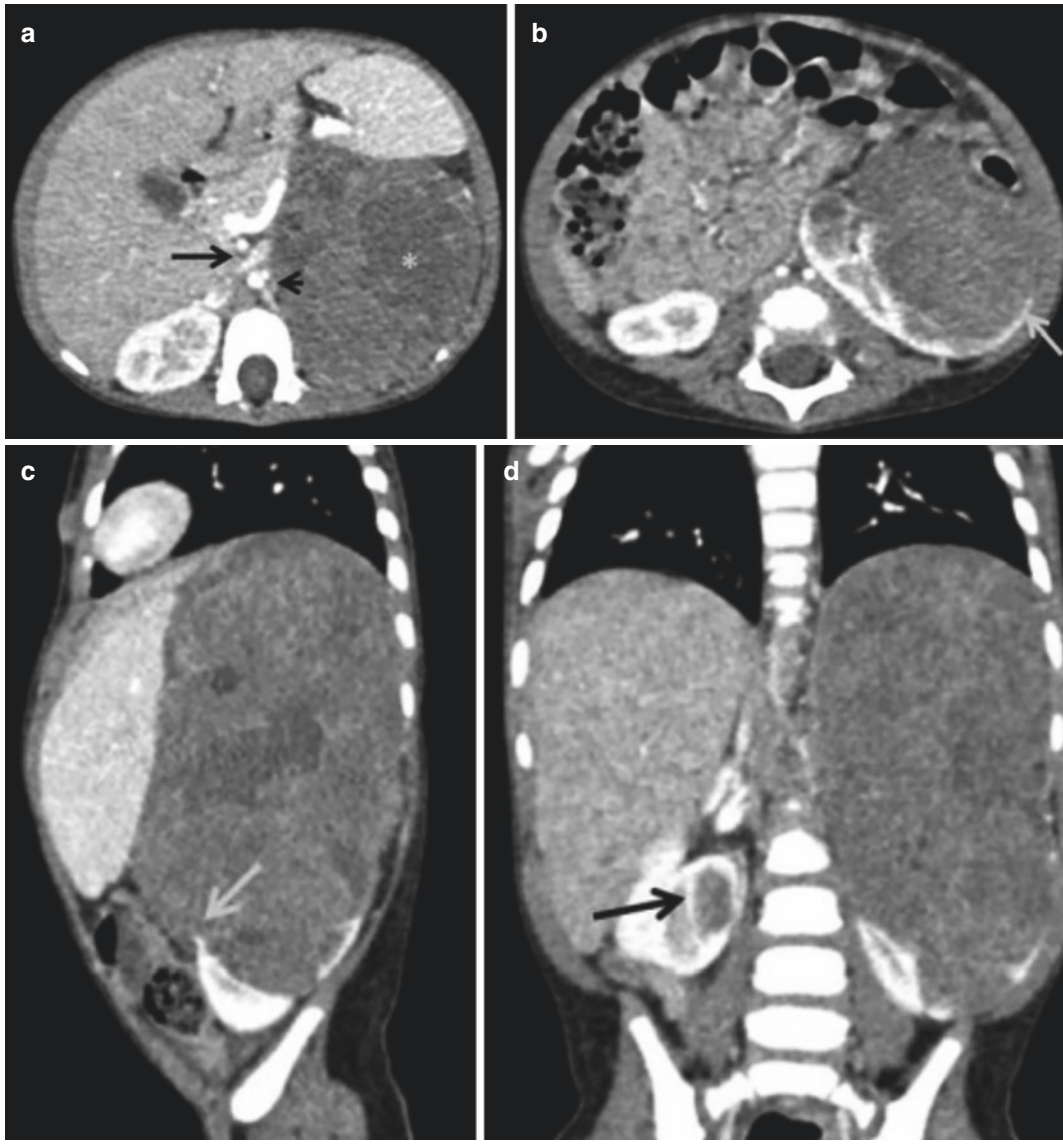

Fig. 10.5 WT of left renal origin in a 2-year-old girl. CECT axial (**a**, **b**), left parasagittal (**c**) and coronal (**d**) reformatted images show a large, well-defined, solid, hypodense, heterogeneously enhancing left flank mass with few non-enhancing areas within (asterisk in (**a**)) likely due to necrosis. The mass is causing anterior displacement of the spleen, splenic vessels, and pancreas with stretching and splaying of the residual renal parenchyma inferiorly at the lower pole showing a "positive claw sign" (grey arrow in (**b**) and (**c**)). The left renal artery (arrowhead in (**a**)) and renal vein (black arrow in (**a**)) are seen opacified in the proximal course of the lesion. A small, oval, hypodense, non-enhancing lesion seen in the lower pole of the right kidney was a nephrogenic rest (black arrow in (**d**))

veins and IVC can also be evaluated on postcontrast CT images to detect tumor thrombus extension (Fig. 10.7). CT may identify enlarged LNs; however, differentiation of neoplastic from reactive lymphadenopathy is difficult on CT. The involvement of adjacent organs, liver metastases, and the presence of intraperitoneal fluid can be well seen. CECT of the abdomen is

more sensitive than USG in defining the extent of the tumor and detecting lymph nodal, hepatic, and contralateral renal involvement. Exposure to ionizing radiation remains the main disadvantage of CT scans.

The advantages and disadvantages of USG, CT, and MRI are tabulated in Table 10.1.

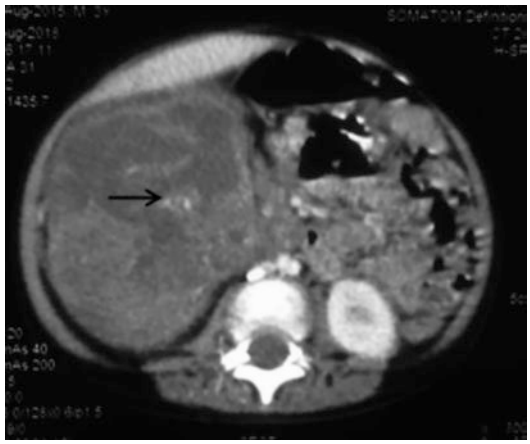

Fig. 10.6 WT in a 3-year-old boy. CECT axial image shows a large heterogeneously enhancing mass lesion arising from the right kidney with areas of necrosis. Calcific foci were seen within the tumor mass (arrow)

Table 10.1 Advantages and disadvantages of USG, CT, and MRI

Ultrasound	MRI	CT
Advantages • Noninvasive modality • Does not use ionizing radiation • Easily available • Good resolution, especially in children • Real-time evaluation • Does not require contrast or sedation	Advantages • Wide field of view • No ionizing radiation • Best soft tissue contrast resolution • Functional imaging is possible	Advantages • Wide field of view • More easily available than MRI • Short imaging time (less than 5 min) • No sedation required in older children (short sedation is required in small children)
Disadvantages • Field of view is restricted • Operator dependent	Disadvantages • May not be easily available • Long imaging time • Long sedation required • Intravenous contrast required	Disadvantages • Ionizing radiation • Intravenous contrast required

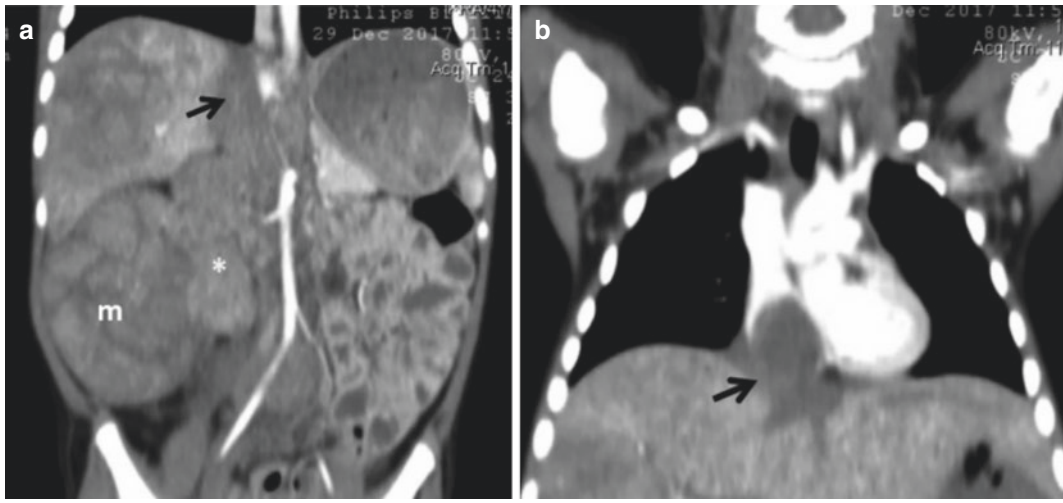

Fig. 10.7 WT in a 4-year-old girl child. Coronal CECT images of the abdomen (**a**) and Chest (**b**) show a large, heterogeneous mass of the right kidney (m) with extensive thrombosis in the right renal vein (asterisk in (**a**)) and IVC (arrow in (**a**)) extending into the right atrium (arrow in (**b**))

10.2 Tumor Staging

Staging of WT is essentially surgico-pathological. However, imaging has an important role in defining the preoperative local extent of tumor mass as this can guide surgeons while operating and assessing the distant metastases to establish the overall disease stage.

CT and MR imaging are considered to have similar accuracy in the loco-regional staging of WT [14]. Different institutions opt for either CT or MRI depending upon the availability of the imaging modality and other patient-related factors. However, MR imaging is more sensitive than CT for the evaluation of venous tumor extension and detection of contralateral synchronous lesions [5, 14, 15].

10.2.1 Local Extent

The key imaging findings that should be carefully evaluated in the abdomen include the following:

a. Infiltration of the tumor into adjacent structures.
b. Intravascular extension of tumor into the renal vein, IVC, and right atrium.
c. Detection of tumor extension into the ureter.
d. Involvement of regional lymph nodes LNs): As the size and morphology-based imaging criteria are not always accurate in differentiating benign from malignant LNs, surgical lymph nodal sampling is imperative for accurate staging [16].
e. Signs of tumor rupture (intraperitoneal and retroperitoneal): It is important to detect tumor rupture for staging and therapy planning, as it is considered an important risk factor for intra-abdominal tumor recurrence. Preoperative detection of tumor rupture on imaging may guide the surgeon in proper planning before surgery [17]. Some of the imaging findings which suggest tumor rupture include poorly defined margins of the tumor, peritumoral fat stranding, presence of fluid in retroperitoneal space, presence of significant peritoneal fluid extending beyond the cul-de-sac (irrespective of Hounsfield units), and ipsilateral pleural effusion [1, 2, 17]. Intratumoral hemorrhage, subcapsular fluid collection, or the presence of mild peritoneal fluid does not necessarily indicate tumor rupture [17]. According to the COG's current staging guidelines and SIOP-RTSG UMBRELLA protocol, imaging diagnosis of tumor rupture needs to be confirmed at the surgery and pathological examination of the nephrectomy specimen to upstage disease to stage III [2, 5].
f. Tumor spread to peritoneum: Peritoneal spread is often associated with intra-peritoneal tumor rupture. This is seen as an irregular peritoneal thickening, peritoneal nodularity, and ascites, along with mesenteric and omental solid masses on USG, CT, and MRI [4].

10.2.2 Size of the Tumor

The size of the tumor can be accurately measured on both CT and MRI. The volume of the tumor can be calculated by measuring the largest dimensions in three planes and using the formula ($A \times B \times C \times 0.523$) (Fig. 10.8). The tumor and kidney should be considered as a single unit and measured in total in a case with a large tumor, not differentiable from the kidney [5].

10.2.3 Distant Metastases

Hematogenous spread of the tumor with distant metastases is seen in approximately 20% of children with WT at the time of initial diagnosis [2]. Lungs are the most common site for distant metastases accounting for 80–85% of cases followed by the liver (Fig. 10.9) [1, 2].

10.2.3.1 Pulmonary Metastases

CT scan has largely replaced chest radiographs to assess pulmonary metastasis owing to its increased sensitivity for detecting very small lung nodules [18]. In the recent SIOP-RTSG UMBRELLA protocol recommendations, a CT chest has been made mandatory for the evaluation of pulmonary metastasis [5].

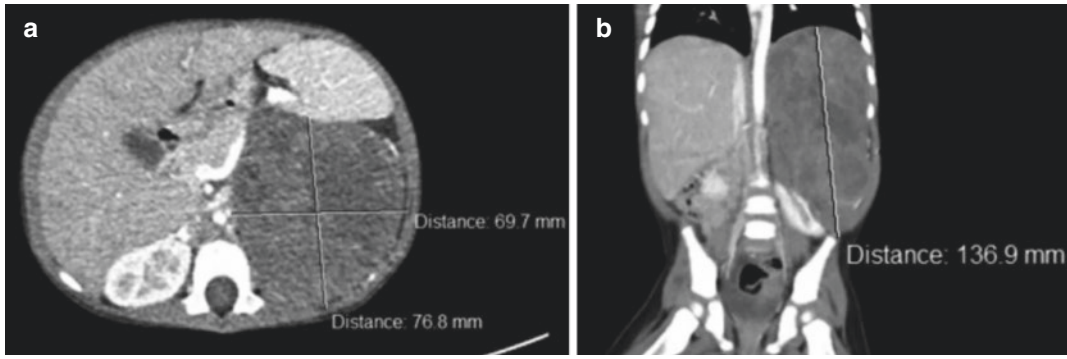

Fig. 10.8 CECT axial (**a**) and coronal (**b**) images of a child with large WT arising from the left kidney show the calculation of the volume of the lesion. The total volume of the tumor (calculated by the conventional method) was 383.2 cc

According to this guideline, intravenous contrast is not mandatory for chest CT; however, it can be used when combined with an abdominal CT scan in the same sitting [5]. It is better to perform the CT chest prior to nephrectomy as adequate evaluation of the lung parenchyma is compromised in the postoperative period by the basilar atelectasis and pleural effusions [2]. The UMBRELLA guidelines also recommend a mandatory baseline chest X-ray to be performed at initial diagnosis for comparison with follow-up chest radiographs [5].

CT-only nodules refer to small pulmonary lesions not visible on chest radiographs. There is ongoing controversy regarding staging the disease when these CT-only lesions are identified on chest CT. This is due to the fact that all CT-only nodules are not invariably metastatic deposits, and histopathological confirmation may be needed in many cases [2]. In a study under SIOP-2001 guidelines, no difference in outcome (both event-free survival and overall survival) was demonstrated between the two groups (those managed for localized disease and those managed for metastatic disease) in cases presenting with CT-only metastatic nodules [19]. On the contrary, results from the trials of Children's Oncology Group (COG), National Wilms Tumor Study Group (NWTS)-4, and NWTS-5 have demonstrated superior event-free survival (EFS) in patients with CT-only nodules and managed for metastatic disease as compared to those managed for localized disease, although the overall survival was found to be similar in both groups [5, 20, 21]. The role of chest CT in unfavorable histology or stage III disease is well established; any suspicious nodules on the CT chest should be considered significant, as accurate staging at diagnosis tends to improve overall survival in this group of patients [7, 19]. According to the latest UMBRELLA protocol, CT-only nodules larger than 3 mm in transverse diameter are managed as metastatic stage IV disease [5].

10.2.3.2 Other Metastatic Sites

About 15–20% of cases of WT can metastasize to the liver [9]. Imaging such as US, CT, and MRI can reliably detect hepatic metastases, which appear as solitary or multiple variable-sized focal lesions within the hepatic parenchyma. On USG, they are usually hyperechoic in comparison to the rest of the hepatic parenchyma (Fig. 10.9). Smaller lesions can be easily detected on CECT/MR imaging of the abdomen done for evaluation of primary tumor and typically appear as hypo-enhancing focal lesions. Metastases to the bone are very uncommon in WT and, if suspected clinically, can be detected by technetium bone scan, whole-body MRI, or FDG PET-CT.

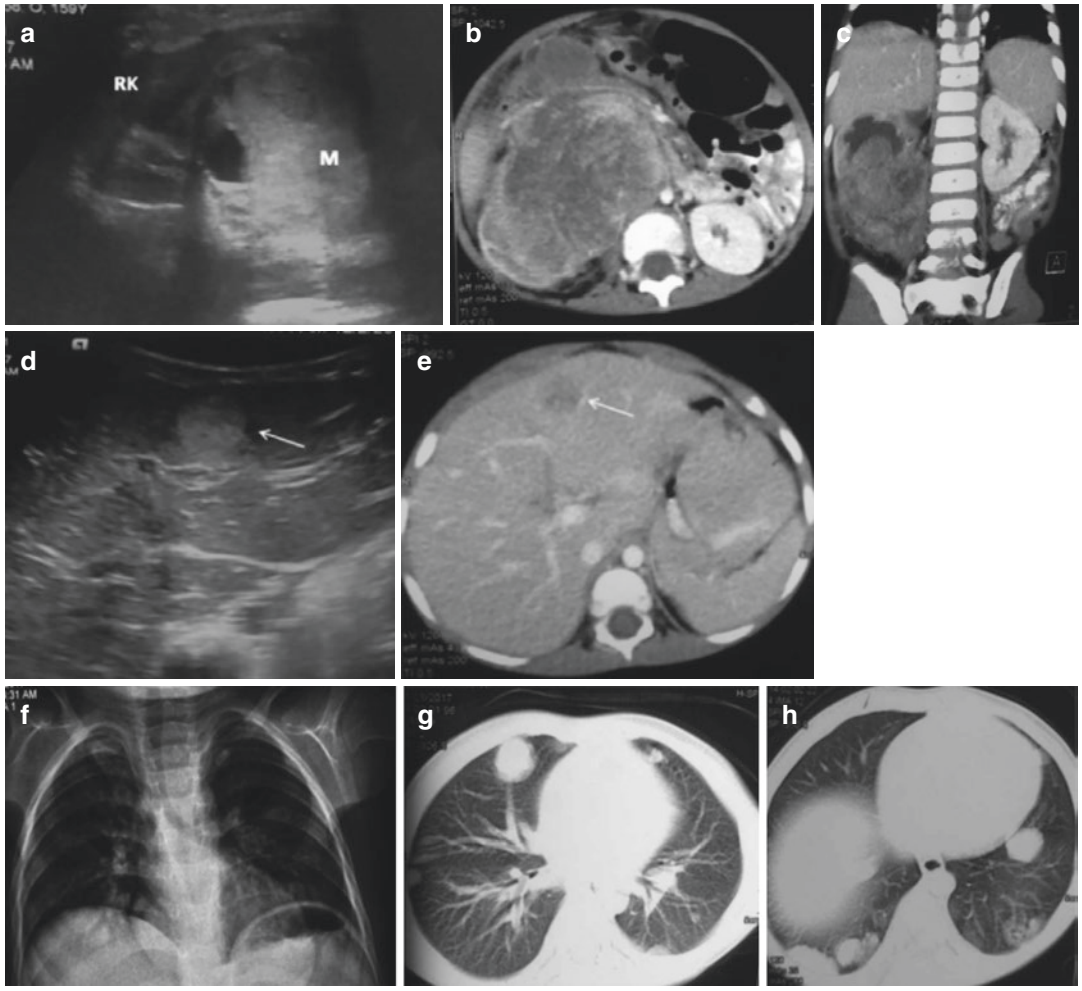

Fig. 10.9 WT in a 4-year-old boy with a history of palpable abdominal mass for 3 months with pulmonary and hepatic metastases. Greyscale USG image (**a**) shows a large, relatively well-defined, heteroechoic, solid mass lesion (M) seen arising from the mid and lower pole of the right kidney (RK). Axial (**b**) and coronal (**c**) CECT images in the same patient confirm the presence of a large, irregular, heterogeneously enhancing mass lesion arising from the mid and lower pole of the right kidney crossing midline and showing non enhancing necrotic areas within. The mass is infiltrating into the renal pelvis with resultant obstruction and dilatation of the residual upper pole calyces. Hepatic metastasis is seen as a well-defined round hyperechoic lesion (white arrow) on ultrasound (**d**) and as a round hypodense lesion (white arrow) in segment IV of the liver on CECT scan (**e**). Chest radiograph (**f**) of the same patient shows suspicious nodular opacities in the right lower zone. Axial CT sections through the chest in the lung window (**g**, **h**) reveal multiple, bilateral, rounded metastatic lesions predominantly in basal and subpleural locations

10.3 SIOP Post Chemotherapy Evaluation

SIOP protocol requires a repeat abdominal imaging preferably an MRI after completion of chemotherapy for reassessing the disease status before going to surgery. A repeat chest CT should be performed only if lung metastases were present at diagnosis [5]. Important imaging criteria to be noted are as follows:

a. *Size of the tumor*: Most of the WTs show a relative reduction in size and volume after

neoadjuvant chemotherapy. No change or increase in tumor size indicates a poor outcome. In the UMBRELLA protocol, post-ChT tumor volume has been described as a risk stratification factor for a subgroup of WTs with tumor volume >500 ml requiring aggressive treatment [5].

b. *Appearance of the tumor*: Most WTs respond by showing increased necrotic areas after ChT, appearing cystic on imaging (Fig. 10.10).

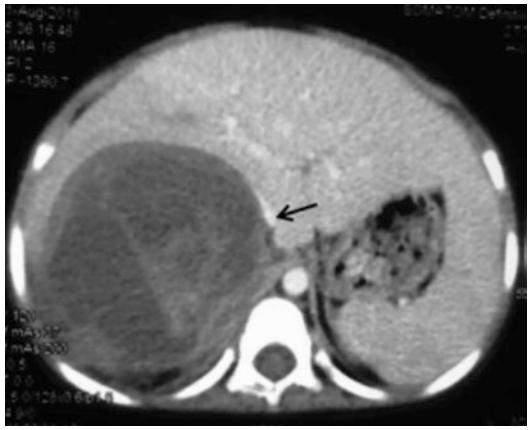

Fig. 10.10 Post-chemotherapy CECT in a case with WT of the right kidney. The tumor shows a large central necrotic component. The IVC is markedly stretched and compressed by the lesion with resultant luminal attenuation (arrow), but no evidence of intraluminal thrombus was seen

c. *Diffusion characteristics and ADC values*: There is a reduction in diffusion restriction (seen as low signal intensity on DW images) with an increase in ADC values in the responding tumor as compared to nonresponders. DWI also helps in the stratification of various histological subtypes of WT [5, 12].

10.4 Evaluation of Contralateral Kidney

It is essential to establish the status of the contralateral kidney to decide the line of management. The contralateral kidney needs to be evaluated to look for the presence of bilateral tumor (Fig. 10.11), NRs, or any co-existing renal malformations which may affect renal function. Current imaging techniques, especially MRI, are highly sensitive in detecting bilateral disease. The contralateral kidneys should be evaluated during surgery if concerning findings are evident on the preoperative imaging [2].

10.5 Nephrogenic Rests

NRs are focal, intra-renal rests, resembling the normal renal cortex on all imaging modalities. USG demonstrates large, irregularly lobulated

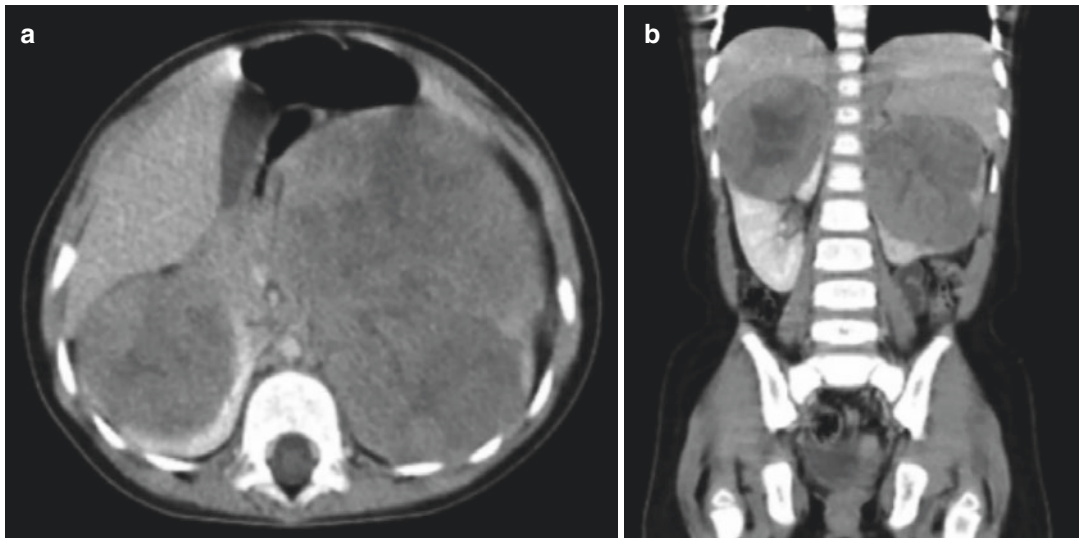

Fig. 10.11 Bilateral WT in a 2-year-old child. CECT axial (**a**) and coronal (**b**) images show two well-defined heterogeneous mass lesions involving right and left kidneys (left larger than right) with areas of necrosis within

kidneys with round or oval-shaped hypoechoic to isoechoic homogeneous renal parenchymal mass-like lesions, often with asymmetric and peripheral distribution [1]. They are better delineated on CECT and MRI as focal nonenhancing mass-like lesions (Fig. 10.5) [1]. The NRs are typically homogeneous in appearance in contrast to WTs, which tend to be heterogeneous. Diffusion-weighted imaging (DWI) can help in picking up small foci of NRs. MRI may help differentiate a sclerotic from a hyperplastic nephrogenic rest. Sclerotic rests tend to lack the potential to develop into a WT and thus considered to be in a regressive phase. CT is unable to make this distinction [22].

Multiple or diffuse nephrogenic rests are known as nephroblastomatosis (NB) [1]. The *diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB)*, also known as *pan lobar NB*, is typically seen as diffuse enlargement of the kidney with a thick hypoechoic rim on USG. This abnormal tissue surrounds the renal periphery and compresses the centrally located residual parenchyma. There may be also a diffuse hyperechoic appearance of kidneys with poor corticomedullary differentiation [1]. At CT, the peripheral rim of NB is homogeneously hypodense and nonenhancing (Fig. 10.12) and causes distortion and splaying of the pelvicalyceal system and renal sinus. On MRI, it shows homogeneous hypointense signal on T1W images and variable iso- to hyperintense signal on T2W images. Contrast-enhanced images better demonstrate these lesions with sharp demarcation from the more enhancing normal renal parenchyma. Sometimes cysts may be seen along with diffuse NBL, simulating adult polycystic kidney disease. CECT and MRI are better than USG in the identification of small tumors, nephrogenic rests, and nephroblastomatosis [2, 22].

Differentiating NRs from a small WT can be difficult on imaging in some cases [2]. Increasing size on follow-up imaging, the spherical shape of the lesion, and heterogeneous enhancement are findings suspicious of neoplastic transformation [15, 23]. At present, DW imaging is unable to distinguish clearly small WT from NRs or NBL, based on mean ADC values [2, 4, 24]. However, DW images are useful in better delineation of small NR/ NB foci and detection of additional NB lesions not visible on conventional MR sequences both at the time of initial presentation and after completion of neoadjuvant ChT [4, 24].

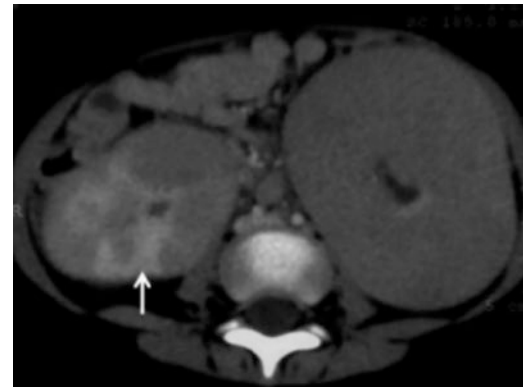

Fig. 10.12 Bilateral DHPLNB in a 1-year-old child. CECT axial image showing enlargement of bilateral kidneys (left > right) with peripheral, homogenous, nonenhancing areas almost completely replacing the normal renal parenchyma on left side. Compressed enhancing normal renal parenchyma is seen on the right side (arrow)

10.6 Role of Imaging in Nephron-Sparing Surgery

Nephron-sparing surgery (NSS) is the primary management of choice in children presenting with bilateral WT at diagnosis [1]. As already mentioned, MRI is the preferred imaging modality in these cases. In these children, DW MRI can be added to conventional MRI for improving the detection and accurately delineating the small lesions (WT, NRs, and NB). This can help the surgeons in optimizing the surgical resection to preserve the maximum possible normal renal parenchyma [4, 23, 24].

Partial nephrectomy and other forms of NSS are also considered in the management of unilateral WT in children with tumor involvement of solitary or horseshoe kidneys, in cases with contralateral genitourinary abnormalities, and in children with syndromic predisposition to develop metachronous WT in the contralateral

Table 10.2 Imaging criteria suitable for NSS [3, 5]

1	Tumor confined to single renal pole or peripheral aspect of mid-kidney
2	Unifocal tumor
3	Volume <300 ml after administration of neoadjuvant chemotherapy
4	Adequate adjacent normal renal parenchyma to achieve oncological safe margin after excision of the tumor
5	Less than 1/3 renal involvement by tumor and sparing of at least 2/3 normal renal parenchyma for function
6	No signs of preoperative rupture
7	No involvement of renal pelvis and calyces
8	Absence of obvious invasion/infiltration of surrounding organs
9	Absence of thrombus in the renal vein or IVC
10	Absence of lymph nodal involvement

kidney [1, 9]. Preoperative imaging using CT with multiplanar reconstructions or multiplanar MRI helps in identifying candidates for NSS and determining the resectability of the lesion by the accurate delineation of tumor margin and its extent [1, 5]. Features on imaging that should be assessed for the feasibility of an NSS are given in Table 10.2. Sometimes, imaging may not be able to detect normal renal parenchyma because of the volume effect of large masses, and in these cases, intraoperative US may be used to accurately delineate tumor margin during surgical excision [9].

Other imaging techniques that are useful in a patient being considered for NSS besides the usual protocol include angiography and renal functional assessment by radionuclide study. Angiographic studies may be of benefit in demonstrating vascular supply and venous drainage accurately [13]. It should ideally be performed as magnetic resonance angiography (MRA) using angiographic sequences with/without an intravascular contrast agent. Renal scintigraphy with dimercaptosuccinic acid (DMSA) is a sensitive technique for evaluating renal function and can be used for assessing the volume of functioning renal tissue. These may guide the surgeons in preserving normal functioning renal tissue while performing nephron-sparing surgery. According to the UMBRELLA protocol, isotope renography should be considered before NSS, to define the expected postoperative function, if the percentage of remnant renal parenchyma cannot be defined on conventional cross-sectional imaging [5]. Another role of imaging in NSS is the assessment of normal postoperative renal function by Doppler sonography usually performed 2 days after surgery [5].

10.7 Role of PET/PET-CT Imaging

There has been an emerging role of FDG PET-CT in the evaluation of WT. FDG avidity has been demonstrated in both primary as well as metastatic WT [3, 25]. At present, FDG PET seems to have no role in the initial diagnostic staging of WT due to the concerns of additional radiation exposure [7, 26, 27]. However, it has an important role in:

1. Evaluating the response to neoadjuvant ChT with a lower maximum standardized uptake value (SUV_{max}) demonstrated in good responders compared with poor responders to ChT [26, 27]
2. Directing biopsy from areas of active tumor activity, if it is deemed necessary [25, 28]
3. Providing additional information over and above the cross-sectional imaging studies about active residual or recurrent disease [27]
4. Accurate staging and detection of the extent of metastatic disease in children with relapse [7]

10.8 Pretreatment Biopsy

The latest SIOP-RTSG UMBRELLA protocol recommends neoadjuvant ChT to be started without biopsy confirmation, thereby increasing the importance of imaging studies in suggesting an accurate presumptive diagnosis of WT [3, 5]. However, to prevent non-WT histology from receiving an inappropriate ChT regimen, a percutaneous core needle biopsy is indicated in the presence of unusual features [5, 10, 29]. Besides unusual clinical presenta-

Table 10.3 Unusual imaging features that warrant a pretreatment biopsy [3, 5, 9, 29]

1	Presence of large lymphadenopathy
2	Presence of significant intratumoral calcifications
3	Inflammation/infiltration of psoas
4	Nonvisibility of renal parenchyma
5	Almost totally extrarenal process
6	Pulmonary metastasis in children with less than 2 years of age
7	Extrahepatic and extrapulmonary metastases

tion, that is, older than 10 years of age, urinary tract infection, septicemia, or presence of hypercalcemia, certain imaging features warrant a biopsy to confirm the histological diagnosis [3, 9, 29]. These have been tabulated in Table 10.3.

In heterogeneous tumors, imaging can help to decide the ideal site from which a biopsy should be taken [29]. The biopsy can be performed under the US or CT guidance to accurately sample from the solid and viable tumor portion, not from necrotic or cystic areas. DW MRI, as well as PET-CT, may help differentiate viable from necrotic components within tumors and therefore is useful in localizing sites for biopsy.

10.9 Differential Diagnosis

Neuroblastoma is the most important differential diagnostic consideration in children with suspected WT. WT classically demonstrates renal origin with clawing of adjacent renal parenchyma, whereas neuroblastoma is often of suprarenal origin and tends to displace the kidney. Differentiation of both these entities may be difficult at times particularly in cases with large exophytic WT and in cases with the renal invasion of neuroblastoma. Imaging morphology that favors WT is internal heterogeneity with intratumoral hemorrhage and necrosis, round to oval shape with regular margins, and lack of calcification. Abdominal neuroblastoma on the other hand usually demonstrates ill-defined margins, intratumoral calcifications, extension across the midline, displacement, and encasement of vascular structures without invasion. The presence of vascular encasement, paravertebral extension, and invasion of the spinal canal are highly suggestive of neuroblastoma, whereas demonstration of tumor invasion of renal vein and IVC strongly suggests WT [1, 7].

Other differentials of intrarenal tumors in children are renal cell carcinoma (RCC), congenital mesoblastic nephroma (CMN), clear cell sarcoma of the kidney (CCSK), and malignant rhabdoid tumor of the kidney (MRTK). These have been elaborated elsewhere in the book.

Occasionally an *infectious process* can also mimic WT—focal bacterial nephritis, xanthogranulomatous pyelonephritis (XGP) and a renal abscess may be misdiagnosed as WT. Clinical features such as fever, flank pain, urinary symptoms, and certain imaging features like the striated pattern of postcontrast enhancement or hypo-enhancing wedge-shaped areas in the adjacent renal parenchyma help distinguish infection from the tumor [1].

10.10 Posttreatment Imaging Surveillance and Screening

Approximately 15% of children treated for WT present with relapse, and most of these relapses are detected within the first 2 years after diagnosis and treatment [30]. Imaging has an important role in the posttreatment surveillance of these patients for early detection of tumor recurrence, even before the onset of symptoms, which may result in better salvage rates with the improvement of postrelapse survival [2]. The lung is the most common site of relapse for WT accounting for 50–60% of cases, followed by local or regional abdominal relapses seen in approximately 30% of cases [25, 31]. There is a higher risk of local recurrence in children with lymph nodal involvement, intraoperative tumor spillage, and unfavorable histology [28].

The duration and frequency, as well as the optimal imaging modality to be used for surveillance, are still debatable; hence, various follow-up protocols are used according to available resources and regional practices. The two most important recommendations cur-

Table 10.4 Recommendations for imaging follow-up of children with WT according to SIOP [2, 5, 8]

Patient group	Radiological investigation	Frequency after the end of therapy
Stage III and IV with high-risk histology Stage IV with Intermediate risk histology	Chest radiograph and ultrasound of the abdomen	At the end of treatment Every 2 months in 1st year Every 3 months in 2nd year Every 4 months in 3rd year Every 6 months in 4th year Annually in 5th year
All other patient groups	Chest radiograph and ultrasound of the abdomen	At the end of treatment Every 3 months in 1st and 2nd year Every 4 months in 3rd year Every 6 months in 4th year Annually in 5th year
Persistent pulmonary metastases after neoadjuvant chemotherapy	Chest CT	At the end of treatment
Bilateral tumors (stage V) and Nephrogenic rests	Chest radiograph and ultrasound of the abdomen	Every 2 months in 1st and 2nd year Every 3 months in 3rd and 4th year Annually from 5 to 10 years

rently in use for clinical and research purposes include the guidelines proposed by the COG and SIOP groups**.** The fundamental difference between SIOP and COG guidelines is that SIOP recommends chest radiographs and an abdominal USG to detect recurrence, whereas COG recommends chest CT and abdominal CT/MRI for the first 2–3 years, depending on stage of the disease and histology of the tumor, before changing to chest radiographs and abdominal USG, respectively [2]. Many recent studies have shown that imaging surveillance of treated WT cases with CT scans provides no significant advantage in terms of detection rate compared to surveillance using sonography and chest radiography while subjecting the children to a large radiation burden [32, 33]. Therefore, ultrasound and radiography-based SIOP guidelines have been preferred for clinical use in many centers. The latest SIOP-RTSG UMBRELLA protocol recommendation for imaging surveillance of WT is summarized in Table 10.4 [5, 30, 34]. Extended surveillance beyond 2 years posttreatment can be considered, but recent studies show that this approach to detect one asymptomatic relapse may not be cost-effective [30].

Children with genetic syndromes have a significantly higher risk to develop WT (>5% risk of WT) and should be screened with abdominal USG every 3–4 months. Imaging surveillance is recommended up to 5 years of age in WT1 mutant syndromes and up to at least 7 years of age in Beckwith-Wiedemann syndrome, isolated hemihypertrophy, and familial WT pedigrees [34].

10.11 Conclusion

Imaging has got an important role in the management of WT including the initial diagnosis, staging of the disease, surgical planning, posttreatment response evaluation as well as follow-up and surveillance. As the management of WT is fundamentally different in both the regimens (COG and SIOP), the imaging protocol also varies (Fig. 10.13). In both cases, a baseline imaging evaluation needs to be done at the time of initial diagnosis, which determines the renal origin of the lesion and its locoregional extent as well as detects distant metastases. As the patients in SIOP guidelines receive neoadjuvant ChT, a repeat imaging is performed after completion of ChT before proceeding to surgery. CT chest for pulmonary metastases is repeated only if pretreatment imaging showed positive findings. USG remains the initial imag-

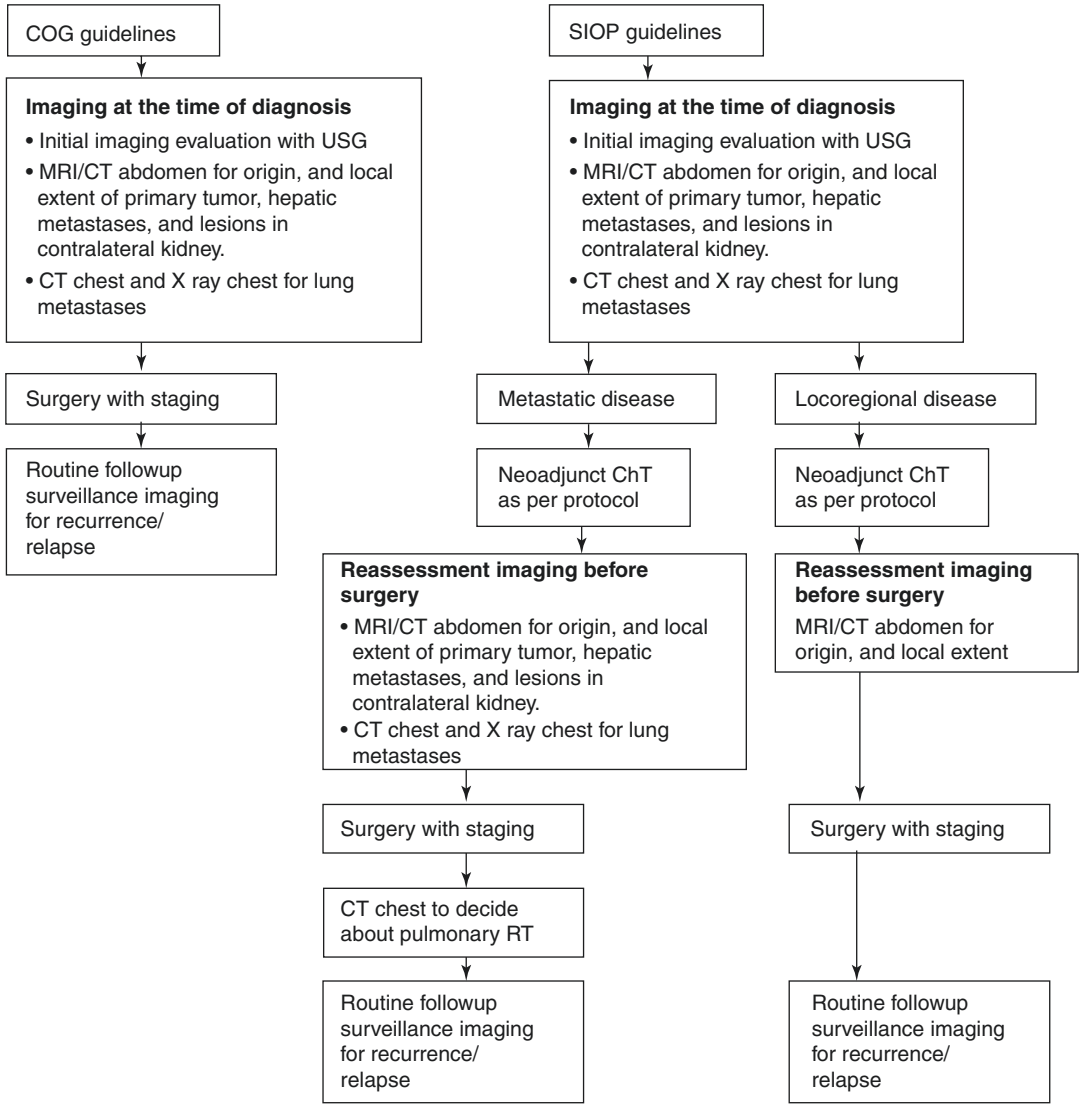

Fig. 10.13 Timing and protocol of imaging in WT according to COG and SIOP guidelines [2, 5]

ing modality of choice for the evaluation of WT. CECT and MRI are both optimal for staging and depicting the locoregional spread of the tumor, although MRI is the preferred modality due to the concerns of radiation exposure in CT. DW MRI has emerged as a promising imaging tool in recent years, as a problem-solving technique that can provide additional functional information with important management implications.

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Diagnostic Biopsy

11

Khalid Elmalik and Brian Davies

11.1 Introduction

The management of Wilms' tumor (WT) is regarded as one of the real success stories in pediatric oncology with an overall cure rate of over 85% [1]. This success is mainly due to the collaborative work of multiple worldwide groups in particular the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (COG) (formerly the National Wilms Tumor Study Group, NWTSG).

COG considers primary nephrectomy as the gold standard in most cases; however preoperative biopsy is recommended in a number of varied clinical scenarios. If primary nephrectomy cannot be safely performed, then a biopsy is recommended, either open or with multiple cores. The contraindications to primary nephrectomy according to the COG protocol include caval tumor thrombus extending up to the hepatic veins, large tumor where nephrectomy would result in significant morbidity/mortality, spillage, or incomplete resection or that involves contiguous structures putting them at risk of removal (e.g., spleen, pancreas, colon, or liver) and finally if the patient suffers from extensive pulmonary compromise from either lung or liver deposits [2, 3]. Bilateral disease usually does not require tissue diagnosis if the patient has classic radiology and falls within the typical age group; nevertheless if one of the lesions is regarded as indeterminate, then pathological assessment is recommended [4, 5]. In the COG protocol, bilateral disease is treated initially with chemotherapy (ChT) and reassessment at 6 weeks, and if the response (tumor shrinkage) is less than 30%, then a biopsy would be indicated to determine the histology. If anaplasia is detected, the ChT regime is changed, and if the histology revealed stromal differentiation, or rhabdomyomatous changes, then definitive surgery is recommended as no further response would be expected [6].

The SIOP protocol recommends preoperative empirical two-drug ChT for 4 weeks with for unilateral localized cases and 6 weeks three-drug ChT for metastatic tumor in children aged 6 months or older without a biopsy. Therapy is initiated purely on imaging and no tissue diagnosis in the majority of cases [7, 8].

Below the age of 6 months, the recommendation is an upfront nephrectomy, and the likely diagnoses are WT or a congenital mesoblastic nephroma (CMN). Renal cell carcinoma mean age for presentation is 14 years; radiographically it is indistinguishable from WT. RCC accounts for approximately 2–4% of childhood renal tumors; however this increases to over 50% in adolescents [9]. So, in the age group >6 months

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to <7 years, biopsy is not recommended, as the likely diagnosis is WT and ChT may be started based on radiology as per the SIOP protocol. There is a caveat however to this strategy, and alternative pathology has to be ruled out by performing a battery of investigations in addition to the standard tests and staging imaging.

Atypical radiology permits a biopsy in both COG and SIOP protocols [3]. On the other hand, small infants below six months of age and cystic tumors are generally resected primarily in both protocols without biopsy globally as the majority will not require ChT, provided the tumors were considered resectable. Biopsy is generally also avoided if rupture is suspected, unstable patient or a patient with known predisposition syndromes, for example, Beckwith-Wiedemann syndrome.

In the United Kingdom, the traditional treatment was an upfront surgery followed by ChT and/or radiotherapy (XRT) depending upon stage and histology (similar to NWTSG). Nevertheless, following the UKW3 study (1991–2001), there was a shift to adopt the upfront ChT as the standard of care including the biopsy [10]. The Children's Cancer and Leukemia Group (CCLG) joined the SIOP-WT-2001 study; however, the routine biopsy at presentation continued to be the standard of care in the United Kingdom. More recently, despite of Brexit, the United Kingdom has moved closer to Europe by adopting the European-SIOP protocol and only performing a biopsy in selected cases following a stringent selection criterion [11].

In countries where the treatment of WT is non-consistent, there is a tendency to follow the COG guidelines for lower-stage disease where surgery is thought to be safe and feasible. However, when risk of intraoperative spillage deemed to be high, preoperative ChT is considered. Few centers believe in performing a biopsy before ChT is instituted [12].

11.2 Fallacies of Imaging Alone

Patients who have classic radiological evidence of WT are exempted from biopsy in European, and now United Kingdom, guidelines provided they fulfill the strict exemption criteria (Fig. 11.1); otherwise there is a small but recognized risk of missing an alternative diagnosis (Figs. 11.2 and 11.3) resulting in suboptimal or unnecessary treatment.

The typical appearance of WT on CT is a mass confined to the kidney and may show a "bear-claw" sign and irregular effacement of normal parenchyma overlying the tumor. On SIOP 93-01 study, about 5% of renal tumors treated with empirical ChT were found to be non-WT; this included 1.8% benign lesions [13].

Miniati et al. reviewed histology reports of nephrectomies and open biopsies of 92 patients

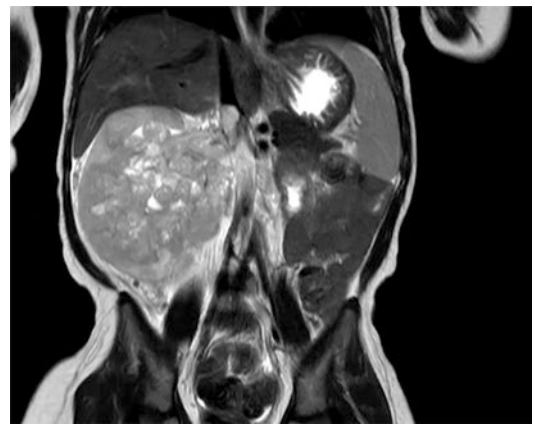

Fig. 11.1 2-year old: typical renal mass with caval extension, hence no biopsy before ChT. WT confirmed on final histology

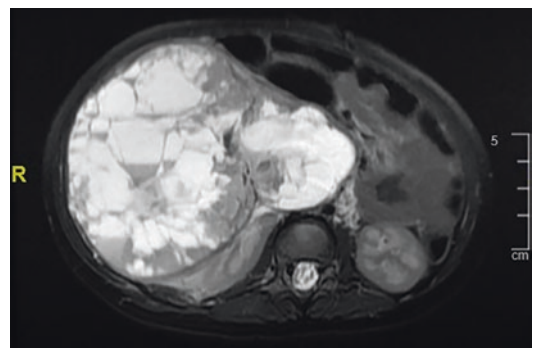

Fig. 11.2 15-month old. Cystic renal tumor. In view of age being atypical for nephroma, a US-guided biopsy by an interventional radiologist was done into the solid component of the tumor. Cytogenetic studies of the sample did not show the typical features of a CMN. Immunohistopathology showed a clear cell sarcoma of the kidney (CCSK)

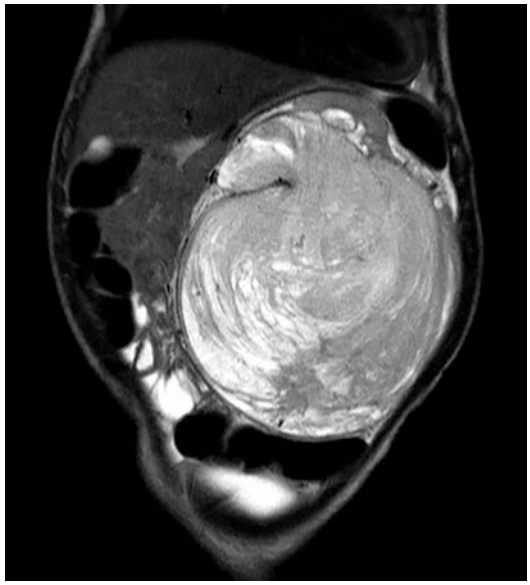

Fig. 11.3 21-month old. Although this was completely solid left renal tumor on imaging, the "swirling" seen on the MRI was not typical of WT; hence, a percutaneous biopsy was performed. This showed it to be a clear cell sarcoma of kidney

at a single institution and calculated the accuracy of the imaging in identifying specific tumors; CT reports stated potential diagnosis in 89% with a diagnostic accuracy of 82% [14].

In 2014, Farmakis and Siegel reported a case of intrarenal neuroblastoma (IR NB) in a 14-month-old boy who presented with a palpable large abdominal mass confirmed on CT to be arising from the left kidney, and there were no calcifications; however there were multiple lung nodules. The diagnosis was secured by sampling one of the lung lesions as there was fear from rupture during a primary nephrectomy [4, 15].

The radiology has to be fairly conclusive to allow commencement of ChT without tissue diagnosis in the SIOP protocol. Reference radiology review is usually carried out for the purpose of quality control in trials in particular. Schenk et al. described reference radiological evaluation can improve the diagnostic accuracy with therapeutic relevance; however they have pointed out that differentiation between the different renal tumors is not completely possible using imaging methods. They concluded that the rate of patients with false preoperative ChT for all renal neoplasms is 5.2% and 1% for benign renal tumors [16].

11.3 Children Cancer and Leukemia Group Guidelines–UK [11]

The UKCCLG recommends consideration of biopsy in the following situations:

1. Children aged 7 years and above.
2. Signs of urinary tract infection that would be consistent with xanthogranulomatous pyelonephritis.
3. Hypercalcemia suspicious of malignant rhabdoid tumor of the kidney.
4. Raised lactate dehydrogenase (LDH) level more than four times the normal value that would be suspicious of neuroblastoma or hematological malignancies.
5. Raised urinary catecholamines—suspicious of neuroblastoma
6. Imaging suggestive of other diagnosis (e.g., psoas infiltration, tumor encasing vascular structures, numerous calcifications in the tumor-all suspicious for neuroblastoma). Renal parenchyma not visible or predominantly extrarenal process, extrahepatic, and extrapulmonary metastases and pulmonary metastasis in a patient less than 2 years of age (suspicious for malignant rhabdoid tumor of the kidney).

11.4 Limitations

The biopsy has its own limitations and cannot always differentiate between WT and nephroblastomatosis, or between the stromal subtype WT and soft tissue sarcoma. The core biopsy may frequently miss areas of diffuse anaplasia too [17].

It appears that overall concordance between biopsy and final nephrectomy remained comparable between the early 1980s at 93% and more recent data at 91.7% to 94%, for all UK data [17–19]. Nevertheless, Vujanic et al.'s study only

included cases where both the biopsy and nephrectomy were sent for central pathology review (CPR). This suggests that where biopsy is performed, CPR may help improve diagnostic accuracy, as is the case for nephrectomy specimens [20].

The biopsy was nondiagnostic in 8% (relatively small sample 36 cases historical data 1982–1986) [18] to more recent 6.5% (20) and 4% in the UKW3 study [17].

The biopsy can be nondiagnostic for a number of reasons, for example, due to necrotic tumor or sampling normal renal tissue. The specimen may be indeterminate if it reveals malignant neoplasm that is not a WT, but it is not clear which is non-WT. All these scenarios can result in delays to initiate definitive therapy with the potential of adverse consequences.

Sebire and Roebuck demonstrated in their systematic review that image-guided needle core biopsies provided adequate tissues for diagnosis in pediatric oncology in about 95% of cases and complications requiring intervention to treat occurred in 1% [21]. They highlighted that a small specimen may be adequate and demonstrate all the necessary diagnostic features, whereas a larger biopsy showing part of a fibrous or stromal area may be inadequate for the pathologist to make definitive diagnostic comment. Immunohistochemical tests, for example, CD56 and nuclear WT1 in the blastema of WT, require only small amount of tissue to diagnose [21].

On the other hand, Jackson et al. found that the biopsy would be expected to correctly change management in only 6.7% cases [19]. However, reviewing the European data showing that with improved imaging and using selective biopsies, the chance of giving inappropriate ChT was around 1%. Hence there is a change of practice in the United Kingdom.

The authors have conducted a similar study of renal tumor biopsy of three regional centers in the United Kingdom, a total of 140 cases; average age 4 years 3 months (5 months to 15 years 5 months) and 5% of the cases had non-WT pathology including clear cell sarcoma of the kidney (CCSK), renal cell carcinoma and nephroblastomatosis. One patient bled post-procedure, but none required emergency nephrectomy.

11.5 The Technique

Someone competent with the technique, usually a pediatric surgeon or an interventional radiologist, performs the biopsy. It is preferable to liaise with the pathologist while the procedure is performed in order to ensure representative and adequate tissue is obtained for histopathology, immunohistochemistry, cytogenetics, and tissue banking if the patient is enrolled in a trial.

It is critical to review the cross-sectional images (more commonly now MR than CT) in all planes in order to locate the best site for biopsy and ascertain the depth in order to adjust the length of the biopsy needle (Figs. 11.4 and 11.5).

The percutaneous procedure is aseptically in the operating theater under general anesthesia using ultrasound guidance (Sonosite® W S-Nerve; SonoSite Inc, Bothell, WA) (Fig. 11.6). Few milli-

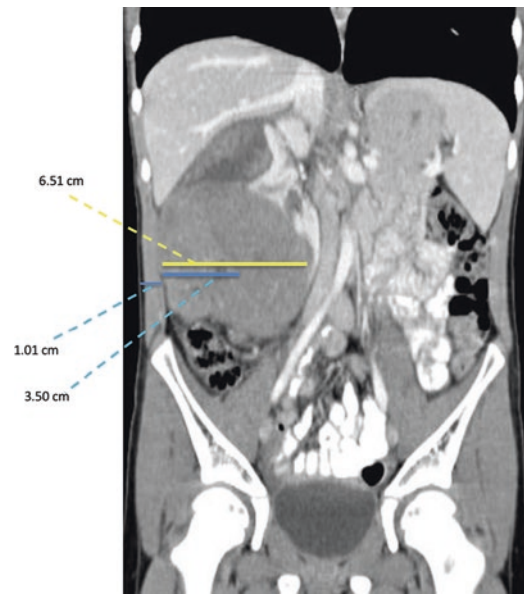

Fig. 11.4 Coronal view of an MR of a right-sided WT, with measurements, showing abdominal wall thickness (1.01 cm), the tumor depth (6.51cm), and the desired depth (3.50 cm)

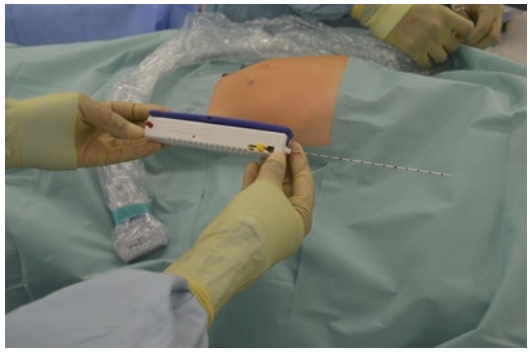

Fig. 11.5 Biopsy site cleaned and draped. The needle's depth is adjusted

Fig. 11.7 It is crucial the sample is sent fresh in a dry, sterile container

Fig. 11.6 Multiple cores are taken using ultrasound guidance

meter incision is made on the skin to avoid unnecessary biopsy of the skin! A cutting biopsy needle is used, for example, full core biopsy instrument BioPince™ Argon Medical Devices, TX, or an Adjustable Coaxial Temno™ (ACT) Biopsy Device, Merit Medical, UT. The main advantage of the latter device is its co-axial sheath which reduces the numbers of points of entry of the needle tract hence allowing multiple sampling cores from one puncture in the capsule of the tumor and reducing hemorrhage and potential tract recurrence, in addition helping minimize damage to surrounding tissue.

The biopsy has to be taken through a retroperitoneal approach for the obvious reason. The two common gauges used are 18 and 16. Several cores are taken to ensure sufficient sample to make the diagnosis, at least three, as WT can be often extensively necrotic. The surgeon needs to appreciate that a short narrow core will have less cells for the pathologist to assess, compared to a wider, longer core.

The surgeon, with experience, tends to get a hunch if the sample is of poor quality and will not hesitate to take more cores. Cores containing tumor tend to be whitish and hold together, whereas necrotic cores tend to look darker and often break up into multiple fragments.

The biopsy is taken promptly to the pathology laboratory fresh and unfixed (Fig. 11.7). To reduce the risk of the sample drying, it can be put into the cut finger of a glove which is then put into a sterile specimen pot that has a small saline damped swab placed at the bottom of it. It then should be transferred rapidly in a closed container, as there is risk of drying artifact during transit of fresh samples to the laboratory. The pathology request form has to be accurately completed and the specimen properly labeled.

The authors prefer to take the specimen themselves to the laboratory and review with the pathologist an imprint smear that only takes few minutes to prepare by the pathologist. Imprint is a simple touch preparation in which tissue is touched on the slide and it leaves behind its imprint in the form of cells on the glass slide; studies are prepared after staining. This technique allows confirmation of the adequacy of the sample usually for no extra time as meanwhile usually a senior trainee inserts a central venous catheter for ChT during the same general anesthetic. If the sample deemed inadequate, the author tends to take extra samples during the same anesthetic in order to avoid further trips to the operating theater. The specimen is then subjected to detailed examination including immu-

nohistochemistry and cytogenetics in addition to any necessary ancillary investigation.

A local anesthetic is infiltrated at either the beginning or end. Usually, the wound doesn't require any suturing, and a postoperative dressing is applied. The patient is usually observed for few hours, and if vital signs remain normal, clear fluids are allowed then built to diet and allowed home in about 4–6 h.

Open wedge biopsy is not recommended, and the disease would certainly be upstaged to stage III. Open biopsy is regarded as a breach or rupture of the capsule.

11.6 Complications

11.6.1 Tract Recurrence

Aslam et al. reported needle tract recurrence in a 2-year-old girl randomized for biopsy and preoperative ChT during the UKW3 study [22]. Rupture and tract recurrence was reported from North America [23]. Nevertheless, in a systematic review, there was no reported similar complication [21]. However, in 2015, a retrospective analysis of the entire UKW3 trial database was performed to evaluate potential risk factors associated with local recurrence of WT, with emphasis on biopsy as a potential risk factor. After a median follow-up of 10.1 years, 5.5% experienced local, 2.4% combined (local and distant), and 9.4% distant relapse. Biopsy, anaplasia, and tumor size were associated with local relapse in univariate analysis; furthermore in multivariate analysis, anaplasia and tumor size remained significant for local relapse, whereas the elevated risk of biopsy was marginal. The investigators concluded that biopsy should not automatically lead to upstaging of WT; nevertheless they felt further assessment of this controversial area is required [24].

11.6.2 Others

Other reported biopsy-associated morbidities include the local pain within the first day, readily controlled with oral analgesics; bleeding, rarely necessitating blood transfusion or emergency nephrectomy; infection and certainly inadequate sample or nonrepresentative sample with the need to repeat the biopsy; and damage to nearby organs which is reduced with the use of image guidance. Finally rupture and tract recurrence may complicate the procedure [17, 18, 23]. In the UKW3 study, the incidences of pain, infection, and bleeding are 19%, 7%, and 5% respectively [17].

11.7 The Future

The biopsy is only one step in the management of WT. The essence is to secure a firm diagnosis, stage, stratify risk, and deliver appropriate therapy in order to achieve cure at the lowest cost and minimum morbidity.

In order to achieve all these goals, the authors believe in the future there will be more utilization of central review of pathology and radiology by experts in the field. Complex cases will be discussed at national level, for example, the National Renal Advisory Panel (NRAP) recently established in the United Kingdom.

MR diffusion-weighted (DW) imaging may allow for differentiation of benign from malignant tumors, histological tumor subtypes, and grade. Using mathematical models of apparent diffusion coefficient (ADC) values from DW MRI may help to identify histological subtypes of WT. This may in the future help stratify risk and guide biopsies to the most malignant part of the tumor [25].

There are ongoing efforts to develop "liquid biopsy" assays as minimally invasive tool to diagnose and monitor childhood solid malignancies including WT. The liquid biopsy utilizes these circulating tumor cells, DNA, RNA, and proteins in order to advance our understanding of tumor biology and its evolution during therapy, and this may open new avenues for personalized therapy [26]. All these advances may allow securing the diagnosis without the need for invasive biopsies in the future.

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General Surgical Guidelines

12

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12.1 Introduction

Surgical resection in Wilms' tumor (WT) is the backbone of multidisciplinary regimen for achieving the objective of complete cure in the child. The first successful extirpation of a WT in a child was performed by Thomas Richard Jessop in 1877 [1, 2]. However, it was not until the beginning of the twentieth century that surgery became the effective therapy for this tumor. The concepts about the extent of surgical expatriation have been forever changing. Both Ladd [3] and Gross [4] recommended simple nephrectomy for WT. Gross [4] suggested removing only fat clinging to the tumor with the affected kidney. It was Robson [5] who championed radical nephrectomy (RN), which includes excision of the entire kidney with the tumor, Gerota's fascia, adrenal gland, and ureter (Fig. 12.1). Most of the cooperative consortia globally consider RN with lymph node (LN) sampling (selective lymphadenectomy) as the benchmark for surgical excision of pediatric renal tumors including Wilms' tumor (WT) and anything short of it is taken as protocol violation. The only concession that is made nowadays is avoidance of excision of the adrenal gland, if possible.

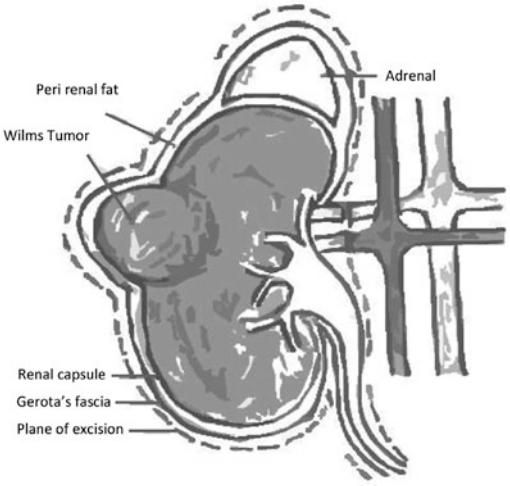

Fig. 12.1 Radical nephrectomy: note the plane of excision is outside that of Gerota's fascia

Notwithstanding this, dissenting voices have been raised from different parts of the world for as long as one third of the century. Philadelphia group first indicated in 1985 that there was no data supporting the need of RN in children with WT [6]. Afterward, Kelalis and Mesrobian [7] also made observations that in children with WT simple nephrectomy (SN), that is, excision of kidney with tumor and perirenal fat, but nonremoval of adrenal gland and Gerota's fascia (Fig. 12.2), may be associated with good overall survival (OS) rates, similar to those obtained

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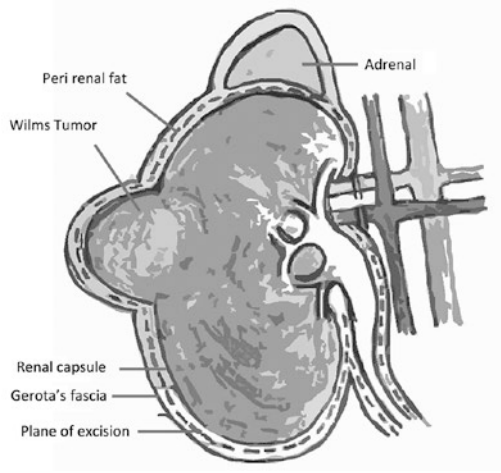

Fig. 12.2 Simple nephrectomy: note the plane of excision is outside the renal capsule; the perirenal fat attached to the kidney is removed along

with RN. Ramon et al. [8], an adult urology group, had begun to doubt the usefulness of RN even in adults with renal cell carcinoma (RCC) and have not found any statistically significant difference between the group of patients with RCC treated with SN and the group treated with RN. Zani et al. [9] justified leaving Gerota's fascia and perirenal fat behind in stages I and II; they had only two patients in stage III so didn't make any clear recommendation for that stage. They felt that as such WT is too large, the distinction between RN and SN is often irrelevant. Szymik-kantorowicz et al. [10] from Poland believed that surgical extent should be also risk stratified, similar to the way it is done for chemotherapy (ChT) and radiotherapy (XRT). They felt RN was non-compulsory in Stage I WT wherein majority of these children could be managed with either simple SN, or nephron-sparing surgery (NSS), based on the size of the tumor. They prescribed SN for tumors of more than 5 cm and NSS for tumors less than 4 cm of diameter. Umbrella protocol of RTSG of SIOP recently legitimized NSS as an acceptable surgical treatment of small volume localized tumors [11].

In this chapter, general recommendations for unilateral nephroureterectomy and surgery for horseshoe kidney with WT are mentioned.

12.2 General Surgical Guidelines for Nephroureterectomy for Unilateral Wilms' Tumor

12.2.1 Access

The patient is placed supine with a rolled towel or bolster placed under the loin on the side of the tumor. Access through a generous transverse abdominal incision is the preferred option. The thoracoabdominal approach may be useful in huge masses located high in the abdomen, but a few authors have reported a higher complication rate with this incision [12]. Whatever the incision, LN sampling must be done. The flank incision, the paramedian incision, and midline incisions are to be avoided; the flank incision doesn't allow adequate LN sampling [13], and the other incisions have been known to be associated with higher rates of intraoperative spill (IOS) [14].

12.2.2 Inspection of the Abdominal Cavity

A self-retaining retracting system is an essential aid to adequate exposure. To start with, any peritoneal fluid, especially hemorrhagic, should be collected for malignant cytological examination. The next step is to inspect and examine the entire abdominal cavity including the liver, LN, and peritoneum for the presence of metastatic lesions, which if present, should be excised (in resectable lesions) or biopsied (in unresectable lesions) and sent for histopathology in a separate container with a clear mention of its origin.

If preoperative imaging is completely normal, exposure of the contralateral kidney is not required except in syndromic WT (risk of bilateral tumors is high) or in WT with high-risk tumor biology [15]. However, if contralateral kidney lesion is diagnosed on preoperative imaging, then the assessment of the contralateral kidney gets precedence over the ipsilateral nephrectomy. Some authors suggest use of intraoperative ultrasound to localize the lesion [16]. Resection of large WT >12–15 cm diameter

increases the risk of IOS due to added on vascularity and intra-tumoral necrosis in large areas [13, 17], and thus, careful handling of the kidney having WT is mandated. Apart from the regular techniques for dissection, bipolar diathermy, ultrasonic dissector can be used (Harmonic®, Ethicon). To increase the intra-abdominal working space and exposure of the tumor, dissecting and transferring all the bowel to bowel bag is suggested by some authors. This technique also helps to prevent any inadvertent bowel injury, heat loss from bowel surface, and also postoperative bowel adhesions [16].

12.2.3 The Procedure

RN including Gerota's fascia, perirenal fat, and adrenal gland should be achieved en bloc (Fig. 12.1). The dissection begins with mobilization of the colon medially to expose the retroperitoneal structures. The colonic mesentery may be left attached on the tumor with preservation of marginal arcade of colonic vessels [16]. In left-sided tumors, the spleen and pancreas may also be mobilized and retracted medially for better access and exposure of the tumor. On the right side, Kocher's maneuver is helpful in exposing the inferior vena cava and renal vein. There has been no consensus regarding the extent of lateral mobilization of the tumor. The "*purists*" believe in no handling or mobilization of the kidney harboring the tumor until after the vessels have been ligated at the hilum (Fig. 12.3a). There are others who choose the middle path and tend to dissect laterally, mobilize, and retract the mass with the kidney partly out of the incision [16, 17]. But few including the principal author believe in delivering the entire tumor outside the abdominal cavity after thorough dissection and mobilization followed by ligation and transaction of renal vascular pedicle for complete en bloc excision (Fig. 12.3b) [18]. This goes against the traditional teaching of control of renal hilar vessels first. In very large or infiltrating tumors, primary ligation of the renal vessels may be in fact difficult or risky, resulting in major vascular complications such as injury to mesenteric arteries/celiac vessels/aorta/IVC, etc. [19, 20]

The ureter is identified at the pelvic brim/pelvic-ureteric junction (depending on tumor size) after mobilization of the kidney and is divided as close to the bladder as possible after division of gonadal vessels and securing all the blood supply of the ureter. In cases of extension of tumor into the ureter (botryoid WT) [21] with-

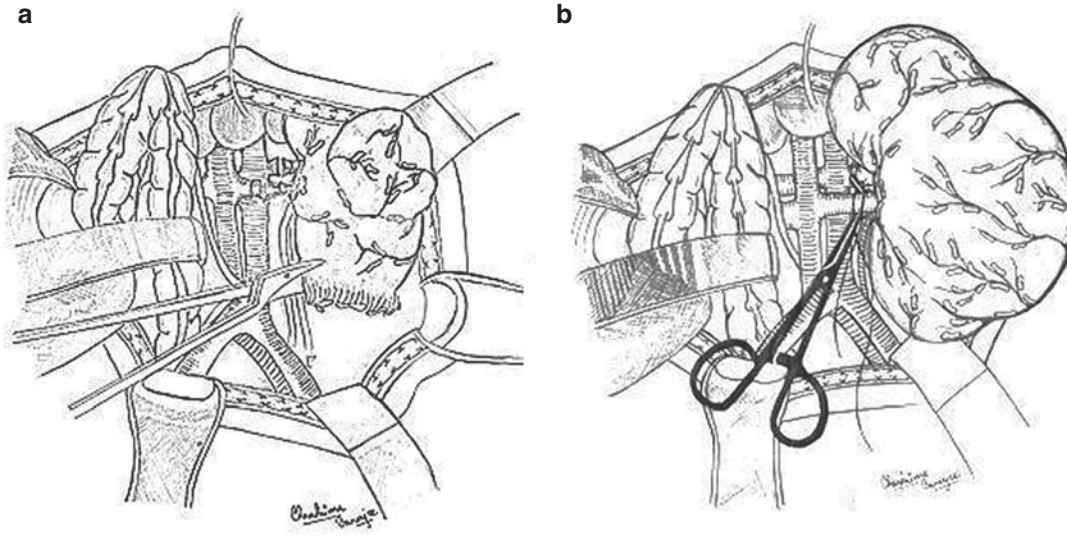

Fig. 12.3 (**a**) Traditional "pedicle first" technique and (**b**) "tumor delivery" technique, where the pedicle is divided the last

out extension into the bladder, the entire length of the ureter up to the ureteric orifice in the bladder needs to the excised taking care of IOS during dissection, ligation, and division of the ureter. All patients presenting with gross hematuria should have cystoscopy just before the surgery to rule out extension up to or beyond ureteral orifice, and in doubtful cases, a cuff of bladder should also be excised along with the ureter, using the distal end of upper divided ureter for traction to expose the renal hilum from below upward.

The *"purists"* believe that when tackling the hilum, the sequence of ligation of vessels is first artery (to avoid venous congestion and possible tumor rupture) and then renal vein. Both artery and vein should be ligated individually to avoid the probability of high output cardiac failure due to renal vessel vascular shunt in the future. Another important feature to be kept in mind is tenting of IVC during renal vein ligation, which could lead to elliptical IVC breach after release of the traction following RN. Before (double) ligating and dividing the renal vein, it is important to palpate it so as not to cut through the intravascular tumor and causing IOS. Extension of tumor in the posterior abdominal wall/diaphragm would require attentive excision and adequate repair of the muscles of these structures [22].

Very extensive and mutilating resections of surrounding organs (e.g., pancreatectomy) are not recommended [23]. Infiltrations into adjacent tissue, affected LNs, macroscopic residues, and macroscopic IOS should be detailed in the operative notes.

As dictated by intraoperative findings, the tumor bed could be prepared for future XRT by marking the site with titanium clips.

12.2.4 Tumor Thrombus in the Renal Vein and Inferior Vena Cava

Preoperative evaluation, by MRI, CT, or ultrasound scan, should state the patency of the renal veins and inferior vena cava (IVC). However, intraoperative examination of renal vein and IVC is suggested. Several surgical options exist depending on the extent of tumor thrombus cranially such as simple thrombectomy for renal vein thrombus with or without complete excision of renal vein, inferior vena cavectomy for extension in IVC below the hepatic veins, and resection without bypass or on cardiopulmonary bypass (CPB) for thrombus extending above the hepatic veins into the IVC/into the atrial chamber [24] and finally staged resection.

For vena cavotomy, the contralateral renal vein as well as IVC on both sides of the thrombus have to be looped with vascular loops before proceeding further. If the defect in the IVC is large, simple closure may cause constriction in which case autologous graft of saphenous or internal iliac vein may be required. In cases where tumor thrombus is densely adherent to the IVC wall, inferior vena cavectomy is the only option which is safe due to the development of multiple alternate collaterals [16].

Cardiopulmonary bypass will be required in the case of intra-atrial thrombus. It may also be very useful in case of a longer thrombus, extending to or above the level of the hepatic veins [16, 24]. Details of these sophisticated procedures are beyond the scope of this chapter.

12.2.5 Adrenal Gland

As per evidence, removal of adrenal gland as a routine has been challenged and rejected by some authors as the involvement of adrenal gland is rare [25, 26]. In situations wherein WT is arising from upper pole of the kidney increasing the risk of local infiltration as well as in difficult dissections wherein risk of tumor rupture increases during attempts to save the adrenal gland, adrenalectomy is advised [17]. van Waas et al. also favored adrenalectomy quoting that one adrenal gland is enough to maintain normal function and does not lead to adrenal insufficiency [27].

12.2.6 Lymph Nodes

Even when LN do not seem involved on gross examination, at least seven LNs have to be excised and sampled for histological examina-

tion; the chances of finding a positive LN increase when more than seven LNs are biopsied [28–31]. The areas of LN biopsies are paracaval supra-hilar, paracaval infra-hilar, paraaortic supra-hilar, paraaortic infra-hilar, right iliac, left iliac, and mesenteric (1 LN from each site) [32]. Appropriate labeling of site and character is crucial before sending the samples for histopathology. Unlike in RCC, radical LN dissection is not recommended for WT as there is no benefit in terms of overall survival.

12.2.7 Translocation of Ovary

The principal author believes in surgically translocating the ipsilateral ovary in girls to the contralateral side with preservation of its blood supply, lest the patient is staged III necessitating ipsilateral flank XRT.

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Nephron-Sparing Surgery

13

Yogesh Kumar Sarin

The increasing evidence that global renal function is better preserved with 2 rather than only 1 kidney will certainly lead to a more aggressive undefined (NSS) approach, not only in children with synchronous bilateral Wilms' tumor. With further experience, the role of NSS for select patients with unilateral Wilms' tumor (WT) and normal opposite kidney will increase in scope and application.... a renal sparing surgical approach should not be considered investigational any longer.—Denis Andrew Cozzi and Francesco Cozzi [1]

13.1 Introduction

Of all the Wilms' tumor (WT) seen in children, 90% are sporadic, unilateral, and unifocal; the other 10% include bilateral Wilms' tumors (BWT) (synchronous or metachronous) and syndromic WT. Partial nephrectomy (PN) or nephron-sparing surgery (NSS) are considered as undisputed standard of care as regards the surgical management of patients with bilateral Wilms' tumor (BWT), syndromic predisposition, solitary kidney, and bilateral nephroblastomatosis. However, in case of non-syndromic unilateral WT (uWT), NSS still stays controversial with many casting doubts that it may compromise the oncological outcomes. The recent literature have recommended NSS in the management of even uWT quoting higher overall survival (OS) rates, better long-term renal functions, and lower occurrence of relapse as compared to radical nephroureterectomy (RN).

13.2 Historical Background

The first ever long-term survivor of BWT was managed by Ladd in early 1950s; he performed a right nephrectomy with pre- and postoperative radiotherapy (XRT) followed by intensive XRT to the left kidney [2]. It was more than 15 years later that Rickham treated the first case of BWT by nephrectomy on the left side (tumor weighed 450 g) and tumorectomy on the right side (tumor weighed 680 g) [3]. Only 40% of the right kidney could be preserved; adrenal glands were spared bilaterally. Surgical margins were negative. Postoperatively, the child was administered whole abdominal irradiation (WAI). She was reported doing well 18 months after the surgery; 1-year OS for BWT used to be 0% before this. In 1966, Bishop and Hope reported the first series of six patients with BWT managed the Rickham way [4]. This surgical approach became the standard of treatment for synchronous BWT. In 1976, Wiener used neoadjuvant chemotherapy (ChT) to shrink the synchronous BWT tumors and performed staged bilateral NSS [5]. This led the pendulum to conclusively move in favor of bilateral NSS for synchronous BWT. The largest series of BWT comprising of 42 patients over a

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13-year period has been reported from St. Jude Children's Research Hospital, USA [6].

Over the years, the role of NSS in the management of WT in BWT, syndromic uWT with bilateral nephroblastomatosis, in the presence of single anatomic or functional kidney, and in fused kidneys (e.g., horse-shoe kidney) was firmly established and has become almost indisputable now.

However, since 1950s when Robson described RN for renal cell carcinoma (RCC) [7], RN along with lymph node sampling has been the standard of care for uWT. Although the first recorded PN for non-syndromic uWT was done in Cuba in 1966 [8], the opposite kidney was abnormal to start with and was later removed. The real push to NSS in uWT came from two groups of authors—Cozzi et al. from Italy [9] and Cost et al. from the USA [10]. Some excellent systematic reviews [11–13] and meta-analysis [14] on the topic of NSS in non-syndromic uWT have been published recently. The first randomized controlled study on the topic has been recently reported from a center in Belgaum, Karnataka, India. A good systematic review of 316 patients undergoing elective NSS for non-syndromic uWT has been recently published by the author [13]. The recent literature supports the use of NSS for non-syndromic uWT. NSS results in better postoperative renal functions and lower incidence of hypertension as compared to the RN. OS and event-free survivals (EFS) with NSS are now known to be even better than RN.

As of the diagnostics, traditionally contrast enhanced computerized tomography (CECT) was done to decide about the feasibility of performing NSS in patients with WT (Figs. 13.1 and 13.2). But recently, few authors and cooperative consortia have emphasized over the use of magnetic resonance imaging (MRI) if NSS is planned

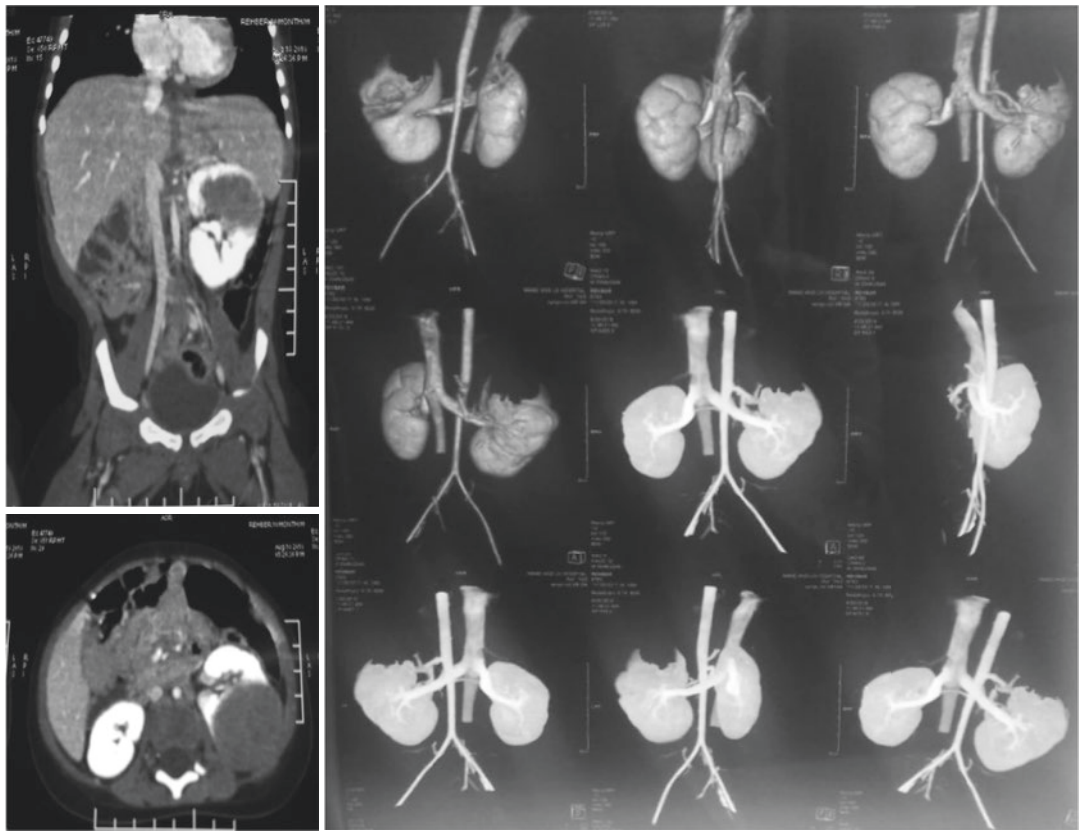

Fig. 13.1 CECT scan of a 10-month-old boy with left uWT

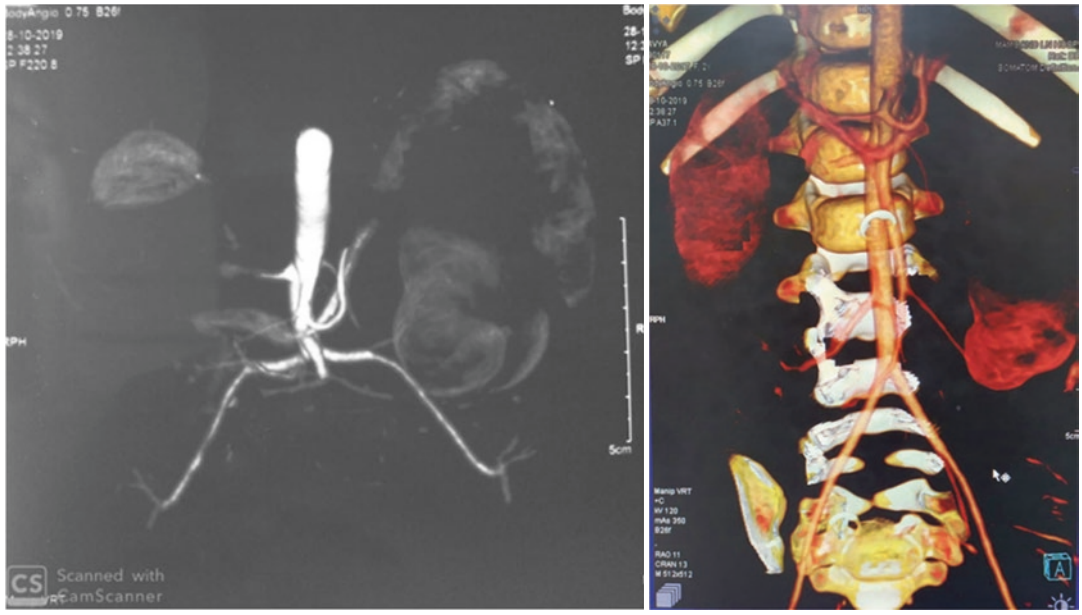

Fig. 13.2 3-D CECT reconstruction of left uWT in a 2-year-old girl

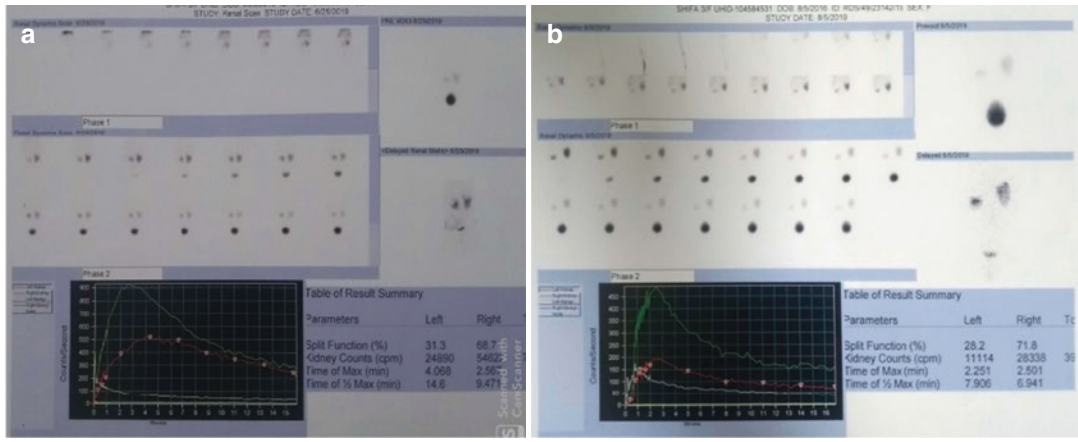

Fig. 13.3 (**a**, **b**) Pre-operative and postoperative Tc-DMSA scans in a patient with BWT undergoing bilateral NSS

[15, 16]. MRI helps better visualization of the soft tissue demarcation between kidney tissue and tumor. Techniques such as diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping added on the preoperative MRI can also provide information on the histological subtyping of WT. The most important disadvantage of MRI is that general anesthesia is usually necessitated to perform MRI in young children. Even if MRI is done, a CECT scan may still be warranted as it exhibits far better vascular imaging [15]. Warmann and Fuchs have also stressed on the use of Uro-MRI and Technetium-99m dimercaptosuccinic acid (Tc-DMSA) scans for the patients planned to undergo NSS to know the differential renal function (DRF) [15]. They also suggested use of intraoperative contrast-enhanced ultrasonography (CEUS) to confirm the preoperative imaging findings and to decide the surgery for tumor removal [15].

The author has routinely used preoperative and postoperative Tc-DMSA scans in all children undergoing NSS since 2018 to study the change in DRF, if any (Figs. 13.3 and 13.4).

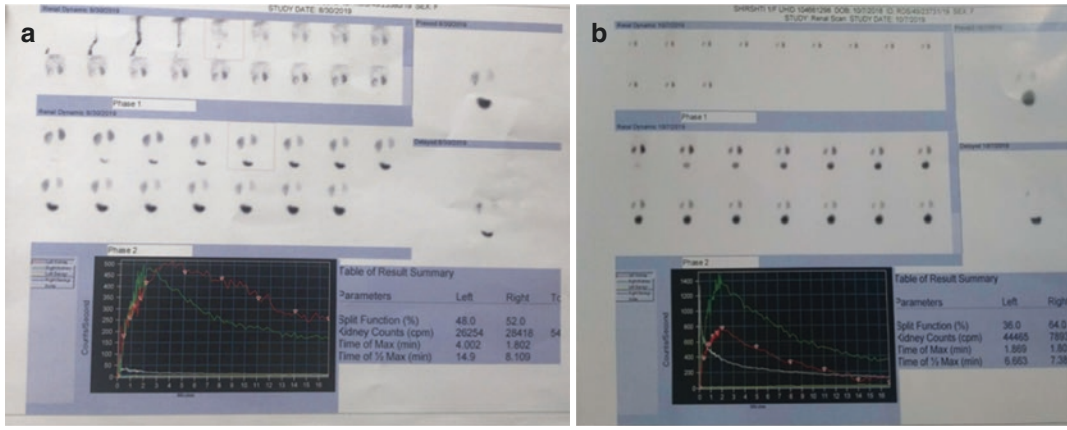

Fig. 13.4 (**a**, **b**) Pre-operative and postoperative Tc-DMSA scans in a patient with left uWT undergoing NSS (75% of original function retained on left side after NSS)

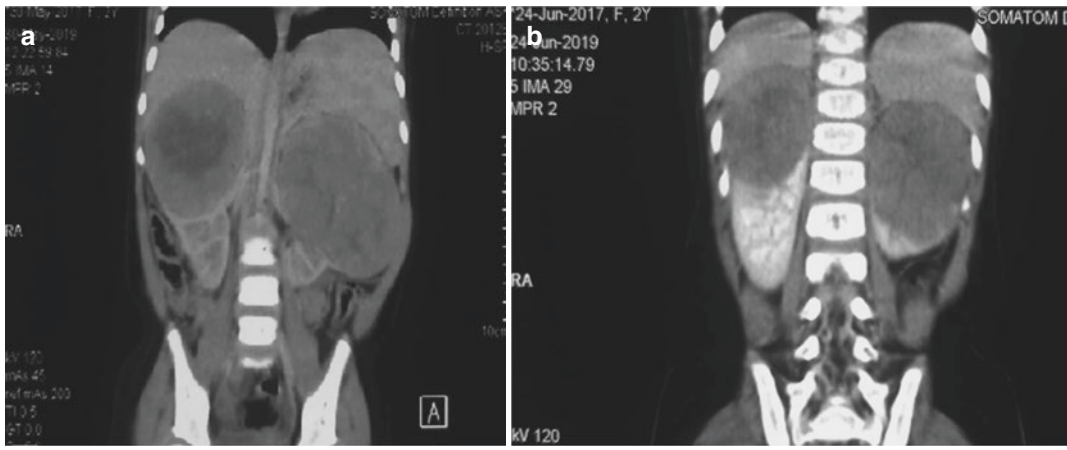

Fig. 13.5 (**a**, **b**) BWT in a 2-year-old girl. Pre-ChT tumor volumes of right and left WT were 250 ml and 320 ml, respectively. Post-ChT tumor volumes of right and left WT were 200 ml and 280 ml, respectively. Reduction in volume was 20% and 12.5% on right and left WT, respectively

13.3 Neoadjuvant Chemotherapy

Bishop et al. in 1977 while reporting outcomes of 30 patients with BWT treated on National Wilms' Tumor Study (NWTS)-1 had concluded that the WT had effectively shrunk after the administration of neoadjuvant ChT, thus making them more amenable to PN [17]. Blute et al. later made similar conclusions after studying 145 children with BWT treated on NWTS-2 and NWTS-3 [18].

The average reduction in tumor volume after administration of neoadjuvant ChT has been 38% and 79% in two different series (Figs. 13.5 and 13.6) [19, 20]. However, some tumors may only have necrotic transformation after neoadjuvant ChT and no significant volume reduction [16]. Other differential diagnoses for non-reduction of post neoadjuvant ChT include a stromal-predominant histology WT that is non-responsive to ChT and a diffuse anaplastic WT in which ChT intensification is mandatory [15]. Its noteworthy that presence of diffuse anaplasia is a definite contraindication for performing NSS in a uWT.

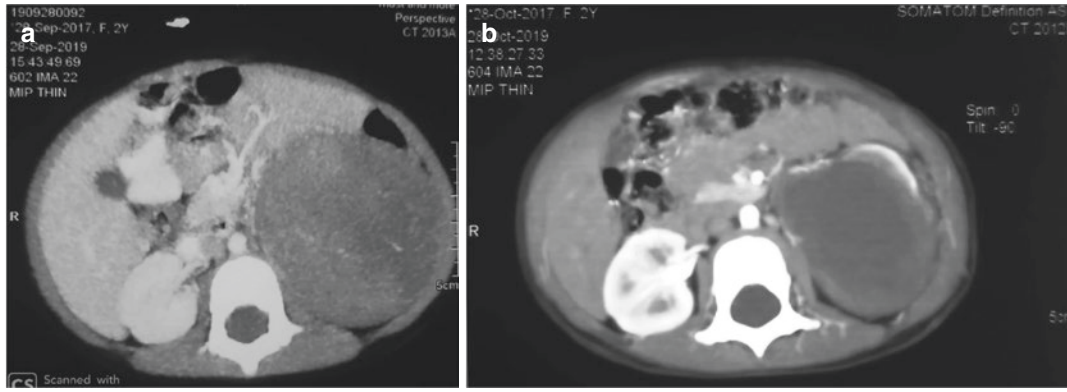

Fig. 13.6 (**a**, **b**) A 2-year-old girl with left WT. Pre-ChT tumor and post-ChT volumes of 186 ml and 85 ml, respectively, with 54% volume reduction

In the non-treated WT, the feasibility of performing NSS on preoperative imaging of WT has been known to be as low as 8% [21].

So, it is more or less universally accepted globally now that if renal preservation has to be facilitated by NSS, then the neoadjuvant ChT is mandatory for children with both BWT and uWT [5, 22–25].

13.4 Operative Technique [22, 26]

Other than maximal nephron preservation, the goals in NSS in patients with WT include total extirpation of all tumor while avoiding positive surgical margins (PSMs), and vascular thrombosis. The operative technique for NSS for BWT and uWT remains the same. Swenson had historically operated one of the patients with synchronous BWT in stages (one WT at a time with 2nd surgery after a week) [27]. The performance of bilateral NSS during a single surgery not only includes avoidance of an additional operation, but it also results in removal of all macroscopic tumor at the earliest so that the chance of developing therapy-resistant disease is reduced, and the postoperative ChT is not interrrupted [22].

In case of synchronous BWT, the kidney with the larger tumor is approached first.

Traditionally, these tumors are operated transperitoneally via a generous transverse upper abdominal incision. A retroperitoneal approach has also been described citing faster postoperative recovery and lesser morbidity, while ensuring similar oncological outcomes [28], but this approach is usually not recommended.

The colon along with its mesentery is reflected away from the anterior aspect of the kidney. The Gerota's fascia is opened, and the kidney is separated from the surrounding perirenal fat. The Gerota's fascia and the perirenal fat overlying the surface of the tumor are left in situ; these would be removed later along with the WT. The author's preference is then to create a surgical plane between the posterior surface of the kidney/renal mass and the posterior abdominal wall by careful blunt dissection. Once fully mobilized, the entire renal mass is delivered outside the abdominal cavity through the incision, while it is left attached to the vascular pedicle and ureter only (Fig. 13.7). Even kidney harboring a very large tumor can be mobilized by this "tumor delivery technique" [29]. A vessel loop is passed around the vascular pedicle so as to provide vascular isolation. This would allow fast access and clamping of the hilar vessels, if required. The renal vein needs to be palpated at this stage even if a negative imaging report in the regard is available; presence of vascular thrombus precludes NSS. A vessel loop is passed around the ureter also.

Intrarenal surgery requires hemostasis and bloodless field to allow a clear distinction between the renal tissue and tumor [15]. The vessel loop when placed on tension results in vessel

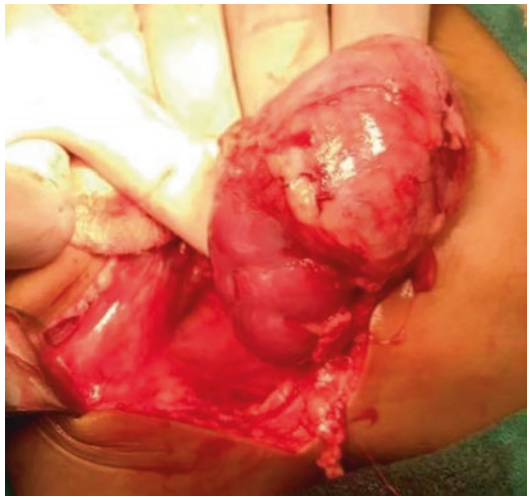

Fig. 13.7 Tumor delivery technique

occlusion and this maneuver suffices most of the time, but few of the surgeons believe in vascular clamping. Preoperative hydration ensures optimal renal perfusion during surgery. Few surgeons believe in administering mannitol intravenously 5–10 min before vascular isolation/clamping; this helps preventing renal ischemia by reducing intracellular edema and intrarenal resistance [26]. Others believe in administering Inj. Heparin (100 IE/kg) before vascular exclusion to avoid the formation of intrarenal microthrombi [15].

Simple clamping of the renal artery without any cooling provides a safe period of "warm ischemia" for about half an hour. If the surgeon feels that the vascular clamping needs to be done for a longer period, then selective local hypothermia should be created to lengthen the ischemia tolerance of the kidney. However, it must be stated here that there is no consensus till date about the ideal cooling temperature in children. "Cold ischemia" could be achieved with the renal surface cooling or perfusion hypothermia. Surface cooling with sterile ice slush allows at least 1 h of safe clamping of renal artery; the ice slush could be reapplied as often as needed in that critical 1 h. However, the ice, which is packed around the kidney, interferes with the surgery; additionally, there is slight risk of necrosis of renal cortex. Millar et al. have described "ice-dam cooling" [30]. De Backer et al. used in situ cold perfusion with solutions that are commonly used during organ transplantation surgery, while performing NSS in a patient with multifocal synchronous BWT [31]. This technique has no added advantage of prolonging the "cold ischemia" time; on the other hand, arteriotomy and the venotomy for continuous perfusion may cause renal artery thrombosis and/or tumor spillage from the renal vein.

Many authors have found that digital pressure on the renal tissue next to the line of resection accomplishes acceptable hemostasis and obviates any requirement of clamping of the renal artery [30, 32]. "Zero-ischemia" NSS (Z-NSS) is now getting popularized where neither clamping of vascular pedicle is done, nor any form of cooling is used [33, 34]. The author uses Z-NSS each time.

The vascular pedicle needs to be carefully handled because traction injury could lead to vascular thrombosis. This issue assumes importance especially if we are applying tumor delivery technique in very young patients. It is pertinent to mention that the optimal age beyond which vascular pedicle clamping is safe is not yet known.

Before proceeding to NSS, frozen sections from regional lymph nodes (LNs) and perirenal fat are sent [26]. If the LNs are positive, NSS is abandoned in favor of total nephrectomy.

PN (NSS A) in the Umbrella protocol classification is the preferred procedure, because excision of the tumor with a rim of normal renal tissue would in all probability not result in a positive surgical margin (PSM) [35]. While margins of 1–5 mm for RCC are recommended to prevent and minimize recurrence, no exact guidelines are available for WT [25]. Surgical margin of 3 mm should be sufficient, although many authors have suggested 5–10 mm surgical margin [22, 26].

Intraoperative ultrasonography (IOUS) with a high-frequency linear transducer may help in a clear distinction of the tumor from the adjacent normal renal tissue and in deciding the resection line [20, 25, 36]; it has been successfully used in RCC [37]. However, IOUS has not been found that advantageous for NSS in WT, and significant positive margin rate (22.5%) was reported in spite of the use of IOUS by Aldrink et al. [25]. Early learning curve with IOUS in children could be one of the plausible explanations [38]. Further, ultrasound, whether done pre-operatively or intraoperatively, fails to distinguish nephrogenic rests from WT [25]. IOUS probe size needs to be standardized.

It must be clearly understood that IOUS can delineate the tumor margin from normal renal parenchyma only before the resection has been commenced with the electrocautery. Once the resection has started, it would be difficult, if not impossible, to differentiate tumor margin or infiltration from a cautery artifact [25].

Once the lesions are identified, an incision is made on the renal capsule with a cautery a few mm away from the visual limit of the tumor; this is followed by both blunt and sharp dissection (Fig. 13.8). The smaller vessels in the renal cortex are coagulated with bipolar electrocautery, argon-beam coagulation, or cavitron ultrasonic surgical aspirator (CUSA) [39], whereas the larger ones in renal medulla are sutured using atraumatic resorbable sutures.

Ideally, the collecting system should not be violated, but it happens often in case of centrally located tumors. If a small breach in the collecting system is suspected but is not visualized, one could inject a diluted methylene blue solution into the renal pelvis to detect it; the ureter may be temporarily occluded with a vessel loop during this maneuver. Once the breach is identified, it is closed with a fine absorbable suture with or without a "double-J" (DJ) ureteral stent.

The German group have described longitudinal partial nephrectomy (LPN) technique in case of complex bilateral central tumors close to hilum; resection may look impossible on preoperative imaging in these patients [15, 40]. LPN entails major reconstruction of the pelvis and dissection of vessels deep into subsegmental areas. In case a part of renal pelvis is infiltrated and needs concomitant resection, one should be careful to leave sufficient pelvis tissue on the kidney side for a tension-free closure (Fig. 13.9).

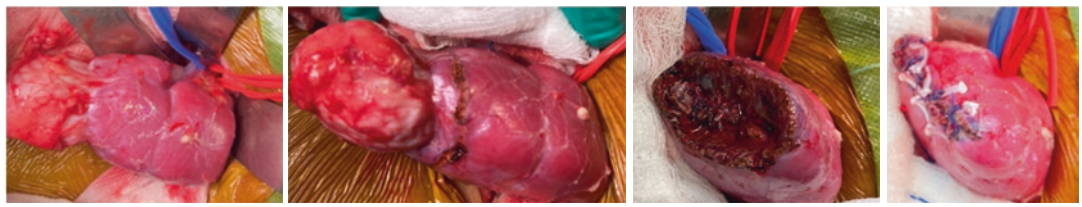

Fig. 13.8 Operative steps of NSS (picture courtesy Dr. M Pathak, AIIMS, Jodhpur)

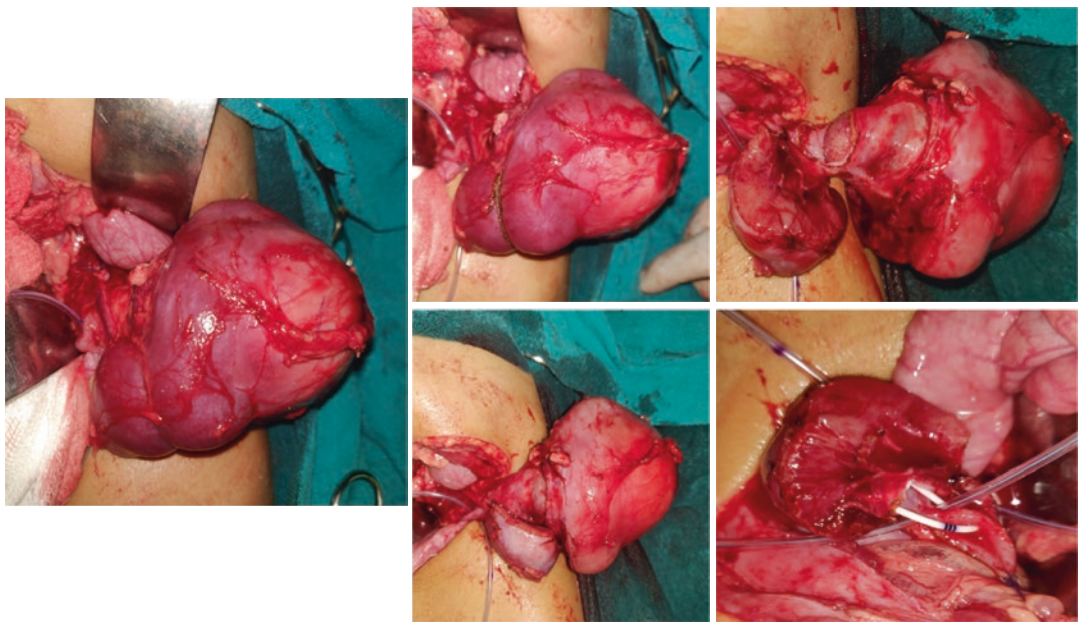

Fig. 13.9 Steps of NSS in a botryoid WT. Note a part of pelvis has been excised and reconstruction done over a DJ stent

Frozen sections are sent from the renal edge to confirm a negative surgical margin. An additional slice of few mm of renal parenchyma is resected if the surgical margins are reported positive. Another modality that can be used to confirm negative margin rates is to perform ex vivo ultrasound imaging on the resected specimen [41].

After the tumor resection, the renal remnant is "folded" over the cut surface over a piece of oxidized cellulose to ensure hemostasis; this also helps in restoring the reniform contour of the kidney. If this is not possible, then perirenal fat, or omentum, or Surgicel® or a tongue of Gerota's fascia is placed over the cut surface of the kidney. This would assist with hemostasis and maintain tissue planes, so that a re-exploration, if required, would be easier. The author believes in pexing the renal remnant to avoid the theoretical risk of its rotation on its pedicle postoperatively leading to a catastrophe.

In a case of BWT, one then proceeds to the opposite kidney, and same steps are repeated.

Berry-picking and excision biopsy of at least seven regional lymph nodes is then performed. No systemic or regional anticoagulation is advised. Flank Penrose or tube drains are put and the abdomen is closed.

The drains are removed before the patient is discharged. DJ stents are removed 1 month later; Davidoff et al. advise the removal of DJ stents after a period of 4–6 months [22].

Enucleation (NSS B), i.e., bluntly shelling out of the tumor along the plane of tumor pseudocapsule, once propagated by Cozzi et al. [9], is not considered adequate local treatment nowadays. Tumor penetration of pseudo-capsule was noted in more than 1/4 of the patients in the NWTS experience [42, 43]. Enucleation involves the risk of local tumor spillage upstaging the disease from stage I to stage III, in which case Umbrella protocol of SIOP-RTSG suggests flank radiotherapy (XRT) if not excision of the whole kidney (completion nephrectomy) [16]. The advantage of this procedure is its simple and rapid ability to remove tumors; the author confirms this statement by his own personal experience without having any incidence of local tumor relapse. The author believes that there is a definite role of enucleation in the central placed tumors where removing a 5–10 mm margin of normal renal tissue is rather impossible. Cozzi et al. believed that enucleation should be safe in young children (<3 years), especially in those with synchronous BWT and having centrally located WT; the risk of anaplasia in such settings is extremely low [9].

PSMs are present in 0–7% of patients after open NSS, in 0.7–4% after laparoscopic NSS, and in 3.9–5.7% after robot-assisted NSS [44].

There has been a paradigm shift about the prognosis in the eventuality of PSMs after NSS. Shamberger et al. in 1999 had reported that PSMs were associated with an enhanced risk of having local relapse that was associated with a poor prognosis; once recurrence occurred, the 2-year OS was ~43% [45]. This view has been challenged by few recent reports. It has now known that PSM status does not necessarily lead to a local recurrence [46] or to a reduced OS [22]. However, these patients with PSMs would need to undergo additional flank XRT [47]. Ehrlich and colleagues recently reported that 9 of the 39 patients (23%) with uWT who underwent NSS had positive margins or intraoperative tumor spill and received additional ChT and XRT [48]. However, the 5-year OS in this subset of patients was ~96%. So, it is established that most patients with PSMs after PN remain without disease recurrence and completion nephrectomy is not indicated in all such patients, but a robust surveillance strategy must be put in place for these patients [44].

Presence of anaplasia is an absolute contraindication to NSS in WT. If anaplastic cells are diagnosed intra- or postoperatively, especially in presence of PSMs, a completion nephrectomy is indicated. The author believes in performing core needle biopsy through retroperitoneal route in all patients undergoing NSS for WT [49]. Preoperative core needle biopsies may diagnose anaplastic WT with a sensitivity of 29% [49]. In case of BWT or with multifocal tumors, core biopsies for each tumor should be taken as discordant pathologies are known to occur. Intraoperative frozen sections from the resection margins may probably detect anaplastic histol-

ogy with a greater sensitivity, in which case completion nephrectomy has to be performed.

As regards positive lymph nodes at pathology after NSS, XRT is indicated but a completion nephrectomy is not warranted.

There are very few reports of bench surgery for renal tumors in children. It should be reserved for patients with centrally located tumors that cannot be removed with the usual surgical techniques. They are discussed in a separate chapter.

13.5 NSS and MIS

Laparoscopic NSS for WT has been infrequently reported [50, 51]. Piché et al. from Canada were the first to report a case of a small polar WT in 2012 [50]. Complications of laparoscopic NSS in WT include intra-operative spill of tumor, risk of peritoneal and port site metastases, and surgical challenges requiring special expertise. Chui and Lee from Singapore reported extensive peritoneal implants with tumor following laparoscopic NSS [52]. As of date, an open surgical approach is the standard of care for NSS in children with WT [16].

13.6 New Classification System for NSS

In 2014, Godzinski, Graf, and Audry suggested a new classification system for NSS, which has now been incorporated in the Umbrella protocol of SIOP-RTSG [53]. Umbrella protocol discriminates the two prevailing NSS techniques into NSS A (PN) and NSS B (enucleation) and states that NSS B is not adequate local treatment [16, 35].

13.7 NSS in Non-syndromic Unilateral Tumors

13.7.1 Rationale and Selection Criteria

Initially, there were only few takers of NSS in management of non-syndromic uWT, but now data is available for over 300 such children who have done well oncologically [14].

Szymik-kantorowicz et al. had quoted in 2012 that "RN is an overly aggressive treatment modality in children with stage I WT." They recommended NSS for uWT of size ≤4 cm diameter and simple nephrectomy for larger stage I uWT [54]. The author believes that NSS is feasible in uWT up to 7 cm in diameter.

Though feasibility of NSS is decided on the pre-operative imaging, it may not always correspond with the feasibility decided intraoperatively by the operating surgeon. In a report from the Netherlands, preoperative imaging showed 87% predictive accuracy for the feasibility for PN in uWT [55].

In the last one decade, some proponents of COG protocol, i.e., upfront RN, from the USA did post hoc feasibility analyses to determine the proportion of uWT that could have been removed by NSS instead. Cost et al. reviewed pathologic specimens from 78 RN performed for uWT [36]. Even having used very strict pathological criteria, they realized that about 1/4 patients met all those criteria and could have been amenable to NSS.

Romao et al. emphasized that it was wrong to support RN in uWT quoting a low incidence of end-stage renal disease (ESRD) [11]. They insisted that many survivors of WT after having undergone RN grow up with under-recognized milder forms of chronic kidney disease (CKD). They suggested that even the newly diagnosed large uWT (>10 cm diameter) with non-aggressive biological behavior and tendency to multifocality or having underlying risk for renal dysfunction could undergo NSS after administration of neoadjuvant ChT. The smaller tumors of course could be managed with NSS (Fig. 13.10).

Umbrella protocol of SIOP-RTSG allows NSS in non-syndromic, non-anaplastic, unifocal uWT provided there is no involvement of renal sinus, renal vein, inferior vena cava, or locoregional LNs and the tumor volume at diagnosis is less than 300 ml [16, 35]. Umbrella protocol of SIOP-RTSG states that NSS is not totally ruled out in the presence of metastatic disease, but it should be considered carefully [16]. Umbrella protocol still

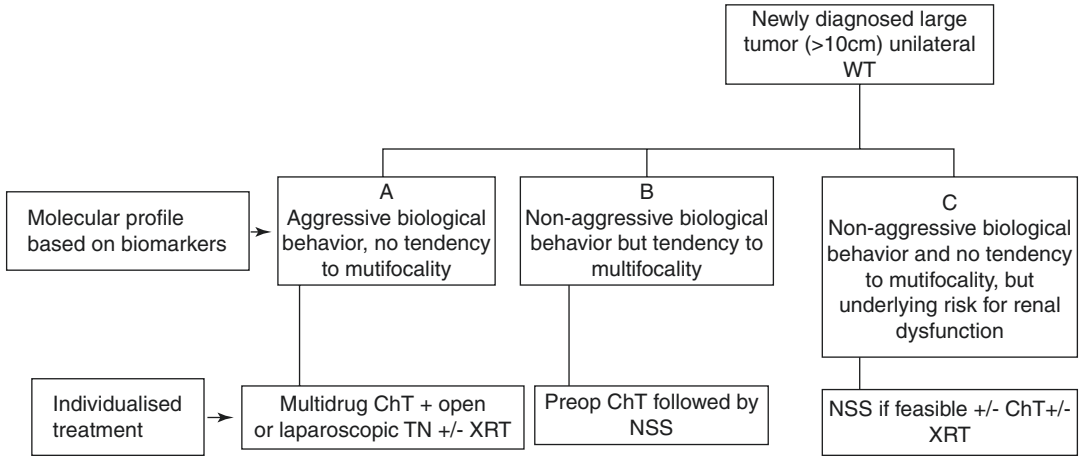

Fig. 13.10 Individualized care of uWT based on molecular stratification based on biomarkers that could influence WT treatment. (Reproduced from Romao et al. [11] with permission from Elsevier)

maintains that at least 2/3 of the renal parenchyma should be spared after the NSS A to provide any worthwhile protection against hyper-perfusion injury. If this is questionable, it would be imperative to do a pre-operative DMSA scan to assess the expected postoperative function.

It is obvious that there is no universal consensus as regards the size of the worthwhile renal remnant post-NSS; it ranges from 2/3 of the kidney [16, 35, 55] to 1/5 of the kidney [56].

Although many authors believe that NSS should be done only in stage I disease [9, 57], but it is impossible to predict the staging on preoperative imaging, and it is no more than an intelligent guess.

Aldrink et al. believed that the routine use of surgical adjuncts, especially IOUS, has the potential to improve renal salvage NSS in as many as 3/4 of the affected kidneys [25].

The author also believes that most of the WT (excluding those having significant local lymph node enlargement on preoperative imaging and/or anaplastic histopathology on pre-therapy core needle biopsy) are amenable to NSS; all it takes is a change in mindset and experience in performing NSS.

13.7.2 Follow-Up

The renal remnant needs to be meticulously monitored after NSS. Doppler ultrasound needs to be done 2 days after NSS. DMSA scan is performed 6 months postoperatively and should record the DRF of the renal remnant.

Nephroblastomatosis in the renal parenchyma of the NSS specimen is a pointer to the fact that a metachronous WT may evolve in the renal remnant; therefore a close postoperative surveillance is warranted.

13.7.3 Prognosis After NSS in uWT

Authors from Germany have recently mentioned NSS in WT as the most promising of the four innovations in the surgical management of childhood solid tumors that would improve the long-term outcomes in the future [58]. They claimed that NSS would play a vital role in the individualized and optimized risk-adapted treatment of children with uWT in the future.

Chen et al. in a recent meta-analysis also recommended the use of NSS for uWT as it resulted in better OS and EFS and preserved renal function as compared to RN [14].

Nerli et al. in a recent RCT on uWTs have concluded that though the oncological outcomes of NSS and RN are comparable, the ones undergoing RN have higher blood pressures and elevated serum creatinine levels as compared to their NSS counterparts [56]. Incidentally, this is the first and only randomized controlled study hitherto on the topic.

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Lymph Node Sampling

14

Kant Shah and Gita Verma

14.1 Introduction

Among the staging criteria of Wilms' tumor (WT), lymph node (LN) involvement has emerged as the commonest (40% in stage III and 16% overall) and single most important criteria for worse local stage and overall outcomes [1, 2]. The patients who do not undergo LN sampling also have a worse prognosis [3–5].

The treatment of stage III tumors involves significant augmentation of therapy. Anthracyclines such as Doxorubicin (DOX), have a long risk for cardiotoxicity—more than 20 years. Radiotherapy (XRT) has a high risk of second malignant neoplasms, impaired renal function, worse pregnancy outcomes, and early mortality [3].

The introduction of molecular genetics has brought forth a worse prognosis in those tumors which show loss of heterozygosity (LOH) at 1p and 16q [6]. National Wilms Tumor Study (NWTS)-5 has shown a higher rate of LOH 1p and 16q in patients with LN involvement in favorable histology (FH) WT (6% vs 2% $p = 0.05$) with a worse prognosis with event-free survival (EFS) 96% vs 73% $p < 0.001$ and overall survival (OS) 99% vs 92% $p = 0.09$ [1, 3].

Such prognostication data has fueled research into impact of LN status with the aim to escalate treatment in those with worse prognosis and de-escalate in those with a better prognosis stage III FH WT [7]. Relapse after stage III treatment has poor outcome with intense salvage therapy and/or autologous hematopoietic stem cell transplantation with overall survival (OS) ~50% [3]. The commonest factors affecting relapse are LN positivity and anaplasia [8].

14.2 Lymphatic Drainage of Kidneys

Renal lymphatics are abundant in the cortex of the kidney in the interstitium surrounding main arteries and veins such as interlobular, arcuate, and interlobar. As these lymphatics do not have valves, they may drain towards the hilum or may join the capsular lymphatics by penetrating the capsule.

The pattern of drainage from the left kidney is towards pre-aortic, para-aortic, and retro-aortic LNs and from the right kidney is towards para-caval, pre-caval, retro-caval, and inter-aortocaval LNs. The kidneys can also send lymphatics posterior to the aorta, which then directly join the thoracic duct. The upper pole may also drain into the posterior mediastinal LNs via the diaphragm.

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14.3 Pattern of Lymphatic Spread in WT

The pattern of LN metastasis in WT is varied and hence unpredictable. The retroperitoneal lymphatic network mentioned above is extensive. The draining LN are inter-connected and finally drain into the thoracic duct. Unlike breast cancer and melanoma, there is no concept of a sentinel node in context of WT.

Commonly, the hilar LN and the regional para-aortic or para-caval LN are involved.

In studies from adult population with renal cell carcinoma (RCC), it was found that 40% of patients had metastasis in the inter-aortocaval region and 30% had skipped the renal hilum. There may be additional lympho-venous spread, which may cause distant metastasis [9].

14.4 Role of Imaging for Assessment of LN Involvement

In smaller children, ultrasonography (USG) may be as useful as computerised tomography (CT) to detect enlarged LN at primary presentation. USG can be very useful in picking up small retroperitoneal recurrences which may often be in LN.

Although USG is considered adequate with many WT protocols, with modern CT scans, imaging of LN has become easier [10, 11]. The common parameters of detecting metastasis to a LN are size, loss of architecture, and drainage location relevant to the organ involved. With a staging CT scan, apart from the primary tumor, the entire anatomical range of renal lymphatic drainage can be studied at once. The main areas are ipsilateral renal hilum, para-caval or para-aortic, inter-aortocaval, and retro-caval or retro-aortic. Further away, if LNs are involved such as at bifurcation or higher up near the diaphragm, it may indicate more extensive spread, although skip metastases are known, as noted above. However, the diagnostic accuracy of CT scans in detecting positive LNs is moderate to poor, and there are no studies with MRI or PET focusing purely on LN involvement [11].

The main parameter of assessment for a LN is size in maximum transverse diameter in millimeters or centimeters. From adult cancers, 1 cm is historically considered as significant size to determine metastatic involvement. However, this may be too big for children, and several papers have suggested 7 or 8 mm as the cut-off size [12]. It is important to note that size does not correlate with involvement too well, and even as small as 3 mm nodes may turn out to be positive and larger ones may just be reactive.

The assessment of nodes on CT may help in identifying the larger (>7 mm) lymph nodes and helps the surgeon have a template in mind before the surgery. Rarely, if a surgeon has missed sampling, review of pre-operative scans may be used to suggest upstaging treatment.

There is no evidence that MRI is better than CT for picking up nodal disease in WT; however the primary tumor characterization is superior and may even characterize histologic subtypes [11].

14.4.1 PET Scan

Although WT is flourodeoxyglucose (FDG) avid on a positron emission tomography (PET) scan, large regional LNs may or may not be avid. Larger than 7 mm LN may hint towards involvement, but this is not definite. There is a role of FDG-PET in recurrent disease as these lesions are often avid [13].

14.5 Method of LN Sampling

During dissection of the primary tumor, the surgeon has to be careful not to include the hilar LN within the primary specimen or if it is inevitable, to label the specimen as tumor plus LN.

Gross identification of involved LN has been shown to have a poor sensitivity (4–11% failure rate in clinically negative LN disease and 40% failure in clinically positive LN disease), and hence sampling of regional LNs is a must [14]. Ipsilateral supra- and infra-hilar, para-aortic, para-caval and inter-aortocaval LNs are sampled

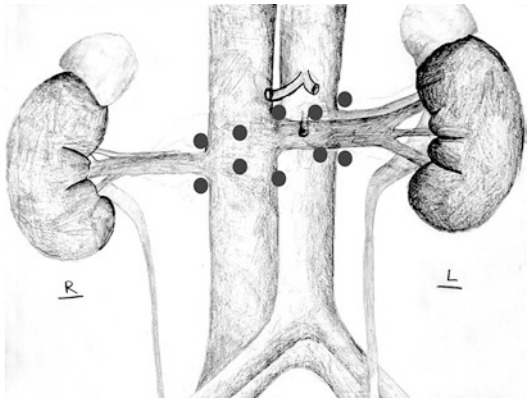

Fig. 14.1 Lymph node groups to be sampled during surgery for WT

(Fig. 14.1). If none are felt, then the fatty tissue surrounding the major vessels is dissected—small pieces only—carefully and sent. A few LNs from the inter aortocaval space at the hilar level may be sampled, as NWTS-4 showed that patients with positive aortic LNs have higher risk of local relapse although the location of positive LN does not affect the EFS or OS [8, 15]. Distant LNs are usually not sampled. A recent study by Qureshi et al. has highlighted the importance of sampling the inter-aortocaval space for tumors of both left and right side as skip lesions from hilar to inter-aortocaval space are common [16]. This is particularly true for the right side; however the group recommends a five station template to be used for all tumors so that positive LNs are not missed.

One must be careful to not reach the inter-aortocaval space too high up in the abdomen to avoid injury to the cisterna chyli. At the end of dissection, a Valsalva maneuver can help identify major chyle leaks.

A formal retroperitoneal LN dissection (RPLND) is not warranted. A combined NWTS 4 and 5 report suggested a minimum of 7 LNs to be sampled to increase the likelihood of getting positive LNs [17]. However, the EFS did not change with increasing number of LNs sampled, and hence extensive sampling is not warranted.

However, there is a linear relationship between the number of LNs sampled and 5-year OS [4]. One method of assessing this is LN density defined as the number of positive LNs divided by the total LNs sampled. LN density < 0.38 was shown with better OS (94% vs 84% $p = 0.12$). LN density was affected by surgeon and institution volume as also stage and tumor size. Hence, a more careful approach is needed in lower stage and smaller tumors to avoid under-staging, as also in case of surgeons who do not perform surgery for WT on a regular basis [2].

14.6 Processing and Reporting of Lymph Nodes

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) do not apply TNM staging to WT; the COG staging system utilizes the findings of metastatic nodes for staging.

LN sampling is carried out, labelled as far as possible and sent with the main specimen, to the histopathology laboratory.

The specimen maybe sent immediately, to the histopathology lab, in an unfixed state. If sent in preservative, it should be put in 10% neutral buffered formalin. LNs are easily found in unfixed specimens, and the best way to dissect them is by palpating the fat carefully to distinguish the node contour. The hilar fat is sampled extensively, and all separately sent nodes are sorted as per the labelling.

The dimensions of the harvested LNs are noted. Larger LNs (>3 mm) are sliced, and then the labelled nodes are left for 12–18 h in 10% neutral buffered formalin. Small LNs are not sectioned. During grossing, on slicing the node, if metastasis is visible, only one section is taken. But if metastasis is not visible grossly, multiple levels are screened on microscopy. The yield of LNs is higher if more time is taken to dissect them, and a higher yield is correlated with better outcomes [4].

Routine processing is carried out and sections are stained by H&E stain. If necessary, immunohistochemistry may also be carried out, e.g., CD45 may help to distinguish between lymphocytes and blastemal cells, particularly in a nodal sinus.

If the patient has received chemotherapy (ChT) before surgery, then non-viable tumor may be seen in the LNs. Replacement of normal LN architecture with foamy macrophages or ChT induced changes can be taken as LN metastasis. Under the SIOP-RTSG UMBRELLA protocol, this upstages the tumor to stage III [18].

Template to report lymph nodes
Site[a]
Total no. of LNs examined
LN metastasis identified, no. of nodes
LN metastasis not identified, no. of nodes

[a]Individual labelling of the nodes, if available, may be used

14.7 Adverse Events of LN Sampling

Radical and limited RPLND for adult and pediatric renal tumors have shown a high incidence of chylous ascites. This can debilitate a child over and above the effects of ChT as also delay adjuvant treatment. In one series of nine children with chylous ascites, five patients underwent extensive lymphadenectomy (four with supra-hilar dissection) and four underwent sampling only. The children presented between 12 and 49 days of surgery, and seven children were successfully treated with total parenteral nutrition (TPN) and/or a diet with medium chain triglycerides (MCT). One child needed a Denver shunt, and another needed a laparotomy and surgical ligation of cisterna chyli channels. The average length of hospital stay was 26 days (6–68 days) [19]. More recently, Qureshi et al. reported only two postoperative chyle leaks, which resolved with conservative management. They also recommend careful identification of chyle leaks during surgery [16].

14.8 Outcomes of LN Positive FH WT

An NWTS-5 study found that the EFS and OS is less in those with LN metastasis (EFS 87% vs 80% $p = 0.066$ and OS 97% vs 91% $p = 0.057$), although not statistically significant [1]. The same study on multi-variate analysis for failure with LN involvement showed a relative risk of 2.24 ($p = 0.003$) for EFS and 2.79 ($p = 0.02$) for OS.

Among children who received pre-operative ChT, the recurrence rate was higher if LNs were not sampled (22%) compared to those who had positive LNs (16.7% with more than 25% LNs positive and 0% with less than 25% LNs positive) ($p < 0.001$) and those with negative LNs (8.9%) [20]. In the same study, children who had less than 7 LNs sampled had a worse prognosis.

14.9 Future Directions

14.9.1 Reducing Toxicity of Treatment

In patients with stage III disease, there is a subset who do not have adverse risk factors such as LN positivity, microscopic residual disease, and LOH 1p and 16q. Such patients may be suitable for reduced intensity treatment including exclusion of DOX and XRT [7]. Conversely in patients with all such risk factors positive, the therapy may be further augmented, and some protocols have already incorporated this.

14.9.2 Rapid Central Pathology and Radiology Review

LN involvement is a major criterion for upstaging to stage III in most of the treatment protocols. Hence, there is a need to formulate uniform guidelines for LN imaging on CT and/or MRI/PET scans and the pathology review of LN slides [10].

14.9.3 Lymph Node Sampling During Surgery

In the future, it is likely that data on LN sampling in terms of number of LN sampled, the LN den-

sity, and location of the LN sampled may be used to deduce the reliability of staging a patient. More importantly, if adequate sampling has been done showing negative LNs, one can use treatment protocols using reduced intensity of therapy [2]. This may not be applicable to those patients in whom adequate sampling has not been done.

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Minimally Invasive Surgery

15

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15.1 Introduction

MIS is one of the mainstay modalities of treatment for benign pediatric surgical conditions in the present era; however, its use in pediatric oncosurgery is traditionally limited to diagnostic endoscopy and biopsy [1]. Pediatric minimally invasive surgery (MIS) experts around the globe have published few papers about its use in cases of neuroblastoma and to some extent for Wilms' tumor (WT) [2, 3]. As per our literature search we have found around 100 plus cases of WT managed sporadically by MIS approach. This literature is comprised of only few case series and case reports [4]. The main reason for this is perceived fear of incomplete excision, tumor spillage, inadequate lymph node (LN) sampling, and port site metastasis [5]. However, increasing evidence is building up in favor of use of MIS in properly selected cases of WT [6].

15.2 Laparoscopic Surgery

The first series of Wilms' tumors (WT) treated by laparoscopic surgery was reported in 2004 by Duarte et al. in children receiving neoadjuvant chemotherapy (ChT) preoperative treatment [7] and in 2009 by Barber et al. in children without preoperative ChT [8]. Since then many authors have published their experience in the management of WT using MIS.

Warmann et al. published the data of 24 children who underwent laparoscopic surgery for WT during the period from 2001 to 2013 [9]. Median age of the studied patients in their series was 39 months, and median volume of the tumor at surgery was 73 ml (range 3.8–776 ml). The median largest diameter of the specimen was 5 cm (range 2.8–12 cm). LN sampling was done in 15/24 children, and number of nodes sampled ranged from 0 to 11. None of the patients studied in this group required conversion to open surgery. The oncologic outcome in these children was encouraging as 23/24 children had event-free survival (EFS) and 24/24 children had overall survival (OS) on median follow-up of 47 months (range 2–112 months).

Similarly, Ezekian et al. published results of laparoscopic management of WT from American Cancer Society's National Cancer Database [10]. During the study period of 2010–2012, 35/695 children with WT were treated by MIS. However, in this study, the patients who were converted to open were also included in laparoscopy group. In this study, the patient characteristics (age, tumor size, metastatic disease, tumor stage) and treatment outcome (positive surgical margins, LN sampling, LN positivity, length of hospital stay, unplanned readmissions, 1-year and 3-year OS) after propen-

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sity matching in open vs. laparoscopic group were not significantly different. They concluded that the MIS and open approach for WT have similar outcomes. Though, not statistically significant MIS is associated with lower rate of LN sampling. As more and more pediatric surgeons are getting comfortable with MIS, its utilization in pediatric surgical oncology including WT surgery is certainly going to increase.

However, as of now, use of laparoscopy in management WT is usually only offered to patients who have received neoadjuvant ChT [11]. The other reported advantage of preoperative ChT is that it leads to tumor shrinkage, formation of pseudo capsule around the tumor helping in easy handling, and decreased possibility of tumor rupture or spillage [12]. In 2014, SIOP had published some guidelines for identifying patients in whom MIS can be considered [13]. These included tumors not infiltrating extra renal structures, tumor not extending beyond the ipsilateral border of the spinal column, and small central tumors with a rim of "normal" renal tissue and no thrombus in renal vein or vena cava. Burnand et al. from Australia have shown in their retrospective analysis that 9 out 20 cases of laparoscopic WT surgery done by them were outside SIOP criteria [13]. They concluded that SIOP criteria for MIS in WT are conservative and with proper treatment planning and surgical expertise tumors adherent to nearby structures or tumors crossing the ipsilateral border of vertebral column can also be successfully treated by MIS without adversely affecting the oncological outcome.

The use of MIS in WT has its known advantages like better magnification, decreased blood loss, less postoperative pain, good cosmesis, and early reinstitution of ChT or postoperative radiotherapy [5]. However, MIS does have a steep learning curve and can be associated with intraoperative tumor rupture/spillage, injury to normal organs, decreased inclination to harvest LNs, increased surgical time, anesthesia implications of CO_2, and increased operative time in small children [5]. It is advised that the surgeon with good experience in laparoscopy should only attempt MIS for WT.

15.3 Indications and Contraindications

The oncosurgical principles of radical nephrouretectomy (RN) must be followed, and the operation should be carried by a surgical team with good experience in pediatric MIS as well as pediatric oncosurgery.

The most important aspect of MIS for WT is proper case selection [14, 15]. However, these criteria have been quite subjective depending on the experience of the surgeon and the size of the tumor and the loco-regional spread.

Duarte et al. in their initial experience of laparoscopy used to select patients based on tumor histology [16]. They used to perform preoperative retroperitoneal core needle biopsy as per SIOP guidelines and selected only patients with favorable histology. Nevertheless, with this initial experience, they found the results of laparoscopy for WT to be very encouraging, and after their first eight cases they stopped doing preoperative biopsy, if the radiology evidence was strongly suggestive of WT.

The other aspect of case selection is tumor size. Laparoscopy was first used in adults for renal cancer. In adults for renal cell carcinoma, tumor size of 7 cm is considered acceptable for laparoscopy. However, it's not feasible to have a specific tumor size for laparoscopy in children as their body habitus is quite variable. Some authors have reported removal of even 10 cm size tumor post ChT. The ratio of post ChT tumor's largest dimension on computerized tomography (CT) scan and height of the patient is a suggested criterion in few studies. On reviewing these studies, it was found that this ratio is 0.04–0.1 [16]. It means tumor dimension was always less than or equal 10% of patient's height. This can be a useful indicator in selecting patients for laparoscopic approach for this neoplasm.

Tumor thrombus in the renal vein or inferior vena cava is also a relative contraindication to MIS [17, 18]. Large tumors not responding to preoperative ChT are not the ideal cases to be considered for MIS and are better treated by conventional open surgery [18].

15.4 Transperitoneal Approach

15.4.1 Patient and Team Positioning

Patient positioning and ergonomics play a vital role in complex laparoscopic surgery. The child should be positioned a little towards the contralateral side of the operating table for ease of moving instruments thus avoiding the edge of the table interfering with the surgeons and assistant's hand movements. A bolster made of a towel roll or gel pad kept under ipsilateral flank can provide more space for trocar insertion. Patient can be tilted anywhere between 30° and 60° ipsilateral flank up depending on the surgeon's preference. Patient should be securely strapped to the operating table but care to be taken that all the pressure points are soft padded to avoid any sores. Surgeon and the assistant stand on the opposite side of the lesion, while primary monitor is positioned at the ipsilateral side of the lesion (Fig. 15.1). Nasogastric tube and per-urethral catheter should be inserted after positioning the patient.

15.4.2 Surgical Technique

Open method for camera port insertion is ideal in pediatric population. Although some surgeons used Veress needle, it is not a preferred method used by the authors of this chapter. Supraumbilical, infraumbilical, or trans-umbilical port can be used as per patient's umbilical anatomy or surgeon's familiarity. Either a 10 mm or 5 mm port can be used depending on the patient size. We preferably used a 5 mm camera port and 30° camera. Three-port or four-port method can be used depending on the experience of the surgeons and ease of the operation (Fig. 15.2). Ports can be 3 mm or 5 mm depending on patients' size and the endoscopic instruments used. An additional port if required should be placed at the site of Pfannenstiel incision for specimen retrieval. After camera insertion a diagnostic laparoscopy should be performed to assess the resectability and to look for intraabdominal metastatic deposits. Dissection begins with reflecting the colon adequately to visualize the complete lesion and the renal hilum. Our preference is to use a hook diathermy for this, but any

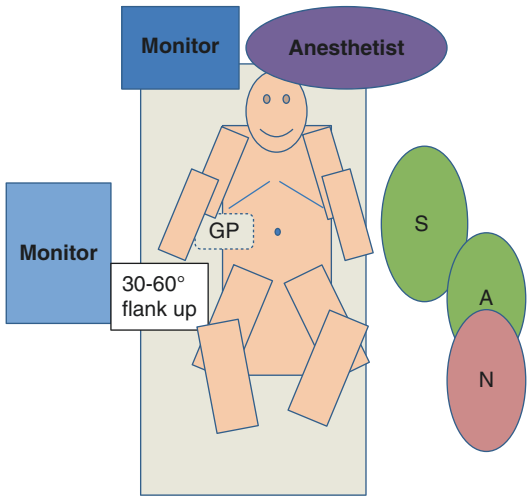

Fig. 15.1 Theatre arrangement for laparoscopic nephrectomy for right-sided WT. Abbreviations: *S* surgeon, *A* assistant surgeon, *N* scrub nurse, *GP* gel pad

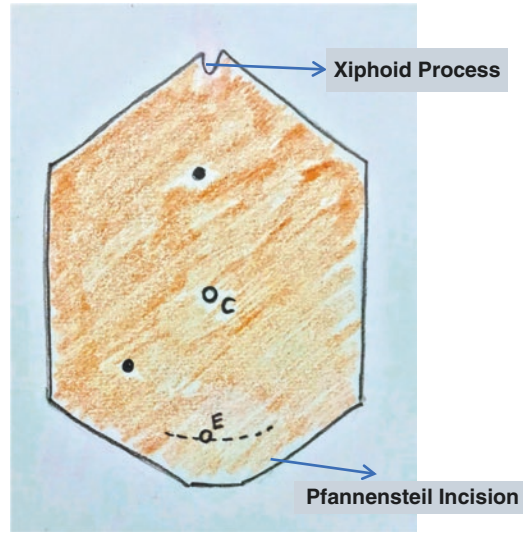

Fig. 15.2 Ports placement for laparoscopic nephrectomy as preferred by authors. *C* camera, *E* extra fourth port if needed

energy device can be used. Once the colon is reflected, the lower part of the ureter is identified and is dissected up to the hilum. Dissection of the hilum should be done very carefully with blunt and diathermy dissection. Adequate Kocherization of duodenum is required on right side to identify the inferior vena cava and renal hilar structures (Fig. 15.3). The renal vein is usually found before renal artery. Artery is easy to identify in MIS because of its pulsations clearly visible due to added magnification. Attempt should always be made to tackle the artery before renal vein to avoid tumor engorgement (Fig. 15.4). Once the artery is identified and dissected out, it can be dealt either with endoclips or an endoscopic energy device like ultrasonic dissector or ligasure. After dividing the artery, renal vein is clipped and divided as well (Figs. 15.5 and 15.6). Depending on the availability, a 5 mm or 12 mm endostapler can also be used for vascular control. Accessory hilar vessels should be identified and tackled appropriately. Ureter is traced up to the bladder and divided as well. The kidney along with the perirenal fat and pseudocapsule are dissected en-bloc. Sometimes the kidney might be adhered to adrenal gland, lumbar musculature, diaphragm, liver, or other related structures. Careful dissection with the help of energy devices like harmonic can aid into dissection. Once the specimen is completely mobilized, LN sampling is to be done from peri-hilar, peri aortic, and paracaval LNs. The specimen and the LNs are placed in an endo-bag and retrieved through a Pfannenstiel incision without morcellation. Port sites are closed without placing any drain.

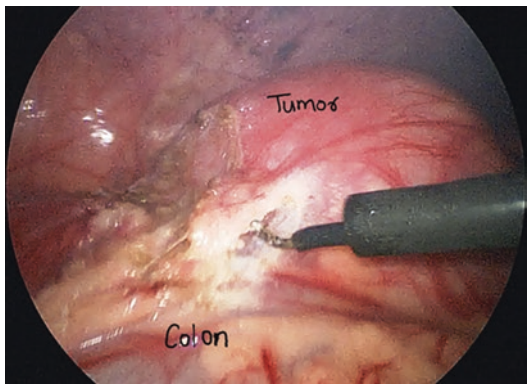

Fig. 15.3 Laparoscopic appearance of right-sided lower-pole WT

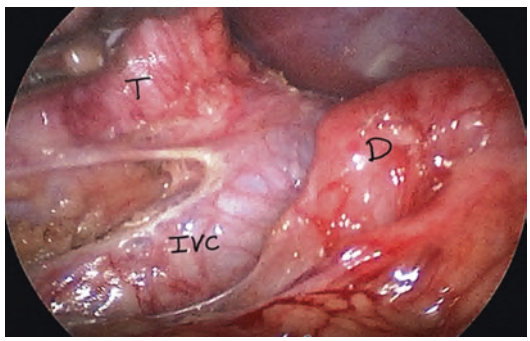

Fig. 15.4 Complete Kocherization of duodenum (D) exposing the inferior vena cava (IVC)

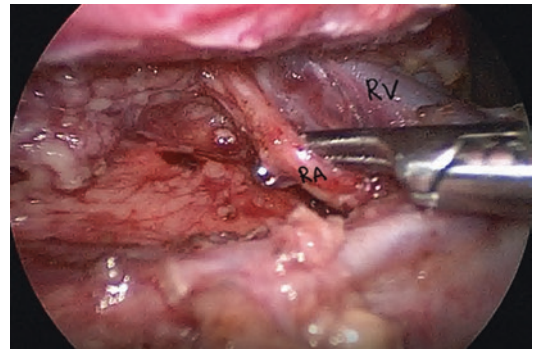

Fig. 15.5 Dissection and isolation of renal artery

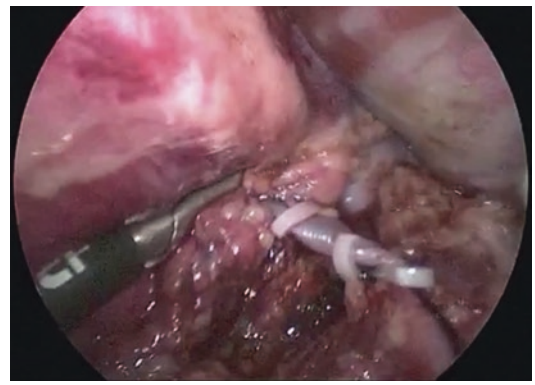

Fig. 15.6 Renal vein clipped using Hem-o-lok polymer clips

15.5 Retroperitoneal Approach

As this approach is technically very challenging, it should only be used by well experienced surgeons familiar with retroperitoneal anatomy in

children and that too if the tumors are localized to lower pole and are small in size; there is only a single reported done by this approach hitherto [19]. In the presence of large tumors, this approach is not recommended as the camera port placement itself can be very difficult and might lead to tumor rupture or rarely insertion of trocar in the tumor.

15.5.1 Patient Positioning

Patient can be placed in either lateral or prone position with the flank region on the breaking point of the table. As with the laparoscopy a towel roll or gel pad should be placed under the patient widening the distant behind ribs and iliac crest. All pressure points should be padded.

15.5.2 Surgical Technique

First incision is placed transversely 1–1.5 cm below the tip of the 12th rib. Incision is deepened, and the muscles are split under vision gently entering the retroperitoneal space. Extreme care has to be taken to avoid injury to the peritoneum. Retroperitoneal space can be created either with a big Foleys catheter, glove finger securely tied over a tube, or commercial balloon. Once sufficient space is created, a 10 mm or 5 mm port for camera is inserted and secured. Two working ports are put under vision as per the ergonomic ease of operating surgeon. Psoas muscle is an important landmark helping in finding the ureter and kidney. Once the hilum is identified, renal artery followed by renal vein is tackled as in previously described laparoscopic approach. Specimen retrieval is big challenge in this approach and might need muscle cutting incision thus taking away one of the important advantage of MIS.

15.6 Nephron Sparing Surgery

SIOP 2016 Umbrella protocol advices against used of MIS for nephron sparing surgery (NSS) in WT and advocate doing open surgery if the patient is a candidate for NSS [20]. However, some surgeons have published successful NSS done laparoscopically in these patients [19, 21]. The important indications of NSS are bilateral WT, tumor in solitary functioning kidney, and in cases of syndromic WT. Laparoscopy is a preferred approach for NSS although retroperitoneoscopy has also been reported for the same [18]. Patient position and ports placement is as described above for RN. The most important aspect of NSS is hilar control, cutting through a normal renal parenchyma and securing any urine leak due to disruption of the pelvi-calyceal system. Control of hilar vessels can be obtained by carefully passing vessel loops or using laparoscopic vascular clamps like bulldog. Some authors have used endo-loops around the normal parenchymal just proximal to the resection margins to avoid excessive bleeding during the parenchymal separation [19]. Bleeding from parenchyma can also be controlled by using topical hemostatic agents like Floseal™. The renal capsule at the margin of excision sometimes needs suturing to prevent urine leak from collecting system. Lopes et al. have published their results in six children who underwent laparoscopic-assisted NSS with encouraging early results as compared to open surgery [21]. Although not seen in their series, peritoneal dissemination due to tumor spillage is a major risk in NSS [21].

15.7 Robotic Surgery

The use of robotic surgery (RS) in the management of adult renal tumor is widely established; however its use in pediatric oncosurgery is limited due to small size of the patient, large robotic ports, and also cost factors [22]. To the best of our literature search, only few centers have published their experience in radical nephrectomy or NSS in management of WT using robotic-assisted laparoscopic surgery [20]. Cost et al. published the first case report in which they did RS for a 6-cm-diameter WT in a 14-year-old girl [23]. This child had not received any ChT before the surgery. Similarly, Yadav et al. published their experience of NSS using RS in an 18-month-old girl with WAGR syndrome [24]. A

study from France described the use of RS in ten children who underwent RN or NSS for renal tumors; six out of the ten patients in their series had WT [25]. They concluded that robotic-assisted total or partial nephrectomy is a viable option for carefully selected patients with renal tumors when strictly adhering with oncosurgical principles.

15.8 Complications of MIS

Immediate complications are hemorrhage, tumor rupture/spillage, injuries to normal organs, and complications due to prolonged anesthesia time. Early complications are infection and urine leak in case of partial nephrectomy. Late complications are tumor recurrence and insufficient LN sampling thereby leading to incorrect staging and thus inadequate adjuvant treatment.

15.9 Postoperative Care

Feeding can be started on same day or by first postoperative day. The patients can be discharged by second or third postoperative day from the surgical ward and rest of the ChT should be completed as per the SIOP protocol.

15.10 Conclusions

In properly selected patients, MIS offers all the advantages like early recovery, decreased length of hospital, less postoperative pain, decrease blood loss, less surgical site infection, and better cosmesis thus having good patient/parental satisfaction. However, it has a disadvantage of increased surgical time and should only be attempted by surgeons well experienced in advance MIS in children.

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16 Bench Surgery and Auto-Transplantation

Yogesh Kumar Sarin, Ilhama Jafarli, and Alexandra Richards

16.1 Introduction

Bench surgery and renal auto-transplantation is a nephron-sparing technique that is indicated in those special circumstances where surgery is difficult or impossible in situ. The fact that the kidney can survive for long periods ex vivo when cooled makes this surgical procedure possible. The four essential components of the bench surgery are nephrectomy, renal perfusion, extracorporeal operation, and auto-transplantation. Though the technical aspects of the procedure are straightforward, and could work for many pediatric conditions such as renovascular hypertension, congenital obstructive uropathy, multifocal Wilms' tumor (WT) in solitary kidney, or synchronous bilateral WT, and occasionally renal trauma, it is not very popular with the pediatric surgeons [1]. An extensive review of literature revealed that the first ever bench surgery and auto-transplantation pediatric WT was reported from the USA in 1976 [2]; this was followed by two cases reported from Japan [3, 4]. Just before the turn of the twenty-first century, the largest series of three patients from a single center was reported from Great Ormond group, UK (Table 16.1) [5].

16.2 Advantages

Of all the WT, bilateral WT comprise of 4–8%, of which ~65% present synchronously and 35% metachronously. Almost one-third of the synchronous bilateral WT are multifocal. So, bilateral multifocal WT comprise 1–2% of all WT [8]. For the bilateral multifocal synchronous WT that are nonresponsive to neoadjuvant chemotherapy, or in those cases in which nephron-sparing surgery is not feasible, bilateral radical nephrectomy (RN) is done, and dialysis is instituted [9]. A hiatus of 1–2 years following completion of treatment of WT is advised before doing a transplant keeping in view of the deaths due to sepsis and tumor recurrence in patients who were transplant early [9, 10]. European best-practice guidelines recommend a 2-year waiting period before transplant [11]. The long-term dialysis in these immunocompromised children has its own attendant problems. If facilities and competency exist, doing bench surgery and auto-transplantation could be a boon in such circumstances:

Of the other advantages quoted in favor of this surgical technique include:

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Table 16.1 Details of children with WT having undergone bench surgery and auto-transplantation [2–7]

Author(s)/ year/country	Age (months)	Tumor description	Surgery	Outcomes
Anderson, Altman [2]/1976/ USA	36	Synchronous bilateral WT	Left nephrectomy and right bench surgery and heterotopic auto-transplantation in pelvis	• No tumor recurrence. • Renal functions maintained. • Compensatory renal hypertrophy.
Okada et al. [3]/1979/ Japan	NA	Aniridia associated bilateral WT	NA	Successful
Ogawa et al. [4]/1983/ Japan	60	Right-sided sarcomatous WT	Bench surgery and heterotopic auto-transplantation in pelvis	• Mild renal impairment. • Long-term steroid treatment. • No anti-hypertensives.
Desai et al. [5]/1999/ UK	11	Synchronous bilateral WT unresponsive to neoadjuvant ChT; right kidney totally replaced with tumor, only left upper pole L kidney was tumor-free	Right nephrectomy and left bench surgery and heterotopic auto-transplantation in pelvis	• Acute hemorrhage post-op day 4 at the reimplantation site. • Follow-up at 3 years, showed no evidence of recurrence and improved renal function (GFR 39 ml/ min/1.73m^2).
	21	Synchronous bilateral WT unresponsive to neoadjuvant ChT; right kidney totally replaced with tumor, left had multifocal WT (3 discrete nodules)	Right nephrectomy and left bench surgery and auto-transplantation	• Ruptured kidney and perinephric hematoma post-op day 14. Required 8 days of peritoneal dialysis. • Follow-up at 30 months showed no evidence of tumor recurrence and improved renal function.
	15	Synchronous bilateral WT; right kidney totally replaced with tumor, left had multifocal WT (11 discrete nodules)	Right nephrectomy and left bench surgery and auto-transplantation	• Recurrence on the right side with paraaortic lymphadenopathy at 7 months post-operatively. • Death at 9 months due to recurrence and metastases.
Millar et al. [6]/2005/ South Africa	7	Synchronous bilateral WT with NBL; right WT was FH triphasic extensive tumor with rhabdomyomatous change not responding to ChT	Bench surgery and orthotopic auto-transplantation; left kidney required partial nephrectomy	Recurrence 16 months later in opposite kidney away from PN site within an area of biopsy-proven NBL which required tumorectomy
Janssen et al. [7]/2018/ Germany	60	WT in solitary kidney	Bench surgery and auto-transplantation	NA

Abbreviations: *FH* favorable histology, *NBL* nephroblastomatosis, *NA* not available, *ChT* chemotherapy

1. Use of operating microscope can result in more precise dissection thus lowering the chances of post-operative recurrence [1].
2. The auto-transplantation if done in heterotopic location (pelvis) could allow better radiotherapy administration to the tumor bed [4].

16.3 Technique

As regards the technique, the exact steps are beyond the scope of this chapter.

The involved kidney is flushed with ice-cold preservation solution, and RN is done and the specimen transferred to the bench. After excis-

ing the tumor(s), the residual kidney is reconstructed and then be heterotopically transplanted onto the iliac vessels; re-anastomosis of the divided ureter or a ureteroneocystostomy may be done depending upon how low the ureter was divided [12]. It is a known fact that autotransplantation is more swiftly done heterotopically than in the renal fossa [1]. Alternatively, the ureter may be left intact, and the tumor(s) is excised in an ice slush container placed within the surgical field, rather than deep down in the renal fossa. In this situation, the vessels are re-anastomosed orthotopically in the renal fossa [12].

16.4 Outcomes

As with all major operations, this technique is not without its post-operative complications. The long-term complications that need to be anticipated include renovascular hypertension and renal failure due to loss of renal tissue [13].

These patients need to be followed long-term for renal functions and oncological outcomes. Regular renal function tests, blood pressure monitoring and urinalysis to assess for the presence of proteinuria are mandatory. Fortunately, in majority of the patients reported in the literature, no significant renal impairment was reported.

All patients will need a follow-up with serial 3–6 monthly ultrasound scans and a yearly contrast enhanced computerised tomography abdomen [5].

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17 Anesthesia

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17.1 Introduction

Wilms' tumor (WT) is the commonest abdominal malignancy in the pediatric population. While these tumors are mostly unilateral, 5% are bilateral, and a smaller percentage of patients (~1%) have intravascular extension of tumor to the inferior vena cava (IVC) and sometimes to the right atrium.

In about 10% of cases, the tumor manifests in conjunction with syndromes such as Beckwith–Wiedemann, Soto's, Denys–Drash, WAGR, and trisomy 18 [1].

Asymptomatic abdominal mass is the most regular presentation of WT. Abdominal pain occurs in 25% of patients [2], while fever, hypertension, and gross hematuria happen in 5–30% of patients. Some patients with intra-tumor hemorrhage may present with anemia and hypotension [3]. Respiratory symptoms in lieu of lung metastases are seen in those with advanced disease.

In addition to general considerations of pediatric anesthesia, WT may pose additional issues due to its occasional massive size, vascular invasion, bilateral disease, and hypertension. Minimal invasive surgery, though seldom used, may add another dimension because of space constraints, pneumoperitoneum, and virtually a compartment syndrome like picture.

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As perioperative physicians, it is our utmost duty to give a child diagnosed with WT a pain-free and unperturbed ride through his/her medical treatment and surgery.

17.2 Preoperative Concerns and Optimization

Children with WT may require anesthesia at several stages of their management process, including that for diagnostic radio-imaging studies- Computerised tomography (CT) or magnetic resonance imaging (MRI) much before being planned for any surgical procedure. A detailed preoperative assessment of the child forms the basis for the anesthetic plan.

Most children with untreated WT are systemically well and asymptomatic. However, malnutrition and concomitant infective pathologies in low-middle-income countries may compromise the general condition of the child. Maintaining good nutrition throughout the course of treatment is gaining acceptance nowadays.

History regarding previous anesthetics exposure, any prolonged hospitalization, intensive care unit (ICU) stay, family predisposition to anesthetic problems like malignant hyperthermia, known allergies, any coexisting medical problems, and current medications must be elicited. Information elicited from the history should lead the physical examination of the child.

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Respiratory signs and symptoms should be elucidated in suspected metastasized disease and the chest X ray/CT chest reviewed. Rarely, pulmonary function tests may be required to know the extent of the pulmonary involvement due to metastases [4].

A baseline blood pressure reading is mandated.

Reviewing a recent complete blood count and serum electrolytes is desirable by the anesthesiologist. Blood dyscrasias, most commonly anemia or thrombocytopenia, occur from occult tumor bleeding into the abdominal cavity. WT being a renin secreting tumor, secondary hypertension is common which causes electrolyte and acid base disturbances. Nevertheless, most cases reveal a normal renal function. In addition, preoperatively, a coagulation profile must be reviewed, and availability of cross-matched blood and blood products should be ensured at the time of surgery.

In cases of syndromic WT, it is essential to do a thorough physical examination for features that may have anesthetic implications. Children with overgrowth syndromes may require airway equipment of a size different from that predicted by weight or age. Among the overgrowth syndromes, Simpson–Golabi–Behmel and Beckwith–Wiedemann syndrome feature hypotonia, macroglossia, and hyperinsulinism, while Soto's syndrome is linked with marked hypotonia and congenital heart disease mandating an additional echocardiographic evaluation [5]. The patients with trisomy 18 (Edward's syndrome) have varied anomalies that include micrognathia (possible difficulty in intubation) and cardiac anomalies like ventricular septal defects and patent ductus arteriosus, once again mandating an essential cardiology clearance. Early renal impairment and secondary hypertension often develop in patients with Denys–Drash syndrome.

Since atrial tumor thrombus may remain asymptomatic, the anesthesiologist should look for any established IVC thrombus by CT angiography or echocardiography.

Some patients are given pre-nephrectomy chemotherapy (ChT) to shrink the size of the tumor in SIOP protocol which is becoming more popular in the developing world. Initial ChT regimens include Vincristine, which might cause the syndrome of inappropriate antidiuretic hormone secretion and Actinomycin-D which damages the liver and impairs hematopoietic function, increasing the risk of coagulopathy. Children with metastatic disease receive Doxorubicin which potentially causes myocardial damage, resulting in acute cardiomyopathy and cardiac dysrhythmias, thus necessitating an echocardiographic evaluation to assess myocardial contractility.

More than 50% of patients planned for surgical resection of WT present with hypertension. The etiology of hypertension is attributed to an increased plasma concentration of renin produced by perivascular spaces surrounding the tumor [6], and the areas of kidney cortex entrapped within it. Normally, renin produced by the juxtaglomerular apparatus acts on circulating angiotensinogen, converting it to angiotensin I. In the lungs, angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II, a potent arteriolar vasoconstrictor, causes hypertension. Hypertension in a case of WT may be labile and severe, the results of which include left ventricular hypertrophy and intravascular volume contraction. Electrolyte disturbances may additionally occur due to renal potassium wasting induced by aldosterone and fluid retention due to hyperreninemia [7, 8]. This may also cause patients to develop lethal congestive heart failure [9].

Centrally acting sympatholytics like methyldopa and clonidine decrease the stimuli for renin formation [10].

Captopril, which is an ACE inhibitor, is particularly effective in treating hypertension preoperatively. It has a plasma half-life of 2 h and a clinical half-life of 4 h; hence the last dose should not be given within 4 h of tumor removal to prevent rebound hypertension [11, 12].

Saralasin, a synthetic angiotensin II receptor partial agonist, has also been used to control severe hypertension in WT [9, 13].

Non-selective beta-adrenergic blockers should be used with caution in patients with uncontrolled hypertension, as the mechanism of the hypertension is not affected by beta blockade and may in turn get exacerbated due to inhibition of the beta-

adrenergic vasodilatory mechanism [9]. Also non-selective beta blockers prevent the reflex increase in heart rate that develops as a compensatory response to sudden hypotension caused by the labile nature of a renin secreting WT in an event of decreased renin secretion. However, propranolol in the dose of 2 mg/kg/6 h (up to a maximum dosage of 6 mg/kg/6 h) is often used in the perioperative management of hypertension.

In the control of preoperative blood pressure various combinations of labetalol, hydralazine, diazoxide, and prazosin have been proven ineffective [11, 12, 14]. Diuretics also fail to affect the mechanism of hypertension in these patients and may in turn worsen electrolyte disturbances.

Adequate preoperative control of blood pressure lessens the incidence of perioperative hemodynamic instability due to fluctuating renin concentrations [15], since preoperative optimization ensures a good cardiac output in the intraoperative period by decreasing the preload and afterload.

17.3 Intraoperative Management

The challenges of anesthetizing pediatric patients with WT are primarily those pertaining to lengthy transabdominal retroperitoneal surgery in small children and infants: fluid balance, thermoregulation, ventilating the child/infant with raised intra-abdominal pressure, intermittent IVC compression, and potential risk of major hemorrhagic complications. One may also encounter the consequences of paraneoplastic phenomena such as coagulopathy and hypertension, tumor thrombus extension to proximal IVC or right atrium, and preoperative or past treatment with ChT.

Though the neoadjuvant ChT used for a fresh case of WT is nearly bereft of any major side effects, some of the patients of recurrent WT would receive high-dose intensive ChT and stem-cell rescue before the surgeon decides to excise the locally relapsed tumor or the systemic metastases. These patients would be prone to develop mucositis, which is characterized by painful, erythematous and ulcerative lesions. This may cause airway bleeding secondary to tissue friability and supraglottic edema resulting in a difficult airway situation. It is usually seen 7–10 days after the start of ChT and remains for 1–2 weeks. Ideally, the surgery should be delayed in such a case, but if there is rare indication for an early surgery after such an intensive ChT, then the anesthesiologist must be very careful intubating such children.

Choice of anesthesia is to be guided by preoperative history and clinical examination findings. Option regarding pain management is to be discussed with the parents. While epidural anesthesia at the lower thoracic levels is a wonderful option for intraoperative and postoperative pain relief, it may be difficult to perform in infants especially those in the initial few months of life. Ultrasound guided epidural anesthesia is a good alternative in such cases.

Adequate nil per oral status must be ensured. The child may be premedicated with Syrup Midazolam (0.5 mg/kg) in preoperative room. Allowing parents/caretakers in at least the preoperative room, if not in the operation theatre (OT) during induction (as done in the western world), could allay child's fears and family's anxiety.

In OT, all standard monitors must be attached. Induction of anesthesia is done with sevoflurane along with 100% fractional concentration of oxygen if intravenous (IV) line is not available initially and the child does not allow placement of IV line. If an IV line is available, IV induction may be done with inj. Fentanyl (2 μg/kg) and inj. Thiopentone (5–7 mg/kg). Inj. Vecuronium (0.1 mg/kg) or inj. Rocuronium (0.6 mg/kg) may be used for muscle relaxation. The child is then intubated with an appropriate-sized endotracheal tube decided according to the age of the patient. A naso-gastric tube is inserted.

If difficult intubation is anticipated, a check laryngoscopy may be done before the administration of a muscle relaxant and Cormack-Lehane (CL) grading assessed. Also, adequate chest rise is ensured by bag and mask ventilation before any muscle relaxant is given.

An arterial line is inserted because of the potential risk of hemodynamic instability during tumor handling, sudden hypotension, and the usual presence of hypertension in these children. Core temperature monitoring is mandatory, as

a warning for both impending hypothermia and hyperthermia if forced air warming techniques are used. The standard practice entails careful positioning, padding of pressure areas, and eye protection.

It is desirable to secure at least two large bore IV cannulas in upper limbs specially if intraoperative inferior vena cava clamping is anticipated. If a difficult IV cannulation is anticipated, placing a central line is a wise option since resection of a large WT is a major surgery involving massive fluid shifts; the central line shall prevent panic moments in case of intraoperative hemorrhage, which may necessitate massive blood and volume transfusion.

After induction and intubation, an epidural catheter is placed by loss of resistance (LOR) technique or ultrasonographically guided in a case of difficult anatomy. A functional epidural catheter reduces the requirement for IV opioids which reduces the chances of post-op respiratory depression.

A urinary catheter must also be placed; urine output is constantly monitored throughout the surgery.

Maintenance of anesthesia is ensured with 2% sevoflurane, regular top ups/infusion of muscle relaxant and fentanyl. For epidural infusion, the common practice is an infusion of 0.125% bupivacaine at the rate of 0.2 mg/kg/h for neonates and 0.4 mg/kg/h for older children.

Goal-directed therapy, titrated according to hemodynamic response, is adopted for administration of IV fluids with an average fluid administration (balanced salt solution) at the rate of 10–20 ml/kg/h during anesthesia [16]. Rarely, a background infusion of glucose (1–2.5%) may be given at the rate of 10 ml/kg/h in younger children and those children prone to hypoglycemia. In surgeries spanning over many hours, blood sugar levels must be measured, and glucose administration adjusted accordingly.

It is often difficult to ensure adequate ventilation is a case of WT because the intraabdominal pressure is typically raised owing to the large size of the tumor. Small tidal volume breaths with a respiratory rate kept on the higher side shall ensure adequate respiratory exchange of gases. The pressure-controlled mode of ventilation is preferred with a vigilant eye on the peak airway pressures to prevent barotrauma and further compromise in ventilation. Also, epidural analgesia plays a significant role here by reducing the intra op requirement of opioids thereby preventing post op respiratory depression.

In 1% cases, where the tumor may extend to the IVC and right atrium a transesophageal echocardiography or Doppler probe is placed to assess the cardiac output.

Intraoperative fluctuations in blood pressure are frequently encountered during tumor handling. If a rapidly shooting blood pressure cannot be brought under control by maneuvers such as increasing the depth of anesthesia or administering opioids, drugs such as phenoxybenzamine, phentolamine, sodium nitroprusside, and Esmolol are used for control of the same.

Episodes of hypotension are also not a rarity. It occurs frequently due to IVC compression by the surgeon or an episode of sudden blood loss. Blood loss must be replaced with crystalloids or blood products as appropriate. Colloids are generally avoided as a replacement for blood loss since studies have shown that colloids potentially cause renal tubular damage via hyperosmotic mechanisms [17]. More often than not blood pressure is immediately restored upon asking the surgeon to stop the surgery for a little while, and to release the retractors that may be causing a possible IVC compression.

Blood gas analysis may be performed at regular intervals. Analysis of blood gas allows us to note changes over time. Serial values of central venous oxygen saturation ($ScVO_2$) may be used as a fast indicator and base excess and lactate concentration as slow indicators of tissue perfusion. In case of a negative trend in these parameters, countermeasures are taken accordingly, before a pathological level is reached.

Hypothermia needs to be avoided both intra- and in the immediate postoperative period. If epidural anesthesia is not being used, local anesthetic (0.125% bupivacaine) should be infiltrated at the incision site (taking care not to exceed the highest permissible dose according to the weight of the child).

Once the surgery is over, an arterial blood gas assessment is done. If the acid base gas (ABG) picture shows conditions conducive to extubation, reversal of the child is attempted with Inj. Glycopyrrolate (0.01 mg/kg) and injection neostigmine (0.05 mg/kg). An antiemetic is also given in older children to prevent postoperative nausea and vomiting. Once the child is extubated, he/she is shifted to the postoperative recovery room. The epidural if inserted is generally kept in situ for postoperative pain relief.

In a situation where extubation is not possible due to reasons such as massive blood loss, acidosis, or inadequate reversal, the child is shifted to the intensive care unit (ICU) and is kept under continuous supervision until it is possible to wean him/her off the ventilator.

17.4 Anesthesia for Special Circumstances

17.4.1 Anesthesia in a Case of Tumor Extension to the Right Atrium

Neoadjuvant ChT is almost necessarily given in all cases of tumor extension to the IVC or right atrium, to shrink the tumor which shall enable surgery without the requirement of cardiopulmonary bypass. However, in some cases, hemodynamic instability caused by the tumor invasion into the right atrium that presses onto the tricuspid valve requires an upfront emergency surgery.

Cardiopulmonary bypass (CPB), with or without circulatory arrest, is used frequently to facilitate the resection of the tumor thrombus extending into the suprahepatic IVC and right atrium (Daum stages III and IV). CPB requiring the use of a median sternotomy, atriotomy, and systemic anticoagulation is associated with significant morbidity from the systemic inflammatory response provoked by the the extracorporeal circuit. There is higher incidence of neurological dysfunctions, systemic inflammatory response syndrome (SIRS), and coagulopathies in such cases. CPB prolongs the operative time, exposing the patient to risk of acidosis, hypothermia, blood transfusion, and cardiac arrest.

In addition to the challenges posed by a regular nephrectomy in a pediatric patient, the anesthesiologist shall have to deal with a plethora of other anesthetic challenges of cardiopulmonary bypass specifically during the transition period, while going into bypass circuit and coming off bypass. Normally the nephrectomy is done prior to intracardiac removal of the tumor with the help of extracorporeal CPB, since systemic anticoagulation that is a necessity for CPB predisposes the patient to unanticipated bleeding, if nephrectomy is planned post bypass in the same sitting. Adequate anticoagulation should be ensured before going on bypass by administration of Inj. heparin (3 mg/kg), titrated to point of care anticoagulant test values. The anticoagulation should be adequately reversed with Inj. protamine after the patient is off bypass, to minimize the chances of further bleeding.

The anesthesiologist should be adept in the management of myriad arrhythmias that are frequently encountered while the patient is coming off CPB. All antiarrhythmic drugs, inotropes, and a functional defibrillator should be ensured in the operation theatre before shifting the patient for surgery. Arterial blood gas should be done at frequent intervals and acidosis if any must be corrected aggressively.

Epidural is not to be put in patients planned for CPB due to risks of bleeding, and thrombus formation associated with systemic anticoagulation and analgesia is achieved mainly with IV opioids.

Since such patients are majorly electively mechanically ventilated postoperatively, postoperative respiratory depression due to opioids is of a lesser concern.

17.4.2 Anesthesia in Bench Surgery

Bench surgery involves the removal of the diseased kidney from its bed while ligating the renal vein, artery, and ureter (close to the bladder), excision of the tumor(s) on the removed kidney in cold preservation solution extracorporeally and transplanting the residual kidney back into the iliac fossa in the same patient.

Apart from the routine anesthetic concerns, our main goal during this surgery is to maintain adequate renal perfusion. Thus, a high normal BP and a central venous pressure (CVP) of 8–12 cm of water is ensured with the help of generous IV hydration before the renal artery is clamped. Ischemic injuries to the kidney are prevented by mannitol infusion [18].

During the bench surgery (extracorporeal surgery interval), our aim is to prevent fluid overload. During that period, CVP is kept on the lower side.

Just before the anastomosis and release of the clamp, CVP is increased and a higher BP maintained to provide necessary perfusion to the transplanted kidney [19, 20].

Furosemide is given to ensure diuresis and to improve graft viability. Oxygen consumption in the renal tubules is also lowered by furosemide thus reducing the chances of any ischemic kidney injury [21].

17.4.3 Anesthesia for Laparoscopic Nephrectomy

Laparoscopy surgery is restricted to only small tumors to be performed by surgeons with reasonable degree of expertise and experience in laparoscopic procedures; a low threshold to conversion to an open procedure is emphasized. General anesthesia with endotracheal intubation without the use of nitrous oxide is ideal as with any major laparoscopic operation. The major concerns are hypercapnia due to abdominal insufflation with carbon dioxide and hypoventilation. Increased intraabdominal pressure caused by pneumoperitoneum causes the diaphragm to displace cephalad resulting in decreased compliance and decreased functional residual capacity. Increased airway resistance increases peak pressure and plateau pressures thereby resulting in an increased work of breathing. Therefore, pressure-controlled ventilation is the preferred mode. Normocapnia is ensured by keeping a high respiratory rate with lower pressure limits and thus lower tidal volume. Care should be taken to monitor the rate of insufflation of gas into the peritoneal cavity. To minimize the cardiorespiratory adverse effects of pneumoperitoneum, insufflation pressures should be limited to 5–10 mmHg in neonates and 10–12 mmHg in older children [22]. Gas embolism is a known complication of any laparoscopic surgery, and the anesthesiologist should be observant of any sudden fall in end tidal carbon dioxide, sudden hypotension, arrhythmias, or desaturation. The treatment would then consist of desufflating the abdomen, ventilation with 100% oxygen, trying to break the air embolus by cardio-pulmonary cerebral resuscitation, and aspirating the embolus through central venous line by Durant's maneuver [23].

Ports sites should be infiltrated with local anesthetic at the end of the operation to provide adequate pain relief. Regional anesthesia such as an epidural catheter may be used for intra op and post op analgesia specially if the Pfannenstiel incision is of a bigger size.

Although both laparoscopy and retroperitoneoscopy have been used for the radical nephrectomy, the latter is associated with increased CO_2 absorption and pulmonary hypertension in children [24]. This may have central nervous system and cardiorespiratory consequences during and after the operation.

17.5 Postoperative Concerns

Once the child is extubated and shifted to the post op recovery room, care must be taken to ensure a pain-free postoperative period to restore normalcy in the child's life as fast as possible. A complete hemogram is done to assess the actual blood loss during the procedure. Blood products are transfused based on reports of the postoperative hemogram.

The epidural catheter, if in situ, is followed up regularly by an anesthesiologist with regular top ups of injection bupivacaine or bupivacaine infusion administered as per patient's requirement. A Prothrombin Time-International Normalized Ratio (PT-INR) report is mandatory before taking out the epidural catheter, and care is taken to ensure that the catheter tip is intact while it is being taken out.

If there is no epidural catheter in situ, other modes of postoperative analgesia must be considered like opioids or even simpler steps such as round the clock dosage of paracetamol goes a long way in ensuring adequate pain relief. If the child is receiving opioid analgesia, vigilant monitoring of his vitals and respiratory parameters must be ensured.

The child must be encouraged to do incentive spirometry to ensure full recovery of his/her pulmonary functions.

17.6 Conclusions

Nephrectomy in the twenty-first century remains a potentially challenging case for any anesthesiologist, more so in children. Comprehensive imaging, multidisciplinary team discussion, and preoperative optimization are frequently necessary across diverse specialities. A good coordination between the surgeon, anesthesiologist, oncologist, and a meticulous planning backed by a harmonious teamwork shall ensure that every child with WT leaves the hospital with a smile and carries good will for his treating doctors in the years to come.

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18 Staging

Manish Pathak

18.1 Introduction

Staging for malignancy is the process of determining the extent of the tumor. The stage generally takes into account the tumor's extension or invasion into the surrounding structures, involvement of regional or distant lymph nodes (LNs), and distant metastasis. Staging for the tumor is important for risk stratification, prognostication, and facilitation of comparison between groups of patients sharing similar stage defining characteristics. As the appropriate therapy and prognosis are based on tumor stage, it is imperative to stage the tumor accurately.

Staging systems for Wilms' tumor (WT) are based exclusively on anatomical extent of the tumor. The staging is not dependent on clinical characteristics, molecular markers, histology, or biology of the tumor [1, 2]. The anatomical extent of the tumor is determined by the pathologic examination of the surgically excised tumor and sampled LNs. Thus, it is a surgico-pathologic system where both surgeons and pathologist have an important role to play.

Stage is an important criterion in the risk stratification of the WT. Advanced tumor stage at the time of diagnosis is associated with an increased risk of recurrence [3, 4]. One of the important benefits of accurate staging is that it enables the universal comparison of treatment outcomes. Multi-center trials have shown that staging still represents a major problem. The large size of the renal tumors at the time of nephrectomy results in difficulty in the assessment of its relationship with normal renal anatomical structures such as the renal sinus and the renal capsule. Thus, it is of utmost importance that the pathologist ensures to take the blocks from all the critical sites and register the location of each block accurately [1, 5].

18.2 COG and SIOP Staging

Currently, two major surgico-pathologic staging systems are in use. Children's Oncology Group (COG) recommends upfront surgery, and staging is based on combination of operative findings at the time of immediate nephrectomy and imaging for distant metastasis [6, 7]. Operative findings determine the local stage, while the disease stage is determined by the imaging done to look for distant metastasis.

Societe Internationale D'oncologie Pediatrique (SIOP) uses the preoperative chemotherapy (ChT) approach, and staging is done after 4–6 weeks of neoadjuvant ChT as per protocol [5, 8]. Localized tumor receives 4 weeks of preoperative ChT, while metastatic WT receives 6 weeks of preoperative ChT. The staging is done again based on local operative findings and preoperative imaging to define metastatic disease.

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Recently, definitions that are more detailed have been introduced to aid correct staging [9].

It is important to understand the concept of local stage and disease stage in WT. The local staging is based on operative findings, while the disease staging on preoperative image findings of presence or absence of distant metastasis. The need for local radiation and its dose depends on local stage, while the disease stage determines the type and duration of ChT to the patient.

Both staging systems for WT are essentially very similar, and both have been found to be useful in predicting outcome; however, stage-wise comparison of two staging systems is not possible due to the difference in the timing of ChT relative to the surgico-pathologic evaluation [10] (Fig. 18.1) (Tables 18.1 and 18.2).

Staging of WT also has changed as the data emerged during the course of multicenter trials that subgroups within stage categories have varying prognosis. The stage definitions have been modified over the years, as per the available data. It was observed that patients with "local tumor spill" have significantly high rate of local recurrence in comparison to the patients without local spill, and this led to reassignment of these patients from stage II to stage III in the recent NWTS/COG staging system [11, 12].

As the appropriate therapy and prognosis is based on tumor stage, it is imperative to stage the

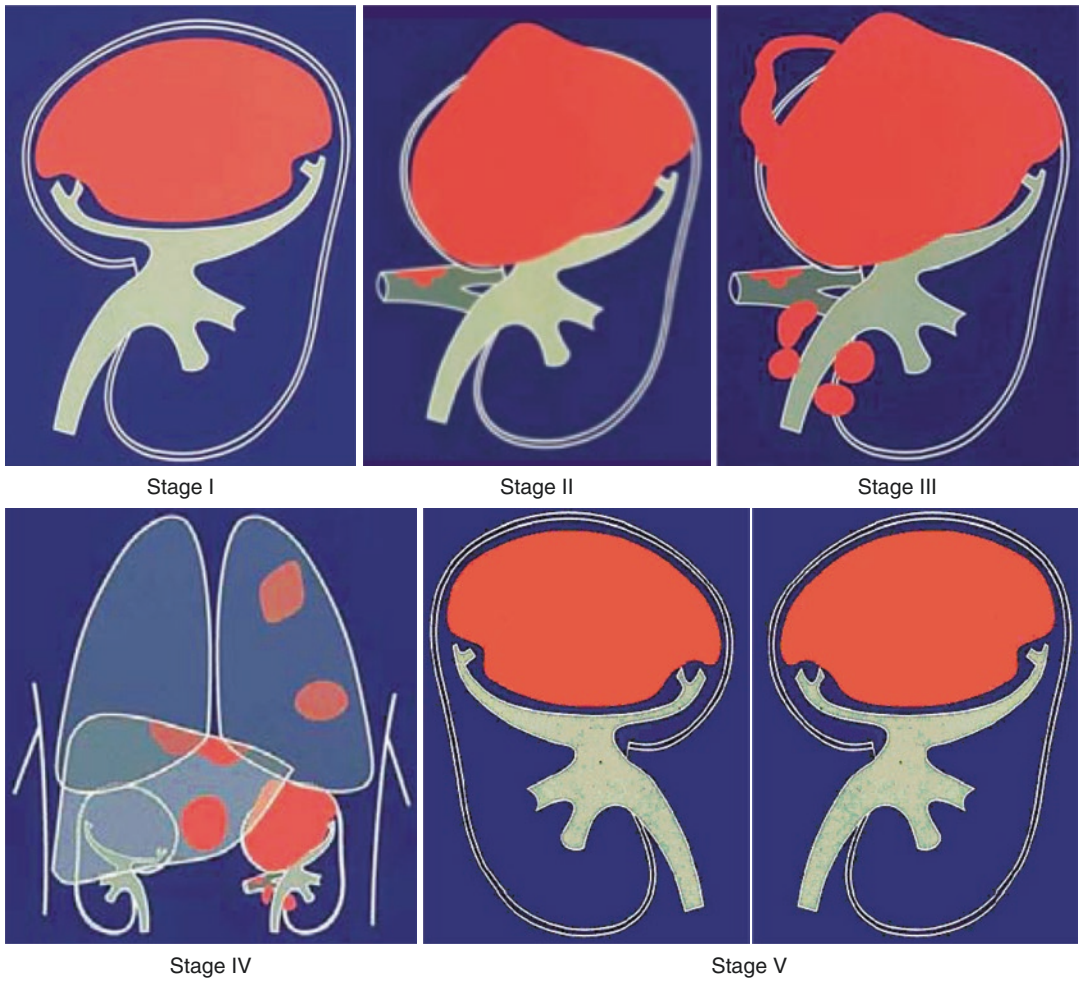

Fig. 18.1 Tumor staging; the general concept

Table 18.1 COG staging

Stage	Criteria
I	Complete resection of the tumor that is limited to the kidney No preoperative or intraoperative rupture of the tumor. Tumor was not biopsied prior to removal There is no involvement of renal sinus or any penetration of the renal capsule
II	The tumor extends beyond the capsule of the kidney but was completely resected with no evidence of tumor at or beyond the margins of resection The tumor penetrates the renal capsule or there is invasion of the renal sinus vessels
III	Gross or microscopic residue postoperatively, including inoperable tumor, positive surgical margins, or tumor spill Preoperative or postoperative tumor rupture Tumor biopsy prior to removal Abdominal or pelvic LNs positive for tumor Penetration of the tumor through the peritoneal surface Presence of peritoneal tumor implants Local infiltration into vital structures making the tumor not completely resectable Patients receiving neoadjuvant ChT Tumor transection during surgery or if tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; transection of the tumor thrombus) Tumor thrombus extension into the abdominal vena cava, thoracic vena cava, or right atrium (adhered to wall) is considered stage III, rather than stage IV, even though outside the abdomen
IV	Lymphatic or hematogenous metastases outside the abdomen (e.g., lung, liver, bone, brain)
V	Bilateral renal tumor at diagnosis (each side is staged separately for local stage)

Table 18.2 SIOP staging

Stage	Criteria
I	The tumor is limited to the kidney or surrounded all around with a fibrous pseudocapsule. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected. The tumor may be protruding into the pelvic system and dipping into the ureter, but it is not infiltrating the walls. The intrarenal vessels may be involved but the renal sinus is not involved
II	Viable tumor in the perirenal fat without any surrounding pseudocapsule but is completely resected. Renal sinus infiltration by the viable tumor. Viable tumor infiltrating the wall of the renal pelvis or of the ureter. Viable tumor infiltrates the vena cava or adjacent organs (except the adrenal gland) but is completely resected
III	Presence of viable tumor at the resection margin. Nonviable tumor or ChT-induced changes at a resection margin are not regarded as stage III. Abdominal LN involvement (viable or nonviable). Preoperative or intraoperative tumor rupture, if confirmed by microscopic examination (viable tumor at the surface of the specimen at the area of the rupture). Transection of viable or nonviable tumor thrombus. Presence of viable or nonviable tumor at resection margin of ureter. Wedge or open tumor biopsy before preoperative ChT or surgery. Intraabdominal tumor implants (viable or nonviable). Peritoneal tumor implants (viable or nonviable)
IV	Lymphatic or hematogenous metastases outside the abdomen (e.g., lung, liver, bone, brain)
V	Bilateral renal tumor at diagnosis (each side is staged separately for local stage)

tumor accurately. Tumor stage is a critical component of risk-stratified therapy [13]. Both the surgeon and the pathologist play an important role in correctly determining the local stage of the tumor. Diagnostic imaging as per protocol and its correct interpretation by radiologist is also warranted for the adjudication of the disease stage [14]. Initial imaging study should be able to confirm the organ of origin to be the kidney, delineate the contiguous spread of the tumor into the ureter or vena cava, status of the opposite kidney, and delineate the metastasis if present. Additionally, a computerized tomography (CT) of chest should be done in order to look for lung metastasis, as it has been found in study trials that CT-only nodules fare worse if the treatment is

administered according to the local primary stage alone [15]. An interesting study was conducted by Gow et al. to find the correlation between local staging based on CT findings and histology findings. Their study concluded that there is a poor correlation of CT scan to histological staging. Therefore, therapy based solely on radiological imaging may lead to under- or overtreatment of patients. Histological assessment of the tumor should continue to be the standard for staging WTs. The authors found it consistently difficult to identify the capsular or nodal involvement thus making them unable to correctly differentiate between stage II and stage III [16]. Failure to sample the LN is one of the most frequent errors committed by the surgeon that may lead to incorrect downstaging and undertreatment to the patient thereby leading to increased risk of local relapse [14]. The operating surgeon must be aware of the surgical factors that may upstage the tumor to avoid any such mishap. These factors include tumor spillage, transection of the tumor thrombus, removing the tumor piecemeal, etc. [16–18]. It is the duty of the operating surgeon to document the operative findings in detail.

The pathologist is expected to gross the specimen correctly and extensively. He/she must ensure to take the blocks from all the critical sites and document the site of each block correctly [9].

18.3 Salient Differences Between the SIOP and COG Staging System

Surgico-pathologic staging in COG staging system is done upfront while in SIOP this staging is done after neoadjuvant ChT. Upfront surgery in COG protocol provides the unique opportunity to do the histological examination of naïve tumor tissue. It also avoids unnecessary preoperative ChT to the benign tumor. In addition, it also avoids the inappropriate preoperative ChT to the tumors with histology other than WT. In contrast, preoperative ChT as per SIOP protocol decreases the tumor size, leads to favorable stage distribution, and reduces the chances of tumor rupture. This significant benefit reduces the need for radiotherapy to almost half of that required in upfront surgery protocol of COG. SIOP staging is often criticized for under-staging the WT patients. However, patients' stages as I or II by SIOP have the same overall and event-free survival as COG stages I and II, thus invalidating the argument of under-staging against SIOP [19]. Another criticism is that it may lead to unnecessary pre-nephrectomy ChT to the benign renal tumors. The SIOP rebuttal is that this incidence is only 1.5%, and it is well balanced by the favorable stage distribution and lower risk of tumor ruptures [19, 20].

Important points to remember:

1. The tumor extending into renal pelvis and ureter does not upgrade the tumor, if it can be removed in toto as the tumor specimen without transecting through the tumor. On the contrary, if the tumor in the ureter is transected at the time of surgery, then it upstages the tumor to stage III. If the tumor extends along the ureter through the uretero-vesical junction and is dipping into the bladder, then the surgeon should remove the cuff of bladder around the uretero-vesical junction so as to remove the tumor in a single piece avoiding the transection through the tumor. This will prevent the tumor to be upstaged to stage III based on surgical resection margin.
2. The tumor extending into renal vein or inferior vena cava makes it minimum stage II.
3. Extension of the primary tumor within the thoracic vena cava or heart that is removed piecemeal or separately from tumor is considered stage III not stage IV, even though outside the abdomen [10].
4. Any residue, even when it is microscopic, makes the tumor stage III.
5. Positive LN makes the tumor stage III, but if the positive LN is present outside the abdominal cavity, then it will be considered metastasis and stage IV.
6. FNAC of the tumor does not upstage the tumor. In COG, core needle biopsy upstages the tumor to stage III.

7. Core needle biopsy will not upstage the tumor in SIOP. However, open biopsy will upstage the tumor to stage III in both SIOP and COG staging system,
8. Even in those with stage IV disease, local stage is still a prognostic feature.
9. In case of a bilateral WT, a local stage should be provided for each tumor.

18.4 Role of Surgeon in Appropriate Staging

1. Trans-peritoneal incision for wide exposure—retroperitoneal surgery may not be able to stage the tumor correctly.
2. The peritoneum and liver should be examined to look for any tumor implant; presence of it will upstage the tumor to stage III or stage IV, respectively. Exploration of the contralateral kidney is no longer mandated before nephrectomy if the preoperative CT or Magnetic resonance imaging (MRI) demonstrates a normal kidney [21].
3. Thorough inspection should be done to look for any evidence of preoperative or intraoperative rupture. Bloody peritoneal fluid suggests rupture, and surgeon should thoroughly inspect the tumor surface. Free communication of the open neoplastic tissue surface with peritoneal cavity is also a sign of tumor rupture. Rupture of the tumor upstages it to stage III.
4. Tumor dissection should be done carefully to prevent any intra-operative spill or tumor rupture during surgery; this will upstage the tumor to stage III [16]. "Spill" refers to a break in the tumor capsule during surgery, whether accidental, unavoidable, or by design. In COG protocol, spill is considered to have occurred if a preoperative or intraoperative needle or open biopsy is performed, thus, upstaging the tumor to stage III. Any tumor spill increases the risk of local tumor recurrence [17, 18]. In SIOP protocol, fine needle or Tru-cut needle biopsy is permitted and does not upstage the disease, while the incisional biopsy upstages it to stage III. In the United Kingdom Children's Cancer and Leukemia Group (UKCCLG) trial, preoperative percutaneous cutting needle biopsy, preferably using coaxial technique through retroperitoneal route to obtain multiple core biopsies, used to be performed routinely in all cases at diagnosis [9].
5. Ureter and renal vessels should be palpated to look for any tumor extension, if the tumor extension is present then it mandates the appropriate technique so as to avoid any transection of the tumor; this will also upstage the tumor to stage III [9].
6. LN sampling: Failure to sample the LNs is the most frequent error committed by the surgeon [22]. This will falsely under-stage the disease leading to undertreatment and high risk of local recurrence. Pathologic assessment of hilar and regional LNs is critical to accurately stage a child with WT. Determination of the involvement of the tumor by simply looking at the LN is highly inaccurate. There is no formal recommendation on the number of lymph nodes that need to be sampled. In a retrospective study of COG, sampling of seven LNs increased the rate of detection of metastasis [23]. Another important point is that the LN even when it contains only necrotic tumor then also it is labelled as stage III in SIOP protocol [9].
7. Proper documentation of intraoperative findings is also one of the primary goals of the surgeon.

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Chemotherapy

19

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19.1 Introduction

The multimodality treatment approach by employing surgery, chemotherapy (ChT), and radiotherapy (XRT) (in select cases) for Wilms' tumor (WT) has led to the survival rate go up to 90% today, with metastatic presentation having overall survival (OS) rates >50% [1].

The surgical principles described by Mixter (1931), later followed by Ladd and his colleagues, have remained the same to this date. With introduction of XRT, first employed in Children's Hospital Boston (1935) and later by Friedlander (1950), the survival rate doubled, from 25% to 50% in unstaged patients [2, 3]. But it was the introduction of ChT for WT that truly served as a game changer.

In 1954, Actinomycin-D (AMD), a derivative from *Actinomyces*, was tested by Ravina et al. and was found to have profound anti-cancer effect [4]. Later, the benefits of AMD in WT treatment were found in 1958 and confirmed by multiple reports [5, 6]. In 1960, Farber et al. reported the combined usage of AMD with XRT, which provided the best yet treatment for WT [7]. Soon, in 1963, a second agent Vincristine (VCR) was also found to be effective against WT [8].

With due course, multiple reports of successful use of anti-cancer drugs along with surgery and XRT were published. But the available scientific evidence was insufficient to clarify the benefits of ChT in WT and to identify the subset of patients who benefited from additional XRT. This issue gave rise to the origin of multiple international cooperative groups, whose years of strenuous research on molecular biology of WT, effects of newer anti-cancer drugs, and evidence-based protocols put shape to the current knowledge and management strategies for WT. Also, these cooperative groups became models for interdisciplinary collaboration between pediatric surgeons, radiation oncologists, pathologists, medical oncologists, molecular biologists, and statisticians/epidemiologists.

The two prominent international cooperative groups include National Wilms' Tumor Study Group (NWTSG) based in America that was started in 1969, and Société Internationale D'Oncologie Pédiatrique/International Society of Pediatric Oncology (SIOP) based in Europe that started 2 years soon after in 1971. NWTSG was later merged into Children's Oncology

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Group (COG) in 2001. These working groups are not only separated by the Atlantic Ocean, but also by their guiding philosophies. The treatment strategies and results should be studied in the context of the particular protocol implemented in a clinical setting.

19.2 NWTSG/COG vs. SIOP Philosophy of Management

NWTSG/COG recommends that children with malignant renal masses undergo surgery before ChT (upfront surgery), while SIOP advocates preoperative ChT followed by surgery. Though the two protocols have different strategies, the OS rates for patients treated by the two guidelines are quite similar with over 90% being cured, though the debate continues regarding relative merits of each approach [9–11].

The proponents of NWTSG/COG believe that the most accurate information needed for individualizing the treatment for a WT patient comes from up-front resection of tumor and highlight various risks for preoperative ChT [12, 13]. Only 80–90% of childhood renal tumors in the western developed world are WT, and in SIOP protocol, ChT may be inadvertently administrated to patients with a benign disease (e.g., a benign cystic partially differentiated nephroma) or inappropriate ChT regimen may be administered to a patient with a non-Wilms' renal tumor (NWRT) such as malignant rhabdoid tumor of kidney, clear cell sarcoma of kidney, or renal cell carcinoma [14]. NWRT would have benefited from alternate treatments strategies, and the delay leads to further increase in tumor burden in those patients.

Further, modification of tumor histology and loss of information regarding staging may occur because of the neoadjuvant ChT.

On the other hand, the opponents of NWTSG/COG [13] quote the several risks and drawbacks of opting for the up-front resection of tumor.

They quote the following advantages of SIOP protocols:

- Allows for a considerable reduction of the tumor size, thereby making surgery easier and also reducing the chances of an inadvertent intraoperative tumor rupture, which in turn reduces the likelihood of local recurrence.
- Makes nephron-sparing surgery (NSS) feasible.
- Allows for an establishment of in vivo chemosensitivity of the tumor to the regimen.

SIOP approach might be the preferred approach for children in developing countries as most cases present with advanced disease and large tumor burden. The neoadjuvant ChT makes surgery easy and gives time to organize resources to operate upon these children safely.

However, there are a few exceptions for both the protocols. SIOP also recommends upfront nephrectomy in babies less than 6 months of age as alternative histology (other than WT) is more common in this age group [4–6]. COG, likewise, suggests using neoadjuvant ChT in certain situations which are discussed in the section below.

19.3 National Wilms' Tumor Study Group (NWTSG)/Children's Oncology Group (COG)

By 1960s, the annual incidence of new WT cases was only 500 per year in the entirety of North America. The available treatment modalities included surgery, XRT, and two new anti-cancer drugs.

Between 1969 and 2002, NWTSG conducted five studies [15]. Each study attempted to answer a few research questions (aims), and the results prompted the next set of research questions (Table 19.1).

Table 19.1 Details of NWTS trials [15]

Study	*N*	Aims	Results
NWTS-1 (1969–1975)	741	• Eliminating XRT for low-risk patients (group I). • Is treatment with one of the two known effective ChT agents (AMD and VCR) better than the other, or will the treatment be improved if they are combined? • To better diagnose each tumor by extent of spread and by pathology review. For the first time a study combined the findings of surgeons, pathologists, oncologists, and other researchers to obtain a comprehensive assessment of a tumor. • Do different histologic types be having different prognosis, and can it be used to assess prognosis? This could possibly result in more aggressive treatment for "bad" histologies and a less aggressive treatment might be sufficient for "good" histologies. • Implementation of the longstanding study of the epidemiology of WT.	• XRT not essential for low-risk group I pts. • AMD + VCR is more effective than either alone. • Favorable histology (FH) and unfavorable histology (UH) tumors identified.
NWTS-2 (1975–1979)	950	• Aimed to answer whether the duration of treatment be decreased from 15 months to 6 months for low risk (group I) pts. • Will outcome or survival be improved by adding ADR to treatment for other groups (II, III, and IV)? • Will the existing outcomes be maintained even while reducing ChT doses by 50% for children <1 year of age?.	• 6 months of ChT is sufficient for group I[a] • Addition of DOX improves survival of groups II to IV[a] • 50% ChT dose reduction is appropriate for infants • Prognosis of FH is better than that of UH. • New staging system introduced (LN involvement is shifted from group II to stage III)[a]
NWTS-3 (1979–1986)	2496	• To intensify the focus on the study of histology and pathology and use these to compare the various treatment and clinical outcomes. • To refine treatment methods and base them according to staging of the tumors in order to prevent various complications and effects of unnecessary treatment. • To test out treatments specifically designed for a specific combination of stages and histologies. • To study the late consequences of successfully treated WT patients. • To frame guidelines for studying survivors of WT and to define forms for data capture.	• Histology and stage specific treatment proposed. • Focal or diffuse anaplasia, clear cell sarcoma, and rhabdoid tumor are classified as UH. • XRT not essential for stage I (both FH or UH). • Stage III FH requires 3 drugs (AMD+ VCR+ DOX) plus XRT. • Stage II–IV UFH requires 4 drugs (AMD+ VCR+ DOX+ CTX).

(continued)

Table 19.1 (continued)

Study	*N*	Aims	Results
NWTS-4 (1986–1995)	3335	• To simplify, shorten, and refine the treatment regimen so as to lessen the socio-economic impact of therapy including time, money, travel, and major lifestyle changes. • To implement a distinct project for the *NWTS late effects study*. This was now a separately funded project with an expanded scope.	• Pulse-intensive ChT gives good results with less toxicity. • Pulse intensive ChT of FH of all stages significantly reduces the cost of care.
NWTS-5 (1995–2002)	3031	• To increase the survival rate of children with FH WT and other renal tumors of childhood. • To determine if a poorer prognosis was seen for patients with FH WT if these patients had a LOH for chromosomes 16q markers in tumor tissue. • To determine if a poorer prognosis was seen for patients with FH WT if these patients had a LOH for chromosome 1p markers in tumor tissue. • To determine if poorer prognosis was seen for patients with FH WT if they had an increased DNA content in tumor cells. • To limit the initial therapy with an aim to decrease the acute and long-term morbidity of treatment of pts. while employing a consistent retrieval therapy for patients who relapse after the limited initial treatment. • To improve the survival and outcomes of patients with UH tumors including those with clear cell sarcoma of kidney and diffuse anaplasia by utilizing a new treatment regimen which used ETOP and CTX. • To study patients with bilateral WT and determine their biology and pathology. • To establish a bank for biological samples containing paraffin blocks, touch preparations, the actual frozen tumor, normal kidney tissue, serum and urine samples that will be available for other scientists to evaluate additional potential biological prognostic variables or for conducting other research. • To provide data regarding LOH for chromosomes 11p14, 16q, and 1p, age at diagnosis, precursor lesions including perilobar and intralobar nephroblastomatosis, bilaterality, and presence of various congenital anomalies.	• Among FH, LOH-1p or LOH-16q has poor prognosis. • Among UFH, LOH-1p has poor prognosis in stage I and II but not for stages III and IV. • LOH-1p plus LOH-16q has the worst prognosis. • Surgery alone is enough for stage I FH tumors of <550 g in children below 2 yrs of age. • Lung secondaries detected by only CT but not by chest X-ray benefit by adding DOX to VCR and AMD. They do not require RT. • High telomerase expression in FH has poor prognosis. • Pathobiology of bilateral WT was documented. • Biological sample bank was established. • ETOP and CTX improves OS and EFS of UH. • Increased DNA content of FH has poor prognosis.

[a]In the first two NWTS the concept of study grouping was used instead of staging

WT Wilms' tumor, *pts* patients, *AMD* Actinomycin-D, *VCR* Vincristine, *ADR* Adriamycin, *CTX* Cyclophosphamide, *ETOP* Etoposide, *XRT* Radiotherapy, *FH* Favorable histology, *UH* Unfavorable histology, *LOH* Loss of heterozygosity, *mon* months, *yr* years, *LN* Lymph nodes, *OS* Overall survival, *EFS* Event-free survival

19.3.1 Role of Neoadjuvant ChT in COG

When one opts for NWTSG/COG protocol, the usual pathway is to diagnose the patient with WT based on imaging, look for resectability, do upfront radical nephrectomy (RN), histological classification, followed by postoperative/adjuvant ChT. However, there are exceptions for this, and there are certain indications where neoadjuvant ChT is recommended before a RN, which include [14]:

1. Bilateral WT.
2. WT in a solitary kidney.
3. Unilateral WT with predisposition syndromes and a possibility of developing metachronous tumor.
4. Extensive pulmonary metastases causing respiratory compromise.
5. Inoperable tumor (deemed as such by the treating surgeon, tumor adherent to inferior vena cava (IVC) on imaging, large tumor which cannot be excised without the risk of rupture).
6. Presence of a tumor thrombus within the (IVC), which was extending beyond the hepatic veins.
7. Tumor that involved the contiguous structures such that the removal of tumor mandates a removal of the organ (e.g., spleen, liver, colon).

In the COG study AREN0532, Fernandez et al. evaluated 23% of the patients who had neoadjuvant ChT and delayed nephrectomy [16]. They identified a subset of patients without LOH 1p or 16q, without LN involvement at diagnosis and with completely necrotic tumors at delayed nephrectomy, in whom Doxorubicin (DOX) and XRT could be omitted without impacting the survival [16].

19.3.2 Treatment Overview of Unilateral WT

Tumor stage and histology are the principal factors that decide the prognosis and further treatment. Historically, right till NWTS-5, these two main factors decided the treatment. The treatment overview of NWTS-5 is detailed in Table 19.2; this may still be useful in the management of WT in low- and middle-income countries (LMIC).

Table 19.2 Treatment overview of NWTS-5 [17]

Stage	Histology	ChT regimen	XRT
I	Favorable	AV × 18 weeks (EE-4A regimen)	None
	Focal anaplasia	AV × 18 weeks (EE-4A regimen)	None
	Diffuse anaplasia	AV × 18 weeks (EE-4A regimen)	None
II	Favorable	AV × 18 weeks (EE-4A regimen)	None
	Focal anaplasia	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank or abd. And to any metastatic sites
	Diffuse anaplasia	VDCE × 24 weeks (regimen I)	10.8 Gy flank or abd. And to any metastatic sites
III	Favorable	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank or abd.
	Focal anaplasia	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank or abd. And to any metastatic sites
	Diffuse anaplasia	VDCE × 24 weeks (regimen I)	10.8 Gy flank or abd. And to any metastatic sites
IV	Favorable	AVD × 24 weeks (DD-4A regimen)	10.8 Gy flank or abd. If local stage III and to any metastatic sites
	Focal anaplasia	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank or abd. And to any metastatic sites
	Diffuse anaplasia	VDCE × 24 weeks (regimen I)	10.8 Gy flank or abd. And to any metastatic sites

A Actinomycin-D, *V* Vincristine, *D* Doxorubicin, *C* Cyclophosphamide, *E* Etoposide

19.3.3 Current COG Protocols

Over a period, it has been recognized that histology and tumor stage alone cannot identify the patients at risk for recurrence. COG identified several other major prognostic variables including clinico-histopathological factors (age at diagnosis, tumor weight, histology, tumor staging, histologic response to therapy) and genetic factors (loss of heterozygosity at 1p and 16q) that are now used to assign risk-stratified management. Since 2006, four clinical trials have been commenced within COG for the treatment of Wilms' tumor under the newly established "AREN03B2: Renal tumor classification, Biology, and Banking study" protocol, which aims to facilitate timely and accurate risk assessment. This protocol assigns the patients to one of the four new protocols (AREN0321, AREN0532, AREN0533, AREN0534), which cover the entire spectrum of WT based on the histology and the risk staratification [18].

If we have to summarize the current regimens in a tabulated form (Table 19.3), the subtle changes in the present risk-stratified management could be readily appreciated.

The different protocols are diagrammatically depicted in Fig. 19.1.

19.3.3.1 AREN0532

The AREN0532 study/trial enrolled patients with WT with Very Low Risk and Standard Risk as

Table 19.3 Treatment overview in new COG trials (AREN0321, AREN0432, and AREN0533)

Stage	Histology	Other clinical or biological factor	LOH 1p & 16q	ChT regimen	XRT
I	FH	Age < 2 years and tumor <550 g	Any	None	None
		Age < 2 years and tumor ≥550 g	No	VA × 18 weeks (EE-4A regimen)	
		Age < 2 years and tumor ≥550 g	Yes	VAD × 24 weeks (DD-4A regimen)[a]	
	FA	Any	Any	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank
	DA	Any	Any	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank
II	FH	Any	No	AV × 18 weeks (EE-4A regimen)	None
			Yes	VAD × 24 weeks (DD-4A regimen)	
	FA	Any	Any	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank
	DA	Any	Any	VDCBE × 29 weeks[b]	10.8 Gy flank
III	FH	Any	No	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank/ abd.; 10.8 boost for gross disease
			Yes	VDACE × 30 weeks (regimen M)[c]	
	FA	Any	Any	VAD × 24 weeks (DD-4A regimen)	10.8 Gy flank/ abd.; 10.8 boost for gross disease
	DA	Any	Any	VDCBE × 29 weeks	20 Gy flank/ abd.; 10.8 boost for gross disease

Table 19.3 (continued)

Stage	Histology	Other clinical or biological factor	LOH 1p & 16q	ChT regimen	XRT
IV	FH	Week 6 lung nodule CR	No	VAD × 24 weeks (DD-4A regimen)	No lung XRT
		Week 6 lung nodule CR	Yes	VDACE × 30 weeks (regimen M)[c]	12 Gy lung[d]
		Week 6 lung nodule no CR	Any	VDACE × 30 weeks (regimen M)[c]	12 Gy lung[d]
	FA	Any	Any	VDCBE × 29 weeks	12 Gy lung[d]
	DA	Any	Any	VDCBEI × 35 weeks	12 Gy lung[d]

[a] Cumulative Doxorubicin dose 150 mg/m^2
[b] Cumulative Doxorubicin dose 225 mg/m^2
[c] Cumulative Doxorubicin dose 195 mg/m^2
[d] Metastases other than lung were also radiated; XRT does varied according to metastatic site
FH Favorable histology, *FA* Focal anaplasia, *DA* Diffuse anaplasia, *AV* Actinomycin D/Vincristine, *VAD* Vincristine/Actinomycin D/Doxorubicin, *VDACE* Vincristine/Doxorubicin/Actinomycin D/Cyclophosphamide/Etoposide, *VDCBE* Vincristine/Doxorubicin/Carboplatin/Cyclophosphamide/Etoposide, *VDCBEI* Vincristine/Doxorubicin/Carboplatin/Cyclophosphamide/Etoposide/Irinotecan

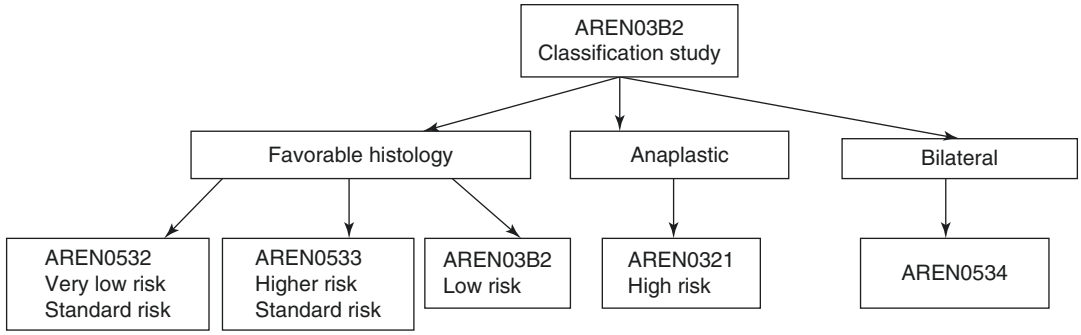


Fig. 19.1 Current COG protocols for patients with WT [18]

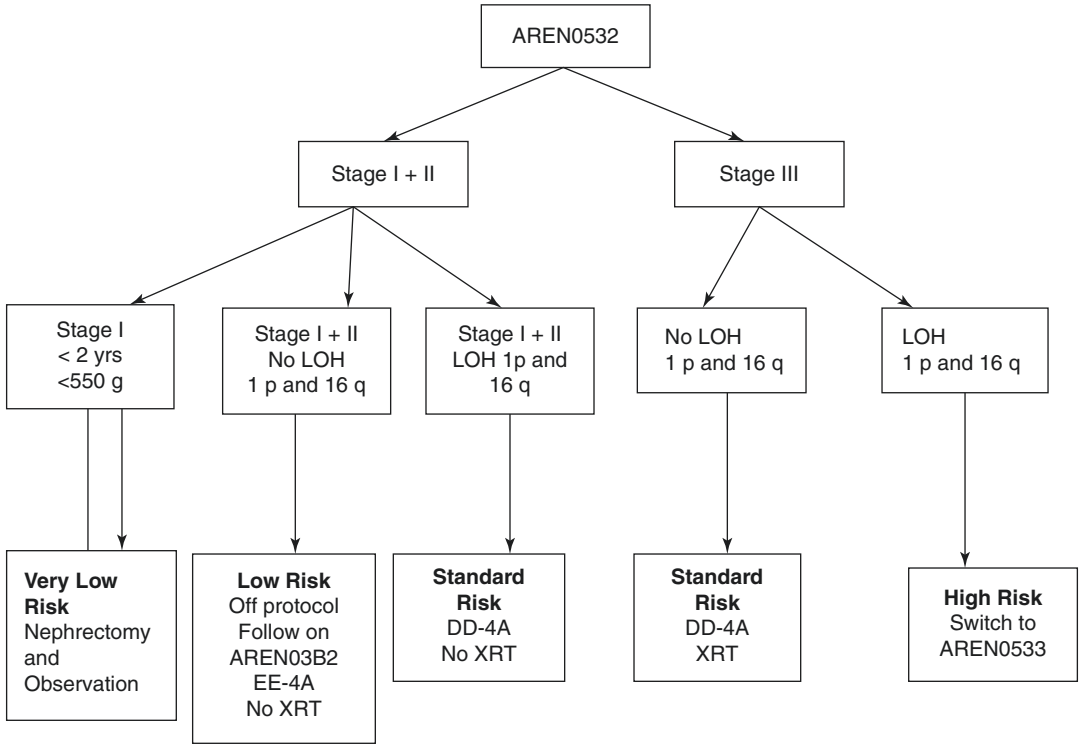
assessed by a Central Review of Pathology, diagnostic imaging, and surgical reports (Fig. 19.2) [18]. The patients with favorable histology (FH) and locoregional (non-metastatic disease) are eligible for this study.

There are two arms in this AREN0532 study:

1. *Very Low Risk group*:

   The patients under 2 years of age, upfront operated with adequate lymph node (LN) sampling, local stage I, with tumor weighing <550 g are included in this arm. One must note that adequate LN sampling is a must for entry into this trial. These patients were treated only with surgery in NWTS-5 study. They targeted a 2-year event-free survival (EFS) at 90%, but it fell short at 86.4%, and the study was stopped according to the predefined criteria. However, the analysis of data revealed that this group had a 5-year OS at 98% that was comparable to 99% OS achieved in those who were treated with adjuvant ChT. Even with recurrence, most of these patients could be salvaged. Hence, this study was revived as part of AREN0532 trial by COG. Currently, the Very Low Risk (VLR) group patients are treated only with surgery.

   A small sub-set of these VLR group patients with WT-1 mutation and Loss of Heterozygosity (LOH) at 11p15 were found to be at an increased risk of recurrence [19]. These patients may benefit from the addition of an adjuvant ChT. These criteria may be used as points of entry into future trials.



LOH loss of heterozygosity; *XRT* radiotherapy

Fig. 19.2 Treatment schema of AREN0532 [18]

Fig. 19.3 Treatment schema of regimen EE-4A

Week	0	1	2	3	4	5	6	7	8	9	10	12	15	18
AMD[a] 45 μg/kg	↓			↓			↓			↓		↓	↓	↓
VCR[b] 1.5mg/m^2 [cd]		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓ d	↓ d	↓ d

[a]Maximum single dose 2.3mg
[b]Maximum single dose 2mg
[c]for all patients weighing >30kg
[d]2mg/m^2 for weeks 12,15,18
AMD Actinomycin D, *VCR* Vincristine

2. *Standard Risk group:*

The patients who qualify as Standard Risk group are:

(a) Stage I and II patients associated with a LOH at 1p and 16q.
(b) Stage III patients lacking a LOH at 1p, 16q.

Stage I (who do not qualify for Very Low Risk group) and Stage II patients with FH lacking a LOH at 1p and 16q are considered Low Risk group and treated with EE-4A regimen, which is same as 18-week 2-drug ChT used in NWTS-5 (Fig. 19.3).

Standard Risk group stage I and II patients are treated with 3-drug regimen including Doxorubicin (DOX) DD-4A regimen postoperatively (Fig. 19.4). For stage III patients, in addition to DD-4A regimen ChT, XRT is also given.

Week	0	1	2	3	4	5	6	7	8	9	10	12	15	18	21	24
AMD[a] 45μg/kg	↓						↓					↓		↓		↓
VCR[b] 1.5mg/m^2 [cd]		↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]
DOX 45mg/m^2				↓						↓			↓[e]		↓[e]	

[a]Maximum single dose 2.3mg
[b]Maximum single dose 2mg
[c]for all patients weighing >30kg
[d]2mg/m^2 for weeks 12, 15,18, 21, 24
[e]30mg/m^2 for week 15 and 21.
The dose of AMD at week 7 and DOX at week 4 should be decreased to 50% if whole lung irradiation (WLI) or whole abdomen irradiation (WAI) has been given
AMD Actinomycin D, *VCR* Vincristine, *DOX* Doxorubicin

Fig. 19.4 Treatment schema of Regimen DD-4A

19.3.3.2 AREN0533

Higher-risk patients with FH WT (either stage III disease with LOH at 1p and 16q or a stage IV disease irrespective of LOH status at 1p and 16q) are eligible for this protocol; the treatment schema is depicted in Fig. 19.5.

The NWTS-5 used regimen DD-4A and XRT treatment of FH WT stage IV associated with lung metastases. However, The AREN0533 study applies an alternate risk stratification and a new treatment strategy to improve EFS, at the same time reducing exposure of lung to XRT [18].

All the stage IV patients lacking LOH at 1p and 16q with pulmonary metastatic lesions only would be reevaluated radiologically after week 6. Those patients where all the pulmonary metastases have already disappeared would be called *rapid complete responders (RCR)* and these will further continue with regimen DD-4A only (Fig. 19.4); no pulmonary XRT is administered (Fig. 19.6).

The patients with stage III or stage IV disease with LOH at 1p and 16q LOH would receive 11 cycles of adjuvant ChT, using VCR, AMD, and DOX, along with the addition of Cyclophosphamide (CTX) and Etoposide (ETOP), known as Regimen M; stage III patients would receive abdominal XRT and stage IV patients will receive whole lung irradiation (WLI).

Then there would be the stage IV patients lacking LOH at 1p and 16q with pulmonary metastatic lesions only that would not have disappeared at 6-week radiological evaluation; these are called *slow incomplete responders (SIR)* and these patients would also be the candidates of 30-week 5-drug *regimen M*; they would also receive WLI.

Lastly, there would be a small cohort of stage IV patients with extra-pulmonary metastases with or without associated pulmonary metastases; these patients would receive regimen M and XRT to abdominal metastases and WLI in case of SIR, or irrespective of the pulmonary response if LOH at 1 p and 16q is present.

Overall, the treatment strategies used under AREN0533 yielded EFS and OS rates that were superior to previous studies.

19.3.3.3 AREN05321

All the patients enrolled in this trial have anaplastic histology [18].

In the NWTS-5, 29 patients with stage I focal or diffuse anaplastic WT (AWT) were treated with VCR and AMD without flank XRT, and they had a 4-year EFS and OS estimates of 69.5% and 82.6%, respectively. Whether the addition of DOX and flank XRT to these patients could improve the survival was evaluated in the COG AREN0321. It was found that the treatment of stage I AWT with VCR, AMD, DOX (DD-4A

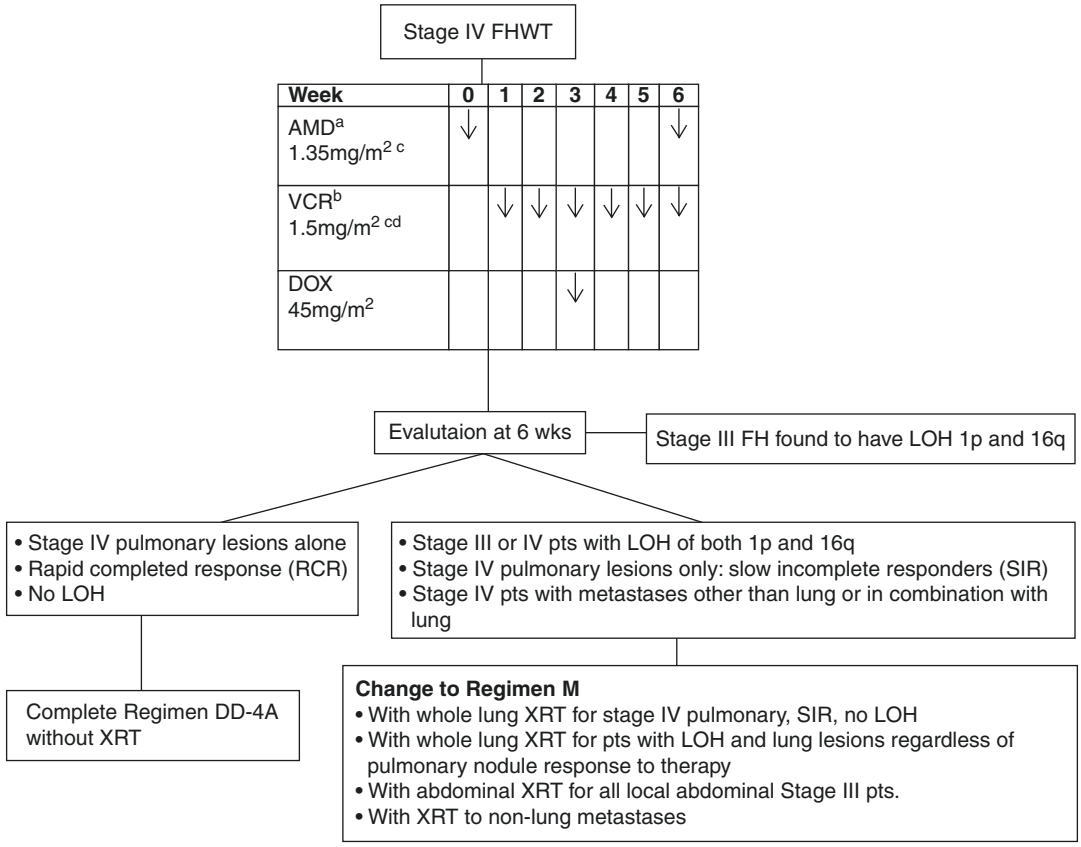


Fig. 19.5 Treatment schema of AREN0533 [18]

regimen), and flank XRT in AREN0321 yielded improved and outstanding survival outcomes [20]. *Stage I with diffuse anaplasia and stage I–III with focal anaplasia are now treated with DD-4A regimen and flank XRT*.

A retrospective analysis of AREN0321 and NWTS patients suggested that the addition of DOX had a greater contribution to the improved outcomes than XRT. Also, NWTS-5 reported 55% 4-year EFS for stage II–IV diffuse anaplasia using *regimen I* (VCR, DOX, CYCLO, ETOP) and XRT (Fig. 19.7).

AREN0321 instead employed UH-1 regimen that has additional Carboplatin (CARB). Stage II–III with diffuse anaplasia, stage IV with focal anaplasia, and stage IV with diffuse anaplasia *without* any measurable disease are treated under regimen UH-1 that is 29 weeks of ChT with CTX-CARB-ETOP and VCR-DOX-CTX) and XRT (Fig. 19.8). XRT is usually administered in week 12. Compared to NWTS-5, UH-1 appears to have better EFS but with higher toxicity [21].

Stage IV diffuse anaplasia *with* measurable disease are treated with a window therapy using VCR-Irinotecan (VCR-I) to evaluate tumor response. This is followed by evaluation to add these on UH-1 regimen. VCR-I used in patients with metastatic diffuse AWT produced a high response rate. AREN0321 treatment also appeared to improve outcomes for patients with stage II to IV diffuse AWT when compared with NWTS-5, but with an increased toxicity. The UH-2 regimen (UH-1+ VCR-I) definitely warrants further investigation with modifications designed to reduce toxicity [22].

Fig. 19.6 Treatment schema of regimen M

Week	1	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	27	30
AMD[a] 1.35mg/m^2 [c]	↓												↓[d]	↓[d]		↓[d]		↓[d]	↓[d]
VCR[b] 1.5mg/m^2 [cd]		↓	↓	↓	↓	↓		↓	↓		↓	↓	↓[e]	↓[e]		↓[e]		↓[e]	↓[e]
DOX 45mg/m^2				↓									↓[f]	↓[f]		↓[f]		↓[f]	↓[f]
CTX 440mg/m^2 **X 5 days**							↓			↓					↓		↓		
ETOP 100mg/m^2 **X 5 days**							↓			↓					↓		↓		
XRT								↓											

[a]Maximum single dose 2.3mg
[b]Maximum single dose 2mg
[c]for all patients weighing >30kg
[d]23μg/kg or 67μg/m^2 for weeks 12, 15, 21, 27, 30
[e]2mg/m^2 for weeks 12, 15, 21, 27, 30
[f]1mg/kg or 30mg/m^2 for weeks 12, 15, 21, 27, 30
AMD Actinomycin D, *VCR* Vincristine, *DOX* Doxorubicin, *CTX* Cyclophosphamide, *ETOP* Etoposide

Fig. 19.7 Treatment schema of regimen I used in NWTS-5 for diffuse anaplasia WT stage II–IV

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	18	21	24
VCR[a] 1.5mg/m^2 [bd]		↓	↓		↓	↓	↓	↓	↓		↓	↓	↓[c]	↓[c]		↓[c]		↓[c]
DOX[d] 45mg/m^2	↓						↓						↓			↓		↓
CTX 14.7mg/kg or 440mg/m^2 **X 5 days**				↓			↓			↓			↓		↓	↓	↓	↓
ETOP 100mg/m^2 **X 5 days**				↓						↓					↓		↓	
XRT							↓											

[a]Maximum single dose 2mg
[b]for all patients weighing >30kg
[c]2mg/m^2 for weeks 12, 13, 18, 24
[d]Maximum cumulative dose 250mg/m^2
DOX Doxorubicin, *VCR* Vincristine, *CTX* Cyclophosphamide, *ETOP* Etoposide, *XRT* Radiotherapy

Week	0	1	2	3	6	9	10	11	12[c]	13	14	15	17	18	21	22	23	24	27	28	29
VCR[a] 1.5mg/m^2	↓	↓	↓			↓	↓	↓	↓	↓	↓				↓	↓	↓		↓	↓	↓
DOX[d] 45mg/m^2	↓					↓			↓[b]						↓[b]				↓[b]		
CTX 440mg/m^2 **X 5 days**	↓			↓[b]	↓	↓[b]			↓			↓[b]	↓	↓[b]	↓			↓[b]			
ETOP 100mg/m^2 **X 5 days**				↓	↓							↓		↓				↓			
CARB[d]				↓	↓									↓				↓			

[a]Maximum single dose 2mg
[b]Omit Doxorubicin on Week 12, 21 & 27 for patients who received 12 weeks of VAD regimen ChT. Omit Doxorubicin on Week 27 for patients who received 6 weeks of VAD regimen chemotherapy.
[c]Imaging at week 12 to look for resectability, followed by surgery (if not operated previously).
[d]Dose titrated against GFR, hold CARBO if GFR <30ml/min/1.73m^2.
DOX Doxorubicin, *VCR* Vincristine, *CTX* Cyclophosphamide, *ETOP* Etoposide, *CARB* Carboplatin

Fig. 19.8 Treatment schema of revised UH-1 regimen

19.3.4 Treatment Overview of Bilateral WT/Solitary Kidney with WT

19.3.4.1 AREN0534

The patients included in this protocol fall into one of the following distinct arms:

1. Bilateral WT/solitary kidney with WT.
2. Unilateral WT or with risk for metachronous tumor in opposite kidney.
3. Diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB)—patient at high risk for developing metachronous tumor.

The common point for all these arms is nephron-sparing surgery (NSS). Each arm has distinct initial treatment and decision points after 6 and/or 12 weeks of treatment.

After 6 weeks of ChT, patients undergo imaging for two purposes:

1. To assess the response to ChT (based on RECIST criteria).
2. To evaluate whether partial nephrectomy is feasible.

The patients are enrolled when diagnosed with WT detected on imaging. It is discouraged to do biopsy or primary nephrectomies. However, occasionally, some patients may be referred to the higher tertiary centers for adjunct therapy after bilateral total/partial nephrectomies; they would be treated as per stage (higher of the two kidneys) and histology (worse of the available histologies).

Biopsy is indicated (recommended to use posterior approach to prevent peritoneal contamination) in case of atypical features like age at

Table 19.4 Initial ChT in AREN0534

Description	Initial ChT regimen
Imaging only, locoregional disease/ metastatic disease	DD-4A
Imaging and biopsy (FH)[a]	DD-4A
Imaging and biopsy (diffuse anaplasia)[a]	Revised UH-1
Total/partial nephrectomies at diagnosis. Treatment based on highest assigned risk for either kidney and systemic metastasis	Based on stage and histology

[a]Biopsy makes the patient stage III, but XRT is administered in presence of positive LNs and anaplastic histology
FH Favorable histology, *XRT* Radiotherapy, *LN* Lymph node

diagnosis >10 years, or atypical imaging features. If a biopsy is obtained, the patients are considered stage III, but XRT is not given unless there's evidence like presence of positive LNs in the excised specimen or abdomen. The mere fact that a biopsy has been done doesn't mandate radiation in these patients.

Initial Therapy

Two cycles of ChT are given over 6 weeks, which differs according to the initial status based on imaging and the fact whether an initial tru-cut biopsy has been performed (Table 19.4).

Therapy at the End of 6 Weeks

After 6 weeks of treatment, reimaging is done, and the treatment response to ChT is judged based on the Response Evaluation Criteria In Solid Tumors (RECIST), developed in 2000, and last updated in 2009 (RECIST 1.1) (Table 19.5) [23].

So, one of the following situations may result after 6 weeks of ChT, and further course will differ accordingly:

1. CR with a complete disappearance of all identified target lesions with no significant LN.
2. Partial response (PR) or greater and bilateral NSS are feasible.
3. PR or greater, but not feasible for surgery.
4. Less than PR.

Table 19.5 RECIST 1.1 criteria

Response	Criteria
Complete response	Complete disappearance of all target lesions (the number of target lesions reduced to only two per organ with a maximum of five target organs in total) Any LN if seen, should demonstrate a reduction in short axis diameter to a size less than 10 mm
Partial response	30% or more reduction in sum of diameters, compared with a baseline sum of diameters of target lesions
Progressive disease	More than 20% increase in sum of diameters (compared to smallest diameters during the course of illness; not necessarily the baseline reference) More than 5 mm absolute increase in diameter (longest) of target lesions Appearance of new lesions
Stable disease	Current size doesn't qualify for neither a partial response nor a progressive disease. Use smallest diameters as reference

Complete Response (CR)

Defined as total disappearance of tumor lesions with no significant lymphadenopathy, i.e., all visualized LNs less than 1 cm diameter. No further surgery is required in these patients.

The same chemotherapy initiated initially would be continued for all, other than those who were diagnosed on imaging alone and had non-metastatic disease initially would be now treated with EE-4A (no more DOX).

PR or Greater and Feasible for Bilateral NSS

After initial therapy, if there is PR or greater, and where surgery is feasible, bilateral NSS is done. Further postoperative treatment depends on histology and staging (higher of the two kidneys) (Table 19.6):

Partial Response or Greater, But Not Feasible for Surgery

These patients would receive the same ChT as before for another 6 weeks and then reevaluation after 12 weeks.

Table 19.6 Postoperative ChT depending on histopathology and staging

Histology (SIOP classification)	Stage[a]	Regimen
Completely necrotic	I–II	EE-4A
Completely necrotic[a]	III–IV	DD-4A + XRT
Intermediate risk	I	EE-4A
Intermediate risk	II	DD-4A
Intermediate risk[a]	III–IV	DD-4A + XRT
Blastemal predominant	I	DD-4A
Blastemal predominant[a]	II	Regimen I
Blastemal predominant[a]	III–IV	Regimen I + XRT
Focal anaplastic WT	I–III	DD-4A + XRT
Focal anaplastic WT	IV	Revised UH-1 + XRT
Diffuse anaplastic WT	I	DD-4A + XRT
Diffuse anaplastic WT	II–IV (after surgery, no measurable disease)	Revised UH-1 + XRT
Nephrogenic rest without WT	Not applicable	EE-4A

[a]Biopsy makes the patient stage III, but the XRT depends on presence or absence of positive LNs
WT Wilms' tumor, *XRT* Radiotherapy, *LN* Lymph node

Less than Partial Response

All patients who had less than PR in *either* kidney shall undergo open biopsy of bilateral tumors after 6 weeks of ChT. The goal is to identify the histology of both the tumors and decide whether additional ChT need to be given, or if any alternate ChT regimen is required. Post-ChT risk stratification is based on histology:

1. Intermediate risk tumors (tumors which are not completely necrotic/ anaplastic/blastemal predominant).
2. Blastemal predominant.
3. Anaplastic (focal/diffuse).

Further treatment will depend upon the histology of this biopsy. *Irrespective of the stage of the tumors*, all patients with anaplasia will be treated with revised UH-1 regimen, the ones with blastemal predominant would get Regimen I, and the ones with other intermediate-risk histology would have DD-4A regimen for next 6 weeks and then would be reevaluated (imaging to assess the tumor response at 12 weeks).

Therapy at the End of 12 Weeks

As mentioned before, the two sub-cohorts where surgery has *not* been performed at 6 weeks would have reevaluation at 12 weeks. If CR is achieved, then the chemotherapy started at 6 weeks shall be continued. If CR is not achieved even at 12 weeks, definitive surgery (total/partial nephrectomy) would be done. Further treatment is based on the stage (higher of the two kidneys) and histology (worse of the available histologies), and the regimens used are the same as those used for patients having undergone NSS after 6 weeks of ChT (Table 19.6).

19.3.5 Treatment Overview of Patients with High Risk of Developing Metachronous Tumors

The patients with syndromic association (Beckwith–Wiedemann syndrome, Denys–Drash syndrome, WAGR syndrome, etc.), multicentric tumors, and nephrogenic rests within contralateral kidney (children under 1-year age) are enrolled for this treatment protocol. The diagnosis is made by imaging in these patients; biopsy is not recommended. However, those who undergo biopsy are also treated in this protocol.

Initial treatment for 6 weeks is followed by reimaging to look for response. If partial response or greater is present, and surgery is feasible, a partial nephrectomy is done. If partial response or greater is present and surgery is not feasible, further ChT is given. If less than partial response is present, nephrectomy is done.

19.3.5.1 Initial Therapy

Patients will receive two cycles of ChT over 6 weeks. Treatment regimen is based on the findings as below (Table 19.7):

Table 19.7 Initial therapy for patients with unilateral WT, and predisposition to develop metachronous tumor

	Initial imaging	Initial therapy
Imaging only (no biopsy done)	Localized disease by imaging	EE-4A
Imaging only (no biopsy done)	Evidence of distant metastatic disease by imaging	DD-A4
Imaging and biopsy (FH)	All patients[a]	DD-A4
Imaging and biopsy (anaplasia)	All patients[a]	Revised UH-1

[a]Biopsy makes the patient stage III, but XRT depends on presence of positive LN and anaplastic histology
FH Favorable histology, *XRT* Radiotherapy

19.3.5.2 Therapy at the End of 6 Weeks

After 6 weeks of initial therapy, reimaging is done to look for response to the ChT.

For the patients who shall achieve CR, no surgery is done. They would continue to receive the same ChT as before.

Those with partial or greater response and where NSS is feasible would undergo NSS and those with less than a partial response would have total nephrectomy. Further postoperative treatment depends on histology of excised tumor and stage as described *for bilateral tumors* (Table 19.6), the only difference being that the patients with intermediate risk stage II would receive EE-4A instead of DD-4A.

Those with partial or greater response where NSS is not feasible, another 6 weeks of same ChT would be administered and revaluation would be done at 12 weeks.

19.3.5.3 Therapy at the End of 12 Weeks

If CR is achieved at 12 weeks, then further therapy would be the same as described in Table 19.7 above. If CR does not occur by 12 weeks, definitive surgery (total/partial nephrectomy) needs to be done. Further postoperative treatment depends on histology of excised tumor and stage as described *for bilateral tumors* (Table 19.6), the only difference being that the patients with intermediate risk stage II would receive EE-4A instead of DD-4A.

19.3.6 Treatment Overview of Diffuse Hyperplastic Perilobar Nephroblastomatosis (DHPLNB)

Under this trial, patients with DHPLNB are diagnosed, based on imaging alone. On imaging (preferably MRI), DHPLN appears as thick rind, with no pseudocapsule separating it from adjacent normal parenchyma. Pathological differentiation between DHPLNB and WT is difficult. Hence, biopsy is of no value in these cases.

As with the other two arms of this protocol (BWT and unilateral WT with predisposition for metachronous tumor), patients with DHPLNB receive EE-4A regimen as initial ChT followed by assessment at 6 weeks of therapy. Treatment response is defined as per RECIST criteria. If the disease is stable or responsive, then EE-4A regimen is continued for 18 weeks.

But in case the disease is progressive, or new masses have developed, then there could be two possibilities. If NSS is possible, proceed with surgery. Further treatment is based on the histopathology of the resected lesion; if histopathology reported as DHPLNB, continue EE-4A regimen ChT for 18 weeks, and if histopathology reported as WT, treat based on stage/histology. If NSS is not possible, proceed with biopsy. Further treatment is again based on the histology; if histology shows WT with viable elements, then treat as bilateral WT (AREN0534 protocol), and if histology is AWT, then proceed with total nephrectomy, followed by ChT Regimen UH-1 and XRT.

19.4 Société Internationale D'Oncologie Pédiatrique (SIOP)

SIOP is a study group based in Europe which was established in 1971 and is also known as the International Society of Pediatric Oncology. The philosophy of SIOP distinctly differs from that of NWTS/COG, in that the SIOP propagates up front (pre-nephrectomy) ChT, followed by surgery, to reduce the need for postoperative radiation ther-

apy. The exception to this is the WT in infants (<6 months old), in whom upfront surgery is recommended by SIOP. So far, SIOP has conducted seven trials between 1971 and 2001 (Table 19.8). The last trial SIOP-2001 was succeeded by a protocol designed by the Renal Tumour Study Group (RTSG)-SIOP, called UMBRELLA SIOP-RTSG in 2016 [10].

Treatment guidelines for WT in UMBRELLA protocol address the localized, metastatic, and bilateral Wilms' tumor in all age groups, as well as for cases who have a relapse.

Since the time of inception, with its focused trials, SIOP has been able to reduce the intensity of ChT and XRT. Meanwhile the rates of survival have increased up to 90% in WT patients managed by SIOP protocols. About two-thirds of the patients with WT receive ChT regimen based on just VCR and AMD, while the rest of them which includes metastatic tumor, and high-risk histology subtypes, are benefited by addition of DOX.

The proponents of SIOP/RTSG are of the opinion that neoadjuvant ChT (preoperative ChT) reduces the tumor size which makes the surgery easier. It slims the chances of intraoperative tumor rupture, thus, decreasing the risk of local and distant recurrence. Since the tumor size is reduced, there is a possibility for NSS as well. With neoadjuvant ChT, the need for anthracyclines in adjuvant ChT is reduced, and XRT is

Table 19.8 Details of SIOP Trials (1971–2001)

SIOP trial	*N*	Results
SIOP-1 (1971–1974)	338	• Pre-op XRT reduces intra-op tumor rupture/spillage. • Post-op AMD of 1 vs 6 cycles have comparable EFS/OS.
SIOP-2 (1974–1976)	138	• Non-RCT reconfirm the findings of SIOP 1. • VCR + AMT for 9 vs 15 m has equal DFS/OS. • Pre-op XRT is beneficial even in small size tumors.
SIOP-5 (1977–1979)	397	• Tumor rupture rate is equal in 4 weeks of pre-op VCR+ AMD vs pre-op XRT+ 1 cycle of AMD. • For pre-op preparation ChT is preferable over XRT due to fewer side effects.
SIOP-6 (1980–1987)	1095	• Post-op VCR + AMD for 17 weeks vs. 38 weeks are comparable in stage I. • No difference in EFS /OS in XRT vs no XRT for stage II; but no XRT group had more relapse.
SIOP-9 (1987–1991)	852	• Pre-op ChT for 4 weeks vs 8 weeks are comparable for stages I to III. • In node negative stage II, epirubicin without XRT reduces tumor relapse.
SIOP 93–01 (1993–2001)	2162	• Post-op ChT for intermediate risk and anaplastic tumors can be reduced to 4 doses of VCR+ 1 dose of AMD without compromising the outcome.
SIOP WT 2001 (2001–2015)	5728	• DOX not required in stage 2 and 3 intermediate risk.
Umbrella protocol[a] (2019 onwards)		

[a]UK IMPORT study which enrolled 692 patients between Oct 2012 and Feb 2020 is now merged with Umbrella Protocol trial

Pre-op preoperative, *Intra-op* intraoperative, *Post-op* postoperative, *EFS* event-free survival, *OS* overall survival, *AMD* actinomycin-D, *VCR* vincristine, *XRT* radiotherapy, *ChT* chemotherapy, *DOX* doxorubicin, *int.* intensive dosage

restricted to only a small subset of patients [18]. But opponents of SIOP are of the opinion that neoadjuvant ChT alters the histology of the tumor. This has been countered by proponents of SIOP/RTSG with description of new risk stratified groups based on post-neoadjuvant ChT histological features and the associated chemotherapy-induced changes.

Staging in SIOP protocol is based on post-ChT surgico-pathological features that are described in another chapter.

19.4.1 Therapy for Unilateral WT in SIOP

19.4.1.1 Preoperative ChT

The diagnosis of WT is made on the clinical presentation along with the imaging features. Biopsy of the tumor to confirm the diagnosis is not advised. The preoperative ChT has been standardized, and the recommendations of UMBRELLA protocol are same as that of SIOP-2001. The patients who are eligible for this regimen are age > 6 months to 18 years, no history of previous anti-tumor treatment, and unilateral WT diagnosed by imaging (or biopsy, though not recommended). Hematogenous metastases in WT majorly happen to lungs, and less frequently to liver, and extra-abdominal LNs. The metastatic lung nodules can be detected on a chest radiograph. Small metastatic lung nodules missed by a chest radiograph and only detected on a CT scan are shown to have poorer prognosis (increased relapse rate and reduced survival) when compared with truly localized tumor of similar stage [10]. Hence, UMBRELLA protocol has included CT (chest) only nodules > 3 mm as metastases and treated accordingly.

Biopsy is done in special circumstances that are detailed in another chapter. Protocol for treatment of bilateral WT is discussed separately.

The WT patients are divided into two groups for preoperative ChT. *Localized disease* patients get 4 weeks of ChT based on two drugs (VCR-AMD), while *metastatic disease* patients get 6 weeks of ChT based on three drugs (VCR-AMD-DOX). The schemata of treatment are given in Fig. 19.9 [24].

Week	1	2	3	4
AMD[a] 45μg/kg	↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓

[a]Maximum single dose 2mg
AMD Actinomycin D, *VCR* Vincristine

Week	1	2	3	4	5	6
AMD[a] 45μg/kg	↓		↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2	↓				↓	

[a]Maximum dose 2mg
AMD Actinomycin D, *VCR* Vincristine, *DOX* doxorubicin

Fig. 19.9 SIOP neoadjunctive ChT for localized and metastatic disease

19.4.1.2 Postoperative ChT Regimen for Localized WT in SIOP [10]

The postoperative ChT regimen is dependent on the stage and histology of the mass/tumor which was excised. Risk groups are identified, and treatment stratification is done accordingly. UMBRELLA protocol has adopted the experimental arm in SIOP-2001 which tested 27 weeks of VCR-AMD in stage II–III intermediate risk patients with 27 weeks of VAD (VCR-AMD-DOX) (5 doses at 50mg/m^2)—the *standard management*. It found that the EFS in experimental group was not significantly less than the standard treatment group, while having no effect on OS [10]. It was found that the use of XRT or DOX could be reduced by 20% in patients who were receiving ChT prior to surgery as compared to the patients treated with upfront nephrectomy with no difference in survival [25]. The SIOP-RTSG takes into account the risk of misdiagnosis of WT by recommending direct surgery instead of preoperative ChT for young children less than

Table 19.9 Umbrella (SIOP-RTG) protocol for postoperative treatment of localized tumor

Disease	Tumor vol after pre-op ChT	Treatment		
		Stage I	Stage II	Stage III
Low risk (only CN)	All	None	AV2 (27 wk)	AV2 (27 wk)
Intermediate risk, all subtypes	<500 ml	AV1 (4 wk)	AV2 (27 wk)	AV2 (27 wk) + flank XRT
Intermediate risk, stromal or epithelial type	≥500 ml	AV1 (4 wk	AV2 (27 wk)	AV2 (27 wk) + flank XRT
Intermediate risk, non-stromal, non-epithelial	≥500 ml	AV1 (4 wk)	AVD[a] (27 wk)	AVD[a] (27 wk) + flank XRT
High-risk blastemal type	All	AVD[a] (27 wk)	HR-1 (34 wk)	HR-1 (34 wk) + flank XRT
High-risk diffuse anaplasia	All	AVD[a] (27 wk)	HR-1 (34 wk) + flank XRT	HR-1 (34 wk) + flank XRT

[a]AVD250 where cumulative dose of Doxorubicin is 250 mg/m^2

A Actinomycin D, *D* Doxorubicin, *V* Vincristine, *wk* Weeks, *CN* Completely necrotic, *XRT* Radiotherapy

6 months of age, and keeping the option of a fine-needle biopsy for patients who have unusual clinical presentations or have unusual findings on imaging. However, to avoid treatment delay, a routine histological assessment before treatment is not advocated. Furthermore, preoperative ChT enables personalized assessment of sensitivity of the tumor to ChT, including identification of the high-risk, blastemal-type WT. Yet, by considering the absolute residual volume of blastema rather than the relative percentage might improve the definition of the blastemal-type histology. This will be further investigated in the UMBRELLA protocol.

SIOP-2001 trial observed the outcomes with omission of DOX for large volume tumor (>500 ml) of stage II–III regressive, mixed, and focal anaplasia type. The EFS was lesser when compared with smaller tumor volume (80% vs. 90%). When DOX was added, the EFS significantly increased from 67 to 93% for large tumor volume cases. Hence, UMBRELLA protocol has added DOX for large volume tumors of stage II–III (non-stromal, non-epithelial tumors). The existing criteria for defining the histological types are tabulated in another chapter. The SIOP-RTSG UMBRELLA protocol for postoperative treatment of localized tumor is detailed in Table 19.9 [10].

AV1

This treatment is given to all patients with local stage I. In German Society for Paediatric Oncology and Haematology (GPOH) in case of focal anaplasia, mixed and regressive type with a tumor volume ≥ 500 ml after preoperative ChT is given according to stage I high risk (AVD) (Fig. 19.10).

Regimen AV2

This treatment is given for all patients with local stage II and III. In GPOH in case of focal anaplasia, mixed and regressive type with a tumor volume ≥ 500 ml after preoperative ChT, DOX is added to AV-2 (treatment with AVD as for high risk stage I) (Fig. 19.11).

AVD Regimen

This treatment is given for all patients with local stage I of high-risk histology. This treatment is also given for patients with stage I, II, and III and focal anaplasia, mixed or regressive type with tumor volume ≥ 500 ml after preoperative ChT.

The total duration of the postoperative ChT in both AV2 and AVD regimens is 27 weeks, the only difference between the two being addition of 5 doses of DOX (cumulative dose of DOX is 250 mg/m^2) (Fig. 19.12).

Regimen HR-1

Total duration of postoperative treatment is 34 weeks. There are two alternating courses of ChT (ETOP-CARB and CTX-DOX) given at 21-day intervals. Both combinations consist of 2 drugs. It differs from UH-1 regimen used in COG that has 5 drugs, the additional drug being VCR.

Week	1	2	3	4
AMD[a] 45μg/kg		↓		
VCR[a] 1.5mg/m^2	↓	↓	↓	↓

[a]Maximum single dose 2mg
AMD Actinomycin D, *VCR* Vincristine

Fig. 19.10 Regimen AV1

The first course starts as soon as the patient has recovered from surgery and clinical condition allows. This should be the case within 21 days after end of preoperative ChT. Use of Cotrimoxazole is recommended for HR regimens as Pneumocystis Carinii Pneumonia (PCP) prophylaxis (Fig. 19.13).

Postoperative ChT for Metastatic Disease (Stage IV) in SIOP [10]

Approximately 17% of patients with WT present with stage IV disease at diagnosis with pulmonary metastases being the most frequently observed site of metastasis. The increasing use of chest tomography as routine imaging for staging has increasingly resulted in the detection of small pulmonary nodules, which are not visible on chest radiographs. CT-only nodules are also included in the definition of lung nodules and are treated as metastases in the UMBRELLA protocol if they have a transverse diameter of 3 mm or more [10]. This Inclusion of CT-only nodules in the definition of metastatic disease will benefit patients with intermediate-risk or low-risk histology who achieve a rapid complete response of their CT-only nodules as these patients do not

Fig. 19.11 Regimen AV2

Week	1	2	3	4	5	6	7	8	11	12	14	15	17	18	20	21	23	24	26	27
AMD[a] 45μg/kg		↓			↓			↓	↓		↓		↓		↓		↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓

[a]Maximum single dose 2mg
AMD Actinomycin D, *VCR* Vincristine

Fig. 19.12 Regimen AVD

Week	1	2	3	4	5	6	7	8	11	12	14	15	17	18	20	21	23	24	26	27
AMD[a] 45μg/kg		↓			↓			↓	↓		↓		↓		↓		↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2		↓						↓			↓				↓				↓	

[a]Maximum single dose 2mg
AMD Actinomycin D, VCR *Vincristine*, *DOX* Doxorubicin

Fig. 19.13 Regimen HR-1

Week	1	4	7	10	13	16	19	22	25	28	31	34
ETOP 150mg/m^2 **X 3 days**		↓		↓		↓		↓		↓		↓
CARB 200mg/m^2 **X 3 days**		↓		↓		↓		↓		↓		↓
CTX 450mg/m^2 **X3 days**	↓		↓		↓		↓		↓		↓	
DOX[d] 50mg/m^2	↓		↓		↓		↓		↓		↓	

DOX Doxorubicin, *CTX* Cyclophosphamide, *CARB* Carboplatin, *ETOP* Etoposide

require pulmonary XRT and have, therefore, a reduced risk of severe long-term sequelae, e.g., cardiac complications, lung disease, or secondary malignancies. As with SIOP-2001, preoperative treatment for metastatic (stage IV) disease in the UMBRELLA protocol also includes a combined VCR, AMD, and DOX regimen for a period of 6 weeks, followed by a reassessment imaging of local tumor (using MRI) and metastatic sites (using CT and/or MRI) before surgery. With 6 weeks of preoperative ChT, the complete response as regards pulmonary nodules is seen in 61–67% stage IV cases.

The cumulative dose of DOX in SIOP-2001 was 300 mg/m^2. UMBRELLA protocol opts to stratify patients to VCR, AMD, DOX (150 mg/m^2), or VCR, AMD, and DOX (250 mg/m^2), or CTX (450 mg/m^2/day), ETOP (150 mg/m^2/day), CARB (20 mg/m^2/day), DOX (cumulative dose 300 mg/m^2) treatments depending on the risk stratification and overall response of metastases to preoperative ChT.

Stage IV patients have been stratified based on the following factors:

1. Tumor stage.
2. Histology of the excised tumor.
3. Histology of the excised metastatic tumor (if done).
4. Size of metastatic lesions.
5. Response of metastatic lesions to preoperative ChT and surgery (if done).

Postoperative ChT for stage IV patients has been described in Table 19.10.

For *Group A patients*, i.e., those with *local stage I/II/III, low- and intermediate-risk (IR) histology* where *metastatic clearance (CR) of lung nodules or very good partial remission (VGPR)* has been obtained by preoperative ChT or completely removed by surgeon would receive AVD150 or AVD250, respectively (Figs. 19.14 and 19.15), depending upon whether the lung nodules were 3–5 mm or >5 mm at diagnosis. These regimens are very similar to the AVD regimen given to patients with non-metastatic disease (Fig. 19.12), the only difference being that in AVD150 regimen, the cumulative dose of DOX (including preoperative ChT) is 150 mg/m^2 and therefore these patients get only one dose of DOX postoperatively. In the AVD250 regimen, the cumulative dose of DOX (including preoperative ChT) is 250 mg/m^2, and therefore these patients get 3 doses of DOX postoperatively, and the DOX is omitted on weeks 20 and 26. If CR is achieved by resection of nodules and viable tumor is found in the biopsy, pulmonary XRT is recommended. The patients with local stage III IR histology receive flank/abdominal XRT; local and lung XRT should be given simultaneously to avoid overlapping fields.

For *Group B patients*, i.e., those with *local stage I/II/III, low-risk (LR) histology with residual nodules/metastasis* after ChT and surgery, it is recommended to resect (one)/multiple representative nodules. Postoperative treatment is recommended according to histology.

Table 19.10 Postoperative ChT for stage IV patients [10]

Metastasis surgery	Histology	Treatment
Complete remission (CR) or very good partial remission (VGPR)[a]		
Surgical complete resection if needed	LR or IR disease. No evidence of metastasis	Treatment as in localized disease
	LR or IR disease and lung nodules 3–5 mm	AVD150; no pulmonary XRT unless complete resection of viable metastasis, then pulmonary XRT
	LR or IR disease and lung nodules >5 mm or other sites	AVD250; no pulmonary XRT unless complete resection of viable metastasis, then pulmonary XRT
Partial response (PR) or stable disease		
Resection of representative nodule(s) feasible	LR or IR disease No evidence of viable tumor	Potentially treatment as localized, *Or* AVD250, CT at week 10: If remaining nodules then surgery recommended to achieve CR if feasible, no XRT to metastases
	LR disease Completely necrotic metastasis	AVD150, CT at week 10: If remaining nodules then surgery recommended to achieve CR if feasible
	LR disease Viable metastasis confirmed	AVD250, lung/metastasis XRT, CT at week 10: If remaining nodules then surgery recommended to achieve CR if feasible
	Intermediate-risk disease Completely necrotic metastasis	AVD250 regimen, CT at week 10: If remaining nodules then surgery recommended to achieve CR if feasible
	Intermediate-risk disease Viable metastasis confirmed	HR2 regimen, XRT to metastasis. CT at week 10: If remaining nodules then surgery recommended to achieve complete response if feasible
Resection not feasible	Low-risk disease	AVD250, CT at week 10: Reconsider resection and discuss XRT to metastasis
	Intermediate-risk disease	HR2 regimen, CT at week 10: If remaining nodules, XRT to metastasis is indicated
Progressive disease		
Representative nodule resection feasible	Intermediate-risk disease Metastasis confirmed	HR2 regimen, XRT to metastasis. CT at week 10: If remaining nodules then surgery is recommended to achieve complete response if feasible
	Intermediate-risk disease No evidence of viable or necrotic tumor	AVD250, CT at week 10: If remaining nodules then surgery: If viable metastasis then CDCE plus XRT to metastases is indicated
All		
	High-risk disease	XRT to metastases, CT at week 10: If remaining nodules consider resection if feasible
Mixed		
Indicated	Confirm metastatic disease by histology	If metastases present, then treat according to worst histology and worst response

AVD150; cumulative dose of Doxorubicin including preoperative treatment is 150 mg/m^2
AVD250; cumulative dose of Doxorubicin including preoperative treatment is 250 mg/m^2
VGPR; very good partial remission (non-progressive or stable disease with and no new lesions and no lesions >2 mm)
AVD Actinomycin-D, vincristine and doxorubicin, *CDCE* Cyclophosphamide, doxorubicin, carboplatin and etoposide, *XRT* Radiotherapy, *LR* Low risk, *IR* Intermediate risk, *CT* Computerised tomography

If no viable tumor but necrotic nodules in a representative number of metastases, proceed with regimen AVD150 postop. Repeat CT assessment in week 10. If nodules are still visible, reconsider complete resection, but no pulmonary XRT is administered.

Fig. 19.14 AVD150 regimen

Week	1	2	3	4	5	6	7	8	11	12	14	15	17	18	20	21	23	24	26	27
AMD[a] 45μg/kg		↓			↓			↓	↓		↓		↓		↓		↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2		↓																		

[a]Maximum single dose 2mg
AMD Actinomycin D, *VCR* Vincristine, *DOX* Doxorubicin

Fig. 19.15 AVD250 regimen

Week	1	2	3	4	5	6	7	8	11	12	14	15	17	18	20	21	23	24	26	27
AMD[a] 45μg/kg		↓			↓			↓	↓		↓		↓		↓		↓		↓	
VCR[a] 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2		↓						↓			↓				↓				↓	

[a]Maximum single dose 2mg
AMD Actinomycin D, *VCR* Vincristine, *DOX* Doxorubicin

Fig. 19.16 4-drug regimen (HR-2 regimen)

Week	1	4	7	10	13	16	19	22	25	28	31	34
ETOP 150mg/m^2 **X 3 days**		↓		↓	↓	↓		↓	↓	↓		↓
CARB 200mg/m^2 **X 3days**		↓		↓	↓	↓		↓	↓	↓		↓
CTX 450mg/m^2 **X 3days**	↓		↓				↓				↓	
DOX[d] 50 mg/m^2	↓		↓				↓				↓	

DOX Doxorubicin, *CTX* Cyclophosphamide, *CARB* Carboplatin, *ETOP* Etoposide

If viable tumor in resected lung nodules, proceed with regimen AVD250 and XRT to the lungs. In that case, it is not a LR tumor and even switching to HR-1 regimen may be considered.

If representative lung nodules cannot be resected, proceed with regimen AVD250 post-op and carry out reassessment CT at week 10. In nodules are still visible, consider lung XRT. Lung XRT may be postponed to week 10 for this purpose.

For *Group C patients*, i.e., those with *local stage I/II/III IR histology with residual nodules/metastasis* after preoperative ChT and surgery, if the number of nodules at diagnosis and at surgery is limited (<10 at diagnosis, <6 at surgery), a complete resection of lung nodules should be contemplated.

If no viable tumor but necrotic nodules in a representative number of nodules is found, proceed with regimen AVD250 postoperatively. Carry out chest CT in week 10. If nodules are still visible: reconsider complete resection or pulmonary XRT.

If viable tumor in resected nodules is found, or if representative lung nodules cannot be resected, proceed with 4 drugs regimen or HR-2 regimen (Fig. 19.16) postoperatively for 34 weeks and reassess at post-op week 10. Pulmonary XRT is indicated even if CR can be achieved at week 10. The patients with local stage III IR histology receive flank/abdominal XRT; local and lung XRT should be given simultaneously to avoid overlapping fields.

For *Group D patients,* i.e., those with *local stage I/II/III with high-risk histology* regardless of metastatic status and patients with progressive disease and IR histology (stromal predominant excluded) and histologically proven metastasis, high dose (HD) ChT and stem cell rescue may be given together with flank and lung XRT (Fig. 19.17). It includes seven cycles of standard chemotherapy with combinations of VCR; VCR/I; CYCLO, CARBO and ETOPO; VCR, CYCLO and DOX; and high-dose melphalan.

Centers that cannot adhere to HD-ChT consolidation may use the dose intensive VCR-I (VI)/ CARB-CTX-ETOP (CCE)/ VCR-DOX-CTX (VDCy) regimen without applying HD-chemotherapy.

Centers that cannot adhere to even the dose intensive VI/CCE/VDCy regimen may use the HR-2 regimen, but it is not going to be that efficacious.

19.4.2 Bilateral WT Management (SIOP) [10]

In the SIOP-2001 study, patients with bilateral disease received preoperative ChT including VCR and AMD until NSS was deemed feasible, with response evaluations performed every 4 weeks. However, several studies have shown that prolonged preoperative chemotherapy is often ineffective (especially as many bilateral tumors are the chemotherapy-insensitive stromal subtype) and could even result in an increased risk of the presence of anaplasia, disease progression, and development of metastases [10].

The SIOP-RTSG UMBRELLA protocol limits preoperative ChT to a maximum of 12 weeks, with time intervals for evaluation fixed to 6 weeks, similar to COG approach [10]. In instances of tumor non-responsiveness or

Week	1	2	4	7	8	9	10+	11	12	13*	16#	17	18	19*	21	22#	23	24	25
DOX 50mg/m^2										↓				↓					
VCR 1.5mg/m^2	↓	↓		↓	↓		↓	↓		↓		↓	↓	↓					
CTX 1.2g/m										↓				↓					
CTX 1g/m^2 **X3 days**			↓								↓					↓			
ETOP 100mg/m^2 **X3 days**			↓								↓					↓			
CARB 200mg/m^2 **X3 days**			↓								↓					↓			
IRI 50mg/m^2 **X5 days**	↓						↓												
Melphalan 200mg/m^2																			↓

SCH, Stem Cell Harvest (week 5-6); in case of unsuccessful harvesting repeat CCE and try second harvesting before XRT of lung or metastatic site(s)
SCT, Stem Cell Transplantation(week 25-26)
XRT: Radiotherapy (week 2-3: flank, week 7-10 metastasis/lung)
OP: metastatic surgery(week 6 after CT evaluation);
CT: CT evaluation of metastasis in case of lung metastasis, with MRI all other sites of metastasis (week 3, 6 & 24)
*: replace VCR/DOX/CTX with CARB/CTX/ETOP (CCE) if no response to preop AVD in week 13 and 19
#: consider 2/3 dose reduction of CCE in case of hematoxic delay in week 16 and 22
+: replace IRI/VCR (VI) with CCE in week 10 in case of PD in week 3 evaluation
DOX Doxorubicin, *VCR* Vincristine, *CTX* Cyclophasphamide, *CARB* Carnoplatin, *ETOP* Etoposide, *IRI* Irinotecan

Fig. 19.17 High-risk and high-dose (HR and HD) regimen

inoperability switching to treatment with ETOP and CARB is recommended, to avoid use of anthracyclines, and biopsy can be considered to determine histology for poorly responding cases.

19.4.3 Management of Patients with Unilateral Tumor and Predisposition Syndromes/ Contralateral Nephroblastomatosis

The treatment strategy of both these cohorts is similar to that of patients with bilateral WT above.

The provision of ChT for these children with WT is a specialized and an exacting job. The complications of ChT and the various dose adjustments in various systemic impairments are considered elsewhere in the book. Provision must also be made for a long-term follow-up of these patients to look for the late complications of the therapies including second malignancies.

The provision for ChT for a recurrence or a relapsed WT is also covered elsewhere in the book.

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Radiotherapy

20

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20.1 Introduction

As in many pediatric tumors, radiotherapy (XRT) forms an important part of the management of Wilms' Tumor (WT), and its evolution is based on the fact that the tissues have a low threshold for XRT induced long-term sequelae. Over the past half a century, there have been considerable improvements in the management of WT in terms of multimodality treatment. XRT at the site of the primary tumor and local lymph nodes (LNs) enables good local control in terms of relapse and recurrence. Multimodality therapy is associated with risk of significant toxicity in long-term survivors of WT. In particular, studies have shown that treatment including XRT is associated with increased risk of renal failure, intestinal occlusion, scoliosis, ovarian failure, high-risk pregnancies, and diabetes. In addition, studies have shown an increased risk of second malignant neoplasm (SMN) most often occurring within the XRT field [1]. Various cooperative trials done over the years have resulted in a significant decrease in the intensity of chemotherapy (ChT) and XRT.

Broadly, there are two approaches studied by National Wilms Tumour Study group (NWTSG)/ Children's Oncology Group (COG) and Société Internationale d' Oncologie Pédiatrique (SIOP). Both employ risk stratified adjuvant treatment based on initial staging, histopathological subtype, and molecular status, while SIOP also takes into consideration the response to preoperative ChT. Children with metastatic WT are treated with XRT to local as well as metastatic sites. Indian Council of Medical Research (ICMR) has come up with consensus guidelines that are similar to COG/SIOP [2]. Recently, SIOP-Renal Tumor Study Group (RTSG) has formulated the SIOP-RTSG UMBRELLA protocol, taking inputs from all the specialists involved in the diagnosis and treatment [3]. This protocol deviates from the traditional indications of XRT in the management of WT and will be discussed in detail.

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20.2 Technical Considerations of Radiotherapy

20.2.1 Pediatric Radiation Oncology

It is essential that XRT where indicated should be administered in a center with experience of pediatric XRT. The staff should be appropriately trained for handling children. The radiation suite must be child friendly, and small points like controlling the ambient temperature goes a long way in gaining confidence of patients and parents both. The support of a pediatric anesthesia team should be in place for easy management of these patients. The parents must be taken into confidence about the short- and long-term complications. There needs to be specific consent and adequate documentation before commencement of therapy.

The support of a pediatric anesthesia team should be in place for easy management of these patients. It is very important that the child does not move during treatment and the patients will be alone for about 10–15 min inside the linear accelerator. In these children, XRT is delivered under sedation and with CCTV monitoring as shown in Fig. 20.1.

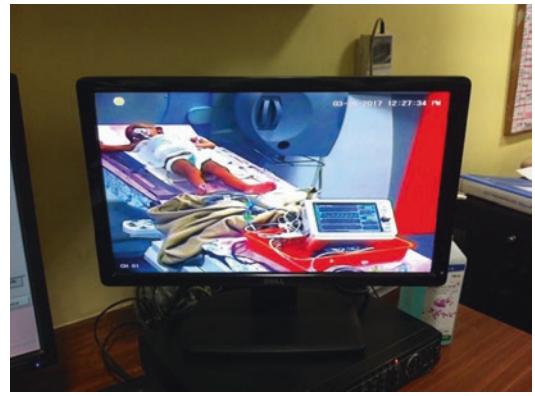

Fig. 20.1 Monitoring of the kid during XRT under sedation

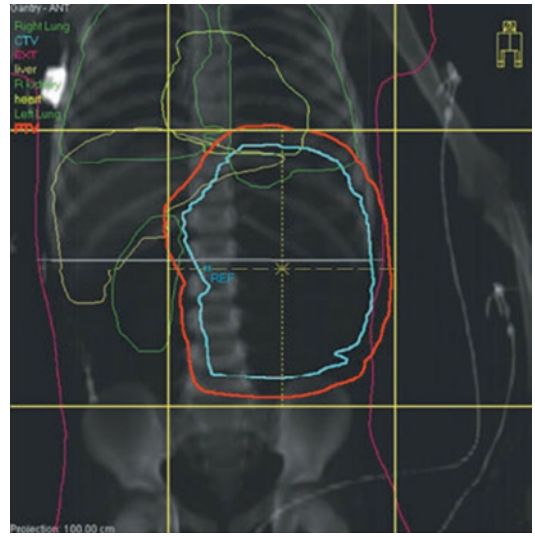

Fig. 20.2 Showing flank irradiation which included the renal bed and the para-aortic nodes

20.2.2 Target Volume Definition

Target volume definition will be performed on a planning CT scan, taking into account the post ChT, pre-surgery magnetic resonance imaging (MRI), or computerised tomography (CT) scans. The surgeon may have placed clips to mark the extent of the tumor or any areas suspicious for residual disease.

The clinical target volume (CTV) is defined as the preoperative extent of disease plus the remaining ipsilateral kidney, as defined on imaging, plus a 1 cm margin. This may be modified by additional information from the operation note, position of clips, and pathology report. The CTV will be extended medially to cover the full width of the vertebral bodies (Fig. 20.2). Any definite residual disease should be volumed as a separate CTV. The remaining kidney and liver should be volumed as organs at risk (OAR). The dose variation within the CTV should not exceed ±5% until ±7–10% of the prescribed dose.

Ideally, XRT should be administered soon after surgery. A delay of XRT beyond 10 days after surgery has shown higher risk of abdominal recurrences, but these studies have a bias of unfavorable histology [4]. The COG protocol recommend starting the XRT for locoregional disease by the 9th postoperative day (POD), if possible and not later than POD 14 [5]. The SIOP Umbrella protocol recommends that abdominal and flank

XRT must commence between 2nd and 4th week after abdominal surgery.

If both abdominal and pulmonary XRT are to be administered in the presence of metastatic disease, they can either be administered simultaneously (Fig. 20.3) or sequentially (Fig. 20.4); both are well tolerated as the dose delivered is very less. In the COG sequential XRT protocol, lungs would be irradiated first, and the abdominal XRT should be delayed and administered after the lung metastatectomy. In cases of high-risk histology (like anaplasia), the abdominal RT should be given as soon as possible, and the lung XRT can be given later.

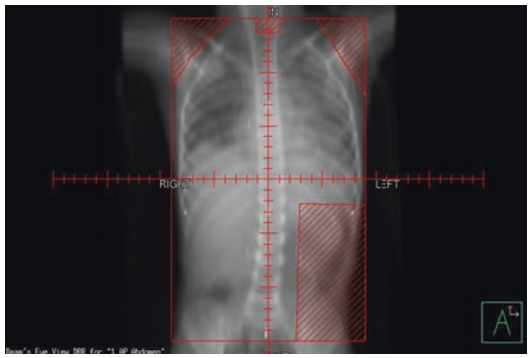

Fig. 20.3 Showing simultaneous thoraco-abdominal irradiation

20.2.3 Equipment and Treatment Techniques

There is continuous evolution of the XRT techniques over the years. Earlier days, XRT used to be delivered with Telecobalt machines using a cobalt source. These machines have been replaced by modern linear accelerator (LA) which is the standard unit used nowadays. It uses an X-ray tube emitting 4–6 MV photons and opposing AP/PA fields. XRT beam, on day-to-day basis, can be verified using on board X-ray or CT scan which is called Image-Guided Radiation therapy (IGRT). Using LA, the XRT beam can be modified to any shape of the tumor using multileaf collimators. This technique is called three-dimensional conformal radiation therapy (3-DCRT).

SIOP-RTSG Umbrella protocol propagates the use of intensity-modulated radiation therapy (IMRT) [3]. This technique offers the greater conformality of high dose volume to target

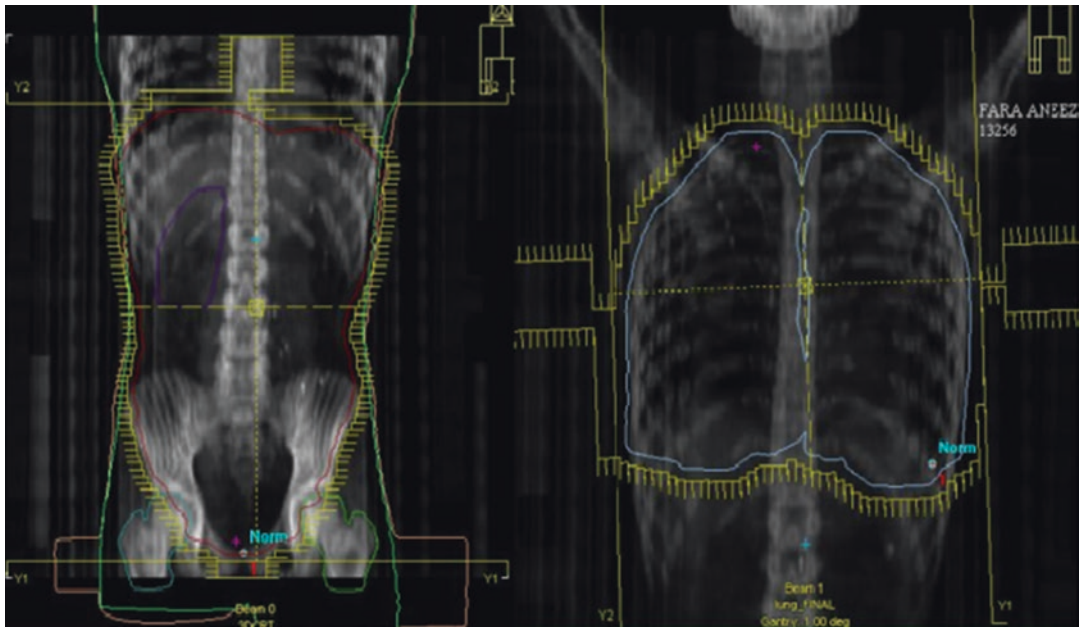

Fig. 20.4 Showing sequential abdominothoracic irradiation

volume thus significantly decreasing the XRT to non-target organs. In view of the low dosage of XRT required in management of WT, the old school of thought wonders if IMRT really matters.

Helical tomotherapy is based on treating the tumor slice-wise, and hence the treatment time is shorter and convenient to the patient.

Intraoperative radiation therapy (IORT) uses 50 kV X-rays to deliver XRT during surgery to a small localized gross disease [6].

The new kid on the block is Proton Beam therapy (PBT). This newer modality has significant advantages in terms improvement in the dosimetric domain as compared to standard beam therapy [7]. It uses pencil beam scanning (PBS) to reduce dose to OAR. PBS plans are more efficient to create than alternative proton modality double-scattered proton therapy (DS-PT) plans [8]. The risk of SMN is also low theoretically; however this needs to be validated by more clinical studies. The major downside of PBT is the escalated costs and unavailability in most parts of the world.

Advanced technologies like IMRT and PBT could be used for recurrent disease, bilateral WT, and WT in horseshoe or ectopic kidney.

20.2.4 Simulation and Shielding

The patient is immobilized using thermoplastic cast in a supine position. This material becomes soft at a temperature of 65 °C and when allowed to cool on the body becomes rigid and takes the shape of the body. The cast is fixed onto the base plate everyday of treatment, and hence the same position is reproduced on all the days of XRT.

CT simulation is done with the cast, and images are imported on to the treatment planning computer system. With the help of preoperative CT scan, the tumor extent is identified in all directions. The same is contoured on every axial CT scan cut as tumor bed and para-aortic LN are also included.

The entire vertebral column is included, and the opposite kidney is completely kept out of XRT portals. Various plans are generated and evaluated, and the best plan which adequately covers the target region and at the same normal structures receive minimal XRT is chosen for execution.

Important organs at risk are the opposite kidney in flank XRT, heart and bilateral humerus in whole lung irradiation (WLI), and opposite kidney, small bowel, ovaries and testis, bilateral head of femur, and acetabulum during whole abdominal irradiation (WAI). The dose in organs at risk is calculated and reported for each organ separately. Critical organ dosage should not exceed 10–12 Gy to the remaining kidney and 20 Gy to the liver. The WLI dosage should not be more than 15 Gy in 15 fractions (high-risk patients) with correction for homogeneity. For WLI, the shoulder joints should be shielded and the hips for WAI.

20.2.5 Radiation Dose and Fractionation

The dose of XRT depends on the protocol that is used for the treatment as there are subtle differences in the risk stratification. The COG categorizes each stage as low, intermediate, and high risk based on the pathological subtype, whereas the SIOP protocol takes into account the response to ChT and the relative proportion of the histopathological subtype. The subtle differences in the dose of XRT are highlighted in Tables 20.1 and 20.2.

In the recurrent settings, the same dose of XRT can be repeated, and the decision of sequencing is decided on a case-to-case basis after discussion in multidisciplinary tumor board.

The fraction size should not exceed 1.8 Gy for flank XRT but should be lowered to 1.5 or 1.25 Gy if large volumes are treated, for example, whole lungs or whole abdomen and pelvis and in very young children, for example, less than 2 years old. If there is macroscopic residue, a boost of additional 10.8 Gy 6 fractions may be considered. Earlier a boost for stage III positive LNs was recommended, but there is little

Table 20.1 Dose fractionation schedules for different stages and risk stratification for children with locoregional disease

	SIOP [3]			NWTSG/COG, AREN0321, AREN0532, AREN0533 [14]		
	Intermediate risk	High-risk blastemal	High-risk diffuse anaplasia	Favorable/without LOH1p, 16q	Favorable with LOH1p, 16q	Focal/diffuse anaplasia
Stage I	Nil	Nil	Nil	Nil	Nil	10.8 Gy/6 Fr
Stage II	Nil	Nil	25.2 Gy/14 Fr	Nil	10.8 Gy/6 Fr	10.8 Gy/6 Fr
Stage III	14.4 Gy/8 Fr	25.2 Gy/14 Fr	25.2 Gy/14 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr
Stage IV	15 Gy/10 Fr	19.5 Gy/13 Fr	19.5 Gy/13 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr

[a]Additional 10.8 Gray-20 Gy/6–10 Fractions is given to the sites of gross disease identified at the time of radiation on the planning CT scan

Table 20.2 Dose fractionation schedules for different stages and risk stratification for children with metastatic disease

	SIOP [3]			NWTSG/COG [14]
	Low risk	Intermediate risk	High risk	Favorable/unfavorable
Lungs	Nil	12 Gy/8 Fr	15 Gy/10 Fr	10.5 Gy/6 Fr <12 months 12 Gy/8 Fr > 12 months
Liver	Nil	14.4 Gy/8 Fr	19.8 Gy/11 Fr	19.8 Gy/11 Fr
Brain	Nil	15 Gy/10 Fr	25.2 Gy/14 Fr	21.6 Gy/12 Fr < 16 years 30.6 Gy/17 Fr >16 years
Bone	Nil	30.6 Gy/17 Fr	30.6 Gy/17 Fr	25.2 Gy/14 Fr < 16 years 30.6 Gy/15 Fr > 16 years

[a]Additional 10.8 Gray/6 Fractions is given to the sites of gross disease identified at the time of radiation on the planning CT scan

evidence to support this now if the resection is complete.

Once commenced, XRT should be delivered in five daily fractions per week without interruption. If an interruption is inevitable, this should, if possible, be compensated for by hyper-fractionation so that the overall treatment time isn't extended.

For non-metastatic disease, surgery to XRT interval should be started between 9 and 14 days. Delay beyond 14 days is associated with a significant increased risk of death with a hazard ratio of 1.04/day [9]. Hence, it is important that a child with WT needs to be seen by a radiation oncologist before surgery so that planning can be done. Wound healing is not an issue as the dose delivered is so low that it will not hamper the process of postoperative healing.

20.2.6 Sequelae of Radiation

Acute side effects like radiation enteritis are rare as the dose of XRT is very less compared to most other pediatric tumors. Late sequelae include kyphoscoliosis and SMN. To decrease kyphoscoliosis, entire vertebra column is included in the treatment volume, and the dose also is reduced. As regards SMN, the cumulative incidence of SMN was 2.3%, 6.8%, and 12.2% at 30-, 40-, and 50-years post-treatment, respectively, in a population-based cohort study of WT survivors treated over 50 years [10]. There was no difference in the occurrence of SMN between children treated with or without XRT [8]. In addition, the dose is presently reduced to 10.8 Gy, and longer follow-up is required to see further reduction in SMN due to radiation.

20.3 Indications for Radiation

Depending on the tumor stage, histology, resection status, and ChT response about 15–25% patients of WT will have one or another indication for XRT. The broad indications for XRT in WT include:

1. Locoregional disease: To reduce the risk of local recurrence and improve probability of cure.
2. Metastatic disease: Control of lung metastasis with residual disease and rarely distant metastasis (including liver and bones).
3. Recurrent/relapsed disease: As an integral part of multimodality treatment used for salvage therapy.

The three principal fields for XRT include the flank, whole abdomen, and lungs in both major protocols. The NWTSG/COG protocols over the years have helped establish the indications, timings, and dosage of XRT to all the fields.

20.3.1 Locoregional Disease

The NWTS 1 and 2 established that XRT can be avoided in stage I tumors, if they receive vincristine and Actinomycin-D [4]. The NWTS-3 results in addition to the above also reported that favorable histology (FH) stage III tumors could be safely radiated with 10.8 Gy as compared to the previous 20 Gy to the flank (renal bed) and lymph nodal areas.

This significantly decreased the dose of XRT and hence the toxicities [5]. In general, the treatment regimens in the SIOP 2001 protocol for loco regional disease are quite successful, and very few changes have been made in the recent UMBRELLA Protocol [2].

The SIOP and the UKCCSG (now termed as UKCCLG) have over the past 40 years looked at indications and the advantages of XRT in the management of WT. The SIOP 1 randomized patients between preoperative XRT and primary surgery. In patients going upfront tumor resection, there was a significantly higher chance of tumor rupture [6]. SIOP 2 looked at a non-randomized set of patients with either preoperative chemoradiation or surgery alone, and there was significantly less tumor rupture in the first group. The SIOP 5 administered chemoradiation vs ChT alone in a randomized fashion preoperatively. Postoperative XRT was given only to stage II and III and not to stage I. Both arms showed equivalence in terms of rupture and overall survival. An important finding from this study showed that 43% of patients were only stage I and did not receive postoperative XRT. This strategy has been followed in SIOP to further reduce the late effects and toxicities of RT [7]. The SIOP 6 randomized node negative and positive patients to receive or not receive XRT, and the study was abandoned as the unirradiated group had an excess of recurrences [7].

The UK Wilms Tumor Study group had an interesting observation [11]. After neoadjuvant ChT, the number of stage III tumors decreased considerably from 29.8% to 9.8%. This meant that there was a reduction in the requirement of XRT by almost two-thirds.

The preoperative findings are also important for a radiation oncologist, especially when the capsule is ruptured. Prior biopsy and capsule rupture during surgery, even if it is accidental, are all labelled as stage III. As per NWTS-4 subset analysis, the local relapse caused reduced survival at 2 years among those with extensive spillage decreases with event-free survival (EFS) plummeting from 90% to 43% [10]. Extensive spillage associated with higher local relapse with a relative risk of 2.86 requires WAI, whereas accidental rupture in an otherwise intact capsule needs flank XRT only [12]. The patients with ascitic fluid positive for malignant cells and those with peritoneal implants would also need WAI. Entire peritoneal cavity from diaphragm till obturator foramen is included for WAI. Boost dose of XRT is required to control gross disease left behind either in the tumor bed (21Gy) or in the peritoneum (10.5Gy); boost doses mentioned are as per COG protocol.

Within a given stage, children with diffuse anaplasia (DA) histology WTs fare badly, and hence they require aggressive ChT as well as locoregional XRT. Daw et al. [13] studied all patients of NWTS I to IV and AREN0321 with anaplastic WT and observed a reduction of local recurrence from 6.2% to 4% with addition of flank XRT for focal as well as diffuse anaplasia; recurrences in this series occurred only in cases of DA. Hence, adjuvant XRT was recommended for all the patients with DA. Both COG and Indian Council of Medical Research (ICMR) recommend flank XRT even for stage I anaplastic WT, though it is not advised in SIOP protocol.

20.3.2 Metastatic Disease

Patients with metastatic disease having local stage I and II do not need adjuvant flank XRT. The local radiation for metastatic patients is considered if surgico-pathological features under stage III are present, and it could be either flank or WAI.

Presently in COG as well SIOP protocol, patients with initial chest X-ray negative CT scan positive lung metastases, who achieve complete radiological response after 6 weeks of ChT, are considered to have lesser tumor burden in the lungs; these patients do not need WLI. In COG protocol, these patients are referred to as "Rapid Complete Responders" [5]. The "Slow Incomplete Responders" however would complete their ChT and then receive WLI (Fig. 20.5). However, all patients with loss of heterozygosity (LOH) at 1p and 16q, irrespective of local extent of disease and response to ChT, would receive WLI [14]. ICMR recommends WLI irrespective of response to ChT [2].

Metastatic sites in the liver, brain, and bone are addressed after ChT. Whole organ is treated if the lesions are diffuse, while discrete ones are treated with localized XRT.

The radiotherapy protocol in UMBRELLA SIOP-RTSG 2016 study is in broad accordance with the COG protocol. In SIOP-2001, the WLI dose was 15 Gy, which was decreased to 12 Gy.

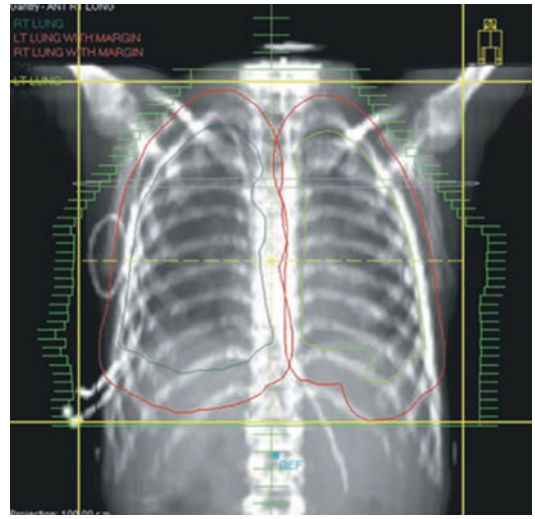

Fig. 20.5 Showing WLI which includes the entire pleural cavity

20.3.3 Recurrent Disease

XRT is used along with ChT with or without surgery in selected recurrent patients. The lesion should be small and could be either locoregional or metastatic; the dose and technique depend on the previous treatment and duration since radiation. In Umbrella protocol, in patients with recurrent disease with lung metastasis without prior lung irradiation, WLI should be administered in all histology types.

20.4 Comparison of Radiotherapy Schedules in COG and SIOP-RTSG (Umbrella Protocol)

There are subtle differences about the XRT protocols that have been highlighted in tabulated form (Tables 20.1 and 20.2). It is obvious that the doses used in COG are marginally less.

20.5 Conclusions

All WT patients should be seen by a radiation oncologist before surgery as it is very important to start adjuvant radiation between 9th and 14th

POD. XRT for WT plays a vital role in preventing local recurrence and thus improving the EFS. It is safe in carefully selected children based on the staging and risk stratification. It has a useful role in recurrent settings too.

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21 Novel Tumor Directed Interventions

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21.1 Intra-tumoral Chemotherapy for Wilms' Tumor

The standard treatment of care for solid tumor comprises of systemic chemotherapy (ChT) that may be given as neoadjuvant or following tumor excision. However, there have been situations where local action of chemotherapeutic drugs has been found beneficial [1]. Intra-arterial, intra-peritoneal, intra-vesical, and intra-pleural instillation of ChT agents has been done with fruitful results. However, all tumors are not amenable to these routes. For a Wilms' tumor (WT) in a small child, the renal artery may not be amenable to the available gadgets. The ChT needs to be repeated as per the cycle. Also, there may be a clot in the inferior vena cava (IVC) in advanced cases that may get dislodged with an intervention in the nearby vessels.

There are times when the patient presents in an advanced stage and is not physically fit to undergo the systemic toxicity of these ChT agents. In order to make them physically fit in terms of anemia and malnutrition, precious time is lost without a guaranteed timeline for fitness. In such instances, there is a role for intra-tumoral ChT (IT-ChT) that may provide timely response without added toxicity.

21.1.1 Indications for IT-ChT

1. Cachexic patients with large tumors.
2. Nonresponsive tumors.
3. Patients with repeated chemotoxicity not allowing timely scheduling and dosing of ChT cycle.
4. Tumors with large necrotic areas interspersed with solid areas.

21.1.2 Mode of Action

The ChT agent reaches the tumor cells directly and destroys the same. It also starts a tumor-specific systemic immune response, which in turn helps to contain the metastasis if any. This immune response originates after the tumor-specific antigens are presented to the immune cells in immunocompetent hosts following IT-ChT [2, 3].

Nelson et al. have called the approach of local immunotherapy as a "Trojan Horse" approach as besides destroying of the local tumor, it also induces a more widespread response that eliminates the metastatic tumor deposits [4].

The tumor microenvironment (TME) consists of tumor cells and stromal cells. The stromal cells

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include blood vessels with endothelial cells and pericytes, fibroblasts, macrophages, and infiltrating immune cells. Among the immune cells are the natural killer cells, monocytes, neutrophils, T and B cells, mast cells, and dendritic cells. Overall, the stromal cells are responsible for the majority of the tumor cellularity [5]. Thus, an interest has now been generated to target the solid tumors and modify the stromal elements. It has been realized that solid tumors consist of different microniches. Some of these microniches are well perfused and oxygenated, while others are poorly perfused and hypoxic. The poorly perfused ones are inaccessible by systemic ChT and may harbor resistant tumor cells that can survive a nutrient- and oxygen-deprived environment [6].

21.1.3 Administration of IT-ChT

IT-ChT for WT is administered under ultrasound guidance after following all aseptic precautions. A spinal needle, usually a thin one (25G), is used to administer the drug. The dose of IT-ChT is generally the same as in systemic ChT. Injection hyaluronidase can also be added along with the ChT drug to boost the local distribution of the drug within the tumor [2, 6]. The first author has given IT-ChT in advanced cases of WT, neuroblastoma, rhabdomyosarcoma, soft tissue sarcomas, and also metastatic carcinoma of the colon presenting on the abdominal wall (unpublished data).

21.1.4 Results

Kumar et al. compared IT-ChT versus systemic ChT in children with WT and neuroblastoma [3]. The authors depicted the response to IT-ChT in 16 patients of WT versus the response to systemic ChT in 14 cases of WT. Seventy percent of patients had completely resectable tumor at the end of 6 doses of IT-ChT as compared to 50% resectability in the intravenous group; this difference in resectability was statistically significant.

21.2 Trans-arterial Chemo-embolization (TACE)

The loco-regional therapy or trans-catheter endovascular cancer therapy of childhood malignancies, also referred as the fourth modality of oncological treatment, is a promising therapeutic option in childhood malignancies. It includes trans-arterial embolization (TACE), chemo-embolization, or radio-embolization; however, radio-embolization is not commonly used. The most common application of this modality has been seen in the form of TACE therapy. TACE therapy was first used in the 1960s for hepatocellular carcinomas (HCCs) in adults. With the miniaturization of the angio-catheters due to technological advancements, it is now possible to use this modality in children with solid organ malignancies [7].

TACE involves selective injection of the ChT agent into the feeding arteries of the tumor leading to tumor necrosis. This not only decreases the tumor size (or volume) and makes it amenable for a safe and precise resection, but also reduces the systemic toxicity of the ChT drug.

21.2.1 Technique

During the procedure, a high concentration of the known ChT agent is administered into the arterial feeders of the tumor along with a carrying agent. The carrying or the embolizing agent can be either temporary or permanent. Although temporary agents are preferred due to less incidence of collateralization, permanent occlusion might be beneficial in children with highly vascular tumors.

21.2.2 Post-procedural Care

Post-embolization syndrome must be anticipated in all cases, and all children must be closely monitored after the procedure. Antipyretics (or analgesics) and anti-emetics must be administered in

all patients for initial 24–48 h after the procedure. Antibiotic prophylaxis can be administered for 5 days to prevent gram-negative bacteremia. However, this is not universal to all the centers. In addition to this, specific side effects of the ChT drugs must be anticipated and managed accordingly. A non-contrast computed tomography study should be performed 24–48 h after the procedure to see the distribution of the chemoemboli. Assessment of tumor response should be done by follow-up imaging.

21.3 TACE in WT

Preoperative TACE has shown to significantly reduce the tumor size in children with WT. This helps in better handling of the tumor and reduces the chances of tumor spill or rupture. Li et al. have demonstrated a significant reduction in the rates of recurrences and deaths occurring within 1 year in children undergoing preoperative TACE versus those undergoing only surgery. Histopathological comparisons reveal that this better clinical outcome is due to enhanced tumor necrosis, interstitial fibrosis, and lymphocyte infiltration. Additionally, it increases the feasibility of nephron sparing surgery (NSS) in a selective subset of patients [8].

In a study by Liu et al., TACE followed by tumor resection was performed in 44 patients of WT [9]. Not only the 2-year EFS was significantly higher in the TACE group, but the unfavorable events (recurrence and death) were significantly less within this subset of patients as compared to the control group [9]. Li et al. have reported their experience of combination of neoadjuvant TACE and systemic ChT in the management of 55 patients of unresectable, metastatic, or diffuse anaplasia histology WT in 2016 [10, 11]. Their protocol includes a platinum-based combination ChT regimen. The basis to employ a combination ChT regimen is to avoid the problems related of drug resistance. Most of the patients (50/55) could undergo complete tumor resection. Following TACE, complete regression of IVC thrombus, shrinkage of atrial thrombus to IVC, and disappearance of distant metastases were seen in 80% (4/5), 50% (1/2), and 67% (4/6) of the patients, respectively. The 5-year event-free survival (EFS) and overall survival (OS) were 92.7% and 94.5%, respectively.

21.3.1 Contraindications

Apart from general contraindications of angiography, TACE is contraindicated in associated advanced liver disease, hepatic encephalopathy, systemic infection and subnormal cardiac function (using doxorubicin), hemorrhagic disorders, and poor renal function [8].

21.3.2 Adverse Events

Post-embolization syndrome featuring symptoms as high-grade fever, nausea, vomiting, and abdominal pain appear to be quite common with the embolization procedure but usually resolve within 2 weeks. Tumor lysis syndrome is also noticed in some children following TACE. Life-threatening complications including anaphylaxis and skin ulceration, gastric ulcers, renal failure, pulmonary embolism, etc. are rare. On the other hand, no specific complications of TACE are reported when it is performed for other tumors [8].

21.4 Ablation Techniques

Gomez and colleagues did a systemic review on ablation techniques like radiofrequency (RFA), microwave (MWA), high-intensity focused ultrasound ablative therapy (HIFU), or cryoablation on malignant and aggressive benign lesions [12]. The underlying principle for these techniques is that the sustained alterations of tissue temperature have cytotoxic effect. RFA and MWA are heat-based techniques that deliver electrical or electromagnetic energy into target tissue by using needle mounted electrodes or antennae. Cryoablation systems instead destroy the tumor

tissues by using rapid tissue cooling to temperatures below −40 °C. This is achieved by direct circulation of liquid nitrogen, or argon gas. These techniques other than cryoablation have been occasionally used in the settings of inoperable or metastatic WT. Some of the examples are briefly mentioned below.

21.4.1 Radiofrequency Ablation (RFA)

Brown and colleagues from Boston in 2005 were the first to report CT-guided RFA as a short-term temporizing palliative procedure to treat a WT in a 5-year-old girl in whom surgical excision of WT was not feasible [13]. RFA could be tried in those children with WT who are poor surgical candidates or who would otherwise require dialysis and renal transplantation. It should be remembered that children have lesser amount of intra- abdominal fat, and need smaller grounding pads when compared to adults in whom the clinicians have much larger experience.

Gandhi et al. used the combined modality of CT-targeted RFA and brachytherapy in an 11-year-old girl with multiple recurrences of anaplastic WT in the same year [14].

RFA ablation has been also used to treat hepatic metastases from WT [15].

21.4.2 Microwave Ablation (MWA)

In 2016, Freedman and Harbut [16] from Sweden described a 6-year-old boy who had right-sided WT with inferior vena caval thrombus and pulmonary metastases at presentation that was successfully treated with multimodality treatment. He had recurrence 6 months later with multiple right sided pulmonary metastases and a single 15 mm metastasis in the inferior lobe of the left lung. Lobectomy was done on the right side, but an ablative procedure was decided for the solitary left lung metastasis. The authors chose MWA over RFA as heating takes lesser time (2 min in the present case); it doesn't depend on direct tissue conductivity and is less affected by cooling effects of nearby vessels (heat-sink effect). Other overriding advantages include possibility of larger near-spherical ablations. The procedure done using state-of-the-art navigated CT targeting, high-frequency jet ventilation, and a standard 1.8-mm, 14-cm antenna resulted in complete ablation of the lesion. He was later treated with high-dose intensive myeloablative ChT followed by an autologous stem cell transplantation.

In 2020, Petrut et al. from Romania successfully used MWA to ablate a subcapsular small remnant lesion in a 3-year-old girl who had presented with bilateral synchronous WT and had bilateral nephron-sparing surgery [17].

21.4.3 MR-Guided High-Intensity Focused Ultrasound Ablation (MR-HIFU)

High-intensity focused ultrasound (HIFU) is a non-invasive, non-ionizing method of producing selective and "trackless" thermal ablation of large tumor volumes in deep-seated targets in the body without damage to overlying tissues; no antenna similar to that used in MWA is required [18]. The technique was first described by Lynn and colleagues in 1942 to destroy selective regions within the brain for treatment of neurobehavioral disorders [19]. A focused beam of ultrasound kills accurately the desired targeted cells, whereas those lying outside the focus are spared; in fact, the tissue destruction can be monitored during treatment because of the availability of sophisticated imaging techniques available these days [18].

Though no published data is available on this intervention as of date, a clinical trial is on to study its safety and feasibility on children, adolescents, and young adults with refractory or relapsed solid tumors that are located in bone or soft tissue in close proximity to bone, including WT [20]. The study is expected to complete by June 1, 2022.

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Wilms' Tumor in Resource-Challenged Nations

22

Yogesh Kumar Sarin

Sharpening the needlepoint of surgical expertise will, of itself, not compensate for the major infrastructural deficiencies, but must proceed in tandem with resource development and allow health planners to realize that pediatric surgical oncology is a cost-effective service that can uplift regional services.—Hadley et al. (2012) [1].

22.1 Introduction

Wilms' tumor (WT) with a quoted 5-year overall survival (OS), ~90% in high-income countries (HIC) cannot still be considered as conquered because 85% of these tumors occur in low-income countries (LIC) where its management still poses enormous challenges and the OS rates are still in the range of 25–50% [2]. The various contributing reasons that are known to exist may vary from country to country, but broadly include late presentations, cultural issues, lack of education, malnutrition, drug toxicity, and limited resources as regards chemotherapy (ChT) drugs, radiotherapy (XRT), and trained pediatric surgeons. Early abandonment of therapy is common. In many African countries including South Africa, the WT patients have been also afflicted with concomitant tuberculosis and/or human-immunodeficiency virus (HIV). In low-middle-income country (LMIC) such as India, the situation may not be very different because of the rampant disparities between different centers as regards the clientele and the available resources. Even the premier teaching tertiary institutions in the capital of India lack local housing, services of pediatric oncologists and radiologists, and intensive care beds for cancer patients. The focus of local governments is still on primary healthcare, and the high-end care available in corporate hospitals is beyond the reach of common people. This results only a few children with WT in LMIC receiving protocolized curative therapy; in LIC; even palliative care is usually not available [3].

Such prevailing situations had made Hadley et al. from South Africa to suggest in 2001 that in the third world, keeping in mind the limited resources that need to be used cost-effectively, the goal of therapy in the high-risk WT such as diffuse anaplastic WT patients should be palliative, and one may choose not to treat this cohort with an intent to cure [4].

It is then obvious that situations are significantly different between LMIC and HIC, and we need to create regimens in LMIC that we could achieve to cure as many children as possible with the locally available resources [5].

22.2 Challenges to WT Care in LMIC

The poor outcomes of children with WT in LMIC could be attributed to many factors; these could be related to the existing healthcare delivery system,

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biological differences in the ethnicities, cultural and socioeconomic factors, and the burden of disease at initial presentation [6, 7]. Late presentation, treatment abandonment, and on-therapy mortality due to gaps in standard of care account for most of the poor outcomes in such settings [7].

22.2.1 Late Presentations

Less than 10% patients of WT are known to be in stage I when they reach the specialized centers in LMIC [8], whereas stage I represented ~40% of WT in HIC even in the 1980s and 1990s [9, 10]. Half to two-thirds of patients of WT reporting to major referral centers in LMIC such as Lebanon and South Africa presented with advanced stage disease [10, 11], whereas most of the patients in North America and Europe would present in stage I or II disease. Not only these advanced stages of WT require more toxic and intensive adjunct therapies associated with their attendant morbidity and mortality, but it is also known that WT that present with advanced stage disease could acquire therapy-resistant biologic features, e.g., *TP53* mutation and *MYCN* alteration [12].

22.2.2 Abandonment of Therapy

Completion of therapy for WT in LMICs remains a significant challenge. An audit of eight referral centers in sub-Saharan Africa revealed treatment abandonment rates as high as 14–48% [13]; Sen et al. reported 23% abandonment rate from Asia [14]. The reasons underlying abandonment of therapy include illiteracy, socioeconomic, and cultural factors, and non-availability of healthcare closeby [15]. In sub-Saharan Africa, ˜20% of children with WT have lost a parent to HIV, thus diminishing the family support; further these children may have concomitant HIV and/or tuberculosis [16].

22.2.3 Malnutrition

Malnutrition is rampant in patients of WT in LMIC. Moreira et al. mentioned that more than one-fifth of patients of WT had clinical nutritional indices less than 2SD; 7% had cachexia defined as clinical nutritional indices less than 3D [17]. Furthermore, 22% presented with anemia (<8 g/L hemoglobin) [17]. Malnutrition is known to affect surgical mortality and morbidity as well as ChT toxicity. The Pediatric Oncology in Developing Countries (PODC) Committee of the International Pediatric Oncology Society (SIOP) suggests administering only two-thirds of the ChT doses to patients with malnutrition [18].

22.2.4 Socioeconomic Factors

Sen et al. emphasized on the socioeconomic factors contributing to late presentation and abandonment of therapy in Asian countries, with many of the patients coming from far-off [14]. Moreira et al. emphasized that the 55% of the children's families had a poor socioeconomic level defined either with an average income below the minimum wage for each household member or, if this was unknown, defined by lack of access to potable water and electricity, in their series; 35% of parents were illiterate [17]. The distance to travel to the center was more than 100 km in half of their patients, and in more than one-third of patients, the travel time was more than 3 h [17].

22.2.5 Cultural Issues

Prevailing cultural issues, poor socioeconomic status of families, illiteracy, and non-availability of primary health services close to home in LMIC help the traditional healers or quacks to flourish. In South Africa, more than three-fourths of WT patients were initially taken to sangoma or nyanga, the traditional healer and a trial of alternative therapy before coming to the hospital [19]. Fear of hospital detention is also known to result in both delayed presentation and abandonment of therapy [20]. These cultural issues need redressal, and society's confidence in modern medicine has to be enhanced before such a situation could be reversed.

22.2.6 Biology

Ethnicity and hereditary predisposition also contributes to a particular outcome. Increased incidence of WT in certain Kenyan tribes pointed towards race disparities in biology. The molecular markers of WT in Kenyan patients when compared to the North American patients (both from black and white populations) pointed to far worse biological behavior and treatment resistance [21, 22].

22.3 SIOP PODC and Adapted Regimens

SIOP PODC have drafted an outline of adapted treatment regimens to manage pediatric cancer including WT in LMIC. The adaptations include focus on preventing treatment abandonment, reduction in doses of ChT drugs to reduce deaths due to drug toxicity, adapting the diagnostic strategy, modification of staging and risk stratification, local control, nutritional assessment, and supportive care [6]. The adapted regimen in LMIC may be of different intensity, than the regimens used in HIC or simply different, e.g., using additional ChT for WT when XRT is not available in a particular center or region. PODC has designed guidelines for at least four malignancies including WT for settings in LIC where only the minimal requirements for treatment with curative intent are available (defined as setting 1) [5–7].

It is not easy to promote the idea of adapted regimens for more than one reason. Above all, there is a general tendency to resist change and preserve the status quo, especially when there is insufficient local data on the follow-ups and outcomes of patients from LMIC. There are also perceived ethical concerns about using modified or totally different regimens. Also, lot of efforts go in formulating the adapted regimens which local LMIC physicians may not be willing to put [5]. So, many continue with the misperception that "more is better" and question why to adapt.

ICMR consensus guidelines published from India in 2017 are not very different from that from SIOP 2001 protocol [23, 24]. There is no denying the fact that there are pediatric cancer units available in India that offer the highest chance of care, but the level of care at various centers is obviously heterogeneous and in the absence of insurance coverage for most, the caretakers have no choice other than to get their wards with WT treated in a sub-optimal center close to their home. We must acknowledge that ChT of solid tumors in majority of the tertiary centers is still being provided by the busy pediatric surgeons for whom pediatric surgical oncology forms less than 3–5% of their total practice, and histopathology reports are often delayed or unreliable as the local pathologists are still not comfortable to report tumors that have undergone ChT-induced changes after administration of neoadjuvant ChT and radiotherapy (XRT) is unavailable, to count a few [25]. We need to wait and see the impact of government schemes in India like Ayushman Bharat—Pradhan Mantri Jan Arogya Yojana (AB-PMJAY) on the heterogenicity of healthcare provided to WT patients.

PODC framework may help selecting an "optimal" adapted regimen that may have the highest probability of cure in the given circumstances. Once put in practice, there should be a willingness for periodic evaluation and constant improvisation, as it is possible that the initially selected regimen may give sub-optimal outcomes. On the other hand, it is possible that the locally available resources get augmented, and even a LMIC center moves on from the best adapted regimen to a situation where a patient with relapsed WT could be treated with the high dose-ChT and autologous transfusion similar to a HIC sitting [5]. This dream could come true when these centers could invest on providing more human resources, better intensive care, better ChT drugs and antibiotics, provision of guest house for patients coming from far, etc.

22.4 Suggested Management for LMIC

The author had switched from COG to SIOP and then to UKCCLG with its earlier philosophy of performing a retroperitoneal tru-cut biopsy in

every renal tumor. Three strategies have worked to reduce the issue of early abandonment for the author. One, admitting children from remote far-flung areas for the entire duration of their ChT as they were unable to complete therapy on an outpatient basis. Two, administering preoperative ChT to all patients not only created better rapports between the families and the caregivers, but also made the families understand that the treatment of WT is multimodal, and surgery alone may not work. Three, starting a dedicated separate pediatric surgical division within the pediatric surgery ward (along with isolation rooms for the patients suffering from febrile neutropenia) helped families of many patients at different stages of management staying together and sharing a rapport between themselves. The families of the patients who were closer to completion of treatment are source of immense encouragement and hope to those families who have just started their arduous path that would keep them busy for next few weeks.

A thorough search and analysis of literature of management and outcomes of WT in the LMIC (also referred to as third-world countries, developing countries, and even non-developing countries), it is realized that probably a flexible hybrid approach should be recommended in LMIC setups [7, 25–27]. Whatever the approach, it may be imperative to have a tumor board, which is a new, if not a non-existent concept, in majority of LMIC centers. With advancing technology, however, *virtual tumor boards* may be set up at the tertiary well-equipped centers. The multidisciplinary expert panel of these centers could support the peripherally placed pediatric surgeons in management planning of individual cases. One such tumor board is run by the National Cancer Grid and hosted by Tata Memorial Centre, Mumbai, India.

If a child presents with a small operable mass and no metastases, then it would be advisable to do nephrectomy first (Fig. 22.1). The staging and histological classification according to

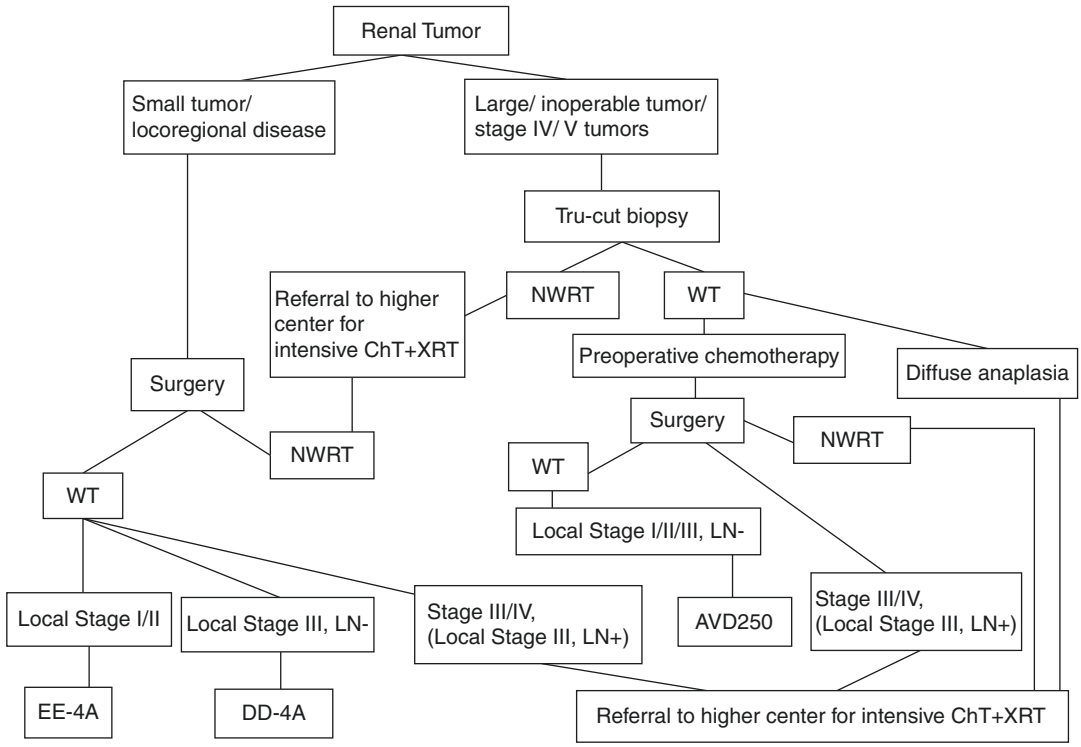

Fig. 22.1 Proposed algorithm for treatment of WT in LMIC

National Wilms Tumor Study Group/Children Oncology Group (NWTSG/COG) criteria are easier for the pathologists than those used in SIOP criteria [27]. It is due to the facts that tumor histology is not altered by preoperative ChT and NWTS criteria for histological subtyping of WT into two broad categories—either non-anaplastic (favorable) or anaplastic (unfavorable)—are simpler. The pathological diagnosis would be easier for the local pathologists and treatment-related errors would be fewer; this is all the more important as rapid central pathology review (CPR) is not feasible in LMIC [27].

Non-anaplastic WTs stage I or II could have the same adjuvant ChT, regimen EE-4A comprising of only two drugs—Actinomycin-D (AMD) and Vincristine (VCR)—administered over 18 weeks, and patients with stage III and IV could be treated with regimen DD-4A comprising of three ChT drugs, AMD, VCR, and Doxorubicin (DOX) [28]. The diffuse anaplasia patients, usually in local stage III at presentation in LMIC, are not going to fare well with regimen DD-4A and would necessitate intensive ChT with its toxic effects, ICU care, and XRT that is definitely not available in LIC. Their treatment with regimen DD-4A alone is not going to be curative; it at best would be palliative.

If a child presents with a large, inoperable WT, or metastatic WT, or bilateral WT, then preoperative treatment for 4–6 weeks of 2- or 3-drug regimen as advised in SIOP should be administered [18]. But in all such patients, a tru-cut biopsy should be considered as considerable data is available from many countries especially India, China, Vietnam, and Japan that the proportion of non-Wilms' renal tumors (NWRT) is higher than as compared to what is reported from Europe [27, 29–31]. In the year 2008, 50% of renal tumors from the principal author's department were reported as NWRT; this prompted him to move from SIOP to UKCCLG approach of doing a mandatory pre-therapy tru-cut biopsy. The Vietnamese study reported WT to represent only 68–76.5% of pediatric renal tumors [27]; this is true for other far-east Asian countries too. An American study showed that the WT comprised of only 73.9% of all renal tumors, and CT studies had diagnostic accuracy of only 82% to pick up the WT [32]. Smets et al. have stated that imaging studies alone cannot distinguish between WT and other non-Wilms' renal tumors (NWRTs) [33]. So, if we give ChT suitable for WT to all patients with renal tumors, a large number of patients with NWRTs would unnecessarily receive non-effective preoperative ChT. Although the UK has subsequently scaled down doing tru-cut biopsy only in few limited situations, the author is not convinced whether any such change of practice is required.

With preoperative ChT, the inoperable WTs would shrink in size and would be less prone to intra-operative tumor spill (IOS). The down-staging effect from preoperative ChT is also expected. This may again curtail the use of XRT postoperatively. The rider is that preoperative ChT would significantly alter the histological types; the excised specimen would show varied extents of ChT-induced changes. It is harder to categorically state the extent of tumor, thus making staging more difficult. It was conceded in SIOP 2011 Congress that there were discrepancies between the institutional pathologists and central pathology review in as many as one-fourth of the patients; 9.5% had diagnostic inaccuracies and 15.5% had staging differences [34]. If these statistics are extrapolated to the local scenarios, many of the WT treated with preoperative ChT would be either under- or overtreated. Some centers have tried taking the benefit of twinning programs and sending the histopathological images of tumors by the Internet for central pathological review in Europe [27], but the specialists could only see limited and selected images. This would be even more difficult for other hospitals in a country that has limited facilities, resources, and international collaborations. But with the advent of 4G and 5G data networks, this situation may change.

So, the institutional policy in all such patients (large, inoperable WT, or metastatic WT or bilateral WT) could be to treat all of them as local stage III and administer 3-drug AVD250 regimen with total cumulative dose of DOX of 250 mg/m^2 (including preoperative ChT).

Whether we use NWTSG/COG or SIOP philosophy, the major ethical dilemma would be

treating patients with local stage III with positive lymph nodes (LN) with ChT alone without any XRT. There is global consensus on the fact that not administering XRT to these patients would mean early local relapses and need of administering intensive and toxic second-line ChT, with consequent secondary malignancies. These patients could be sent for an intensive adjuvant treatment including XRT to an advanced tertiary center. Along with these patients, patients with diffuse anaplasia WT and NWRT such as Clear Cell Sarcoma of Kidney (CCSK), Malignant Rhabdoid Tumor of Kidney (MRTK), etc. could also be sent to advanced tertiary center.

22.5 SIOP PODC Clinical Guidelines for LIC [18]

It would be imperative to mention here the SIOP PODC clinical guidelines for the management of children with WT in LIC that were published in 2013 and later used in many LIC African countries [18]. The minimal requirements suggested by SIOP PODC for treatment with curative intent mentioned were as below [18]:

1. Basic laboratory services: full blood count, thick blood film for malaria parasites, HIV antibody test, stool and urine microscopy.
2. Basic radiology facilities: chest X-ray, ultrasonography.
3. ChT drugs: AMD, VCR, and DOX and their safe administration.
4. Supportive care: safe blood transfusions, intravenous broad-spectrum antibiotics, adequate pain-relief drugs, and reasonable degree of nursing care.
5. A trained (pediatric) surgeon, adequate facilities for surgery and perioperative care.
6. Free medical treatment and social support (meals, money for travel) for poor families so that therapy is not abandoned.

There is no mention of pediatric oncologist in the requirements above as many members of the writing group believed that in Africa, surgeons were inescapably true generalists and, with little training, were capable to administer ChT to WT patients provided ChT regimens are simple and drug toxicity is minimized [35]. Even in some of the good teaching institutions in India, the ChT for most solid tumors is administered by trained pediatric surgeons.

Preoperative ChT in setting 1 is similar to that of SIOP 2001 protocol [18]. It is identical for the patients with localized disease. In metastatic disease, chest X-ray and/or abdominal ultrasound scans is done at week 6 to assess the regression and resectability of metastases (Fig. 22.2). ChT is administered for 3 additional weeks if the metastases are still present. If metastases have not disappeared or not become resectable after 9 weeks, curative treatment is stopped, and the child is sent home with caretakers for palliative care. Treatment flow sheet of metastatic disease is shown below:

The patients with localized disease are operated upon, and the adjuvant ChT is decided as per the histopathology and staging as shown in Table 22.1. If the histopathological staging is unsatisfactory, then it was proposed that the adjuvant ChT can be based on *surgical staging* (staging assigned by the surgeon himself based on the intraoperative findings, IOS, and the extent of resection) [15]. *Surgical stage I* is tumor limited to the kidney and completely

Week	1	2	3	4	5	6*	7	8	9*
AMD 45μg/kg (Day 1 of wk)	↓		↓		↓		↓		↓
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2 (Day 2 of wk)	↓				↓				↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine
*Chest x-ray and US abdomen to assess the regression and resectability of metastases

Fig. 22.2 SIOP PODC treatment schema for metastatic disease

resected; *surgical stage II* is tumor outside kidney, but completely resected; *surgical stage III* is IOS or incomplete resection. This stage also includes assessment of the LNs by the surgeon by gross inspection [15].

It is obvious that intensive ChT regimens and XRT are not used. Neither the tumor volume post ChT is taken into consideration, nor the histological subtypes in a particular risk-stratification category. Further, ChT regimens are simplified [15].

The ChT regimens mentioned in Table 22.1 are further detailed below (Fig. 22.3):

As regards the supportive care, the issue of all prevailing malnutrition in LIC was considered as the preoperative ChT was known to be associated with a higher morbidity and mortality [36]. It was also noted that infectious complications are the most common cause of treatment-related mortality. So, nutritional support and treatment of febrile neutropenia with appropriate antibiotics were given utmost importance [37]. The ChT drugs are administered at two-thirds of the doses to the malnourished children. Three practical recommendations and priorities mentioned in this protocol need to be highlighted—provision of free medical treatment, provision of social support (travel money, free boarding, and lodging), and provision of excellent counselling on diagnosis and need to complete treatment.

The above SIOP PDOC protocol could be easily reproducible even the interiors and most difficult Indian terrains; the only difference the author suggests is that the patients with the metastatic disease who do not show regression of metastases after 9 weeks of ChT could be referred to higher centers rather than their abandonment to respective homes to await their impending death.

There had been many other studies that have adapted changes in regimens. Two of these are worth a mention.

One is GFAOPNEPHRO 01 study (years 2001–2004) using SIOP 2001 protocol approach, comprising of eight African pilot units, namely, Algiers, Casablanca, Rabat, Oran, Tunis, Dakar, Yaounde, and Antananarivo [17]. All patients were treated preoperatively with ChT by the standard SIOP 2001 protocol. Postoperatively, the stage I patients irrespective of histology were treated with two cycles of AMD and VCR with a break in the 5th postoperative week. The stages II–IV patients were treated with AVD regimen

Table 22.1 Risk stratified adjuvant ChT suggested by SIOP PODC

	Treatment		
Disease	Stage I	Stage II	Stage III
Low risk	None	AV X 5 cycles	
Intermediate risk	AV X 1 cycle	AV X 5 cycles	AVD X 5 cycles
High risk	AVD X 5 cycles	AVD X 5 cycles	AVD X 5 cycles

Abbreviations: *A* actinomycin-D, *V* vincristine, *D* doxorubicin

Fig. 22.3 SIOP PODC treatment schemata for adjuvant ChT regimens

Week	1	2	3	4
AMD 45μg/kg	↓			
VCR 1.5mg/kg	↓	↓	↓	↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AMD 45μg/kg (Day 1 of wk)		↓			↓			↓			↓			↓	
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AMD 45μg/kg (Day 1 of wk)		↓			↓			↓			↓			↓	
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓
DOX 50mg/m^2 (Day 2 of wk)		↓			↓			↓			↓			↓	

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine; DOX, Doxorubicin

for 27 weeks. Flank XRT was administered if LN were positive, incomplete resection was done, or there was a localized intraoperative spill. Whole abdominal XRT in case of diffuse intraoperative spill or there was an unresectable tumor. Same group repeated their study (GFAOPNEPHRO 02; years 2005–2011) with minor change in the postoperative management—the stage I tumors were treated with 9 weeks of AV instead of 4 weeks [38].

The other study was by Sen et al. describing the experience from Christian Medical College Hospital, Vellore, India (1985–1995), and from King Faisal Specialist Hospital, Riyadh, Saudi Arabia (1988–1995) [11]. They recommend postoperative XRT for stage I–II disease of favorable histology with features that make relapse likely, such as invasion of the tumor capsule, the presence of an inflammatory pseudocapsule (manifested as tumor adherence to surrounding tissues at surgery), renal-sinus invasion, and tumor in intrarenal vessels [39]. Such a recommendation for large late-presenting tumors in the developing world is unacceptable globally as of today, but is worth a mention nonetheless.

22.6 Post-treatment Surveillance in LMIC

Post-treatment surveillance of children with WT is difficult and has been known as one of the reasons of poor outcomes in LMIC; the referral centers in African countries reported lost-to-follow-up rates of 15–43% in the first year after treatment [40]. Situation is not very different in Indian subcontinent and many other Asian countries. In Malawi, pediatric oncology patients are followed by a field worker using a donated motorcycle. GPS records enable the field worker to trace the patient repeatedly [35]. It is a model worth emulating in other LMIC. In India, Accredited Social Health Activists (popularly now as ASHA workers) that provide primary medical care for minor ailments in the villages and remote communities could be taught clinical features of common childhood cancers; they could help in early diagnosis and referral as well as in post-treatment surveillance.

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23 Management of Resected Wilms' Tumor with Unknown Staging Status

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23.1 Background to the Vexed Problem

Staging for Wilms' tumor (WT) is based on combination of preoperative imaging for distant metastasis and anatomical extent of the tumor judged on post-operative histopathological findings of the excised tumor and sampled lymph nodes (LNs), and it is not dependent on clinical characteristics, molecular markers, histology, or biology of the tumor. Thus, it is a surgico-pathologic system where surgeons, pathologists, and radiologists have an important role to play.

As the appropriate therapy and prognosis is based on tumor stage, it is imperative to stage the tumor accurately. Tumor stage is a critical component of risk-stratified therapy. In simple words, by using proper staging and risk-stratified therapy, we are trying to achieve that all patients of WT are optimally treated; no patient is to be under-treated or over-treated. Failure to do adequate LN sampling may result in understaging and inadequate treatment of the child with the potential for an increased risk of local recurrence and inferior outcomes as regards event-free survival (EFS) and overall survival (OS). Such patients would eventually need second-line chemotherapy (ChT) drugs and radiotherapy (XRT) with their associated toxicities. Second malignant neoplasms (SMN) could ensue. Overtreatment due to upstaging because of intraoperative spill (IOS) of tumor would also eventually translate into similar consequences.

But complete staging happens only in a Utopian world. Even in the developed world, many protocol violation or deviations occur; NWTS-5 quality assessment report from the USA stated that ~9% surgeons had failed to sample LNs. There were total of ~11% IOS; ~5% of these IOS were definitely avoidable [1]. A few surgeons may operate WT via an inappropriate retroperitoneal approach through a flank incision. Some daring surgeons may even attempt excising "all so-obvious" "unresectable tumor" and end up in removing the tumor piecemeal rather than an en bloc specimen. Or they may cause intraoperative spill (IOS) of the tumor, or the tumor thrombus in the vessel may be transected. Then there could be an over-enthusiast but inexperienced young surgeon who wishes to perform nephron-sparing surgery on bilateral Wilms' tumor, but is scared to cause IOS, so he/she leaves residual disease behind. A recent retrospective study from Tunisia mentioned about incomplete resection in few cases that was associated with significantly lower 4-year OS [2].

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Even when such sinister events occur, the patient can be bailed out if the surgeons record such events accurately in the operative notes; the disease would be upstaged, and risk-stratified stage-appropriate adjuvant therapy can be instituted.

All suspicious structures once biopsied or resected are supposed to be marked, described precisely, and sent to the pathologist in separate containers. The intact surgical specimen should be delivered to the pathologist without being opened by the surgeon. The sutures need to be placed on the ureter, renal vein, and artery so that the pathologist is able to find them easily for histological examination.

Now comes the all-important role of the pathologist. The pathologist is expected to gross the specimen correctly and extensively. He/she must ensure to take the blocks from all the critical sites and document the site of each block correctly. Histological assessment of the excised mass is the standard for staging WT. The capsular or nodal involvement should be commented upon, or else the treating surgeon may be unable to correctly differentiate between stage II and stage III.

We all know that in a large part of this world, the surgeon may not have the luxury of having the services of a local pediatric oncologist, a local tumor-board, what to talk of Central Pathology Review. So, unless he/she is trained to administer ChT, the patient is referred to a higher experienced center. Depending on the socioeconomic status and cultural beliefs of the caregiver, the further treatment may be abandoned, or the family may waste precious time in getting alternative medicine and not heed to the surgeons' advice. The outcome is written on the wall for such a patient—local or systemic or combined relapse.

If the caregiver is well-motivated and financially sound, then the patient may reach the higher center, with preoperative imaging (reports and films), and ill-documented operative notes. The caregiver may or may not be able to bring the histopathology slides or blocks.

A Swedish study (study period 1982–1990) had reported that ~16% of the referred patients of WT had incomplete information [3]. A leading cancer tertiary Mumbai center had reported in 2005 that a sizable number of the WT referred to them in the late 1990s were referred to their institute after primary surgery performed elsewhere [4]. Whenever surgery was done outside, every effort was made to stage the disease based on the referring clinician's preoperative and intraoperative examination findings and imaging studies and most of these patients treated as per the standard institutional protocol which included three-drug ChT (vincristine, dactinomycin, and doxorubicin) for all the patients as given for advanced stages in the NWTS-4 to compensate for lacunae in staging [4]. The situation is not much different after 2 decades in some of the states of India and major part of African continent.

This chapter deals with management of such a child who underwent surgery for WT at an outside center and has incomplete information regarding the staging, and adequacy of surgery or intra-operative spillage during surgery. He/she may have arrived within the days of surgery or after having a local relapse. Further, the biopsy report may be able to say about the presence or absence of anaplasia, but the local staging of the tumor (stage I–III) may not have been elicited.

23.2 Management

The treating physician/surgeon at the tertiary referral center needs to perform detailed examination and repeat imaging studies, if the preoperative imaging is not available, or if the patient has arrived late. Undoubtedly, the imaging studies (chest X-ray, abdominal CT scan ± chest CT scan) can easily differentiate between the locoregional and the metastatic disease. One can discern about the presence or absence of lung and liver metastases (the two common sites of metastases) from the available imaging. It is worthwhile to remember that RTSG-SIOP Umbrella protocol considers any lung lesion more than 3 mm diameter as metastasis unless proved histopathologically otherwise [5].

Also, the presence or absence of bilateral disease (stage V) can be ascertained on imaging, but the local stage of each diseased kidney cannot be confirmed. As per the COG protocol, the patient is administered the systemic ChT ± local XRT relevant to higher of the local stages of the two kidneys.

Capsular infiltration differentiating stage I from II cannot be ascertained on CT scan. Similarly, it would be impossible to know whether the LNs, if enlarged, are due to disease involvement or reactive hypertrophy; thus it would be impossible to designate the disease to stage III. Due to poor correlation of CT data along with histopathological data, it would be impossible to differentiate between low-stage (stage I and II) tumors requiring 2-drug ChT from advanced stage III disease requiring 3-drug regimen ± local XRT.

3-D reconstructions may not be possible on the available preoperative imaging, so the volume of the excised tumor may not be calculated; however, the diametric dimensions could be known to give a rough idea whether the excised tumor was small, average, or too large. It should be remembered that chance of intraoperative spill is known to be higher if the diameter of the tumor is more than 12–15 cm [6]. Whether these large tumors should be treated with flank radiation or whole abdominal radiation just on the suspicion of a possible IOS that the surgeon has failed to record, could be a contentious issue.

If fresh imaging has to be ordered, then one must consider the feasibility of doing magnetic resonance imaging (MRI) abdomen instead of contrast enhanced computerized tomography (CECT) abdomen and CT chest (without contrast) be performed. MRI is a better modality to pick up a missed intravascular thrombosis and the residual tumor [7].

The available histopathology report is expected to reveal at least whether the tumor was of favorable histology (FH) or anaplastic histology. If the patients could bring the slides or formalin-fixed paraffin-embedded (FFPE) tissue blocks, they should be sent for review, which will confirm whether the tumor is favorable or unfavorable. This histopathological differentiation would offer very vital prognostic information to guide the risk-stratified therapy.

Futuristically, it may be possible to extract DNA and mRNA from FFPE tissue blocks and know the status of TP53 or the presence or absence of LOH at 1p and 16q and management of patients tailored accordingly [8].

23.2.1 Management of Favorable Histology Tumors

A flank incision on the patient is difficult to miss, and its presence should immediately label this patient as the one whose local LN status is not known. If the patient has arrived within a week or 10 days of the initial surgery, and no information in this regard could be deciphered from the initial surgeon, then the patient may be taken up for laparoscopy or transverse transperitoneal laparotomy for LN sampling, and an attempt be made to assign the correct local stage of the tumor as per COG protocol. If the local LNs are positive, then the patient should be risk stratified as stage III standard risk and treated with adjunct therapy DD-4A and flank XRT. However, if the local LNs are negative, this patient should be treated as low risk and treated with regimen EE-4A.

In most of the centers of low- and middle-income countries (LMIC), the biological markers would not be available and the status of loss of heterozygosity (LOH) at 1p and 16q won't be available, so one may choose to treat this patient with the 3-drug regimen of DD-4A instead, especially where there was a suspicion of the excised tumor being large on the preoperative imaging. However, the side effects of anthracyclines should be kept in mind and informed consent of the caregivers be taken.

In the situation, where the caregiver does not give the consent for a re-exploration or if the patient has come quite late but doesn't have any local or systemic relapse as evidenced clinically or on fresh investigations, then this patient could be treated as stage III, and one can administer adjunct therapy for standard risk WT, i.e., DD-4A and flank XRT.

23.2.2 Management of Anaplastic Tumors

These patients would be stratified as high risk and be treated with COG AREN0533 protocol that is detailed in another chapter.

23.2.3 Management of Metastatic Tumors

It is important to understand the concept of local stage and disease stage in WT. The local staging is based on operative findings, while the disease staging on preoperative image findings of presence or absence of distant metastasis. The need for local XRT and its dose depends on local stage, while the disease stage determines the type and duration of ChT to the patient. If local staging is not known, then it is imperative to treat this patient as local stage III.

23.2.4 Management of Small-Sized Favorable Histology Tumors in Young Children (<2 Years)

The weight of the excised WT may not have been mentioned in the histopathology, and it would be impossible to know whether the excised had weighed 550 g. This weight would equate roughly with 7 cm in diameter if the excised tumor was spherical. Even if such dimensions were known from preoperative scans, it would be foolhardy to follow these tumors without any adjunct therapy. It would be preferable to treat such patients as *low risk* rather than *very low risk* and treat them with EE-4A regimen. In infants, the dosages of the ChT drugs need to be suitably reduced.

In a study from Tata Memorial Hospital, Mumbai in 2005, the authors had proposed that three-drug chemotherapy (vincristine, dactinomycin, and doxorubicin), what we know as DD-4A regimen in COG protocol today, be instituted for all the patients to compensate for lacunae in staging. The overall survivals for stages I–IV were 83%, 81%, 47%, and 75%, respectively [4].

23.2.5 Management of Tumors Where Both Histopathology and Staging Are Not Known

Such a patient should also be treated with adjunct therapy for standard risk WT, i.e., DD-4A and flank XRT. A close follow-up is mandatory as we may be treating an anaplastic WT with the adjunct therapy meant for FH tumor.

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Bilateral Wilms' Tumors

24

S. Kumaravel

24.1 Introduction

Bilateral Wilms' tumors (BWT) though not very common, the occurrence of bilateral tumors in kidneys of children especially less than 10 years, is almost always WT. BWT with an overall incidence between 4 and 8% may either present simultaneously at presentation, i.e., synchronous (6.3%) or at a later date in the opposite kidney (metachronous 0.85%) [1, 2]. BWT differ from unilateral WT (uWT) by presenting earlier—peak incidence about 12–14 months earlier than uWT [3], having much rarer incidence (only one in 20 of all WT), being frequently associated with germline genetic or epigenetic aberrations, and having a higher association of constitutional predisposing syndromes. Associations with syndromes not only pose difficulties during current management, but also have serious significant implications for long-term management, surveillance, and predisposition for poor renal outcomes. BWT is also associated with a much poorer outcome both oncologically—a 4-year event-free survival (EFS) of 56% for BWT vs. 85% for uWT [4] and poor renal functional outcomes, i.e., with 20-year cumulative incidence of *chronic kidney disease* (CKD) III or above of 12% in BWT against a measly 0.6% in uWT cases. The further challenges of BWT management include the complexity of decision-making, lack of clear guidelines or confusing guidelines, and lack of high-quality multicentric trials/studies exclusive to BWT until very recently [5]. Historically, neoadjuvant chemotherapy (ChT) used to be administered for long durations expecting a favorable response and resultantly the surgical treatment used to be inordinately delayed. Prolonged ChT has its own short- and long-term morbidity. Balancing appropriate timely surgical resections to maximize renal preservation at the same time obtaining good oncological outcomes is the greatest challenge of BWT [6, 7].

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24.2 Definition of BWT from a Management Point of View

WT is managed as per principles of BWT when [4, 6]:

1. Tumor masses more than 1 cm are present in both kidneys simultaneously (synchronous), or a single lesion of > 1 cm or multiple lesions of any size in the contralateral kidney.
2. A second tumor develops in the other kidney in a patient who has previously been treated for WT (metachronous).
3. WT in one kidney with nephroblastomatosis (NBL) in the other kidney.

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4. Syndromic patients with an initial presentation of uWT but carrying a high probability of BWT later may also benefit from being treated similar to those patients presenting with BWT.

24.3 Molecular Genetics and Predisposing Factors

Genetically predisposed tumors are likely to occur earlier as well as bilaterally, either synchronously or metachronously. Nephrogenic rests (NRs), which signify early disruption in renal development, are also associated with bilateral lesions [3].

BWT are frequently associated with germline genetic or epigenetic aberrations and a higher association of constitutional predisposing syndromes like WAGR syndrome (17%) and Denys–Drash syndrome (DDS) (20%). BWT has been shown to develop in 17–52% of various WT1 germline alterations. About 17% of Beckwith–Wiedemann syndrome (BWS) develop BWT; the penetrance of these aberrations is lower. However, incidence of BWT in patients Perlman syndrome is about 55%.

A pertinent question could be "why don't these syndromic patients develop bilateral WT in all cases"? This is because of the necessity of a second event (second hit) separately for each kidney prior to the development of a tumor. It is also shown that there exists a differential selection pressure for development of a second event for different mutations, case in point: DIS3L2 of Perlman's syndrome shows a greater incidence of BWT as compared to the IGF2/H19 mutations of BWS. Also, mosaicism exists in children, i.e., different organs or tissues or even cells in tissues may or may not demonstrate the aberration. Hence, each kidney may or may not have the mutation especially if the aberration occurs later in renal development.

24.4 Epidemiology

One of the important differences is the early age of onset. It has been shown in several studies that BWT occurs predominantly in 15–42 months (3.6 years) [3, 8], almost about 12–14 months earlier than the peak incidence of uWT cases. Moreover, the younger the age at presentation, higher is the chance of syndromic association. Two groups of syndromes are commonly associated with BWT in a majority of the cases—one associated with genitourinary abnormalities and the other with overgrowth syndromes.

24.5 Clinical Features

While the usual clinical features of uWT are also seen in BWT, the differences include earlier presentation, association with typical syndromes, aniridia, hemihypertrophy, and genital abnormalities/ambiguity in patients with BWT. Isolated genitourinary anomalies (not related to syndromes) are more common in association with BWT, mostly cryptorchidism and hypospadias. Hypertension should be looked for and documented.

24.6 Investigations

The child is investigated similar to any WT; however following additional points may need to be remembered and addressed.

A contrast-enhanced computerized tomography (CECT) (Fig. 24.1) scan of the abdomen and thorax, or a magnetic resonance imaging (MRI) of the abdomen, is necessary, more so in suspected cases of BWT (Fig. 24.2). Since smaller lesions and NRs are usually isoechoic to renal parenchyma on ultrasound (US), CECT or MRI is more sensitive in picking up BWT [9]. Additional information sought include number (in multifocal tumors), size, and volume of the tumor(s) in each of the kidneys, presence of enlarged retroperitoneal lymph nodes (LNs), preoperative tumor rupture, presence of ascites, and metastatic disease in liver and thorax. The goal in management of BWT is to maximise renal preservation without compromising on adequacy of oncological clearance and the 3-D computer volume rendering images and the 3-D printing models could help the surgeon to plan and execute complex sur-

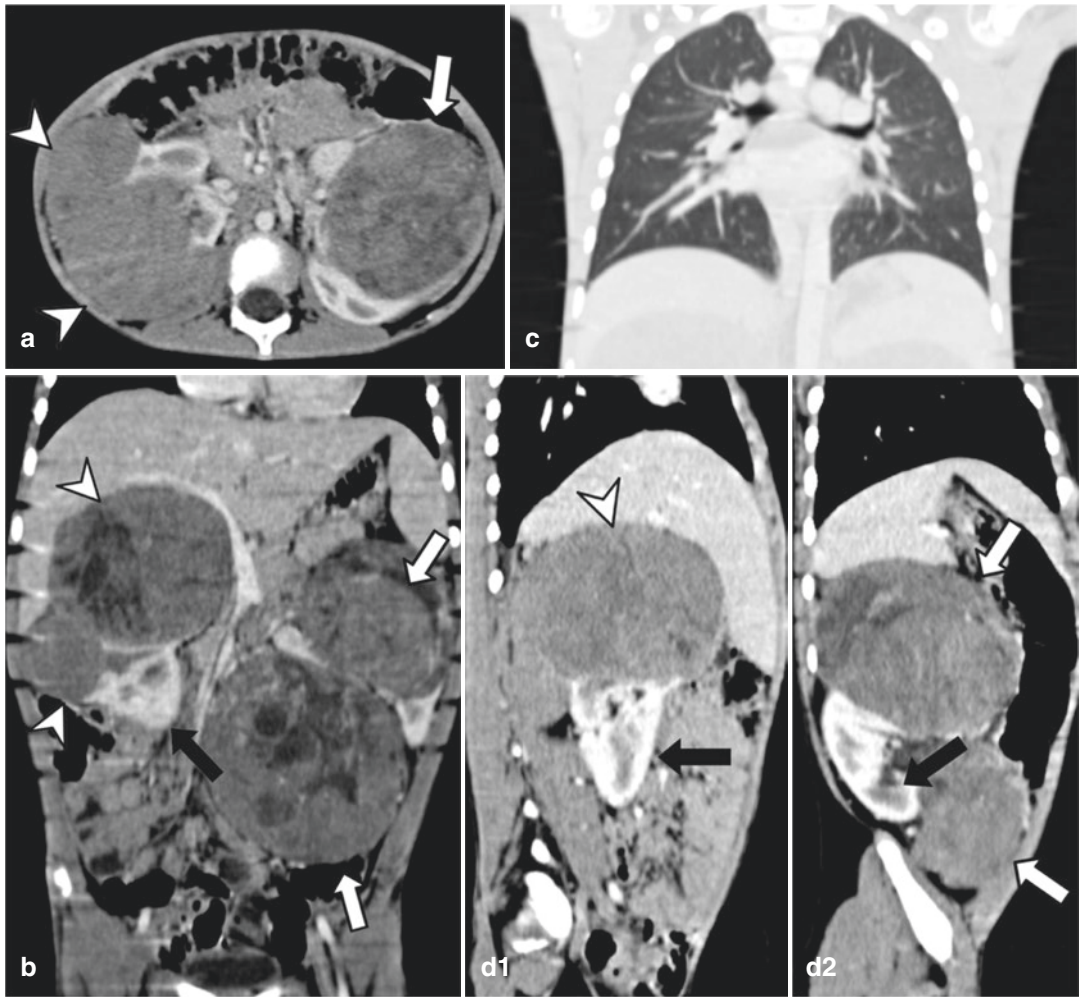

Fig. 24.1 CT abdomen, pelvis, and thorax showing bilateral multiple tumor masses (white arrows-tumor masses, black arrows-normal kidney). (**a**) Axial sections. (**b**) Coronal sections showing bilateral masses, left renal pedicle sandwiched between the two masses, right side vessels stretched over the upper pole mass. (**c**) CT Thorax- lung window showing no metastases. (**d**) Sagittal sections showing right kidney in **d1** and left kidney in **d2**

geries, preservation [7, 10]. Although MRI is nowadays being preferred for the abdominal examination, non-contrast CT scan of the chest is mandatory to rule out pulmonary metastases. Though CECT and MRI have shown to similar diagnostic accuracy as regard the locoregional disease, MRI has some distinct advantages in differentiating NBL. In T_1 weighted images, NBL is usually hypointense compared to the cortex; however, it is hyperintense in T_2 weighted images similar to the cortex [3, 11]. NR are also more lenticular or ovoid, smaller (<2 cm) and of uniform signal intensity, while WT is likely to be rounded [12]. MRI in post-ChT patients show bright lesions in T_2 and Short-Tau Inversion Recovery (STIR) sequences in case of active NR/WT; inactive NRs are dark on the same sequences. MRI, however, requires specific protocols to maximize its utility so that high-spatial-resolution post-contrast images are obtained. One can take advantage of diffusion-weighted MR images to detect smaller lesions, both WT and NR. Histological risk assessment especially in the post-ChT preoperative scans using whole tumor *Apparent Diffusion Coefficient* (ADC) is the new kid on the block, as it can predict stromal subtype histopathology, thus having a

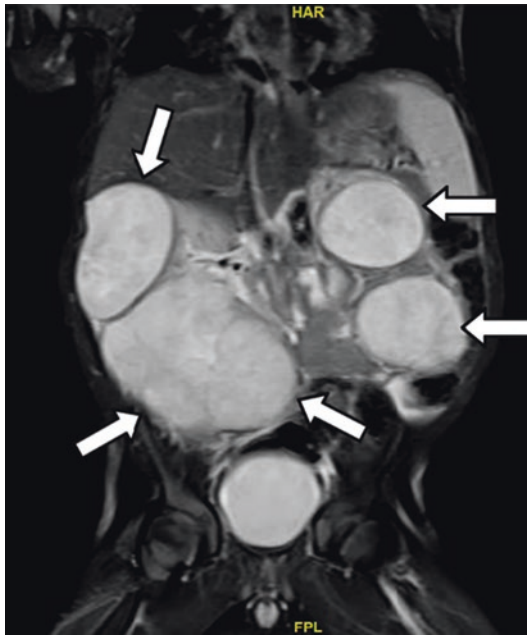

Fig. 24.2 MRI T2 coronal section showing multiple, hyperintense tumors in the right kidney (3 nodules) and left kidney (2 nodules)

prognostic role based on the inverse relation of ADC to the cellularity of the tumor. However, it is not shown to be useful in differentiating WT from NRs [9].

18-FDG PET-CT studies are currently not shown to have much role in the evaluation of BWT as it does not differentiate WT from NR [11].

24.7 Management of BWT

Unlike uWT, BWT has currently uniform management policy across the world. Upfront bilateral radical nephroureterectomies for BWT would render the child anephric and, hence, upfront ChT followed by conservative surgery is universally accepted as the ideal management with improved outcomes [4, 6, 13]. Neoadjuvant ChT is instituted to make bilateral nephron sparing surgery (NSS) a possibility in a majority of the cases without increasing local recurrences. Historically, two mistakes in management were done- too much/too long ChT preoperatively hoping for the tumor to shrink resulting in significant morbidity and performing too much radical a surgery resulting in unnecessary renal loss. These stand corrected today with the concerted efforts of multidisciplinary teams. Postoperative ChT and radiotherapy (XRT) is instituted appropriately keeping in mind to minimize the additional risks of morbidity including additional nephrotoxicity.

24.7.1 Neoadjuvant Therapy

The goal of neoadjuvant therapy is to reduce the size of the lesions so that bilateral NSS can be attempted in the majority of patients. Historically, multiple drugs with varied doses were administered. The current COG protocol (AREN 0534), also endorsed by Indian Council of Medical Research (ICMR) [14], is to administer two 3-weekly cycles of 3-drug regime VAD utilizing Vincristine (VCR), Actinomycin D (AMD), and Doxorubicin (DOX). SIOP, however, still advises VCR (1.5 mg/m^2) and AMD (45 μg/kg) for 4 weeks for non-metastatic BWT initially.

After 4 of 6 weeks of ChT as per the protocol being followed, the tumor response is assessed by US (SIOP) or CECT (COG) to document any decrease in size of the tumors and to assess the feasibility of NSS using RECIST criteria.

In *COG* protocol (AREN 0534), in case the tumor is responding to the ChT as demonstrated by a decrease in 50% volume reduction or 30% reduction in the sum of the diameters of target lesions (using Response Evaluation Criteria in Solid Tumors [RECIST]), but NSS is still not feasible, ChT can be continued for a further period of 6 weeks [4, 6]. Surgery is performed regardless of tumor status at the end of 12 weeks. The reason to avoid prolonged ChT beyond 12 weeks is that poor response may be due to unfavorable histologies. These include diffuse anaplasia (DA), non-responding blastemal predominance, which do not respond to further ChT. It may also be due to the contrasting scenario of stromal predominance, which may have adequately responded but has not shrunk in size. Rhabdomyomatous transformation

does not shrink or may even increase in size; however, this is a sign of good response to ChT. There is also a concern that anaplastic transformation is associated with prolonged administration of neoadjuvant ChT [15]. For the above reasons, the true picture is revealed only on histopathological examination of the excised specimen.

However, if the initial response after 6 weeks of neoadjuvant ChT is poor, i.e., <30% reduction in tumor volume, then bilateral open wedge biopsies are advocated in these patients. If anaplasia is detected, then an intensified ChT with VCR, AMD, DOX, Cyclophosphamide (CTX), Carboplatin (CARB), and Etoposide (ETOP) is used for further 6 weeks. If blastemal predominance is detected, regimen I, i.e., VCR, AMD, DOX, CTX, and ETOP, is advocated for 6 more weeks. For all other histologies, VAD is continued for 6 more weeks. In any case, surgery is carried out after 12 weeks of ChT. Though bilateral NSS is strongly recommended, if it is not feasible, then unilateral radical nephrectomy on the worse side with NSS on the contralateral kidney is carried out.

In *SIOP* protocol, if the disease is stable or progressive on US review at 4 weeks of 2-drug regimen, then DOX (50 mg/m^2) is added and second assessment at 8 weeks is carried out with CECT. Newer recommendations of CARB, ETOP, in lieu of DOX so as to spare the child from doxorubicin toxicity are also noted [16]. If tumor response is present, ChT is continued for a further 4 weeks and NSS is carried out. Note the avoidance of prolonged use of neoadjuvant ChT beyond 12 weeks in SIOP also, at which point, the patient would be subjected to surgery [17]. In any case, at some stage, bilateral NSS is performed either in a single stage approach or in two separate operations performed not more than two post-operative cycles apart. If staged, then the less involved kidney should be operated on first. Complete nephrectomy on one side with NSS on the opposite side is acceptable providing enough functional renal tissue can be preserved. Rarely, the patient may need to undergo bilateral nephrectomy with a planned renal transplantation a year or 2 later if complete response (CR) is achieved.

A biopsy is not indicated in either of the two protocols prior to starting neoadjuvant ChT unless there are very atypical features like age more than 10 years, unusual imaging findings like encasement of vessels, voluminous lymphadenopathy, unusual metastasis like bone(<2 years) or brain, etc. are present [12, 18].

24.7.2 Surgical Management

Several surgical options are available in the management of BWT [6, 11].

They include:

1. Bilateral NSS.
   (a) Partial nephrectomy—ensuring a rim of normal renal tissue separating tumor from the resection margin.
   (b) Marginal resection—tumor along with its pseudocapsule intact; however, no normal renal tissue margin is present.
   (c) Longitudinal partial nephrectomy for central tumors [19].
   (d) Bench surgery with ex situ perfusion and autotransplantation [20].
2. Nephroureterectomy on worse side and NSS on the contralateral side.
3. Bilateral nephroureterectomy and delayed renal transplantation.

The twin goals of adequate oncological clearance with maximal renal preservation are best met by Bilateral Marginal Resections of all tumors, however, may not be feasible in all. Large series from some of the acclaimed centers reiterate that this is feasible in about 90% of cases despite of seemingly unfavorable initial imaging [6].

After administration of neoadjuvant treatment, the surgical team has to consciously decide whether decision to operate both sides simultaneously, or sequentially with a 1- to 4-week gap. SIOP recommends sequential surgery with the better side carried out first and carry out the next after 1–2 weeks for recovery [17]. However, acclaimed centers like St. Judes, Memphis, recommend simultaneous NSS citing no proven

advantage of sequential surgeries [21]. Given the rarity of BWT and the duration and blood loss associated with NSS, varying levels of expertise/experience available, prudence suggests sequential surgery may be carried out until evidence from suitable studies suggest that simultaneous NSS is superior.

Radical nephroureterectomy is recommended even in BWT in certain situations, and these are the presence of DA and supra-hepatic IVC tumor thrombus not responding to ChT (incomplete regression). It is however extremely rare for both the kidneys to have DA, and hence usually NSS on the contralateral side is feasible.

Evaluation of the feasibility of NSS is usually carried out using multiphase contrast-enhanced CT scan of the abdomen and pelvis (Fig. 24.3). 3D reconstructions are also carried out. Even though predefined criteria are not available at present, polar and/or peripheral lesions, with no encasement or invasion of the renal vessels, are easy to excise. Even though the large tumors or those with proximity to renal vasculature, masses abutting the vessels, central masses, and multiple tumors may appear ominous on imaging, it may be feasible to undertake NSS safely with minimal risk of positive margins by one of the techniques mentioned above. It is to be remembered that WT grows by compressing adjacent parenchyma, which forms a pseudocapsule (or even a fibrous capsule), which lends itself to careful dissection outside the tumor margin, irrespective of the size of the tumor (Fig. 24.4). Acceptance of additional expertise or referral may save the patient from nephrectomy in some of these cases [6].

Given the varieties of nephron sparing methods described and the different terminologies used leading to great confusion (e.g., wedge resection, partial nephrectomy, polar nephrectomy, tumorectomy, enucleation, etc.), a standardized format for reporting NSS is essential. Such a standard reporting format has been described [13, 22] with four parameters, viz., *Surgical Technique*

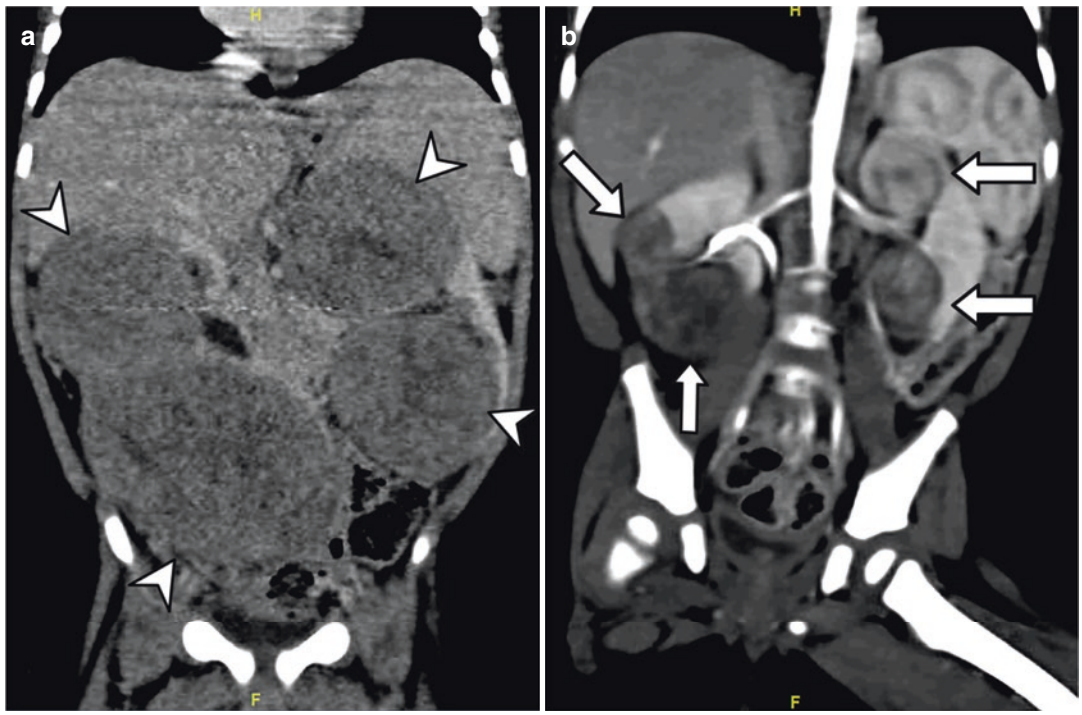

Fig. 24.3 CECT abdomen showing response to ChT (**a**) at presentation. (**b**) After post-treatment drug ChT reduction of more than 50% volume noted (arrowheads, pretreatment lesions; white arrows, post-treatment preoperative lesions)

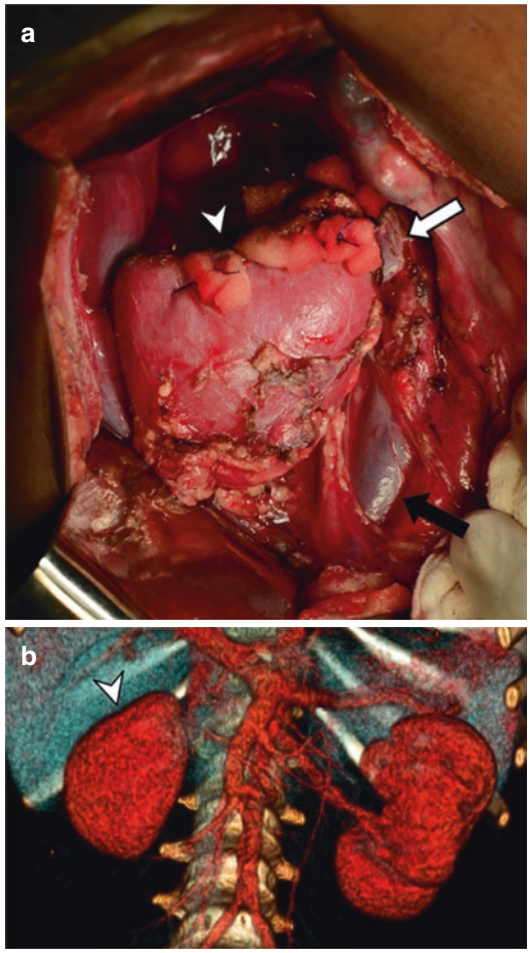

Fig. 24.4 (**a**) Intraoperative photo after completion of marginal excision and in folding of edges sutured with pledgeted sutures (arrowhead). Renal vein is shown by white arrow and IVC shown by black arrow. (**b**) Tumors post bilateral NSS; CECT (volume rendered image) showing tumor remnant of the right kidney (arrowhead) with approximate reniform shape

(partial nephrectomy: i.e., with a rim of normal tissue or enucleation, i.e., without a rim); *Surgical Resection Margin* (surgeon's description of presence of tumor breach or doubtful breach or with intact pseudocapsule); *Pathological Resection Margin* (i.e., intact or tumor breach present); and *Remaining Renal Parenchyma* (estimated by the surgeon as a percentage at end of surgery).

Use of standardized reporting will at least in the future ensure accurate comparable data to understand and apply the best possible surgical intervention.

24.7.3 Adjuvant Therapy for BWT

All cases of BWT require some form of adjuvant therapy. The actual adjuvant therapy depends on staging (factors including tumor margins, LN status, the occurrence of tumor rupture preoperatively or during surgery, etc.) and risk stratification based on histological criteria (anaplasia, blastemal predominance, percentage of necrosis, etc.) [23, 24].

Staging and risk stratification (according to SIOP 2001 protocol) is similar to uWT, and each side has to be staged (stage I–III) and risk-stratified separately. Treatment is based on the higher stage and risk stratification recorded. As far as SIOP recommendations are considered, the adjuvant treatment is same as that for uWT of comparable stage and risk except for stage I low risk, where ChT of stage II low risk, i.e., 27 weeks of VA, is advocated [16, 17].

AREN 0534 has recommended the following adjuvant treatment based on histological and stage criteria [4]:

1. BWT with stage I and II *completely necrotic tumors* and stage I *Intermediate Risk (IR) tumors* are treated with 19 weeks of VCR and AMD.
2. BWT with stage I *blastemal predominant*, stage III and IV completely necrotic tumor, stage II–IV IR, stage I–III *focal anaplasia*, and stage I *diffuse anaplasia* are treated with 25 weeks of VAD.
3. BWT with stage II–IV blastemal predominant receive VCR, AMD, DOX, CTX, and ETOP for 28 weeks.
4. Stage IV focal anaplastic tumors and stage II–IV diffuse anaplastic tumors in BWT will receive VCR, AMD, DOX, CTX, CARB, and ETOP for 31 weeks.

Significant differences in drugs used exist between SIOP and AREN0534, especially in the higher-risk groups.

In bilateral WT, paraaortic nodes cannot be accorded to the one or the other side. If only LNs are positive, then XRT is given only to paraaortic LNs. However, the local renal specimen will be

staged individually and could be stage I, II, or III (positive margins, residual disease left after surgery, tumor rupture). If one or both sides are stage III (any histology) or stage II anaplastic, then accordingly unilateral or bilateral flank XRT along with XRT to paraaortic LNs would be administered. Dose to the whole kidney should not exceed 10–12 Gy (12 Gy maximum dose), even if there is unfavorable histology (UH). Brachytherapy could be given in selected cases. Whole abdominal irradiation (WAI) is reserved for large tumor spill intraoperatively involving areas outside the tumor bed as determined by the surgeon, tumor rupture before surgery, and presence of peritoneal metastases [4].

24.8 Special Circumstances

24.8.1 Completely Resolved Tumors

BWT that have completely disappeared on 6 and 12 weeks of neoadjuvant ChT are treated as per the stage of the disease, i.e., localized disease or metastatic disease before ChT. Non-metastatic CR in both kidneys is treated with a further two-drug regime of VCR and AMD for a duration of 19 weeks and metastatic disease with CR with VAD for 25 weeks; no surgery is performed [4].

24.8.2 Metastatic Disease

Metastatic disease at presentation with CR bilaterally with only neoadjuvant ChT is treated with further VAD for 25 weeks [4, 6].

24.8.3 Positive Margins

Positive margins on histology convert the disease to stage III, and the patient receives flank XRT. However, in the presence of diffuse anaplasia with positive margins, completion nephrectomy with adjuvant flank XRT should be seriously contemplated, considering the poor prognosis of patients with diffuse anaplasia.

24.9 Renal Transplantation

Children who are rendered anephric due to bilateral nephrectomy either in synchronous or metachronous disease or develop *End Stage Renal Disease* (ESRD) due to any reason are in requirement of renal transplantation. Traditionally, this has been delayed for 2 years of EFS before being offered as this is the duration of maximal relapse. However, newer data suggests earlier transplantation as equivalent outcomes [25]. In cases where live-related donors are available, 1-year wait period has been suggested to be sufficient.

24.10 Follow-Up and Outcomes

ICMR adapting from SIOP provided the following guidelines for follow-up of children with BWT [14]:

1. Along with clinical examination including blood pressure monitoring, all children with BWT should undergo chest X-ray and ultrasound evaluation every 2 monthly for the first 2 years followed by 3 monthly for the next 2 years and annually for 10 years.
2. Six-monthly evaluation for proteinuria and serum creatinine is also recommended indefinitely.

24.11 Prognosis and Long-TermOutcomes

Unlike in uWT, BWT is prognosticated against two parameters—oncological and renal functional outcome.

Oncologically speaking, metastatic disease at onset, UH including diffuse anaplasia, advanced loco-regional stage, and age at diagnosis of more than 3 years seem to be associated with poor prognosis [11]. Surprisingly, positive tumor margin in NSS does not seem to increase recurrences provided XRT is given [26].

Renal functional prognosis is related to the type of surgery performed, prolonged ChT and/or concurrent XRT, metachronous disease, associ-

ated syndromes especially WT1 related, e.g., DDS and WAGR (20-year ESRD rate of 82.7 and 43.3, respectively) and progressive disease ending in bilateral nephrectomy. Earlier age at disease (i.e., <24 months) is also associated with higher ESRD [18].

BWT has been associated with a much poorer prognosis compared to uWT, a 4-year EFS of about 56% (NWTS-5) and 10-year overall survival (OS) of only 69% (SIOP) [7]. Historically, long-term renal outcome in context of ESRD is of crucial importance and found to be 4% at 3 years in synchronous and 19.3% in metachronous BWT [14]. The same increases to 12% at 20 years and much worse for syndromic children up to 80%. Poor outcomes are multifactorial including increased anaplasia in BWT, inappropriate staging, and prolonged ChT [15].

Several single-institution studies and the recently reported multicenter trial AREN 0534 report improved outcomes with an enhanced application of NSS and better utilization of preoperative ChT. Davidoff et al. reported (about 90% NSS rate) a 3-year EFS of 64% with a 4-year OS 85.7% [1]. With a maximum follow-up of 13 years, none had estimated glomerular filtration rate (eGFR) <60 and 8.3% had CKD stage 2. AREN 0534 reported a 4-year EFS and OS of 82% and 94.9%, respectively. These remarkable results seem to stem from two interventions, i.e., decreasing the overall duration of preoperative ChT and tailoring the postoperative ChT according to post ChT histological response [4]. The utilization of 3-drug preoperative ChT which has been shown to cause greater shrinkage may also have led to greater utilization of NSS.

While the short-term renal functional outcomes of increased use of NSS bilaterally is encouraging, more long-term data with a larger number of patients will provide greater clarity.

24.12 Future Directions

While there are many unanswered questions specific to BWT, some appear more urgent than others.

The utility of three drugs vs. two drugs as preoperative ChT seems to have been established both in AREN 0534. Assessing response to neoadjuvant ChT seems to be still dependent on imaging, and current imaging techniques seem inadequate. The alternative of performing open biopsies seems too invasive. Tumor shrinkage or reduction as assessed by CECT is currently accepted. Failure of ChT to result in significant size reduction does not always mean failure of ChT for reasons mentioned previously and is currently the Achilles heel of preoperative ChT evaluation. Advanced functional imaging may be the solution. Solutions are being searched using advanced functional imaging. Apparent Diffusion Coefficient (ADC) can be calculated using diffusion weighted MRI. It has been shown that the higher the cellularity of tissues, the lower is the ADC; conversely poorly cellular areas show higher ADC value [27, 28]. This inverse relationship of ADC with cellularity of tissues can be harnessed to differentiate response to ChT.

A second area of constant debate: whether enucleation/marginal resection is adequate, or partial nephrectomy is superior. While single-center studies have tried to answer this question with small but significant numbers, large multicentric trial-based data would help surgeons globally to make informed decisions.

Thirdly, the question of evaluation and assessment of renal function in the post-operative patient. Absolute eGFR, the current standard for evaluating renal function, has been criticized as not being clinically significant in patients undergoing renal resections as it is for patients developing CKD due to medical conditions [29]. There is also considerable variability in evaluating and reporting renal outcome measures and standardizing the same will help enormously.

Epidemiological studies along with molecular genetic analysis when carried out may also be of great help not only in assessing the contribution of the various mutations to bilateral disease but will also clarify their role in the risk of developing renal failure. It may also provide clues to which patient may require NSS, thus helping in adapting and making personalized treatment plans for individual patients.

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Wilms' Tumor in Horseshoe Kidney and Solitary Kidney

25

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25.1 Wilms' Tumor in Horseshoe Kidney

Wilms' tumor (WT) in horseshoe kidney (HSK) presents as a unique diagnostic and a surgical challenge. The incidence of HSK in general population is 1 in 400 [1]. WT occurs uncommonly in HSK and the incidence is 0.4–0.9% of all WT [1, 2]. Renal cell carcinoma and other renal pelvis tumor are more common in HSK than WT [1, 3]. Still, a child with HSK has twofold increased risk to develop WT than the general population [1, 3, 4]. WT can arise in either moiety or the isthmus in HSK and can be unifocal or multifocal. In a National Wilms Tumor Study Group (NWTSG) report, WT was present in both moieties of HSK in 7% of patients and was considered bilateral disease [2]. Metanephric blastemal elements sequestered in the isthmus have malignant potential and cause WT. Other theory is the embryologic alteration causing HSK itself, after second event may give rise to WT [1, 3, 4]. The NWTS did not identify any WT1 mutations in patients with WT and HSK. The incidence of nephrogenic rests in HSK with WT was also found similar to that in unilateral WT [2, 5]. Routine screening of people with HSK for WT is not warranted as the overall incidence of WT development is less than 0.001% [1].

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Presentation of WT in HSK is the same, as for any other case of WT with respect to age, sex, clinical stage at presentation, and histological pattern [4]. Asymptomatic abdominal mass is the most common presenting symptom. Others can be abdominal pain, hematuria, anemia, and hypertension [6]. Other congenital anomalies like chromosomal (Edward syndrome, Turner syndrome), cardiac, genito-urinary, and musculoskeletal abnormalities were present in 44% patients of WT with HSK [2].

Pre-operative imaging including ultrasound and computerized tomography (CT) scan for WT can miss the diagnosis of HSK. More often than not, the diagnosis of HSK is made intra-operatively. In the NWTS, the diagnosis of HSK was missed pre-operatively in 13/41 WT patients (32%). A large size tumor crossing midline may obscure the isthmus and HSK may be missed. Also, it is difficult to distinguish a tumor in the isthmus from a lower pole tumor [2, 7, 8]. HSK has a lot of anatomical variations in shape, blood supply, and collecting system. There may be duplicated or triplicated renal arteries, unilaterally or bilaterally. The isthmus may get its blood supply from either of the renal arteries, aorta, inferior mesenteric artery, or iliac arteries [4]. The ureters may be displaced anteriorly and medially or laterally depending upon the origin of tumor. Hydronephrosis may be present due to compression of one or more ureter [3]. Pre-operative knowledge of vascular anatomy and collecting system can help in planning safe

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resection and minimizing complications. CT-angiography with 3-D reconstruction or a magnetic resonance (MR) imaging with MR angiogram with arterial and venous phase study can assist in localization of the tumor and clearly defining vascular anatomy in the presence of HSK [1, 2].

A supra-umbilical wide transverse incision is considered the best. HSKs are usually located lower than normal kidneys within the abdomen. In the majority, the isthmus lies just in front of the aorta and IVC, at the level of the 3rd to 5th lumbar vertebral bodies. Pre-operative insertion of ureteric stents helps identifying the ureters and averting ureteric injury [9].

WT arising in either moiety of HSK is staged and treated the same as WT in a unilateral normal kidney, other than that there is a global consensus about administering neoadjuvant chemotherapy (ChT) in every patient [10]. Removal of the involved kidney with isthmus, along with meticulous hemostasis, is recommended followed by the stage appropriate ChT [1–3]. Removal of isthmus is important because if the remaining kidney does not drain its urine, a urinary fistula may form. If the tumor is arising from the isthmus, then isthmusectomy along with removal of both lower poles is done. Lymph node sampling protocol also remains the same as in unilateral WT.

In cases with multifocal disease, an accurate estimation of normal uninvolved renal parenchyma needs to be done pre-operatively, and the patient should be treated with NSS as per protocols for bilateral WT. The aim of surgery would be maximal preservation of unaffected renal parenchyma without sacrificing oncological control [11].

Neo-adjuvant ChT can downstage and reduces the bulk of the disease enabling safe and a complete resection, lesser chances of tumor rupture/spill, and maximal preservation of renal parenchyma and function. Of the 41 cases of HSK in NWTS, 37% were deemed inoperable at the time of initial exploration. But after ChT, all were amenable to resection [2]. Pre-treatment FNAC/biopsy is recommended before starting neo-adjuvant ChT.

Abnormal anatomy and blood supply makes the resection difficult. There is increased risk of urine leak and ureteral injury. Any injury to urinary collecting system must be repaired.

The prognosis of WT in HSK depends on the stage and histology. The incidence of anaplasia in WT in HSK is similar to general WT population [2]. The estimated 4-year overall survival (OS) of WT in HSK was 86%, similar to the patients with unilateral WT. [2]

25.2 Wilms' Tumor in Solitary Kidney

Management of WT in solitary kidney is a difficult proposition. Other kidney may be non-functional due to unilateral renal agenesis, dysplasia due to severe reflux, or nephrectomy of previously involved kidney and development of metachronous WT in the remaining kidney [12, 13]. Children's oncology group (COG) recommends nephron sparing surgery (NSS) after neo-adjuvant ChT with Vincristine, Actinomycin-D, and Doxorubicin under certain special circumstances such WT in a solitary kidney, bilateral WT, suprahepatic inferior vena caval (IVC) thrombus, and severe respiratory distress due to extensive pulmonary metastatic disease [14]. It reduces the amount of tumor burden, thus enabling NSS, and decreases the incidence of tumor spillage [15]. Pre-treatment biopsy is advisable, but is not mandatory. After 4–6 weeks of ch ChT, partial nephrectomy, i.e., complete excision of tumor with a rim of healthy renal parenchyma is performed. Partial nephrectomy is preferred over enucleation, which involves bluntly dissecting outside the pseudocapsule of the tumor. It may be rapid but has a higher risk of tumor spillage and positive margins [16, 17]. Davidoff et al. reported positive margins in 7/51 resected specimens (14%) after enucleation in a series of NSS in bilateral WT [15].

NSS may still not be feasible following neo-adjuvant ChT in certain patients. Polar tumors localized within the kidney but outside the hilum and sparing the sinus, not involving the renal vein or IVC in whom more than two-thirds to half of renal parenchyma can be preserved and have favorable histology, are amenable to NSS [18]. A

technique of performing longitudinal partial nephrectomy for central tumors involving the renal hilum has also been described [19]. The patients can develop end stage renal disease (ESRD) after NSS. A functioning remnant of at least 25–33% of one kidney is sufficient to avoid ESRD [16]. In most series with bilateral WT, progression to ESRD occurred in 8–18% of patients [15, 18]. ESRD may develop immediately following surgery because of the removal of bulk of renal parenchyma or may develop later due to chronic kidney disease (CKD) as a result of hyperfiltration injury in remaining nephrons [20]. Risk might increase during puberty due to decrease in glomerular filtration rate and increased deterioration of renal function in CKD [21, 22]. The patients in the second group who develop ESRD late following CKD had good opportunity to receive transplant (79% within 5 years) and have higher overall survival (81% at 5 years) [20].

The patients with ESRD after NSS/nephrectomy require permanent renal replacement therapy (dialysis + renal transplant). Renal transplantation can be done after completion of ChT. Matsukura et al. report a case of a 2-year-old girl with WT in a solitary kidney who after pre-operative ChT underwent resection of the tumor followed by hemodialysis and received a kidney transplant from her mother after completion of her ChT [23]. A delay of 1–2 years following WT treatment before doing a transplant was recommended because of deaths due to sepsis and tumor recurrence in patients who underwent transplant early [24, 25]. European best-practice guidelines recommend a 2-year waiting period before transplant [26]. Grigoriev et al. re-evaluated the recommended waiting time and proposed that patients of WT who subsequently develop ESRD should not be subject to a 2-year delay and can immediately be considered for kidney transplant [20].

WT in solitary kidney poses a unique surgical challenge, and the involvement and extent of disease may not allow application of generally applied principles. There are even reports of successfully treating WT in solitary kidney in whom surgery was not possible without rendering the child anephric with ChT alone [12, 13]. Such adversity mandates an individualized treatment plan. A long-term careful follow-up is necessary to support and safeguard future of such children.

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26 Very Large Tumors Not Responding to Chemotherapy/ Locally Infiltrating Tumors

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26.1 Introduction

Surgery remains the mainstay of treatment in management of Wilms' tumor (WT). In majority of the cases even when tumor is infiltrating into the adjacent organs, the organs can be freely dissected from the tumor. The goals of surgery are to perform a safe operation, remove the kidney without intraoperative spill, sample adequate number of lymph nodes (LNs), and document all findings such as preoperative or intraoperative tumor rupture, extension into other structures, and the presence of peritoneal metastasis [1, 2]. In case of very large or locally infiltrating tumors, primary surgery may not be feasible. Contraindications to upfront resection of WT are few and include unacceptably high risk of anesthesia or surgery due to the disease burden in cases with very large or locally infiltrating tumors which may cause increased risk of operative morbidity [3]. Preoperative chemotherapy (ChT) in some of these high surgical-risk cases provides a window to improve the nutrition, hydration, and general health status of the patient so that subsequent major surgery can be undertaken with acceptable risk.

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26.2 Definition of Large Inoperable Tumor

Despite an aggressive upfront surgical approach, the recent COG studies (AREN0532 and AREN0533) have incorporated surgeons' judgment for eligibility for resection of large tumors with involvement of contiguous organs, which have often undergone delayed resection to avoid spill, residual disease, and surgical complications [3]. The factors which help the surgeon to decide operability are the size of the tumor, large tumor mass that is immobile or fixed to adjacent organs, tumor that is poorly encapsulated and infiltrating into surrounding structures, and tumor mass lacking clear margins on imaging or seen to be having enlarged LNs extending beyond tumor margins [4].

Relationship of tumor size to prognosis has been addressed in several studies including that of Provenzi et al. from Brazil who observed that tumor volume after preoperative chemotherapy (TVAPQ) was the only variable statistically associated to the prognosis as in their study every increase of 10 ml in tumor volume increased the risk of death by 2% [5].

Japan Wilms Tumor Study-2 (JWiTS-2) has recommended that tumor size greater than 12 cm or tumor volume more than 1000 ml should receive preoperative ChT to reduce surgical risk [6].

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26.3 Imaging Technology

Modern advanced imaging technology aids, such as 3-D computer reformatting, and printing models may assist the surgeon in better assessment of tumor operability in management of very large WT [3]. Besides the size of tumor, it was observed in JWiTS-2 that contralateral extension of tumor and compression of great vessels are other important imaging-based surgical risk factors [7]. In their study, more than half of the tumors became stage III due to surgical procedures, and hence their recommendation is that all large tumors with image identified surgical risk factors should undergo needle biopsy for confirmation of diagnosis followed by preoperative ChT instead of attempting aggressive primary tumor resection [6].

26.4 Pre-treatment Core-Needle Biopsy

Pre-treatment core-needle biopsy is advised in only selected patients with specific clinical and imaging characteristics (age above 7 years, with septicemia or UTI or psoas infiltration, hypercalcemia, imaging showing very large LNs or intratumoral calcification or almost totally extrarenal tumor or no visible normal renal parenchyma, or presence of lung metastasis in child below 2 years, or presence of extrahepatic or extrapulmonary metastases) [8]. High proportion of blastemal cells in the needle-biopsy has been known to be associated with greatest decrease in tumor volume; so this may have some prognostic value too [9].

26.5 Preoperative Chemotherapy

The management approach of this subgroup of WT in both COG and SIOP protocols is somewhat similar as preoperative chemotherapy (ChT) is preferred.

In the *COG* protocol, tumors that do not undergo upfront surgery are considered stage III and administered initial chemotherapy with 3 drugs—Vincristine (VCR), Actinomycin-D (AMD), and Doxorubicin (DOX) for 6 weeks [1, 3]. If sufficient (~30%) tumor shrinkage has occurred, then patient could be taken up for surgery, or another 6 weeks of ChT could be administered (a maximum of 12 weeks of preoperative ChT). If at initial imaging at 6 weeks, no appreciable tumor response is seen, they undergo percutaneous core-needle biopsy (PCNB) or open wedge biopsy for confirmation of diagnosis and treated accordingly. All such patients are considered local stage III from the point of postoperative ChT.

In *SIOP* protocol, the neoadjuvant ChT given includes 2 drugs—VCR and AMD for 4 weeks followed by surgery. Response evaluation criteria in solid tumors (RECIST) is a widely accepted imaging-based assessment of the response to neoadjuvant ChT in solid tumors, and 30% or more reduction in maximum tumor size at the end of 4 weeks of ChT is considered as partial response [10]. In children due to concerns of excessive radiation exposure with repeated CT imaging, there is a trend towards favoring functional imaging options such as magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG PET), but still the anatomical response to treatment can best be judged by conventional radiology.

UKW3 study has also shown that delayed nephrectomy preceded by preoperative ChT is associated with fewer surgical complications compared with upfront nephrectomy [11]. It has been reported in another UKW-3 study that downstaging of the tumor with preoperative ChT also helps spare 20% of the patients from XRT or DOX and its attendant toxicity [12].

However, progression or increase in size of localized WT has been also reported in 5% of patients during preoperative ChT in the SIOP 93-01 study, and these patients had poorer event free survival (EFS) and overall survival (OS) independent of the stage distribution and histopathological risk group [13]. Similarly, intratumoral bleeding is also known to result in increased tumor size but without compromising treatment outcome. In SIOP 93-01 and 2001 studies, a cut point volume of 500 ml in patients with

intermediate-risk tumors, excluding those with epithelial and stromal subtypes, showed a significant difference in outcome—the 5-year EFS and OS were 88% and 95% for smaller tumors, compared to 76% and 90% for larger tumors [14]. A worse outcome for post ChT large volume tumors was reported by Graf et al. also [15].

26.6 Tumor Embolization

Occasionally, neoadjuvant ChT may be ineffective or may cause tumor necrosis and hemorrhage into the tumor with sudden significant enlargement of the tumor necessitating early or emergency surgery. In such cases of inoperable WT, in acute life-threatening situations like this, interventional radiology procedure of endovascular selective angio-embolization of affected artery to control the hemorrhage can be undertaken which allows the patient to be stabilized prior to subsequent nephrectomy [16, 17]. In advanced "inoperable" WT, preoperative transcatheter arterial chemoembolization (TACE) has been advocated as an effective modality of treatment. Li et al. have reported that preoperative chemoembolization combined with short-term systemic ChT is safe and effective treatment option in these patients as it helps induce more massive necrosis of tumor and periaortic LN metastases, and thus further improves the tumor complete resection rate and helps achieve a high EFS rate [18].

For children where there is inadequate response to ChT with no tumor shrinkage or progression of tumors despite upgrading the ChT (± TACE), surgery should be performed as soon as possible. R1 resection is acceptable, but it classifies the tumor as stage III and further postoperative ChT and radiotherapy (XRT) has to be given accordingly.

26.7 Surgical Considerations

Very large tumors are likely to be hyper-vascular and have large areas of necrosis and hence require careful handling of tumor to prevent intraoperative rupture. A generous transabdominal approach (large, transverse supraumbilical incision) is best for resection of these large tumors [4]. For tumors arising from upper pole of kidney and extending up to diaphragm, a thoracic extension of the abdominal incision through the 8th or 9th rib and converting to a thoracoabdominal incision helps with improved exposure for easier and safe tumor resection [1]. Majority of WTs do not invade other organs and are very responsive to ChT; hence, radical en-bloc resection of part of liver, spleen, pancreas, or colon are generally not required and should be avoided as this is associated with increased frequency of complications [1, 4]. In rare cases, advanced right-sided tumors may extend into the liver, and en-bloc wedge resection or even hepatic lobectomy may be necessary in these patients. In cases where tumor is adherent to a small part of diaphragm or psoas muscle or tail of pancreas, then that small part can be resected in continuity at the time of nephrectomy. Adrenal glands were found to be involved in 4.4% of patients in NWTSG data, and intraoperative tumor spill was reported to be higher in patients undergoing adrenalectomy which is likely to be due to larger tumor size or technical factors [19]. Hence, adrenalectomy should not be considered mandatory during radical nephrectomy for WT, and adrenal glands should be preserved but not at the risk of incomplete excision of tumor or rupturing the tumor. In large tumors, it may not be possible or safe to ligate the hilar vessels first, and in such cases tumor mass is adequately mobilized by lateral and posterior dissection so as to clearly visualize, isolate, and ligate the vessels at the hilum [4]. The risk of duodenal and mesenteric vascular injuries is also higher.

After removal of tumor mass, titanium clips should be placed to outline the extent of the tumor area or to mark any suspicious residual disease. Placement of titanium clips helps in providing further targeted XRT with minimal side effects.

26.8 Role of MIS

In very large tumors, minimally invasive surgery (MIS) has very little role except for may be helping with tissue diagnosis which is more safely done with image-guided percutaneous core-needle biopsy. MIS is recommended only for small tumors involving less than one-third of kidney, with less than 300 ml volume, those which are centrally placed with a rim of normal renal tissue and not infiltrating extrarenal structures. No outcome advantage has been reported with MIS in WT [20].

26.9 Adjunct Therapy

Post-operative ChT is continued as per the stage and histological risk category. In the SIOP protocol, only patients who have stage III disease because of positive lymph nodes (LN), positive surgical margins, tumor rupture, or peritoneal implants receive flank or abdominal XRT. This cohort of patients usually receive 10 cGy flank XRT; whole abdomen radiation (40 cGy) reserved for those with intra-operative ruptures with diffuse contamination and anaplastic histology [1, 3]. Unlike COG protocol, the patients who had needle biopsy and/or preoperative ChT but no other indications mentioned above are not upstaged to stage III and are not administered flank XRT in SIOP protocol. Irtan et al. [21] observed that in the UKW3 trial, the patients with initially large, inoperable WT at diagnosis, after receiving fairly prolonged three-drug preoperative ChT, ultimately did not have stage III tumor and had a good outcome without abdominal XRT. UKCCLG has shown that omission of XRT does not have an adverse impact on survival in these patients [22].

26.10 Situation in Developing Countries

In developing countries like India where large tumors with advanced stage are common due to delayed presentation and in children with poor nutritional status, the importance of neo-adjuvant chemotherapy increases many folds [23, 24]. Hence, it is prudent to recommend neo-adjuvant ChT for all patients of WT in India although high volume centers, that have developed expertise over the years, can develop the best strategy suited to their population. Meta-analysis of the effect of preoperative ChT on WT published by Liu et al. has concluded that preoperative ChT combined with surgery can increase the EFS and OS and improve the prognosis of patients with WT [25]. In a recently published study by Qureshi et al., more objective criteria for delayed surgery, after a biopsy and preoperative ChT, have been suggested based on image identified high-risk features, including perinephric spread or adjacent organ infiltration, tumors crossing the midline, intravascular thrombus, and extensive adenopathy, which are associated with increased risk of rupture or incomplete resection [26]. In their experience with customization of the timing of surgery, the outcomes with delayed nephrectomy remained similar to that reported in the UKW3 study, while there was favorable improvement in the stage and outcomes in the upfront nephrectomy group.

26.11 Conclusion

Although this subset of very large, locally infiltrating WT, not responding to ChT, requires special considerations in their management, yet it is apparent that with proper risk stratification and an individualized approach involving delayed nephrectomy after neo-adjuvant ChT, has made it possible to achieve favorable oncologic outcome in these children.

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27 Intravascular Extension and Tumor Thrombosis

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27.1 Incidence

Intravascular extension of WT is a well-known phenomenon. WT vascular thrombus can extend to the renal vein, inferior vena cava (IVC), and right atrium, and in some cases it can cross the tricuspid valve and enter the right ventricle [1, 2]. The incidence of vascular extent up to renal vein is variable and ranges between 25 and 30% [3], up to the IVC is about 4–10%, and atrial extensions are rare with reports ranging between 0.7 and 1%. Studies have shown that these cases are diagnosed at a slightly older age (3.75 years vs 2.97 years) [4]. In view of the short course of the right renal vein, the right-sided tumors cause nearly 85% of vascular extensions [2].

27.2 Clinical Features

Most children diagnosed with WT with vascular thrombus are asymptomatic for the thrombus. Symptoms of abdominal fullness and pain may be present in a good number of cases of WT with or without vascular extension. Cases of intra-atrial thrombus may also be asymptomatic. Detailed history taking and clinical examination is essential to suspect vascular involvement. These patients may present with varicoceles, hepatomegaly, and ascites [5]. They may occasionally present with hematuria. These patients may also present with liver lobe infarctions, causing severe abdominal pain [6]. One case has been reported to present with extensive lower limb thrombosis requiring anti-thrombolytic therapy in the preoperative period [6].

27.3 Preoperative Diagnosis and Imaging

The evaluation of preoperative patients with suspected vascular thrombus is multimodal. The commonest initial diagnostic modality is ultrasound and with additional use of ultrasound Doppler (USD). Different centers use computerized tomography (CT) angiography, contrast enhanced (CE) CT abdomen, and magnetic resonance venography (MRV) for the diagnosis.

USD has a good reliability [7] and can even be used for intraoperative scanning, if required [8]. It is easily available and almost always the first line of imaging. There are different schools of thought on CT scan and its efficacy in detecting tumor thrombus, preoperatively. Several studies show that multidetector CT scans with reformatting and expert radiologists can diagnose the thrombus easily. However, they also mention no role of Doppler ultrasound after a CT scan has already been done in these patients [9]. The limi-

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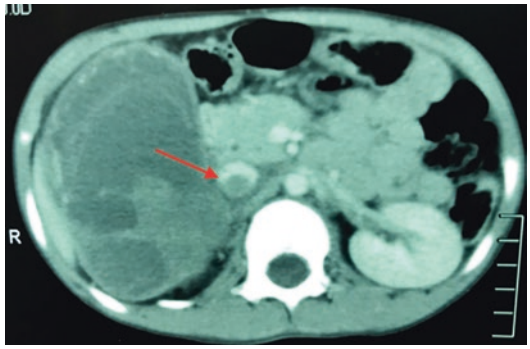

Fig. 27.1 CT scan with IVC thrombus (red arrow)

tation of CT scan is in describing the extent of the thrombus [10] (Fig. 27.1).

Magnetic resonance imaging (MRI) and MRV has reasonably good specificity and sensitivity for preoperative detection of vascular thrombus in these patients. The advantages of MRI are the lack of ionizing radiation, multiplanar ability, and importantly assessment of vascular anatomy without administration of contrast. The problems in the developing world are non-availability at several centers, high costs, prolonged times, and the use of anesthesia. MRI also has a poor sensitivity for the diagnosis of lung metastasis [11]. Venography and intravenous pyelography used in the past are no longer recommended for the diagnosis of these tumors.

There is enough evidence to note that the sensitivity and specificity of CT scan and ultrasonography (USG) improve after the administration of preoperative ChT [9].

Echocardiography must be carried out in all cases of documented vascular thrombus, to rule out intra-cardiac involvement. It has high sensitivity and specificity for the same [12]. Cardiothoracic surgeons, when involved, may want CT pulmonary angiography for proper preoperative planning.

27.4 Staging and Classification

The extent of thrombus is variable in all cases where the extension may be from renal vein to right atrium and even right ventricle in rare cases. It is important to ascertain the extent of the thrombus, so that proper preoperative planning may be done. Historically, the WT thrombus extension has been studied on basis of thrombus in renal cell carcinoma (RCC) in adults. Many staging systems are available in literature.

Initial classifications described by Cummings for RCC in 1982 [13]. Staehler's staging system initially used for RCC was modified by Daum for WT thrombus (Table 27.1) [14].

Several other classifications have been described by various authors like Pritchett [15]. However the modified Abdulla's classification is the most relevant clinically. They modified Daum's staging and added involvement of the hepatic veins, and tumor extending into the right ventricle. The importance of preoperatively establishing this lies in the anesthetic approach. Positive pressure ventilation may cause tricuspid valve obstruction and immediate loss of cardiac output [2] (Table 27.2). The involvement of the endothelium may be difficult to diagnose preop-

Table 27.1 Daum's staging for WT thrombus

Stage	Anatomical/intraoperative description
I	A small <5 cm tumor thrombus in the IVC below the level of the hepatic vessels
II	A large thrombus >5 cm in the IVC, but still below the level of hepatic vessels
III	IVC tumor thrombus extending to the level of the hepatic vessels
IV	IVC tumor thrombus extending to the atrium

Table 27.2 Abdullah's classification

Stage	Anatomical/intraoperative description
Ia	Small (<5 cm) intracaval thrombus below the junction of the hepatic veins
Ib	Subintimal attachment of small (<5 cm) intracaval extension below the junction with hepatic veins
II a/b	Large thrombus (> 5cm) below the level of hepatic veins
III a/b/c	Thrombus extending to level of the hepatic veins
IV a/b	Thrombus extending to the right atrium
V a/b/c	Thrombus extending to the right ventricle

a, free from vessel wall; b, intimal involvement/adherent to endothelium; c, extension into the hepatic vessels

eratively and is usually an intraoperative finding. Adequate level of preparedness is essential in the preoperative period.

27.5 Neoadjuvant Chemotherapy

Both SIOP and the COG agree on the requirement of preoperative chemotherapy (ChT) in patients with vascular thrombus. Neoadjuvant ChT decreases the tumor thrombus in varying degrees. This downstaging of the thrombus is known to significantly decrease surgical complications and even negate the requirement of cardiopulmonary bypass (CPB) in a reasonable number of patients as shown by Shamberger et al. [5]. Some series have reported complete resolution of the thrombus in ~20% patients [2]. Neoadjuvant ChT also has the advantage of treating metastasis in disseminated disease [16, 17]. The details of ChT recommended in patients with vascular thrombus is mentioned elsewhere.

27.6 Surgery

Vascular thrombus extension is a difficult disease to treat and is known to present significant challenges in the surgery. It requires a certain amount of expertise before one can entail upon these operations. Multidisciplinary approach with the pediatric surgeon, cardiothoracic surgeon, anesthesiologist, medical oncologist, radiologist, radiation oncologist, and pathologist is mandatory. Immediate preoperative imaging is essential to clearly know the extent and level of the thrombus.

Tumor thrombus with Abdullah's stage I and II can be safely carried out without CPB support or backup [1]. After a Chevron laparotomy, the vascular controls are taken at the infrahepatic IVC, opposite side renal vein, and infrarenal IVC or bilateral iliac veins. Stay sutures are taken at the IVC renal vein junction, and cavotomy is then carried out with complete removal of the thrombus (Fig. 27.2a, b). If the thrombus is adherent to the intima, then stripping of the endothelium is done. Rarely, a vein patch may be required to be used in very adherent cases. Cavotomy site is then repaired. Following this low molecular weight, heparin may be used for 7–10 days. There is no recommendation for long-term anticoagulation in these patients.

All Abdullah's stage III and above thrombi are managed in a cardiothoracic operating room with cardio-pulmonary bypass (CPB) backup. After anesthesia, a trans-esophageal echo probe is inserted for real-time monitoring. After abdominal incision and mobilization of the affected kidney, midline sternotomy is done by the cardiac team. After systemic heparinization, the ascending aorta, right atrium, and superior vena cava (SVC) are cannulated with Ch 14–16 cannulas. The right femoral vein or IVC is then cannulated (Ch6). The pulmonary artery is slinged to prevent pulmonary tumor embolus [15]. Moderate to deep hypothermia can be induced using cold Ringer's and mannitol solution to bring the patient's core temperature to 16–20 °C. Cardiac arrest or aortic cross-clamping can then be used. Cardiac arrest can be extended to 40 min during hypothermia with reduced morbidity [16]. A cavotomy is then done and tumor thrombus gently extracted. If the tumor is adherent, the thrombus may have to be removed piecemeal, and stripping of the mucosa needs to be done. The caval repair should be done either primarily or using patches (bovine or autologous pericardium).

27.7 Cavectomy

Rarely situations may occur, when the entire IVC has become occluded with the thrombus, and at the same time developed multiple collaterals over the course of time. In such cases a total cavectomy may be carried out. It was first described by Pathak, from PGIMER, Chandigarh. He performed an "incidental" cavectomy in a child with WT. [18] There seems to be no anatomical basis for establishing a collateral circulation, even then this approach is considered safe in these cases [19].

In situations with an unstable thrombus on a narrow talk, Budd-Chiari syndrome and pre-ChT

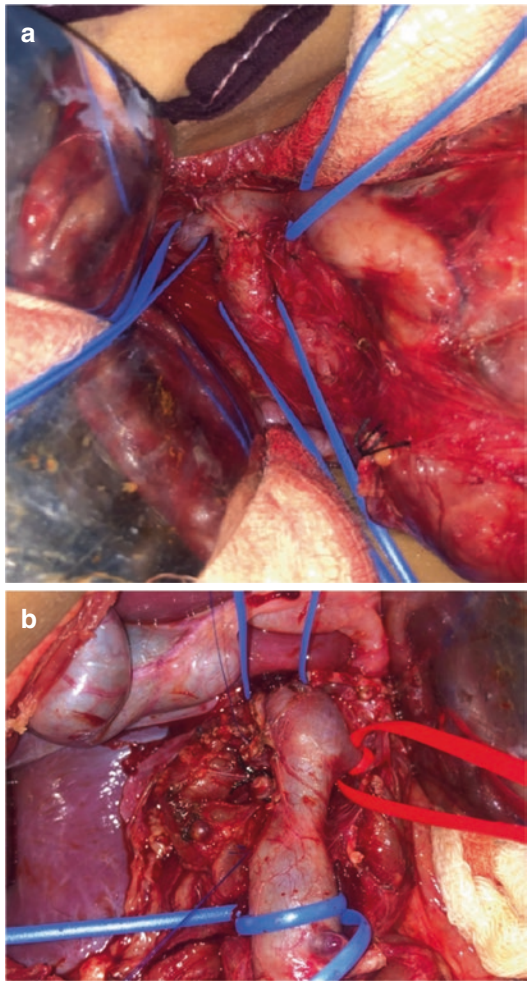

Fig. 27.2 (**a**) Left-sided WT with vascular controls. Tumor thrombus seen in left renal vein. (**b**) Post cavotomy and tumor thrombus removal in a right-sided WT (Personal collection)

tumor rupture, high-risk upfront surgical resection with CPB may be the only option available.

27.8 Radiotherapy

Radiotherapy (XRT) is delivered usually in the post-operative period as per the histology and staging of the disease. The patients undergoing piecemeal excision of tumor thrombus are considered as having intraoperative spill and classified as stage III requiring XRT to the flank.

27.9 Complications and Outcomes

There is a statistically significant increase in the frequency of surgical complications in patients with vascular thrombosis, especially in cases with involvement of the right atrium. There is increased risk of massive hemorrhage, tumor thromboembolism, complications of CPB, and those associated with preoperative chemotherapy.

Survival rates for children who underwent a removal of a tumor thrombus are not significantly different from children with uncomplicated WT. Both level of thrombus and CPB has no detrimental effect on the outcome. The oncological outcome follows the favorable or unfavorable histology and not the extensive surgical approach.

27.10 Conclusions

Surgical resection of intravascular extension of WT remains challenging. Pre-operative ChT is strongly advocated to downsize the thrombus and ease the operative procedure. The approach should be decided based upon the extent of the thrombus. Since the oncological outcome of this subset of patients is reasonably good, all efforts should be made to reduce the operative complications to the minimum. The surgical approach should be a multidisciplinary one, and CPB standby is essential in increased stages of vascular invasion.

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Ureteral Extension

28

Vikram Khanna

28.1 Incidence, Presentation

Although involvement of renal collecting system is common in Wilms' tumor (WT), ureteral extension is rare [1–5]. In National Wilms Tumor Study (NWTS)-5, incidence of ureteral extension was 2% [1]. Half of such patients present with gross hematuria which indicate towards the involvement of collecting system [1, 6]. Patients with ureteral extension may also pass tissue per urethra or can rarely present with a urethral mass [1].

28.2 Pathology

Ureteric extension in WT is present in the form of either prolapse into lumen without invasion or direct ureteric wall invasion. Majority of the studies have demonstrated ureteric prolapse than invasion [2, 7]. In the largest study till date on WT with ureteral extension by Ritchey et al., no patients had any histological evidence of tumor invasion through the ureteric wall [1]. However, in another study by Singh et al., of the 32 WT patients with ureteral extension, 21 (65.6%) patients demonstrated only ureteric prolapse, while 11 (34.4%) patients had invasion of ureteric wall. They followed the Société Internationale D'oncologie Pédiatrique (SIOP) management protocol for WT, which stages WT with ureteric prolapse as stage I, ureteric invasion as stage II, and incomplete excision of ureteric tumor as stage III, and stage-appropriate treatment protocols were followed [6].

In the National Wilms Tumor Study (NWTS), intralobar-nephrogenic rests (ILNR) were present in 50% of these patients with ureteral extension suggesting an association between ILNRs and the development of WT involving the pelvicalyceal system and ureter [1]. Botryoid WT, a rare form of WT, which expands into renal collecting system are thought to arise from ILNR and have protrusion of tumor into the ureter and bladder [8]. Fetal muscle histology, as seen in tumors that arise from ILNRs, is often seen in ureteral tumor extension [9, 10]. Prognostic significance of this is uncertain, but none of these WT with fetal muscular histology developed metastatic disease or had recurrence.

28.3 Diagnosis

Pre-operative imaging especially computerized tomography (CT) scan can detect tumor extension into ureter. It was possible in 30% (14/45) of the patients in the study by Ritchey et al. In 22 patients, ureter extension was noted at the time of surgery and in the remaining nine patients, only on pathological examination [1]. Presence of hydronephrosis or non-functioning kidney on CT

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scan or intravenous pyelography (IVP) also hints towards the possibility of tumor extension. When WT with ureteral extension is suspected, cystoscopy combined with retrograde urethrogram can aid in diagnosis. Tumor/blood emanating from the ureteral orifice and filling defects in the ureter may be seen.

28.4 Treatment

NWTSG classifies WT with ureteral extension removed en-bloc, as stage II disease. Radical nephrectomy with partial or complete resection of the ureter as low as possible to remove the tumor en-bloc is performed. In some patients, bladder cuff might need to be removed for complete clearance of distal ureter. Stage II WT patients are treated with two-drug regimen without the need for radiation (XRT). It is important to ascertain the extent of ureteral extension to avoid cutting across the tumor, which will amount to intraoperative spill (IOS). Separate removal of ureteric extension from the renal tumor bulk is also considered IOS, and would upstage the tumor to stage III. Post-operative intensification of therapy with addition of Doxorubicin and XRT is required in such cases. The level of ureteral extension should also be precisely identified to avoid leaving behind any residual disease [1].

28.5 Outcomes

The prognosis of these WT children with complete resection of ureteral component remains excellent. Some reports have suggested that WT with ureteral extension is more resistant to therapy [7, 11]. However, in the study by Ritchey et al., it was concluded that the deaths that occurred were more likely attributable to the poor prognosis rather than the ureteral extension per se. Total resection of the ureteral component is the most critical factor to reduce the risk of local recurrence and improve outcome.

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Ruptured Tumors

29

Alpana Prasad and Nidhi Sugandhi

29.1 Introduction

Ruptured Wilms' tumor (WT) is an important subset in the spectrum of WT, which needs careful diagnosis and meticulous management according to well-established guidelines to optimize outcomes. The incidence of tumor spill varies from 2.8 to 11.7% in various treatment protocols [1, 2]. According to studies, tumor rupture or spill increases the risk of relapse by almost six times to around 20% [3–5]. The overall survival (OS) of relapsed patients, despite intensive multimodality treatment, is still a dismal 43% compared to >90% OS in even stage III uncomplicated favorable histology (FH) tumors [6]. Intensification of therapy presents with its attendant side effects of increased toxicity and late side effects. This underscores the necessity of making every attempt at avoiding tumor spill and further treating the tumor rupture/spill, should it occur.

Though tumor rupture and spill are terms that are used interchangeably in general language, however, there is a difference between the two. "Rupture" refers to preoperative break in the tumor capsule leading to local escape or generalized dissemination of tumor contents. "Spill," or intraoperative spill (IOS), on the other hand, is defined as intraoperative breach of the tumor mass, whether due to inadvertent incision in the tumor capsule or piecemeal removal of the tumor or the thrombus. The term "peritoneal soiling" is also used for all these situations, which basically lead to diffuse dissemination of tumor cells in the peritoneal cavity. Regardless of the timing and term used, the connotation remains the same, i.e., increased risk of relapse and need to intensify therapy.

29.2 Defining Tumor Rupture/Spill

Tumor rupture/spill can occur in one of the following circumstances:

- Preoperative rupture can be traumatic or spontaneous. Large tumors are particularly susceptible to traumatic ruptures. The incidence of spontaneous preoperative rupture of WT remains low, around 2% [7].
- Intraoperative spill (IOS) during surgery includes breach of a thin stretched out capsule, incision through the primary tumor or lymph nodes (LNs), piecemeal removal of the tumor or thrombus, and transection of the renal vein or ureter in the area of tumor extension.

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- Preoperative or intraoperative open surgical biopsy.
- Presence of separate tumor or nodules on the peritoneal or serosal surfaces is considered as preoperative tumor rupture.

Not much can be done to prevent the preoperative spontaneous or traumatic rupture, but efforts must be concentrated on the other situations to minimize the incidence of IOS to as low as possible.

29.3 Preoperative Chemotherapy

The incidence of IOS varies according to different treatment protocols. Published SIOP studies have reported much lower IOS rate of 2.8% to 6% as compared to the COG studies where there is reported intraoperative tumor spillage of 12.6% [2, 8]. UKCCLG (UKW3) trial suggests that preoperative chemotherapy (ChT) helps prevent tumor rupture in surgically operable WT patients [9]. The significant difference in IOS rates is due to the preoperative ChT in SIOP protocol causing significant tumor shrinkage, decreased vascularity of tumor, and a firmer tumor to handle, which makes subsequent surgery easier and less likely to result in tumor rupture [8, 10]. Preoperative ChT is not usually given in the COG protocol except in special situations, and this accounts for the higher rates of IOS. The criteria for preoperative ChT in NWTSG/COG protocol are well-defined tumor thrombus above the level of the hepatic veins, pulmonary compromise from a massive tumor or extensive pulmonary metastases, resection requiring removal of contiguous structures (other than adrenal gland), and bilateral WT and tumor in a solitary kidney. Based on this decreased incidence of IOS seen in SIOP studies, an additional category of patients that may benefit from preoperative ChT has been added. These are patients in whom ChT may be given based on the surgeon's presumption that attempting primary nephrectomy would entail a very high risk of rupture or residual tumor [2]. However, unlike SIOP, these children still need to undergo biopsy, thus rendering them to COG stage III with requirement of three-drug ChT and radiotherapy (XRT) [2].

29.4 Tumor Size and Volume

Relationship of tumor size to prognosis has been addressed in several studies including that of Provenzi et al. from Brazil who observed that tumor volume after preoperative chemotherapy (TVAPQ) was the only variable statistically associated to the prognosis as in their study every increase of 10 mL in tumor volume increased the risk of death by 2% [11]. Japan Wilms' Tumor Study (JWiTS)-2 has recommended that tumor size >12 cm or tumor volume >1000 mL should receive preoperative chemotherapy to reduce surgical risk [12]. Gow et al. analyzed the factors contributing to IOS and found that the size of the tumor is directly proportional to the incidence of IOS, especially for tumors >12 cm [2]. Simple logistic regression in their study found the maximum risk of spill at tumor diameter of 15 cm. Previous NWTS studies had also classified tumor diameter >10 cm as having high risk of spill [6]. Large size results in limited operative field, difficulty in tumor handling and separation from adjoining structures, problems in accessing the renal pedicle, and thinner capsule more at risk of rupture during handling. The size factor is particularly pertinent in developing countries, where children present late with huge tumors, which may not regress suitably even after ChT. The surgeon needs to always keep in mind the high possibility of IOS and proceed with meticulous and slow dissection.

Increasing tumor volume is also thought to be a factor affecting IOS rates. Barber et al. have shown that tumor volume >1000 cm^3 is the only significant risk factor identifiable preoperatively for WT rupture and the risk increased in direct proportion to the increasing volume [13]. The recent COG trials for children with WT (AREN03B2) have concluded that tumor size >15 cm is associated with a high risk of intraoperative rupture [14]. Despite these find-

ings, the COG group currently does not recommend neoadjuvant ChT based on the sole criterion of size.

29.5 Laterality

Right-sided WT are more likely to have IOS intraoperatively [2]. This is possibly due to the limited operative field due to the presence of liver. Right-sided tumors have shorter renal veins, which may present some difficulty in ligating leading to increased tumor handling. Right kidneys are also known to have more varied vasculature with anomalous arteries and veins lending themselves to difficult dissection [15, 16]. Because of these unique anatomical features, right-sided tumors are more predisposed to IOS, and a right renal vein tumor thrombus may be particularly difficult to handle [17].

29.6 Surgeon Skill and Quality Assurance

There is no substitute to a skilled and meticulous surgeon in WT surgery. The surgeon needs to proceed slowly but efficiently and dissect painstakingly. He should be prepared for sudden change in preconceived plans. There should be no unnecessary hurry or impatience to complete the surgery. Careful judgment needs to be exercised. For example, though it is recommended to achieve vascular control as an initial step, if the tumor seems too large to do this safely, the surgeon should instead change strategies timely rather than risking IOS. No controlled trial is specifically possible to measure the surgeon factors, but it is well recognized that the judgment, skill level, and surgeon experience have an important impact on the risk of spill [2].

Not only is the skill of surgeon significant, but what is also important is the timely and accurate identification and recording of intraoperative findings and events. A study by Shamberger et al. noted that undocumented IOS was one of the two important surgical causes of increased local recurrence, the other being inadequate LN sampling [6]. It cannot be emphasized enough that any breach of tumor has to be documented without fear. A patient with IOS, if treated with upgraded regimen, can have the same outcomes as those with no IOS, rather than continuing the same regimen and compromising the eventual outcomes. The AREN03B2 protocol also directs surgeon to note the type of IOS and details as whether tumor was removed en bloc or piecemeal, whether tumor extended to the renal vein/vena cava or ureter and if so where was it transected for removal, and whether tumor thrombus was removed completely or not. It is for the same reason that the AREN03B2 protocol emphasizes on central review of surgical findings also, in addition to central pathological and radiological review. There have been speculations about interrater variability in rating the surgical findings. However, studies found that assessment of the surgical findings in real time by group of experienced and specially trained experts had a high degree of concordance and was highly reliable and satisfactory [18]. The fundamental contribution of such a central review remains proper assignment of stage and thus appropriate further treatment. This also highlights the value of experience and special training of surgeons to correctly assess and perform surgery for WT. In fact, it is highly recommended by the COG that WT patients should be referred to centralized institutions with high WT caseload and specially trained and experienced surgeons.

29.7 Diagnosis and Investigations

The question of diagnosis arises only in cases of preoperative rupture. IOS is self-evident and just needs proper documentation. Surgeons need to be aware of all the conditions that qualify as tumor spill, namely, breach of capsule, transection of primary tumor or transection of the renal vein/inferior vena cava or ureter in area of tumor, and piecemeal removal of tumor or thrombus. Peritoneal masses separate from the main tumor also indicate previous dissemination and perito-

neal soiling and qualify as rupture. COG protocol treats patients by primary nephrectomy and, hence, insists that the documentation of rupture needs to be done intraoperatively. SIOP on the other hand treats with neoadjuvant ChT and, hence, allows the diagnosis of rupture to be made on pre-ChT imaging. COG studies have also identified imaging characteristics, which may indicate tumor rupture so that the surgeon is better prepared for dealing with the situation intraoperatively [19].

Certain clinical signs may raise the suspicion of tumor rupture. These include sudden severe abdominal pain, abdominal distension, anemia, and rarely shock [20]. However, these signs have low sensitivity and specificity and cannot be relied upon for a definitive diagnosis of preoperative rupture. Preoperative rupture may be totally asymptomatic presenting later as painless peritoneal masses.

Contrast enhanced computerized tomography (CECT) abdomen is the investigation of choice to detect tumor rupture. Recent COG trials for children with WT (AREN03B2) have shown that CT scan imaging has moderate specificity but relatively low sensitivity in the detection of preoperative tumor rupture [14]. Features that suggest rupture are peritoneal fluid beyond pouch of Douglas; hyper-dense hemoperitoneum; peritoneal, mesenteric, and/or omental solid masses; nonlocalized subcapsular or perirenal hemorrhage; poorly circumscribed primary tumor; fat stranding around the tumor; extracapsular retroperitoneal fluid; and ipsilateral pleural effusion [19, 20].

29.8 Management

Risk stratification of children with ruptured WT has evolved, and treatment is based not only on the extent of spill or contamination but also on the stage and histology [14]. Once the tumor rupture or spill is documented, the management is intensified. Current SIOP study advises 4 weeks' preoperative ChT in ruptured WT children, and thereafter postoperative ChT and XRT are tailored according to the histological features [21]. The Children's Oncology Group- Renal Tumor Committee (COG-RTC) has advocated upstaging all patients with tumor rupture to stage III (COG protocol AREN0533) [14]. All ruptures and IOS are upgraded to stage III and receive three-drug treatment with vincristine (VCR), actinomycin-D (AMD), and doxorubicin (DOX) along with flank or abdominal XRT.

29.9 Local Versus Diffuse Spill

In earlier NWTS studies, there was a distinction made between "local spill," limited to the tumor bed, and "diffuse spill" involving the whole peritoneal cavity. In NWTS-3 and NWTS-4, those with local spill were not upgraded to stage III and rather received only two drugs without abdominal radiation. A study by Shamberger et al. subsequently showed that such an approach resulted in higher local relapses as compared with those treated as stage III [6].

The current recommendations of the North American study groups state that any IOS should be classified as stage III and should be treated with 10 Gy of XRT to the area of contamination (flank or whole abdomen as the case may be) and addition of DOX to VCR and AMD is advocated [14]. On the other hand, it has also been reported that 85% of children with stage II FH (favorable histology) WT with rupture will not have local recurrence or relapse despite not receiving DOX and abdominal XRT [4]. Hence, the upgraded ChT and XRT can be added when there is local recurrence or relapse in these children, and this does not alter the OS in these children and also minimizes the treatment-related long-term morbidity. Administration of 10 Gy or 20 Gy of XRT to flank or whole abdomen reduces abdominal tumor recurrence rates following tumor rupture. IOS in stage II patients reduced event-free survival (EFS) and OS, but only the latter was of statistical significance.

Rutigliano et al. have reported that patients presenting with radiologic evidence of contained retroperitoneal tumor rupture or spillage at presentation should be treated with preoperative ChT which would minimize the risk of abdomi-

nal rupture leading to diffuse or generalized spillage at the time of subsequent nephrectomy and would thus be able to avoid total abdominal XRT of higher dose (20 Gy or more) in favor of more localized flank XRT of much lower dose (10 Gy) [22].

In UKW3 study, local spill confined to flank was considered stage II irrespective of whether it occurred in the preoperative ChT with delayed surgery group or in immediate nephrectomy group. In analyzing the data of their randomized patients, they did not find any case of IOS in the group pretreated with ChT as compared to 14.6% tumor spill in the immediate nephrectomy group [9]. UKCCLG distinguishes between retroperitoneal and intraperitoneal rupture diagnosed on CT abdomen by expert radiologist. Those with purely retroperitoneal rupture are offered only flank XRT, whereas those with intraperitoneal rupture receive WAI, thus avoiding the adverse effects of WAI in many patients [20].

29.10 Tumor Biopsy and Its Repercussions on Tumor Spill

A major area of controversy has been the status of preoperative biopsy in WT. It is debatable whether a diagnostic biopsy leads to tumor cell dissemination or needle tract seedling and, hence, should be considered as tumor spill. Shamberger et al. compared the effect of preoperative open surgical biopsy followed by nephrectomy with immediate nephrectomy and found increased local recurrence in patients undergoing biopsy in patients under NWTS-4 [6]. Based on this seminal study, the COG group considers all open biopsy as spill. As discussed above, it has also been recommended to stop treating this open biopsy as stage II and instead upgrade to stage III. Notably, biopsy in COG is only indicated in limited case scenarios such as cases with tumor thrombus extending above the level of the hepatic veins, gross involvement of contiguous structures so that tumor removal entails sacrifice of essential contiguous organs/extensive mutilating surgery, bilateral WT, extensive pulmonary compromise from compression by a massive tumor or widespread metastatic disease, and for obtaining tissue for biological studies, if upfront nephrectomy cannot be done [4, 6].

In contrast in the UKCCG protocol, all tumors used to be routinely biopsied prior to treatment initiation. A percutaneous trucut core-needle biopsy is done through the retroperitoneal route under image guidance with a coaxial needle that is believed not to cause needle tract seeding, and hence no upstaging of tumor is done. The UKW3 trial studied the effect of percutaneous biopsy and found that if the outcomes were adjusted for anaplasia, distant metastasis, older age, and tumor size, then there was no effect of tumor biopsy on recurrence or outcomes [23, 24].

SIOP now permits a percutaneous biopsy taken retroperitoneally at treatment initiation in special situations (unusual clinical, biological, or radiological presentation, tissue for genetic and biological studies) without upgrading the tumor stage but does not recommend it routinely [25]. UKCCLG has also adopted this concept recently. An evident tumor rupture on preoperative imaging is a contraindication to percutaneous biopsy under SIOP protocol [20].

29.11 Prevention of Tumor Rupture/Spill

To prevent increased risk of local recurrence and avoid the side effects of intensified ChT and XRT, it is a surgeon's fundamental responsibility to make every attempt to avoid IOS. Certain considerations can aid in this endeavor. Preoperative XRT has been proven to decrease the IOS as evidenced by the significantly different spill rates in SIOP (2.8%) and COG (11.7%) [1, 2]. It causes tumor shrinkage, makes the tumor firmer and less vascular, and decreases the extrarenal extension and thrombus, therefore easier to handle. This could especially be helpful when dealing with late presenters with huge tumors, a situation that is very common in developing countries.

Thorough preoperative imaging to identify all extrarenal extension, LNs, intravascular throm-

bus, and necrotic areas in the tumor can help the surgeon plan the surgery without any tumor transection or spill. Any abnormal anatomy or vascular variations need to be noted for safe dissection.

In SIOP and UKCCLG protocols, as a precautionary measure, the maximum diameter recommended for the percutaneous core biopsy needle is 18G, as thicker needles theoretically may increase the risks of needle tract metastasis [20].

Surgical skill and patience in dealing with large tumors is irreplaceable. Pedicle first approach may be abandoned, if it presents a high risk of IOS due to tumor handling. Extrarenal extension, intravascular thrombus, and LNs need to be removed in totality without any incision through the tumor. A tumor with large areas of liquefaction and necrosis needs special care and gentle handling to prevent IOS.

Minimally invasive surgery, though being increasingly attempted in WT, needs to be avoided where high risks of spill are anticipated as it may be difficult to get negative margins or completely clear the extrarenal disease en bloc with laparoscopy [26]. Most importantly, it is the surgeon's obligation to correctly document IOS if it occurs, so that appropriate intensification of treatment can be done offering the same chances to the child as that without IOS.

29.12 Conclusion

Preoperative tumor rupture or IOS in WT is an unfavorable event with severe consequences. It requires upstaging of tumor to stage III and consequent treatment with three-drug regimen and XRT, which increases the drug toxicity and long-term side effects and subsequent quality of life of survivors. There is higher risk of local recurrence in ruptured WT patients irrespective of the cause of rupture or the extent of soiling, and this decreases the EFS significantly. Hence, it is mandatory to perform individual risk stratification in management of children with ruptured WT, with a reduced treatment intensity in low-risk histology lower stage tumors. In the event of IOS, if treated intensively with upgraded regimen, the eventual outcome in terms of EFS is comparable to children with no IOS. So, all efforts should be made to prevent IOS or, in case IOS does happen, to identify it and treat accordingly.

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Metastatic Wilms' Tumor

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30.1 Introduction

The remarkable success story that is the treatment of Wilms' tumor (WT) over the years is in a large measure due to the comprehensive treatment of metastatic disease, to the extent that even widely disseminated WT has a treatment success rate of 70–80%—a feat unmatched in the treatment of any other solid tumor [1, 2]. Fortunately, WT is usually picked up early by the parents, and only about 11–17% of tumors are diagnosed with metastasis at presentation, in contrast to tumors such as neuroblastoma, in which two-thirds of whom may have metastatic disease at presentation [3–5]. Regrettably, the presence of metastases does decrease the overall survival (OS) and increases incidence of relapse, apart from long-term side effects like cardiac dysfunction, musculoskeletal problems, and risk of second malignancy [6, 7]. The current research strongly focuses on ways to treat the metastasis aggressively while at the same time avoiding unnecessary chemotherapy (ChT) or radiation (XRT) so as to decrease the undesirable long-term sequelae. To this end, there has been a constant endeavor to use investigations of increasing sensitivity or find new methods to diagnose and quantify smallest of metastases and tailor treatment intensity according to their biological potential. Over the years, there have been refinements in the investigations, such as adoption of non-contrast computerized tomography (NCCT) chest as the primary investigation for pulmonary metastases, instead of simple chest X-ray (CXR) and attempts to chart the biological characteristics of the tumor to fathom the metastatic and response potential. The research is also aiming to stratify risk groups in metastatic disease based on the biological features of the tumor. Loss of heterozygosity (LOH) at 1p and 16q and gain of chromosome 1q are important targets in this endeavor [8–10].

30.2 Pathophysiology

Metastatic WT, also categorized as stage IV WT, is defined as the presence of hematogenous spread of the tumor to the lungs, liver, brain, bones, or extra-abdominal lymph nodes (LNs). The lung is the most common site of metastases (80%), followed by the liver. Brain and bone metastases are unusual in classical WT and rather indicate an alternative diagnosis like malignant rhabdoid tumor of the kidney (MRTK), with predominantly brain metastasis, or clear cell sarcoma of the kidney (CCSK), with predominantly bone metastasis [4, 11]. Metastasis is independent of the local size and stage of tumors and may be present in local stage I tumors also. Biological factors, which are just being investigated, may have a role in the propensity of a tumor to

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metastasize. Few studies have demonstrated that metastases from WT contained predominantly blastemal component with lesser amount of differentiated elements [12]. It is also proposed that intensive ChT and XRT may initiate differentiation in these metastatic nodules and cause maturation or fibrosis in at least some of the patients, which is the rationale behind requirement of histological confirmation in nodules persisting after chemotherapy and radiation [1, 12]. However, it needs to be noted that this is not a universal phenomenon and may depend on the biological characteristics of the tumor.

30.3 Metastasis to Other Sites

Though this chapter largely describes the management of pulmonary metastasis as the lung is the most common site, the same principles of management apply to the other metastatic sites. It is to be remembered though that metastasis to less common sites such as the brain and bone or rarely the pancreas, spine, gonads, etc. should prompt histological confirmation of the primary tumor.

Unusual sites of metastasis in classical WT have rarely been reported. This includes the spinal canal, pancreas, and gonads [13]. The mechanism of such spread is not clear, but some evidence of it being lympho-vascular and perineural/intraneural (in case of spinal spread) has been reported [14]. Though general principles of management remain the same largely, modifications of investigations and treatment may be required according to the unusual sites. In particular, the metastasis at unusual sites may need a preferential treatment with surgical excision in addition to the adjuvant chemotherapy and radiotherapy. Some symptoms such as spinal compression may need rapid alleviation, and response to chemotherapy may not be predictable [14].

30.4 Diagnosis

Pulmonary metastases, if extensive, can cause cough, tachypnea, and respiratory distress, whereas liver metastasis may cause ascites, anasarca, abdominal pain, prominent abdominal veins, and hepatomegaly or coagulation disorders. Bone pains, seizures, headache, and vomiting are rare occurrences due to metastasis in typical WT. However, usually no specific symptoms are attributable to the metastatic disease, and each child needs to be actively investigated thoroughly to confirm metastasis. Since 80% of metastases are to the lungs, a CT chest is therefore a routine part of work-up of WT. Investigations for metastasis at other sites are guided by the presence of symptoms.

30.4.1 CT Chest

Before the National Wilms Tumor Study (NWTS)-5 and SIOP 2001, CXR was the recommended investigation to look for pulmonary metastasis, and a chest CT was optional. Only the nodules clearly demonstrated on a CXR were treated as metastatic disease. With increasing use of CT by the turn of the century, there arose a distinct cohort of children with small lung nodules <10 mm, demonstrable on a CT, but not visible on plain CXR, and thus arose the dilemma of CT-only nodules. The reason for dilemma regarding the treatment of CT-only nodules arises from the fact that 17–26% of these may actually be benign, incidentally detected lesions such as lung scars or granulomas. Additionally, there is a lot of inter-reader variability among the reporting radiologists regarding these small-sized nodules [15–18].

Studies from the National Wilms Tumor Study Group (NWTSG) comparing the outcomes of treatment of patients with CT-only nodules treated as metastatic vs. localized disease found that addition of doxorubicin (DOX) improved the event-free survival (EFS) in the group treated as metastatic disease, but there was no difference in the EFS and OS in those treated with radiotherapy (XRT). This was found to be due to increased events in the form of second malignancies [4, 16]. These studies also found that the patients with CT-only nodules treated as localized disease had a very high incidence of lung recurrence to the tune of 79%, suggesting that the pulmonary metastatic disease was being undertreated. The

second UK Children's Cancer Study Group Wilms' tumor study (UKW2) and SIOP 2001-RTSG analysis also report similar findings. It was seen that stage I patients treated as localized disease only, even in the presence of CT-only nodule(s), had a higher relapse rate [19, 20].

These findings confirmed the hypothesis that even CT-only nodules would have to be treated as metastases, even though there may be a slight chance that these may be some benign lesions such as lung granulomas in a small percentage of cases. Thus, CT chest is now the recommended investigation to look for pulmonary metastasis in all WT treatment protocols.

To decrease the possibility of benign pulmonary lesions being overtreated as metastases, certain radiological criteria have been defined. The COG group considers lung nodules as metastatic disease if they were round, non-calcified, and not in a pulmonary fissure [1]. To improve the accuracy of diagnosis and remove subjectivity, it also recommends all CT scans to be centrally reviewed in the beginning and to assess the response to therapy. Though it has correlated the treatment response rates according to size of nodules also and found best response in nodules <3 mm, however, it does not define size criteria for the pulmonary nodules to be considered metastatic [1]. On the other hand, SIOP-RTSG UMBRELLA protocol considers lung nodules as metastatic disease only if >3 mm in maximum transverse diameter [2]. The UKCCLG group finds CT chest desirable to look for metastases but recommends clinician decision in conjunction with central expert review to confirm the relevance of any positive findings and assess response [21].

30.4.2 CT Chest for Response Assessment

The response of metastatic disease to ChT needs to be carefully assessed as further treatment depends on it. This is done by repeat CT chest at week 6 of ChT.

In the NWTS/COG protocol, those with complete response (CR) of lung nodules at this stage are labeled as *rapid complete responders (RCR)*. They are treated with three-drug ChT; lung XRT can be avoided in these patients, subject to certain biological criteria (no LOH at 1p and 16q and no gain of 1q). Those with slow response or progressive disease (PD) are labeled as *slow incomplete responders (SIR)* and are treated as per Regimen M and whole lung irradiation (WLI) [1].

SIOP also notes disappearance of pulmonary nodules at 6 weeks as an important factor to decide further treatment. However, it stratifies the subsequent treatment further based on histology of primary and metastatic tumors, nodule size, and response to the preoperative ChT or surgery [2].

30.4.3 Volumetric Assessment

The volumetric assessment of residual primary tumor post-ChT by MRI is now an important part of UMBRELLA protocol [2]. There are suggestions that volumetric assessment of pulmonary nodules at the beginning of therapy and post neoadjuvant ChT may also help in a more accurate response assessment [2, 21]. However, more studies are required in this aspect before its usefulness is documented.

30.4.4 CECT Abdomen

This essential investigation for primary tumor assessment also helps in picking up liver metastases that are present in 2% of WT. The number of metastatic nodules, lobes involved, and the remaining healthy liver parenchyma should be noted. Unusual metastases such as pancreatic and gonadal may also be revealed [2, 21].

30.4.5 MRI Head and Spine

MRI head and spine needs to be done in case of suspicion of central nervous system metastases [2, 21].

30.4.6 Bone Scan and Skeletal Survey

Suspected bone metastases should be investigated for site and number by nuclear scans and X-rays. This is required only in patients with clinical symptoms suggestive of bony metastases like bone pains, pathological fractures, etc. Importantly, the primary tumor should be reexamined for alternative pathology like CCSK [2, 21].

30.4.7 Biological Studies

In COG protocol, certain biomarkers, namely, loss of heterozygosity (LOH) at 1p and 16q and chromosome gain at 1q, have a crucial role to decide treatment of metastatic nodules [22]. Even in RCR with CR of nodules at 6 weeks, LOH at 1p and 16q mandates aggressive treatment with Regimen M and WLI. In the AREN0533 study, even after CR and aggressive treatment as detailed above, the 4-year EFS was significantly lower for patients with 1q gain. However, *RCR* with LOH at 1p and 16q, treated aggressively with upgraded Regimen M and XRT, showed similar outcomes to those patients without LOH (Table 30.1) [1].

30.4.8 Biopsy

Histological confirmation of metastatic disease is a controversial issue. On one hand, it is desirable to confirm metastases to prevent overtreatment in incidental lesions such as lung granulomas. On the other hand, it increases morbidity, and if done at the beginning of therapy, it prevents response monitoring and the possibility of omission of lung XRT in cases of CR [11]. Approximately 17–26% of the pulmonary nodules may be proven benign by biopsy [15]. In fact, for this reason, COG recommends full upgradation with three-drug regimen and XRT in patients in whom pulmonary nodules are fully resected at the beginning of therapy and found to be true metastases. These patients may have been *RCR* and could have avoided DOX and WLI but, in the absence of any remaining lesion to monitor response, have to be treated with full metastatic regimen.

The histological confirmation of persistent pulmonary lesions after 6 weeks of ChT is deemed desirable, but not mandatory, by the COG. In the AREN0533 study, 16 out of 175 patients with persistent lung nodules on CT underwent lung nodule biopsy and were classified as having CR on the basis of the biopsy results [1].

On the other hand, the UMBRELLA protocol recommends mandatory resection of any persistent pulmonary nodules to be done at week 10 of ChT. In fact, this is recommended not just for histological confirmation, but the intent is to achieve complete clearance of the pulmonary metastatic disease. WLI is then given only in stage II–IV, high-risk tumors or in those where complete surgical resection was not possible [2]. UKCCLG has similar recommendations [21].

In all the protocols, any pulmonary nodules that persist after completion of all ChT and XRT need surgical removal.

Unusual metastatic sites like the pancreas may require a biopsy to confirm the metastasis.

Table 30.1 Outcomes according to 1q gain status [1]

Group	No. (%)	4-year EFS % (95% CI)	*P*	4-year OS % (95% CI)	*P*
Incomplete lung nodule response					
1q gain+	42 (36.2)	86 (72.2 to 99.3)	0.15	93 (83.1 to 100)	0.45
1q gain−	74 (63.8)	92 (84.4 to 99.8)		96 (90.4 to 100)	
Complete lung nodule response					
1q gain+	21 (21.9)	57 (73.4 to 100)	0.001	89 (73.4 to 100)	0.16
1q gain−	75 (78.1)	86 (73.4 to 100)		97 (73.4 to 100)	

30.4.9 18F-Flourodeoxyglucose (18F-FDG) Positron Emission Tomography (PET)-CT

Though FDG-PET is not currently the standard of care for WT, it has potential to be a very useful noninvasive investigation, especially in metastatic disease. WT is 18F-FDG avid, and it can be a useful adjunct to conventional imaging in monitoring response to preoperative ChT. It is possible that *SIR* with doubtful remaining lesions where biopsy is recommended currently to confirm the metastatic activity may be able to avoid surgical biopsy depending on the 18F-FDG avidity, which corresponds to histologically confirmed active disease [23].

30.5 Management

The entire focus of metastatic WT management is to attempt regime intensification while minimizing secondary and long-term effects of the treatment. The analysis of patients with metastatic disease in NWTS-4 and NWTS-5 and SIOP 2001 revealed that though intensification of ChT and XRT increased cure rates, it did not lead to better OS or EFS in all patients due to increased toxic late effects [6, 7]. Thus, the AREN0533 protocol by COG and UMBRELLA protocol were specifically designed to take into account the stratification of treatment based on the biological behavior of the metastatic disease. Rather than just the presence of metastatic disease, the response of the metastasis to preoperative ChT guides the intensity of the treatment and also the outcomes. Timely monitoring of response thus becomes imperative.

The following section describes the treatment of the lung metastases, but the same principles apply to metastases elsewhere too.

30.5.1 COG Protocol

The AREN0533 study outlines the COG principles of metastatic disease treatment. The study design was inspired mainly by the analysis of patients with CT-only nodules in NWTS-4 and NWTS-5 studies, where a better outcome was achieved with a three-drug treatment, but more late effects toxicity was seen with addition of XRT. This study then sought to provide differential treatment to patients with metastatic disease depending on their response to initial ChT, thus decreasing toxicity in a large proportion of cases.

After confirmation of metastatic disease, all patients are started on three-drug regimen with vincristine (VCR), actinomycin-D (AMD), and DOX (preop cumulative dose of 45 mg/m^2) over 6 weeks [1].

The *RCR* are further treated according to the biomarker status. Those without LOH at 1p/16q continue receiving 3 drugs for 19 more weeks (total 25 weeks) with a cumulative DOX dose for the entire therapy of 150 mg/m^2. The *SIR* and the patients with radiological CR but positive for LOH1p/16q receive the upgraded Regimen M—four doses of cyclophosphamide (CTX) and etoposide (ETOP) in addition to VCR, AMD, and DOX; total ChT is of 31 weeks in addition to WLI. Reassessing the lung nodules and withholding XRT in the *RCR* avoid lung XRT in around 40% of patients [1]. Biopsy of lung lesions in *SIR* is strongly recommended. Any residual metastatic lesion after completion of ChT and XRT needs to be surgically removed. Abdominal XRT is administered if the tumor is local stage III. When both WLI and whole abdomen irradiation (WAI) are given, the radiation fields overlap at the margins to prevent inadequate dosing at the junction.

The recommendations for XRT according to the COG AREN0533 (NCT00379340) study are as in Table 30.2. XRT should be started preferably within 14 days of nephrectomy, and AMD and DOX should be withheld during the duration of XRT.

The treatment protocol for metastasis at any other site remains same as for lung nodules. Pulmonary metastases as also the metastases at any other site too, remaining after the completion of therapy, need to be surgically removed if possible.

Table 30.2 Recommended radiotherapy doses for metastatic sites in WT under COG treatment protocol (Source: AREN0533 NCT00379340 study trial document) [1, 38]

Lung (whole ± boost) (total/fraction dose)	Liver (whole ± boost) (total/fraction dose)	Brain (whole ± boost) (total/fraction dose)	Bone (total/fraction dose)	Unresected LLN metastasis
12.6 Gy/1.8 Gy ± 9.0 Gy/1.8 Gy (boost to gross residual disease)	10.8 Gy/1.8 Gy (whole liver) ± 9.0 Gy/1.8 Gy (boost to gross residual disease)	21.6 Gy/1.8 Gy (whole brain) + 0.8 Gy (boost to gross residual disease)	25.2 Gy/1.8 Gy (lesion +3 cm)	19.8 Gy/1.8 Gy (entire nodal region)

30.5.2 SIOP-RTSG UMBRELLA 2016 Protocol

Like the COG protocol, the SIOP-RTSG UMBRELLA 2016 protocol recommends 6 weeks of preoperative ChT with three drugs—VCR, AMD, and DOX—followed by response assessment by CT. There is difference though in the cumulative dose of neoadjuvant DOX which is 100 mg/m^2 in this protocol compared to 45 mg/m^2 in the COG protocol. Further treatment is stratified according to the disappearance of pulmonary nodules, size, and histology of pulmonary nodules if persistent, tumor histology, and local tumor stage. In the best-case scenario, that is, complete disappearance of the metastatic tumor along with low- or intermediate-risk stage I–III of primary tumor, lung XRT is avoided and DOX is given at the cumulative dose of 150 mg/m^2. For the rest of the patients, detailed guidelines are provided for the stratification of postoperative ChT, in which the cumulative dose of DOX is kept as low as possible to reduce cardiac toxicity. This involves stratifying patients to VCR and AMD plus DOX either with a cumulative DOX dose of 150 mg/m^2 or VCR, and AMD plus DOX with cumulative DOX of 250 mg/m^2, or a four-drug regimen including ETOP (150 mg/m^2/day), carboplatin (CARB) (200 mg/m^2/day), CTX (450 mg/m^2/day), and doxorubicin (cumulative dose 300 mg/m^2). The detailed stratification and treatment plan post neoadjuvant ChT and nephrectomy are tabulated in another chapter.

The UMBRELLA protocol also strongly encourages resection of any residual metastatic disease by week 10. This gives us a correct histological picture and avoids further treatment intensification in benign lesions. Also, it achieves complete surgical clearance of disease in a large number of cases and help to avoid therapy intensification and consequent late effects. This approach has eliminated the requirement for WLI in 59–67% of patients [2].

Metastatic disease resection should be carried out as soon as possible after nephrectomy and preferably before the start of postoperative ChT. Though extensive surgery can be done to completely eliminate metastatic disease, potentially mutilating surgeries need to be avoided. Thus, whereas wide wedge resections of the lung and liver, segmentectomies, and even lobectomies are acceptable, pneumonectomy should be avoided. Metastasis outside the lung and liver should be resected as far as possible while avoiding damage to vital organs [2].

The XRT protocol in UMBRELLA protocol is in broad accordance with the COG protocol (Table 30.3). In SIOP 2001, the WLI dose was 15 Gy, which was decreased to 12 Gy. This was done considering the previous NWTS experience of high EFS and OS (72% and 78%) for favorable histology (FH) tumors with only 12 Gy XRT to the lungs [24].

30.5.3 UKCCLG Protocol

The UKCCLG protocol is similar to the UMBRELLA protocol in terms of stratifying the postoperative treatment on the basis of residual metastatic disease and tumor histology. It uses similar drugs and dosages [21].

Table 30.3 Radiotherapy guidelines in UMBRELLA-SIOP-RTSG 2016 for metastatic disease [2]

	Lung (whole ± boost) (total/fraction dose)	Liver (whole ± boost) (total/fraction dose)	Brain (whole ± boost) (total/fraction dose)	Bone (total/ fraction dose)
Low-risk	No	No	No	No
Intermediate-risk	12.0/1.5 Gy (± 10–13 Gy)[a]	14.4/1.8 Gy (± 10.8/1.8 Gy)[a]	15.0/1.5 Gy (± 10.8/1.8 Gy)[a]	30.6/1.8 Gy
High-risk	15.0/1.5 Gy (± 15–20 Gy)[a]	19.8/1.8 Gy (± 16.2/1.8 Gy)[a]	25.2/1.8 Gy (± 10.8/1.8 Gy)[a]	30.6/1.8 Gy

[a]Boost dose indicated for residual tumor at the time of XRT only

30.6 Management of Unfavorable Histology Metastatic WT

There is a subgroup of children with unfavorable histology (UH) of the primary tumor (focal or diffuse anaplasia) and metastases. Further treatment intensification is required in these patients. In NWTS-5, these children were treated with Regimen I—VCR, DOX, CTX, and ETOP. The 4-year EFS treated such was 55% [25, 30]. In the AREN0321 study by COG, designed for high-risk unfavorable histology stage II–IV, diffuse anaplasia WT showed that regimen UH-1, a more intensive regimen containing CARB in addition to agents used in Regimen I (CTX, CARB, ETOP, and VCR-AMD-DOX plus XRT for 30 weeks) for patients with stage II–IV and focal anaplasia, and regimen UH-2 (UH-1 plus VCR and irinotecan) for patients with stage II–IV and diffuse anaplasia, improved EFS (69%, 95% CI: 56–80%) [25]. This however comes at the cost of significant toxicity to cardiac, respiratory, and musculoskeletal system along with a high risk of second malignancy. This high toxicity decreases the overall EFS and OS and is stimulating further research for therapies with more favorable therapeutic benefit ratio. The novel approaches are aimed at targeting the tumor via biological therapies rather than intensifying ChT and XRT, which seem to have reached a plateau of therapeutic benefit vs. side effects [26, 27].

The UMBRELLA protocol is also broadly consistent with the above approach for the high-risk metastatic tumors though this is one of the areas that the current ongoing study envisages to prospectively collect data on. High-dose ChT followed by autologous stem cell transplantation is also a suggested approach at the discretion of the treating physician, but the outcomes need to be further studied [28].

30.7 Response, Outcomes, and Late Effects

The AREN0533 study reported CR in 42% of the participants after 6 weeks of neoadjuvant ChT, and lung XRT could be avoided in these patients. The proportion of patients achieving CR at week 6 correlated with the initial maximum lung nodule size: The response rates were 22% CR for nodule size >10 mm, 59% CR for nodule size 6 to 10 mm, 69.2% CR for nodule size 3–5 mm, and 86.2% CR for nodule size 1–2 mm. Also, the response rates depended on the total number of lung nodules: 17.6% for >10, 42.3% for 6–10, 59.5% for 2–5, and 72.9% for a solitary nodule [1].

In contrast, 61–67% of patients have complete metastatic response before surgery following the SIOP protocol. An additional 17% achieved CR by surgical metastectomy [29]. The higher rates of CR in SIOP are probably due to higher dose of DOX in the preoperative ChT (100 mg/m^2) as compared to the COG protocol (45 mg/m^2). Also the fact that SIOP allows pulmonary CR to be achieved by surgical metastasectomy definitely improves the response rates.

30.7.1 Outcome

In the COG AREN0533 study, the EFS and OS in metastatic disease with CR at 6 weeks were 80% and 98.3%, respectively, whereas in *SIR*, it was 88% and 92%. The lower-than-expected EFS in *RCR*, though not significant, is thought to be due to the adverse effect of 1q gain, which can be overcome by Regimen M used in *SIR*. The outcome of high-risk anaplastic stage IV tumors treated with UH1 or UH2 was expectedly poorer with an OS of only 46% [30].

30.7.2 Late Effects

The persisting concern with the intense regimen used in metastatic disease is the possibility of late effects. Regimen M, notably, can lead to an increased risk of secondary leukemia associated with CTX and ETOP [31, 32]. There is also a risk of infertility, particularly in boys, related to the use of CTX, which has a cumulative dosage of 8.8 g/m^2 on Regimen M [33].

Lung XRT is an important factor leading to delayed cardiorespiratory failure, pulmonary fibrosis, breast cancer, and musculoskeletal problems in survivors. With the current concept of treatment stratification, fortunately this can be avoided in 40–60% of cases. It is estimated that there is a substantial increase in premature deaths (22.7% as compared to 5.4%) in WT survivors 30–50 years after treatment. This is attributable mainly to secondary neoplasms and cardiac illness, related primarily to XRT [34].

The presence of liver metastases at diagnosis is not an independent adverse prognostic factor in patients with stage IV WT [35].

30.8 Follow-Up

Meticulous and strict follow-up of recovered patients is imperative to detect early relapses. In addition to routine clinical examination and abdomen ultrasound every 3 months, a chest X-Ray (both AP/PA and lateral view) is recommended 3 monthly for the first 2 years for patients that recovered from metastatic disease. In high- and intermediate-risk cases, the CXR needs to be done 2 monthly. A NCCT chest is recommended after the end of therapy, if complete clearance of metastatic disease was not documented after the neoadjuvant treatment [36]. Six-monthly serum creatinine and 2-yearly echocardiography are also essential to look for delayed effects of treatment. Patients receiving bone irradiation for bony metastasis also need to undergo a yearly X-ray till full growth followed by a 5-yearly spine and pelvis X-ray thereafter [37].

30.9 Future Directions

Even though we have come a long way in treatment of WT, a large amount of work remains to be done to improve the quality of life of WT survivors, especially in metastatic disease.

A very important aspect to be studied is the effect of 1q gain, especially in *RCR* currently being treated only with three-drug regimen and showing more events than expected and consequently a lower EFS of 80% compared to the targeted 85% EFS. Both the COG and UMBRELLA protocol aim at collecting more data about the biomarkers, especially 1q gain and their effect on treatment and outcomes.

High-dose ChT followed by autologous stem cell transplant is an approach showing positive outcomes in many pediatric malignancies and is now being tried in metastatic WT too. Though presently this option rests with the treating physician and the local facilities, it is envisaged to assess this option very seriously.

Another important area of work is the treatment of focal or diffuse anaplastic metastatic WT. Currently being treated with Regimen UH1 or UH2, the treatment is handicapped by the severe side effects of these regimens, and there is a constant effort to attempt dose reduction or replace drugs such as irinotecan with those having higher benefit/side effects ratio.

Recently, dendritic cell-based immunotherapy against the WT1 gene protein is being investigated as a potential new targeted therapy, especially for disseminated/relapsed cancers

which have exhausted all other possible treatment approaches. The vaccine against the WT1 gene protein is hypothesized to act by encouraging an immune response by the host's dendritic cells against the cancer cells containing the WT1 protein. Though this is in a very nascent stage, more research into this may present an entirely revolutionary treatment option in the future [39].

30.10 Conclusions

Whereas almost 100% survival has been achieved in stage I and II WT, nevertheless treatment of metastatic WT is still work in progress. After the initial rapid strides in the EFS and OS with stronger ChT drugs and higher doses, along with XRT, there is now a pause in further improvement owing to the unwanted short- and long-term harmful effects of the therapy. Treatment stratification based on response in all the protocols has definitely helped in choosing the patients requiring treatment intensification while ensuring optimum results with less toxic therapy in others. However, this stratification begs for additional refinement, and further progress will depend on identification and understanding of biomarkers affecting tumor behavior.

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Recurrent/Relapsed Wilms' Tumor

31

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31.1 Introduction

The management of Wilms' tumor (WT) has undergone a sea change with the introduction and refinement of multimodal therapy, which includes surgery, chemotherapy (ChT), and radiotherapy (XRT). With these advancements, children with these tumors can expect an overall survival (OS) rates approaching 90% [1].

However, relapse/recurrence of WT is not uncommon. About 15% of patients with favorable-histology (FH) WT experience a recurrence, whereas half the patients with an anaplastic WT (AWT) have a recurrence [2]. The incidence of recurrences in low and middle income countries (LMIC) have been high, with even the latest rates being reported up to 30% [3]. Most recurrences in WT occur within 2 years from the time of diagnosis. Late recurrences are rare and can occur up to 25 years from the initial diagnosis [4–7]. In a retrospective study in more than 13,000 children across various WT trials, the rate of late recurrence were only 0.5% [8]. Lung and pleura account for 50–60% of recurrences, whereas the abdominal recurrences contribute toward 30% of relapses. Other sites like the brain and bone are involved in 10–15% [9–11].

In contrast to the primary WT, the recurrent Wilms' tumors (RWT) carry poor prognosis, with only 3-year OS of only 24–40%, while a subset of patients with FH have an OS of 77% [3, 12].

The surveillance protocol for a patient treated for WT is discussed in another chapter and is not repeated here.

31.2 Site(s) of Relapse and Presentation

The recurrence can occur in the lungs and abdomen (with or without involvement of the lungs) and rarely in the brain and bones. Most common recurrence is seen within the lungs (58–63%), followed by the abdomen, with or without involvement of other sites (29–49%) [8, 12]. RWT in the brain or bones is a rare event (13%). Abdominal RWT can involve the previous site, liver, and opposite kidney and, sometimes extremely rare, unusual sites like the uterus and cervical lymph nodes (LN) [5, 13]. The distribution of the site of recurrence was similar, irrespective of whether the patients had received XRT or not.

Recurrences, in cases with FH in initial diagnosis, confined to the lungs only tend to have better prognosis compared to abdominal or other site recurrence, with 3-year OS of 44% vs. 28%

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vs. 11% [12]. Unfavorable histology (UH) has poor prognosis irrespective of the site of relapse. Though recurrence in the liver carries poorer prognosis, with 4-year OS of 14%, successful surgical excision of these tumors can have good prognosis.

The RWT may or may not cause symptoms in these patients. The prognosis of patients who present with asymptomatic relapses, which are detected during the surveillance imaging, is better compared to those that present with symptoms (nearly twice the mortality) [14]. Abdominal recurrences may present with lump in the abdomen due to recurrence at previous site or liver or gross distension due to ascites, contralateral kidney mass, or pelvic mass. Pulmonary recurrences manifest as difficulty in breathing due to parenchymal masses or pleural effusion, cough, and very rarely pneumothorax [15]. For those with intracranial recurrences, presentation features include seizures, headache, vomiting, paresis/paralysis, and impaired consciousness [11].

31.3 Time of Recurrence

RWT are more prevalent within 2 years after treatment. Recurrences occurring beyond 5 years of treatment are termed as late recurrences. In the largest study that observed late recurrences, the distribution of recurrences in both alive and dead cases had no correlation with gender (equal incidence in both the genders), initial tumor stage, or type of previous treatment received. However, most of these cases had FH in the previous tumor [8]. Late recurrences can be either true recurrence or a metachronous WT in the contralateral kidney (attributed to persistence of nephrogenic rests). The survival in such case is better (87% vs. 45%) compared to recurrences elsewhere. The exact etiopathogenesis of late recurrences is not known. Quiescent tumor stem cells in such sites might escape the immune vigilance and may get activated by unknown stimuli (e.g., hormones in adolescents).

Grundy et al. measured the time to relapse and divided the period into early (0–5 months), intermediate (6–11 months), and late relapse (12+ months). The early relapse cases were mostly UH types at initial diagnosis and had the poorest 3-year-OS among the above strata (18%) [9].

31.4 Factors Influencing Occurrence of Relapse

Stage and histology are two of the most important factors that dictate the course of the disease. With respect to relapse, though no specific identifiable factors causing relapse are identified, the risk of relapse can be predicted in certain subgroups.

Stage III–IV WT, which have gained access to the lympho-vascular structures, can lead to seeding of tumor cells at local and distant sites, potentially causing more recurrences than the stage I–II tumors. The patients with initial stage I FH WT had better post-relapse survival compared to stage IV FH (57% vs. 17%) [12].

AWT and pretreated tumors with blastemal-type histology, which are considered as high-risk types, are again resistant to treatment and cause early relapses.

Biological markers have been much discussed in recent times. Especially the loss of heterozygosity (LOH) at 1p and 16q, which, in even the FH WT, have caused more relapses [16].

The initial treatment received also holds significance with respect to post-relapse prognosis. Patients who received two-drug therapy, vincristine (VCR) and actinomycin-D (AMD), had better survival rates compared to patients who received three-drug therapy (VCR, AMD, and doxorubicin) (42% vs. 26%), in an analysis done for stage II–III (FH) cases. Perhaps patients who received only two drugs had better sensitivity of RWT for the third drug during post-relapse treatment.

XRT to the abdomen doesn't predict the future risk of relapse. But previously unirradiated abdominal RWT are better salvageable compared to RWT in previously irradiated cases. RWT in the lungs occurred more frequently in unirradiated sites.

Percutaneous biopsy of renal tumor at initial presentation has been considered a risk for

recurrence for a long time. But a study from UK found the initial biopsy increased the risk of local relapse (abdomen, other than liver) while having no effect on distant relapse [17]. But the significance was less when histology and size were considered in the multivariate analysis for local relapse.

Another factor to be considered here is the size of the tumor at initial diagnosis. Tumors >12 cm in size are significantly large and have high risk of rupture. This is more significant for those above 15 cm in size. Rupture of tumor is associated with increased risk of local recurrence [18].

Males fare slightly worse than females [19].

In a multivariate analysis of adverse prognostic factor in children with RWT who had been enrolled under the SIOP-6 or SIOP-9 treatment strategies, SIOP identified various adverse factors for RWT [20]:

1. Stage IV disease.
2. UH.
3. Time to recurrence of 6 months or less after initial diagnosis.
4. Multiple sites of recurrence.
5. Previous history of XRT.

Other studies have analyzed 95 patients and demonstrated an association of LN involvement and anaplasia as an adverse prognostic factor correlated with an increased probability of relapse [21]. A European group analyzed 170 patients with relapse and found the following adverse risk factors for a relapse [22]:

1. Initial stage III or IV.
2. High-risk histology.
3. Time to recurrence of 6 months or less after initial diagnosis.
4. Site of relapse.

The precise effect of site of relapse in a RWT is vitiated by the fact that many abdominal recurrences may occur in irradiated fields and many published reports may include contralateral kidney as a recurrence along with tumor bed, liver, or LN. Similarly, many lung recurrences may occur in previously unirradiated areas but may also include mediastinal recurrences. There is a definite need to further evaluate the site of relapse as a prognostic factor for a recurrence.

31.5 Therapy for RWT

There is a limited experience available for the optimal rescue therapy for RWT. Most patients receive VCR and AMD, with or without doxorubicin (DOX), as part of the initial therapy for the primary lesion. Before the 1990s, the same ChT agents were used for the treatment of both primary and recurrent disease. However, the salvage rates with the same ChT agents in recurrent disease were as low as 25–40% [2]. With the introduction of alternate treatment combinations, the outcomes started improving up to 60% in the last 20 years [23]. As a general principle, it is preferable to avoid the agents that have been previously used as part of the initial therapy and to tailor the therapy using a risk-stratified approach. It is common to use ifosfamide, carboplatin (CARB), and etoposide (ETOP), either as a single agent or in combination (ICE regimen) (Fig. 31.1) [24].

ETOP has demonstrated an efficacy of 42% in clinical trials [25], whereas ifosfamide and CARB have shown a 52% objective response [25, 26]. Recent studies have documented the activity of topotecan in FH RWT but have not demonstrated any efficacy in AWT [27]. The introduction of these drugs led to event-free survival (EFS) rates ranging from 50 to 70% [23]. However, the best combinations, dose intensity, and the duration of

Week	0	3	6	9	12
IFO 1.8 gm/m^2 x 5 days	↓	↓	↓	↓	↓
CARB 400 mg/m^2 **x 2 days**	↓	↓	↓	↓	↓
ETOP 100 mg/m^2 **x 5 days**	↓	↓	↓	↓	↓
IFO ifosfamide, *CARB* carboplatin, *ETOP* etoposide					

Fig. 31.1 ICE regimen *IFO Ifosfamide* [24]

therapy still remain to be fleshed out. Moreover, the prognosis of the patients with RWT depends upon many other factors including the initial tumor stage, histology, previous modalities of therapies, site of relapse, and the time from the initial diagnosis to relapse. It also becomes difficult to standardize the various other modalities for treatment, viz., local surgical excision and XRT, especially for already irradiated relapses. High-dose ChT with stem cell rescue (SCR) is being increasingly utilized for the treatment of RWT with improving survival rates [28].

31.6 Management: Patient Risk Stratification Approach

A number of potential prognostic features influence the outcomes post a relapse. However, it is often difficult to determine the effect of each factor independently, as the numbers are low, and it is difficult to compare the subgroups of these patients. Also, the prognostic factors seem to be changing over time as the understanding and the therapy of primary and RWT evolve [21, 22].

Based on the current state of science, the following risk categories for RWT can be identified (Table 31.1) [29, 30]:

1. Standard risk [30].
   (a) FH RWT with initial therapy with therapy with VCR and/or AMD.
   (b) Account for 30% of all recurrences.
   (c) Event-free survival (EFS) of 70–80%.
2. High risk (HR) [31].
   (a) FH RWT with initial therapy with three or more ChT agents.
   (b) Account for 45–50% of all recurrences.
   (c) EFS of 40–50%.
3. Very high risk (VHR) [32].
   (a) Anaplastic, or blastemal-predominant RWT.
   (b) Account for 10–15% of all recurrences.
   (c) EFS of 10–15% only.

However, it is expected that with changes in treatment and further refinement in treating WT, the factors identified for risk stratification may lose their significance. More aggressive regimens which are more effective in dealing with RWT along with a judicious use of radiotherapy may also affect the significance of factors identified.

31.6.1 Management of Standard Risk RWT

The data on the management of standard risk RWT is limited due to a limited cohort of patients. However, the management of the standard risk RWT has revolved around two main protocols-one from National Wilms Tumor Study (NWTS) Group and the other from United Kingdom's Children's Cancer and Leukaemia Group (UKCCLG):

31.6.1.1 Stratum B of the NWTS-5 Relapse Protocol [33]

NWTS-5 relapse treatment consisted mainly of alternating courses of VCR-DOX- CTX and ETOP, which is similar to the Regimen I used as standard treatment for WT (Fig. 31.2). Surgical excision is employed only in locations which are amenable to surgical excision. XRT may also be used in selected cases. Four-year overall survival (OS) was 81.8% for all patients with a slightly lower EFS rates for children who had lung relapses.

Table 31.1 Risk stratification in RWT

Risk group	Includes	Incidence	EFS	Treatment recommendations
Standard risk	FH, initial therapy VA	30%	70–80%	CTX/DOX-CARB/ETOP
High risk	FH, initial therapy VAD	45–50%	40–50%	I/CARBO/ETOPO—ICE regimen
Very high risk	Diffuse anaplasia WT, blastemal-predominant WT	10–15%	10–15%	ICE regimen with high-dose melphalan

VCR vincristine, *AMD* actinomycin-D, *DOX* doxorubicin, *CTX* cyclophosphamide, *CARB* carboplatin, *ETOP* etoposide, *I* ifosfamide, *VA* VCR/AMD, *VAD* VCR/AMD/DOX

Fig. 31.2 Stratum B of the NWTS-5 Relapse Protocol [33]

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	18	21	24
VCR[a] 50 μg/kg or 1.5mg/m^{2bd}		↓	↓		↓	↓	↓	↓	↓		↓	↓	↓[c]	↓[c]		↓[c]		↓[c]
DOX[d] 1.5mg/kg or 45mg/m^2	↓						↓						↓			↓		↓
CTX 14.7mg/kg or 440mg/m^2 **X 5 days**				↓			↓			↓			↓		↓	↓	↓	↓
ETOP 3.3mg/kg or 100mg/m^2 **X 5 days**				↓						↓					↓		↓	
XRT							↓											

[a]Maximum single dose 2mg
[b]for all patients weighing >30kg
[c]67μg/kg or 2mg/m2 for weeks 12, 13, 18, 24
[d]Maximum cumulative dose 250mg/m^2
Dose of DOX at week 6 should be decreased by 50%, if WLI or WAI has been given
Abbreviations: DOX, Doxorubicin; VCR, Vincristine; CTX, Cyclophosphamide; ETOP, Etoposide; XRT, Radiotherapy

Week	0	1	2	3	4	5	6	7	8	9	10	12	13	15	16	18	19	21	22	24	25	27	28	30	31	33	34
AMD 1.5mg/m^2		↓			↓			↓			↓		↓		↓		↓		↓		↓		↓		↓		↓
DOX 30mg/m^2		↓			↓			↓			↓		↓		↓		↓		↓		↓		↓		↓		↓
VCR 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		↓		↓		↓		↓		↓		↓		↓		↓	

Cumulative dose of DOX is 360 mg/m^2
If patient is about to receive pulmonary radiation therapy, then DOX should be administered from week 1 to 28.
Cumulative dose is reduced to 300 mg/m^2
Abbreviations: VCR-, Vincristine; AMD, Actinomycin D; DOX, Doxorubicin

Fig. 31.3 UKW-R Protocol [34]

31.6.1.2 UKW-R Protocol of UKCCLG [34]

Here, patients with recurrences were managed by either a pulse intensive regimen of VCR, AMD, and DOX or an alternating course of DOX-CYCLO and CYCLO-ETOPO (Fig. 31.3).

31.6.2 Management of High-Risk RWT

The management of these difficult cases has revolved around either a conventional-dose ChT or a high-dose ChT with an autologous SCR.

31.6.2.1 Conventional-Dose Chemotherapy

A study published on the treatment of 60 children with relapse reported the management of these children by alternate courses of CTX and CARB with CARB and ETOP over a period of 90 weeks as part of the Stratum C of the NWTS relapse protocol [35]. They reported a 4-year EFS and OS of 42.3% and 48%, respectively. Abu-Ghosh et al. reported 63.6% EFS and OS with high-risk (HR) RWT treated with ICE ChT along with other therapies like surgical excision and XRT [36].

31.6.2.2 High-Dose ChT with Autologous SCR

High-dose myeloablative ChT is utilized along with bone marrow transplantation (BMT) and autologous SCR in an effort to treat the HR RWT. However, most of these treatments are outside the realm of controlled clinical trials. The aim is to obtain a better outcome than historical controls and various centers reporting higher 4-year OS rates (60–73%) [36, 37]. The French Society for Paediatric Oncology reported on 28 HR RWT treated with high-dose ChT with SCR and achieved an OS of 60.9% [37]. The regimen used in these studies utilized either a high dose ICE Regimen or a therapy using elphalan, ETOP, and CARB (MEC regimen) [35]. The German Cooperative Wilms Tumor Study Group reported on patients with HR RWT with ChT utilizing alternating regimen of CTX-ETOP with CARB-ETOP. Children who achieved complete response (CR) were continued on the same therapy, whereas who had partial response (PR) or and no response received ablative ChT with autologous SCR [38]. Campbell et al. reported on 13 children with relapsed WT treated with high-dose ChT with SCR and reported a 4-year OS of 73% [39].

Topotecan has been variably incorporated in the treatment of patients with RWT who failed initial treatment with three or more effective drugs. Topotecan is a camptothecin analog that has demonstrated antitumor activity in various childhood cancers including WT. A retrospective review of 16 children who received topotecan as part of their salvage regimens for HR RWT demonstrated no effectiveness in the treatment of HR histology RWT patients. However, its role is still equivocal in standard risk histology [39].

Thus, the current state of literature suggests that high-dose ChT with SCR might be an effective treatment for patients with HR RWT.

31.6.3 Management of Very-High-Risk RWT

Patients with AWT or advanced tumors on initial therapy who present with a recurrence have generally demonstrated abysmal survival rates to the currently employed treatment strategies [23, 40, 41]. Overall, in these patients, a very poor response to any drug combination due to intrinsic drug resistance has been reported and only a handful of survivors. Other ChT agents and novel strategies may be required to improve the outcomes in this group of patients.

31.7 Other Strategies

Most patients with RWT can be rescued with salvage therapy especially in the standard risk group. However, the HR and the VHR groups demonstrate poorer survival rates with almost very poor survival rates in the VHR. There is a need to identify newer novel agent and targeted therapies for the treatment of these children. A systematic review of literature for published phase I and II clinical trials that registered patients with WT had identified 62 trials. Fifty of these were phase I and 12 were phase II trials, and these enrolled a total of 214 patients with RWT [42]. Overall, only 33 WTs demonstrated any degree of tumor control with these strategies with only 5 patients (2%) demonstrating CR and only 15 patients (7%) demonstrating a PR. This highlights the currently dismal outlook with newer strategies. Various agents that have been attempted in the management have been oxaliplatin, thiotepa, VEGF, bevacizumab, and all-trans-retinoic acid among other agents [43].

31.8 Role of Surgery and XRT in the Management of RWT

Logically, surgical removal of operable tumors should be helpful, but the evidence for the same is lacking in literature. The NWTS group suggests that a surgical removal of all pulmonary metastasis is unlikely to improve survival rate when compared to ChT [43]. Fuchs et al. reported on children with liver metastasis and the outcome of surgical excision in those group [44]. They reported that the patients who could be managed

by a complete surgical excision survived. Similarly, an excision of solitary lung metastasis might avoid the toxicity of lung XRT. There have been no clear guidelines for administering XRT in this select group of patients. However, reports of administration of whole abdominal irradiation (WAI) for abdominal or hepatic recurrence and whole lung irradiation (WLI) for pulmonary recurrence(s) do exist [43].

31.9 Treatment of RWT in SIOP-RTSG Umbrella protocol

In the UMBRELLA protocol, patients with relapsed tumours are classified into three groups AA, group BB, and group CC, based on these factors [45]. Treatment of group AA relapsed WT, defined as patients with initial stage I–II low-risk or intermediate-risk tumours, who received only VCR and/or AMD (no XRT) in their first-line treatment, will include four drugs (combinations of DOX and/or CTX and CARB and/or ETOP). The combination of these drugs are same used in NWTS-5 relapse protocol and UKW-R protocol and the, but drug combinations and doses vary. Treatment of group BB relapsed WT without initial diffuse anaplasia or blastemal-type histology, who have already received DOX in their initial treatment receive an intensive reinduction drug regimen (including the combination of ETOP and CARB with either IFO or CTX), followed by either high-dose melphalan and autologous stem cell rescue (ASCR) or two further reinduction courses [29]. Relapsed group CC includes patients with initial diffuse anaplasia or blastemal-type tumours. For patients in this category, and for the other relapsing patients showing no response to salvage treatment, the UMBRELLA protocol advises trying camptothecins (irinotecan or topotecan) or novel compounds, as these patients will have already received most conventional active agents in their first-line therapy and are likely to develop ChT-resistant disease [46]. UMBRELLA protocol also provides structured guide-lines for administering XRT and surgery at relapse [45].

31.10 Surveillance Schedule After a Complete Response (CR) Following Relapse

There is scarce evidence about optimal surveillance schedules and methods for detection of tumor relapse after a CR following a relapse. Since there are no optimal guidelines for surveillance schedules available in literature, a surveillance schedule detailed for WT with high risk of recurrence might be suitable. In view of the late effects of highly intensive and toxic ChT and XRT, a long-term surveillance protocol may be required to capture recurrent relapse, second malignancies, and/or other effects [43].

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Wilms' Tumor in Less Than 6-Month-Old Infants

32

Vivek Manchanda and Yogesh Kumar Sarin

32.1 Introduction

Wilms' tumor (WT) is the most common renal tumor seen in children representing >90% of all renal tumors [1], but if we focus only on the cohort of children <6 months of age, then non-Wilms' renal tumors (NWRT) are more prevalent [2, 3]. Congenital mesoblastic nephroma (CMN) is the most common renal tumor seen in the first 3 months of life [4]. In a National Wilms Tumor Study (NWTS) report, of the 27 renal tumors seen in the neonatal period, 18 were CMN, 4 were WT, and 1 was Malignant Renal Tumor of the Kidney (MRTK) [5].

WT is not commonly seen in early infancy; neonatal WT comprise only 0.2% of all WT [6, 7]. Incidence of neonatal renal tumors has been reported as 1 in 700,000 live births in a population-based study [8].

32.2 Clinical Presentation

32.2.1 Antenatal Diagnosis

Only 15% of babies born with renal tumors are identified on prenatal ultrasound [2, 3, 9, 10]. The first case of antenatally diagnosed bilateral WT was reported by Gordon in 1996 [11]. Antenatal detection of WT as early as 29 weeks has been also known [12]. Some are identified due to investigations for associated polyhydramnios or fetal hydrops. Hydrops can be either due to abdominal compartment syndrome and compression of infra-diaphragmatic great vessels because of exceptionally large tumor or due to intratumoral shunting [10, 13].

32.2.2 Presentation

Majority of the neonatal renal tumors (40–80%) are diagnosed incidentally as palpable asymptomatic abdominal mass on routine postnatal examination (Table 32.2) [6, 9]. Others may have nonspecific symptoms like pallor, vomiting, lethargy, abdominal distension, or failure to thrive or specific symptoms like hematuria or polyuria [3, 9]. Hypertension due to renin produced either by the tumor cells or by entrapped juxtaglomerular cells may be present [2, 14]. A neonate with WT in rare association with jaundice and consumption coagulopathy without venous thrombus has been also documented [15].

Syndromes such as WAGR syndrome, Beckwith-Wiedemann syndrome, Denys-Drash syndrome, Simpson-Golabi-Behmel syndrome, etc. are infrequently apparent in the neonatal age [9, 16]. If and when these syndromes are recognized, these syndromic patients should have continued surveillance to identify WT at an early stage [17].

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Rarely, WT may be seen in association with many other congenital abnormalities. Mitra et al. had reported a case of congenital bilateral triphasic WT associated with nephroblastomatosis, perilobar nephrogenic rests, ductal plate malformation, pulmonary hypoplasia, splenic-uli, and multiple skeletal malformations who succumbed on first day of life due to pulmonary insufficiency [18].

32.3 Diagnosis

Differential diagnoses to a palpable abdominal renal lump in a neonate or young infant are neuroblastoma, renal vein thrombosis, ectopic kidney, horseshoe kidney, fetal hematoma, and CMN [19].

Laboratory investigations may reveal anemia, hypertension, hypercalcemia, increased renin levels, or bone marrow infiltration [9]. Hypercalcemia is due to secretion of parathormone-like proteins or prostaglandins [2].

Ultrasound abdomen is the initial recommended imaging study. Computerized tomography (CT) scan or magnetic resonance imaging (MRI) may be done to confirm the organ of origin and local extent of tumor evaluate for lymph nodes (LNs), inferior vena cava (IVC) thrombus, contralateral kidney, and liver metastasis but has limited role in identification of type of renal tumor [20]. These may also help in identification of presence of nephrogenic rests (NRs) or nephroblastomatosis (NB) [21]. As MRTK are commonly seen in this age group, CT scan of the brain to look for metastasis may be done [9].

32.4 Pathology

Among WT presenting in early life, triphasic histology is predominant [12]. In large series of infants with WT <6 months of age, not a single case of anaplastic WT was reported [3, 6]. Anecdotally, User et al. had described a 6-month-old infant with bilateral anaplastic WT, who died in postoperative period [22].

32.4.1 Preoperative Biopsy

Role of preoperative biopsy is limited; both COG and SIOP-RTSG protocols recommend upfront radical nephroureterectomy. Neoadjuvant chemotherapy (ChT) is not recommended in this age group [4, 23]. The sample has been reported to be inadequate or inconclusive in 4–24% of preoperative biopsy specimens [9, 23, 24]. Of the two common renal tumors in this age group, it is particularly difficult to differentiate between cellular variety of CMN and stromal component of WT on needle biopsy specimens [9].

32.5 Staging

Infantile WT are usually early-stage tumors. Ritchey et al. reported on 15 neonatal WT, all of them being either stage I or stage II [6]. In reports from NWTS and SIOP groups, >80% of children presented with stage I or II WT; only <1% had metastasis at presentation [2, 4–6]. Rarely, even neonatal WT have been known to have metastases [25–27]; the metastases to the liver and brain have been reported.

Of the NWRT presenting at this age, clear cell sarcoma of kidney (CCSK) patients also present in stage I or II. However, those with MRTK present with advanced stage III or IV [4].

32.6 Management

Management of antenatally diagnosed WT requires multidisciplinary team approach inclusive of obstetricians, pediatricians, pediatric surgeons, and oncologists [7]. Antenatally diagnosed WT being very low risk (stage I, FH, weight < 550 grams) are usually managed by surgical excision only [21].

Though neoadjuvant ChT is not recommended for children younger than 6 months with renal tumors [23, 28], it may however be considered in cases of bilateral renal tumors, syndromic patients with high risk of metachronous malig-

nancy to preserve renal function, or solitary kidney with WT [1, 4, 9].

32.6.1 Surgery

As it is difficult, if not impossible, to differentiate WT and CMN preoperatively, the recommended surgery is radical nephroureterectomy (RN) including en bloc removal of perirenal fat as CMN often shows infiltrative growth into perirenal fat [29, 30]. For the same reason, partial nephrectomy (PN) or nephron sparing surgery (NSS), is not usually advocated for unilateral renal tumor in this age group [29]. Toussi et al. presented feasibility of performing laparoscopic nephroureterectomy with LN sampling in a neonate with WT [31].

NWTS-5 studied surgery only for children <2 years with stage I disease, tumor <550 grams, negative LNs, and favorable histology (FH). This subgroup had higher recurrence (84% 5-year EFS vs. 97% EFS for ChT group, $p = 0.002$). However, the salvage rate with standard treatment was high and 5-year OS was 98% (vs. 99% for ChT group, $p = 0.70$). But the study was abandoned due to stringent criteria [1, 32, 33]. Considering good overall prognosis, current COG protocol has surgery only in infants with a hope to spare them of side effects of toxic ChT [3, 32, 33].

32.6.2 Chemotherapy

Adjuvant ChT is rarely indicated in the situations mentioned above [9]. Due to higher toxicity of ChT agents associated with the usual doses in NWTS-2 trial, the recommended dose for children <6 months has been reduced to 50% without altering therapeutic benefit. The same dose reduction has been adopted by the COG and SIOP protocols as well as Indian guidelines [6, 30, 34–36]. In SIOP-RTSG, the dose is reduced to two-thirds in children <12 kg of weight due to increased risk of hepatotoxicity and veno-occlusive disease [13].

32.6.3 Radiotherapy

Radiotherapy (XRT) is poorly tolerated by young infants [3, 6, 31]. Although the recommendation for XRT is same as that for older children, most clinicians reserve XRT only for local relapse [3].

32.7 Prognosis

A recent review of 5631 children registered in SIOP studies from 1993 to 2016 has shown reduced EFS and OS with increasing age [37]. The long-term EFS and OS is better in early age due to early stage, smaller tumor size, and histological low risk category of tumors presenting in early age [2, 3, 9, 28, 37]. In a single-center survival analysis from 1949 to 2014, 5-year OS and EFS among 65 infants with WT were 88% and 83%, respectively [3]. In a systemic review of 433 WT (among 750 renal tumors) in infants <7 months of age, 5-year OS and EFS were 86% and 93.4%, respectively [4]. Table 32.1 depicts presentation, histology, staging, and outcomes as seen in various studies.

However, those operated in early neonatal period have been reported to have significant mortality, especially those having abdominal compartment syndrome associated with hydrops (Table 32.2) [7, 10, 13, 38, 39]. This may be related to aggressiveness due to unknown genetic factors and poor tolerance to adjuvant ChT and XRT [6]. High expression of minichromosome maintenance 2 (MCM2) by immunohistochemistry has been suggested to be related to poor prognosis [40].

Table 32.1 Characteristics and outcome of WT in children <6 months in various studies

Authors/year	Study group	*N*	Tumor histology	Presenting symptoms	Stage	5-yr OS	5-yr EFS
Ritchey [6], 1995	<1 mon	15	FH WT 15 (100%)	Abd mass (73%) AN USG (20%) BWS screening (7%)	Stage I—12 (80%) Stage II—3 (20%)		
Levie [5], 2000	<6 mon	26	WT 21 (81%) CMN 5 (19%)		Stage I—12 (57%), stage II—2 (10%), stage III—7 (33%)		
Glick [2], 2004	<6 mon	11	FH WT 3 (27%) CMN 7 (64%) others 1 (9%)	AN USG Hydrops and polyhydramnios 1 (33%) Abd mass 2 (67%) HTN 2 (67%) Hematuria 1 (33%)	Stage I—3 (100%)	67	67
Kullendorf [19], 2007	<1 yr	7	FH WT 5 Low grade 1 Intermediate 1	Abd mass 6 hematuria 1			
Akyuz [41], 2010	<2 yrs	50	FH WT 48 (96%) UH WT 2 (4%)		Stage I—16 (32%) Stage II—27 (54%) Stage III—4 (8%) Stage IV—3 (6%)	91	83
Lamb [3], 2017	<1 yr	89	WT 65 (73%) CMN 18 (20%) MRTK 1 (1%) Others-5	Abd mass (80%) Hematuria (12%) vomiting (6%) HTN (3%) Abd distention (3%), incidentally on imaging (1%)	Stage I—40 (56%) Stage II—13 (86%) Stage III—9 (13%) Stage IV—2 (4%) Stage V—7 (10%)	88	83

yr year, *mon* months, *Abd* abdominal, *HTN* hypertension, *FH* favorable histology, *UH* unfavorable histology, *WT* Wilms' tumor, *CMN* congenital mesoblastic nephroma, *MRTK* malignant rhabdoid tumor of the kidney, *AN USG* antenatal ultrasonography

Table 32.2 Neonatal cases reported in literature

Authors/year	*N*	Presenting complaints/N	Stage	Histology	Post-op ChT	Survival	Other features
Favara [42], 1968	4	Polyhydramnios Abd mass 4	I	Blastema Predominant WT		Yes	
Wright [43], 1970	1	Abd mass	I		No	Yes	
Giangiacomo [44], 1975	1	Potter's facies	V		No	No	B to C translocation
Wexler [45], 1975	1	Abd mass	IV	FH	VCR/ AMD	No	Metastasis to LN, liver, contralateral adrenal, bone marrow. Also had medulloblastoma with hydrocephalus; NEC died of chemotoxicity
Kalousek [25], 1977	1	Hydrocephalus	II	Anaplastic	VCR/ AMD	No	Metastasis to the brain, LN, liver
Procianoy [15], 1986	1	Abd mass Jaundice	I	FH			
Hrabovsky [5], 1986	4	Abd mass	Stage I 2 Stage II 1 Stage III 1	FH	No ChT [1], VCR/ AMD [2], VCR/ AMD/ DOX [1]	Yes	
Ritchey [6], 1995	15	AN USG 4 Abd mass 11	Stage I 12 Stage II 3	FH	AMD/ VCR [10]	1 death	
Gordon [11], 1996	1	Abd mass	V	FH	VCR/ AMD	Yes	R PN (HPE PLNR) and L tumorectomy (HPE FH WT)
Suresh 1996 [39]	1	AN USG	–	FH (biphasic)	–	No	Stillborn
Applegate 1999 [21]	1	AN USG Abd mass	I	FH	No	Yes	
Vadeyar [10], 2000	1	AN USG	–	FH (triphasic)	–	No	Stillborn
Parigi [46], 2002	1	Bilious emesis	II	FH	VCR/ AMD	Yes	
Hussain [47], 2004	1	Abd mass, jaundice	III		Yes	Yes	
Leclair [7], 2005	2	AN USG 2 Hydrops, polyhydramnios	I	FH	No	Yes	Operated at D7

(continued)

Table 32.2 (continued)

Authors/year	*N*	Presenting complaints/N	Stage	Histology	Post-op ChT	Survival	Other features
Kullendorff [19], 2007	1	Abd mass	I	FH	No	Yes	
Van den Heuvel-Eibrink [4], 2008	163						92% 5-year EFS and OS
Jain [38], 2011	1	Abd mass	III	FH	DD4A regime	No	
Sarin [13], 2014	1	AN USG Hydrops, polyhydramnios	I	FH	–	No	Pre-op FNAC—Round blue cell tumor
Matondo [48], 2015	1	Abd mass, fever	I	Blastema Predominant WT	No	No	
Yin [49], 2015	1	AN USG	I		No	Yes	Questionable diagnosis
Raciborska [50], 2016	3	AN USG 2, Abd mass 1	Stage I 2 Stage II 1	FH 2 Intermediate1	ChT given to 2	Yes	
Mitra [18], 2016	1	Oligohydramnios Autopsy	5	FH	–	No	Stillborn; Ductal plate malformation
Toussi [31], 2017	1	AN USG	I	FH	EE4A regime	Yes	Laparoscopic nephrectomy
Rampersad [27], 2019	1	AN USG	I	FH	No	Yes	
Ogawa [12], 2019	1	AN USG Abd mass	III	FH	DD4A regime	No	Interstitial loss on the long arm of chromosome 2 at q12.1q13

AN USG antenatal ultrasonography, *FH* favorable histology, *Abd* abdominal, *ChT* chemotherapy, *L* left, *R* right, *PN* partial nephrectomy, *PLNR* perilobar nephrogenic rests, *WT* Wilms' tumor, *VCR* vincristine, *AMD* actinomycin-D, *DOX* doxorubicin

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Wilms' Tumor in Adults

33

Anjan Kumar Dhua and Sachit Anand

33.1 Introduction

Wilms' tumor (WT) is the most common renal malignancy in the pediatric age group, with around 500 new cases diagnosed in the USA annually [1]. In the adult population, however, WT is very rare. The 5-year overall survival (OS) rates among children have significantly improved with multimodal therapy based on the knowledge distilled out from the multicentric cooperative trials carried out by the two major WT research groups (i.e., the National Wilms Tumour Study Group/Children's Oncology Group [NWTSG/COG] and the International Society of Pediatric Oncology [SIOP]). On the other hand, the extreme rarity of WT in adults (WTA) precludes the conduct of such large-scale studies to design management strategies specially directed toward WTA. In literature, WTA is generally reported as individual case reports or as case series with treatment modalities tailored to the clinical situation taking cues from prevalent pediatric WT protocols.

33.2 Incidence

Among older patients (≥16 years of age), WT is extremely rare. It is estimated to have an incidence of less than 0.2 per million per year [2]. A population-based European epidemiological study (1983 to 1994) from the European Cancer Registries study on cancer patients' survival and care (EUROCARE) project, including 67 cancer registries that encompassed a population of 100 million distributed among 22 European countries, demonstrated that the median age of diagnosis for WTA (defined as >15 years of age) was 34 years [3]. However, cases have been diagnosed in adults as late as 60 years also [3].

33.3 Genetics and Pathology

In children, genetic mutations have been noticed in 10% of the cases with WT. More than 40 genes, primarily responsible for kidney development, have been implicated in the etiopathogenesis of WT. Apart from mutations in the WT1 gene, aberrations involving the Wnt pathway, IGF locus, TP53, etc. have also been described in pediatric cases. In comparison, evidence regarding the role of these genes in patients presenting during adulthood is lacking. Also, the syndromic association of WTA is rarely seen [4, 5].

The pathological basis of the diagnosis of WTA is based on the following criteria developed by Kilton et al., which include:

1. Tumor primarily arising from the kidney.
2. Evidence of primitive blastemic spindle or round cell component.

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3. The formation of abortive or embryonal tubules or glomerular structures or no area representing renal cell carcinoma histopathology.
4. Confirmation of the diagnosis in the histopathological tests.
5. Age > 15 years old [6].

Additional diagnostic features can include immunohistochemical staining for demonstrating the presence of cytokeratin, actin, desmin, vimentin, and WT1 that aids in distinguishing between other rare renal malignancies such as mesoblastic nephroma, renal sarcoma, rhabdoid tumor, or clear cell sarcoma. The WT1 expression is diagnosed in the blastemic region and the proliferating epithelial areas, but not in the region of mature stroma and the mature epithelial tissue [7].

33.4 Clinical Presentation

Data on clinical features of WTA are limited, but the existing literature suggests that the most common complaints are local/flank pain and painless hematuria, unlike in children wherein presentation as an abdominal lump is more common. Nonspecific symptoms such as malaise, weight loss, and even, less frequently, hypertension have also been documented as presenting features in WTA [8, 9].

33.5 Diagnosis

Although the diagnosis of WT primarily relies upon the histopathological findings, clinicoradiological characteristics also form an integral part of the diagnostic evaluation. No significant histological differences are noticed among the tumors presenting during adulthood versus those presenting in children. Establishing the diagnosis of WT can be a challenge to the general pathologists. Immunohistochemistry (IHC) and molecular biology studies need to be conducted to rule out common renal neoplasms in this age group. Thus, it is imperative to consult an expert pediatric pathologist for histopathological confirmation of WTA [5, 10].

33.6 Staging

Like pediatric WT, the recommended investigations for staging include computerized tomography (CT) scan of the chest and the abdomen. It helps in the assessment of tumor extension, inferior vena cava involvement, status of contralateral kidney, and detection of liver or lung metastases. Investigations to detect metastases at unusual sites, including the brain, bone, and bone marrow, are not recommended unless the patient is symptomatic. Also, when present, metastases to these sites confer an unfavorable prognosis [4].

The staging system used in these cases is similar to that in children. For children undergoing immediate nephrectomy, a COG staging system is followed. For all those who have received a preoperative chemotherapy (ChT), the tumor stage is considered at least stage III.

In these ChT treated patients, it is recommended to follow the SIOP WT 2001 classification system [4]. Also, in those adult patients receiving pre-nephrectomy ChT, it is recommended to treat blastemal predominant histology cases after preoperative ChT as “high risk” as is also done for pediatric cases [4].

Various studies have depicted the incidence of advanced tumor stages (III or IV) to be higher in adults as compared to children. Also, the incidence of bilateral WT is extremely rare in adults as compared to children [4, 5].

33.7 Management

Management of WTA involves a multimodality approach. The majority of the patients would have already undergone nephrectomy when the diagnosis of WT is made. However, a subset of patients may get the benefit of preoperative ChT [4]. The basic principles of ChT regimens are the same as in pediatric WT, with low-stage and high-stage tumors receiving two- and three-drug combinations, respectively [4, 5]. On the other hand, there are few differences in the ChT protocols. Due to lower survival rates, it is recommended to add doxorubicin (DOX) to stage II adult tumors. Also, the intensity of vincristine

(VCR) is decreased due to a higher propensity of neurological toxicity in adulthood [5]. In patients receiving preoperative ChT, SIOP risk classification must be adopted. It is also recommended that any degree of anaplasia is to be considered as unfavorable or high-risk histology [10].

Nephrectomy followed by stage appropriate adjuvant ChT with or without radiation therapy (XRT) is the preferred approach in majority of the patients. Surgical guidelines for WTA are also not well established, as the majority of these cases are incidentally diagnosed on operative histopathology after nephrectomy for suspected renal cell carcinoma. Nephrectomy with adequate lymph node (LN) sampling is practiced by most of the centers across the globe. Nephrectomy must be performed as per adult nephrectomy guidelines for renal tumors. Patients undergoing laparoscopic nephrectomy must be given a three-drug ChT regimen as adjuvant therapy. Tumors localized to either pole can be treated with nephron-sparing surgery (partial nephrectomy), taking adequate margins [4].

Adjuvant XRT must be administered as per the standard recommendations [4]. It is also advised to start XRT within 14 days of surgery to improve overall survival (OS) [8, 11]. A significant decline in the OS was noticed when adjuvant therapy was delayed beyond 30 days after surgery [2].

33.8 Treatment Toxicity

There is evidence of higher ChT-related adverse effects in adults [6]. Common side effects associated with ChT include nausea, vomiting, alopecia, diarrhea, etc. Apart from these, neurotoxicity and hepatotoxicity (or veno-occlusive disease) are specific adverse effects of VCR and actinomycin-D (AMD) administration. It has been noticed that approximately 48% (13/27) of the patients with WTA suffer from severe VCR-associated neurotoxicity, leading to delays/discontinuation of treatment and dose reduction [9]. In the majority of the cases, this neurotoxicity is partially reversible. The incidence of veno-occlusive disease after AMD administration in children is around 5–8%. However, this complication is uncommon in WTA cases. Renal function impairment and cardiotoxicity are seen in patients who have received DOX. Therefore, it becomes imperative to follow these cases and assess the glomerular filtration rate (GFR). The cardiotoxicity associated with DOX is more when the total cumulative dose exceeds 300 mg/m^2 or when lung irradiation is combined [4].

33.9 WT in Pregnancy

WTA in the scenario of pregnancy is even rarer. Less than 20 cases have been described to date (Table 33.1) [12]. Management of cancer during pregnancy, in general, is difficult due to lack of strong evidence, scarcity of standard treatment guidelines, and complexity of issues pivoting around the mother and the fetus, and WT is no different. Initial staging ideally should be done utilizing nonionizing radiation such as ultrasonography (USG) or magnetic resonance imaging (MRI). If a malignancy is confirmed, a multimodality team comprising of surgery, obstetrics/maternal-fetal medicine, pediatrics, medical oncology, and radiation should discuss the options of local and systemic therapy, considering how the treatment will affect both the mother and fetus. Extensive counseling of the would-be parents would aid them in making tough decisions.

The decision of multimodality team is expected to be based on the following general principles: As far as timing of surgery (nephrectomy) is concerned, there are case reports that document the safety of nephrectomy during pregnancy in patients of renal cell carcinoma from which the safety of surgical intervention in WT has been extrapolated [24, 25]. It is recommended that, for renal cancer, nephrectomy can be offered in the first or third trimester of pregnancy. The operation should be delayed till the 28th week of gestation if malignancy is diagnosed in the second trimester so as to allow pulmonary maturation of the fetus. ChT drugs can have a deleterious effect on the fetus and predispose spontaneous abortion, fetal death, and congenital malformations, and it depends on the specific drug and the

Table 33.1 Summary of WT in pregnancy [12]

S no	Author/country	Age (Yr)	Timing of detection in pregnancy	R/L	Size of mass (cm)	Timing of surgery/surgery	Timing of other therapies/ ChT agents	Follow-up after completion of treatment (in mon)	Remarks
1	Davis et al. [13]	19	32 wk	NS	NS	Prenatal RN	Postpartum ChT: AMD and VCR	15 mon/metastatic disease	–
2	Bozeman et al. [14]; USA	21	32 wk	L	20 × 14	Postpartum	– Adjuvant ChT: Three cycles ICE – Postpartum XRT: Whole abdomen (3000 rads), lungs (1200 rads) – Postpartum lung wedge resection	40 mon/disease-free	Postpartum switched to VAD because of severe myelosuppression and to avoid nephrotoxicity of IFO on solitary kidney
2	Wynn et al. [15]; USA	35	34 wk (during delivery)	L	9.5 × 11.5 × 13	After 12 wk	None	Died after 6 mon with progressive disease	Had R RN for WT16 yrs ago. Became anephric after current operation
4	Corapcioglu et al. [16]; Turkey	19	25 wk	L	NS	None this time	ChT after diagnosis with VCR and AMD till LSCS at 28 weeks XRT (30 Gy) after delivery + ICE/VAC alternatively (four courses)	11 mon/disease-free	This was local recurrence with lung and spinal metastasis of a previously treated L WT 8 mon back. Pt had refused adjuvant therapy that time
5	Byrd et al. [17]; UK	31	30 wk	L	10 × 11	Left RN 12 days after induction of labor done at 32 wk	Adjuvant ChT (NS) 9 mon, followed by 4 wk of XRT	Follow-up CT scan suggested recurrence within R kidney, necessitating further ChT	–
6	Rehman et al. [18]; USA	36	3rd trimester	L	18 × 9	Postpartum lap L RN	Postpartum ChT—18 wk VCR + AMD	18 wk (no mention of disease status)	–
7	Maurer et al. [19]; Germany	31	18 wk	R	8 × 6 × 4	19 wk /RN	VCR+ AMD 22 wk onward 3 weekly/LSCS at 33 wk, subsequently six more cycles of VAD	36 mon/disease-free	–
8	Rodrigues et al. [20]; Brazil	17	NS	L	8 × 8 × 7	20 wk /RN	Refused adjuvant therapy	24 mon/disease-free	

S no	Author/country	Age (Yr)	Timing of detection in pregnancy	R/L	Size of mass (cm)	Timing of surgery/surgery	Timing of other therapies/ ChT agents	Follow-up after completion of treatment (in mon)	Remarks
9	Khan et al. [21]; India	23	22 wk	R	5 × 5	2nd trimester/ PN	NS	12 mon/disease-free (both mother and child)	
10	Brown et al. [22]; USA	34	1st trimester	L	3.2 × 2.5 × 4.9 cm	15 wk/lap PN	Antenatal/VCR, DOX, CTX	12 mon/disease-free (both mother and child)	
11	Walker et al. [23]; USA	23	14 wk	R	17	Immediately after LSCS (done at 28 wk)	14 days after LSCS-XRT to flank and lungs + 30 wk of alternating high-dose CP, VCR, and DOX and low-dose CTX, CARB, and ETOP	14 mon/disease-free (both mother and child)	

Wk weeks, *ChT* chemotherapy, *AMD* actinomycin-D, *VCR* vincristine, *XRT* radiotherapy, *DOX* doxorubicin, *NS* not specified, *LSCS* lower-section caesarean section, *CTX* cyclophosphamide, *CARB* carboplatin, *mon* months, *ETOP* etoposide, *IFO* ifosfamide, *VAD* vincristine, actinomycin-D, doxorubicin, *ICE* ifosfamide, cyclophosphamide, etoposide, *VAC* vincristine, actinomycin-D, cyclophosphamide, *L* left, *R* right, *RN* radical nephrectomy, *PN* partial nephrectomy, *XRT* radiotherapy, *Yr* years, *Lap* laparoscopic

gestational age at which it is administered. For example, cyclophosphamide may be chosen as it is a cytotoxic agent commonly used in WT protocols and has been found to be safe in pregnancy. During the fourth week to the 12th week of gestation, organogenesis occurs in the fetus, and therefore it is prudent to avoid cytotoxic drugs during the first trimester. The risk of congenital malformations decreases significantly as low as 1.5% when these drugs are administered in the second and third trimester [26]. However, the risk of intrauterine growth restriction and premature delivery still exists in about 50% of the fetuses who are exposed to ChT even during the second and third trimesters. Due to the direct effects of XRT on the fetus, XRT to the abdomen or pelvis during pregnancy is contraindicated.

The available literature precludes generalization of treatment modalities that can be offered to this subset of WTA. A pragmatic approach would be to borrow the management principles from prevalent pediatric WT recommendations to expect a favorable outcome to both the mother and the fetus until such time that specific robust evidence is available for the management of WTA.

There are no recommendations on how to follow up a child who is born to a pregnant woman with WT. Till date there are no reports of fetal metastasis of WT. Walker et al. reported that in a situation like this, they had performed a whole-body MRI and chest CT at 6 months of age for surveillance, and thereafter they planned to follow up with investigations based on symptoms that the child may develop [23].

33.10 Prognosis

The prognosis of WT in cases presenting during adulthood has improved since 1982 when the NWTSG first reported the outcomes of this subset of patients [27]. From a dismal 3-year OS of 24% (stage III/IV—11%) reported in NWTSG-1 report, it had improved to 3-year OS of 82.6% in (stage III/IV—70%) in NWTS-4–NWTS-5 era [28]. Apart from this, favorable histology is associated with a superior OS and disease-specific survival ($p < 0.001$), while the advanced stage is associated with an inferior OS and disease-specific survival ($p < 0.001$) [29]. Stage-related prognosis is detailed in another chapter.

33.11 Conclusions

WTA is an intriguing and rare form of WT. Evidence and recommendations for evaluation and management of this form of WT are still evolving. Of late, some improvement in the survival of WTA has been documented by following the same management principles which are available for children.

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34 Nephrogenic Rests and Nephroblastomatosis

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34.1 Introduction

Nephrogenic rests (NRs), as suggested by Beckwith, are aggregates of primitive embryonic nephrogenic cells or persistent embryonic derivatives akin to the developing kidney, capable of induction to form Wilms' tumor (WT). Diffuse groups of multifocal NRs are referred to as nephroblastomatosis (NB), forming the other end of the spectrum. Hypertension and congenital anomalies are accompaniments of elaborate forms of NB [1, 2].

34.2 Incidence

Neonatal postmortem examination has revealed the presence of NRs in about 1%, which scores higher than the incidence of WT to the tune of 100 times. Nephrectomy specimens of WT contain NRs almost 30% of the time, ranges varying from 41% in unilateral WT and 95% in bilateral WT [1].

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34.3 Types

Broadly NRs are categorized into perilobar and intralobar types depending on the relative location with respect to the renal lobe. These types are distinct and well characterized, as shown in Table 34.1 [1–4].

34.4 Embryo Pathology

Renal development is from ductogenic and nephrogenic tissues, evolving from the mesoderm and running through three phases: pronephros, mesonephros, and metanephros. At term (36 weeks of gestation), the metanephric blastema is expected to disappear, which when overstays the welcome persist as NRs.

34.5 Ectopic NRs

Reports of ectopic NRs, variously known as extrarenal nephroblastomatosis, ectopic immature renal tissue, extrarenal nephrogenic rest, hamartoma with primitive renal tissue, and mesonephric remnant tissue, have been noted to occur in inguinal and retroperitoneal regions. Awareness of these is essential in view of their potential to pursue a neoplastic route even in the ectopic sites [5].

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Table 34.1 Characteristics of perilobar and intralobar types of NR

	PL (perilobar)	IL (Intralobar)
Site	Periphery of lobe, sinus, subcortical	Centrally located, Anywhere Cortex/medulla
Type of tissue	Blastema/tubules, scanty stroma	Stroma rich
Borders	Smooth, well defined	Irregular, intermingle
Numerical	Numerous, diffuse	Single
Embryo pathology	Late appearance	Early appearance
Association	BWS, hemihypertrophy, Perlman, trisomy 18	Aniridia, WAGR, DDS
Mutation	11p15	WT1
Risk of WT contralateral	+++	–
Occurrence	More common	Less common
Foci	Multifocal	Solitary
Other mutations	–	CTNNB1 mutations
Risk of neoplastic transformation	Less likely	More likely

BWS Beckwith-Wiedemann syndrome, *WAGR* Wilms', aniridia, genitourinary anomalies, retardation, *DDS* Denys-Drash syndrome

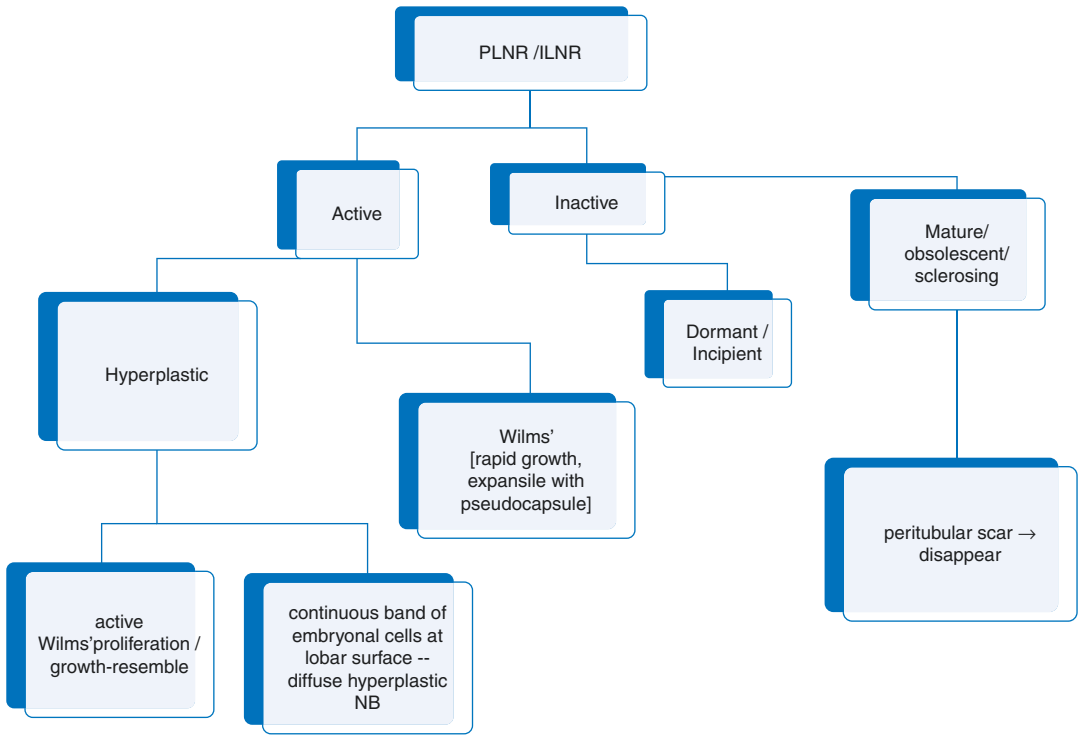

Fig. 34.1 Demonstration of the natural fate of NRs [8]

34.6 Natural History

NRs can become dormant or sclerosing or involute commonly with a small proportion taking up the neoplastic route (Fig. 34.1). Methylation and epigenetic mechanisms are supposed to be the driving forces for this critical transformation. Sonic hedgehog signaling is proposed to play a vital role in this [6]. It takes about 4 months of age for the bulk of the NRs to undergo resolution, leaving about 1% to undergo malignant makeover [7].

Increase in size, changing heterogeneous nature, and spherical appearance of NR are in line with neoplastic transformation. PLNR in

infants and diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB) carry the greatest risk for WT on the opposite side [9].

34.7 Pathology

Based on the ultimate fate/behavior of the NRs, they can be grouped into the following categories.

34.7.1 Subtypes

Most NRs are in the dormant or sclerosing phase.

1. *Dormant/incipient*—microscopic, rare mitoses, blastema, few well-formed tubules, no proliferation. Remaining unchanged over years with respect to size and composition and retaining their tiny focus qualify the dormant subtype. Incipient type is seen typically in newborn/younger infants, while dormant type is associated with older infants/children.
2. *Mature sclerosing obsolescent*—stromal/epithelial cells with hyalinizing stroma, occasional blastemal. Most common fate of NRs. Increase in fibrosis and loss of vascularity lead to the sclerosing NR.
3. *Hyperplastic*—large enough to be seen macroscopically, including areas of blastema, embryonic or sclerosing. At times, they may substitute most of the kidney substance. Coordinated proliferation of all susceptible cells progresses to form a thick crust of abnormal tissue at the renal surface. Formation of small mass can act as a confounding factor in differentiating from Wilms'. Ovoid/elliptical/lenticular shape of hyperplastic can be point of differentiation from a spherical appearing WT. For better distinction from WT, study of the tumor/normal tissue border can be of assistance in that pseudocapsule is a constant finding in a WT. The size of nodule >1.75 cm is also in favor of WT. They can take the form of irregular subcortical yellow tan lesions in the intraparenchymal region. Epithelial elements with nodular expansive growth are representative of hyperplastic type. Diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB) is a distinct variety forming a rind around the periphery of the kidney causing the formation of large unilateral or bilateral flank masses. On imaging, the renal configuration is preserved without necrotic patches.
4. *Neoplastic*—appears in the inside of a rest, evidently expansile, globular, and compressing the rest. The nephroblastomatous/incipient subtype has frequent mitoses, and the adenomatous subtype with rare instances of mitoses is subgrouped under neoplastic type [1, 2, 9].
5. *Anaplasia*—though a possibility, is a rarity [10].

34.8 Diagnosis

A percutaneous biopsy may not be of use if it fails to include the representative area of interphase between normal and malignant zone. Special stains and immunohistochemistry may not be contributory to the diagnosis or differentiating from WT.

34.8.1 Differential Diagnosis

1. Lymphoma.
2. Leukemia [11].
3. Dysplastic medullary ray nodules (most commonly in Beckwith-Wiedemann syndrome) [12].
4. Embryonal hyperplasia (often in multicystic dysplasia and end-stage kidneys) [13].

34.8.2 Imaging

34.8.2.1 Ultrasonography

PLNR may cause enlarged renal size with loss of cortico-medullary differentiation. NR and NB on sonography may appear iso–/hypoechoic. Multifocal NB may not be identifiable by ultrasonography (USG). As such, the pickup rate of NR of 1–2 cm size may be very low. Among magnetic resonance imaging (MRI), computerized tomography (CT), and USG, USG is the least sensitive diagnostic modality but may have a role

in repeat/follow-up studies when the lesion is initially distinguishable on highresolution USG.

34.8.2.2 Computerized Tomography

NRs are hypoattenuated, enhancing less/poorly in comparison with the normal renal cortex in contrast enhanced CT [14].

34.8.2.3 Magnetic Resonance Imaging

Detection of NR beyond 5 mm is possible by MRI. NRs on T1 weighted MR appear as isointense whereas hypointense on T2 weighted sequence. Gadolinium enhancement does not make them intense resulting in hypointense appearance with low signal intensity on postcontrast T1 weighted sequence, due to the poorer perfusion as such. Overall, NRs are homogeneous in contrast to the heterogeneous appearance of WT.

MRI volumetric analysis can determine the volume of NB, through post processing software. This is especially of use in the background of WT on chemotherapy (ChT), as any size increase may indicate a likelihood of WT or unresponsiveness to therapy.

A particular sequence of MRI, known as diffusion weighted imaging, is of value in imaging NR/NB. Based on the hydromolecular level diffusion features ("Brownian motion"), the water particles of tissues are quantified by the apparent diffusion coefficient (ADC). NR/NB in view of their inherent cellular nature and altered tissue architecture with high resistance to diffusion are of low ADC, which is the basis for differentiation from the normal parenchyma on MRI. Magnetic resonance spectroscopy is another armamentarium of MRI which may help in distinguishing benign and malignant lesions [15, 16] (Table 34.2).

Table 34.2 Differentiating features of NR vs. WT on MR imaging

	NR	WT
Nature	Homogeneous	Heterogeneous
Appearance		
– T1 weighted	Iso–/hypointense	Hypointense
– T2 weighted	Iso–/hypo–/hyperintense	Hyper- to isointense
Contrast enhancement with (gadolinium)	–	+
ADC (Apparent Diffusion Coefficient) value	Low	High

34.9 Clinical Significance

In general, painless bilateral or unilateral palpable abdominal masses in the early infancy (<4 months of age) are the clinical presentation of NB [8].

Although benign, NRs have a potential for malignant behavior, which may be likely only in a small minority, when the stage is set in the form of background germline mutations and other additional adverse events triggering the transformation [17].

Identification of NR leads to the likely possibility of synchronous bilateral WT. Metachronous tumor development in the background of ChT is indicative of the fastidious nature of NRs [4].

Anaplasia is found in cases of tumor development in the background of NB, following ChT.

Diffuse hyperplastic perilobar nephroblastomatosis (DHPLNB) requires administration of ChT due to the associated markedly increased hazard of neoplastic change to anaplastic WT. Also, the danger of renal function deterioration due to the load of nonfunctional malignant WT would preempt ChT initiation. Inadequate response would mandate surgical intervention. The unpredictable clinical course, with lesions varying in size over time, and the increased risk of renal insufficiency, prolonged hypertension, and pulmonary complications, if untreated, make its importance felt toward initiation of ChT [9, 18, 19].

34.10 Management

ChT has a definite role in reduction of the proliferative element of NRs, but whether it has any preventive effect on malignancy development is questionable. Overall, renal parenchymal preservation is the objective of ChT in diffuse NB. 13Cis retinoic acid in isolated cases has been used to achieve stable disease. Surgery is not recommended as the initial treatment for nephrobla-

stomatosis and should be avoided as long as possible because of the increased chance of a metachronous tumor developing in the contralateral kidney [20, 21].

34.11 Follow-Up

Baseline CT at 6 months of age to document the findings, followed by a 3–4 monthly USG till 8 years of age so as to detect new lesions in comparison with the baseline imaging pattern [22].

34.12 Future Directions

Keeping in mind the various advances, like molecular diagnosis, microscopic characteristics, and response to therapy, use of genetically engineered mouse models and chemically induced models has been advocated in the study of NR/NB [23].

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Extrarenal Wilms' Tumor

35

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35.1 Introduction

Wilms' tumor (WT) is the most common childhood tumor and accounts for >90% of renal tumors in children. Extrarenal Wilms' tumor (ERWT) is the diagnosis of nephroblastoma occurring outside the kidneys, in the absence of a renal primary tumor, which was described by Moyson et al. in 1961 [1]. The incidence of ERWT is unknown but has been reported to be around 0.5 to 1% of Wilms' tumor with more than 100 cases reported in the literature [2]. ERWT occurs mostly seen in children with more than 60% of ERWT reported in age <4 years, but few authors have reported it in adults [3, 4]. A female predominance was observed [3]. As this is an uncommon condition, no clear guidelines are available in the literature, and it has remained a topic of academic interest. This chapter highlights the recommendations and controversy surrounding the embryogenesis, pathogenesis, staging, and management of ERWT.

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35.2 Embryogenesis

Largely, the embryogenesis and the exact etiology of primary ERWTs are debatable, and there are several unanswered questions. The various possible tissues of origin include malignant transformation of cells with embryonal potential (Connheim's cell-rest theory), ectopic metanephric blastema, and primitive mesodermal tissue of mesonephric duct remnants [5, 6].

Nephrogenic rests (NR) may be observed anywhere in the craniocaudal migration line of the primitive mesonephros and metanephros cells [3, 7]. NRs are precursor lesions found in the kidneys, which usually undergo involution during development. Ectopic or displaced NRs may result in the development of ERWT at various locations ranging from retroperitoneum to distant locations. So far, Connheim's explanation is most widely accepted. The above postulate is further supported by a finding that WT1 mRNA expression, which is characteristic of renal WT, is found in a subset of this rare tumor [8].

The other theories have been studied but are poorly supported by the evidence. The ectopic blastematous cell theory explains occurrence of ERWT in the craniocaudal migration pathway of primitive metanephros cells. Mesonephric duct theory explains gonadal ERWT which results due to the persistence of juxta-gonadal mesonephric glomeruli [9]. Teratomas along with nephroblastic tissue have also been reported raising the

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doubt of teratomatous origin, which is now considered a type of germ cell tumor and not an ERWT [10].

35.2.1 Location

ERWT is most commonly found in the retroperitoneum [11–13] and occasionally inguinal canal, lumbosacral region, pelvis, mediastinum, chest wall, female genital tract, spermatic cord, and paratesticular region [13]. While making a diagnosis of ERWT in locations near the kidney, the possibility of a primary renal tumor with extrarenal extension/metastasis or a diagnosis of WT in a supernumerary kidney should always be excluded. The second most common location is in the pelvis including the inguinal canal, the female reproductive organs (vagina, uterus), the round ligament of the uterus, the ovaries, and the testicles [14–16]. The retroperitoneal location is reported to be typical of males, whereas the inguinal region is believed to be common in females. Out of all cases reported with ERWTs, 7% were found to be associated with horseshoe kidney due to the fusion of metanephric blastema during the sixth to seventh week of intrauterine life and occurrence of the "ectopic" metanephric blastema [7].

35.3 Pathology of ERWT

The classic microscopic feature of ERWT consists of the triphasic pattern that includes mesenchymal, epithelial, and blastemal elements in the absence of any teratoid component. Beckwith and Palmer recommended that a diagnosis of ERWT should be based on histology showing classic triphasic Wilms' pattern outside the kidneys without teratoid or anaplastic elements and both kidneys should be free of tumor on imaging [17]. Multiple sections of the specimen are highly recommended to miss a diagnosis of the teratoid variant [18]. ERWTs are classified as favorable histology (FH) (more common) or unfavorable histology (UH) based on the presence of atypical mitoses and marked pleomorphism [11].

35.3.1 Teratoid ERWT

The presence of heterologous elements along with components of nephroblastoma can be seen in retroperitoneal tumors. Teratoid WT is labeled in the presence of heterotopic teratomatous elements in more than 50% of total microscopic and is a separate entity, of germ cell origin [10]. Teratoid WT represents the heterologous differentiation and is not an individual entity; therefore, it should not be termed as a final diagnosis [19].

35.4 Clinical Presentation

The manifestation of ERWT depends on the location and stage upon the diagnosis. The most common presentation is nonspecific pain and a palpable mass and may be associated with nonspecific symptoms, such as weight loss, fever, and effects due to its location. Symptoms are related to the tumor site and size, usually present as mass and compression symptoms depending on location, and are not uncommon [20, 21].

35.5 Diagnosis

Ultrasound (USG) and triphasic computerized tomography (CT) scan of the abdomen is done routinely to assess the size, site, and spread. ERWT does not have any characteristic radiologic findings, and the diagnosis of ERWT is only after a histological examination is done. But time old teaching of evaluating both kidneys for its anatomy and function is stressed in any case of an abdominal tumor and holds to exclude any intrarenal tumor. Magnetic resonance imaging (MRI) is helpful in paraspinal and thoracic tumors, especially with cord compression symptoms [22]. ERWT can be differentiated from germ cell tumors with the help of tumor markers such as AFP (alpha-fetoprotein) and βHCG (beta-human chorionic gonadotropin). A systematic survey should be done for the spread, although ERWTs rarely metastasize. Three percent of the reported ERWT cases are metastatic, most com-

monly in the lungs and liver [23]. CT chest, whole-body scintigraphy, bone scan, etc. are useful for metastatic workup, and the use of such modalities follows the protocols used for WT. Exclusion of primary renal WT is of utmost importance, as metastases to sites, including the retroperitoneum, chest wall, mediastinum, ovary, vagina, and scrotum have been reported in WT, which may be misdiagnosed as ERWT [24]. Need for histopathological assessment is according to the protocol adopted and is a must if SIOP is followed.

35.6 Staging

The National Wilms' Tumor Study (NWTS) system is applicable for ERWT staging and is as follows [17]:

Stage I—organ-confined tumor, resected completely, no injury to capsule, clear surgical margin. However, the NWTS states that completely resected ERWTs with no evidence of tumor at or beyond the margins should be considered as stage II for treatment purposes [23].
Stage II—regional tumor, biopsied before removal or invading blood vessels; resected completely, clear surgical margin.
Stage III—tumor not completely resected, regional lymph node (LN) metastasis present, tumor spread to the abdominal organs and peritoneum.
Stage IV—hematogenous metastases.

Few authors recommend TNM staging to compare therapy and survival data. The high incidence of stage IIIa (microscopic residual tumor) can be explained by preoperative misdiagnosis resulting in inadequate tumor surgery or an invasive disease [25].

Most ERWTs have FH, and the chance for local recurrences and distant metastases is similar to classical WT. The majority of ERWTs are in stage II and the next common is stage III, while distant metastasis was reported in very few patients [23]. However, Coopies et al. in their series of 34 cases of ERWT found that stage III was the most common (57%) followed by stage I (30%) [25].

35.7 Treatment

Radical surgical excision with adequate oncological margin following the basic oncological principles remains the key upfront treatment of ERWT [26]. Regional LN sampling and careful inspection of solid organs and peritoneum should be done for abdominal locations of ERWT. The role of intraoperative frozen section in ERWTs has not been reported before and is not recommended.

Similar to renal WT, adjuvant chemotherapy (ChT) is recommended for all cases. Radiotherapy (XRT) of tumor bed is indicated for stage III–IV disease with FH and stage II–IV disease with UH. XRT to involved sites is indicated if there is unresectability, residual disease, relapse, or distant metastasis [27].

35.7.1 Prognosis

The outcome, event-free survival (EFS), and overall survival (OS) of ERWT match with that of WT [26]. Two-year EFS of ERWT is comparable to renal WT, and good prognosis is due to identification in early stages and FH [23, 25, 28]. The risk stratification of ERWT is based on tumor volume, weight, histology, stage, and LN involvement and should follow NWTS-5 protocol [26].

35.8 ERWT So Far: A Systemic Review

We reviewed the cases of ERWT reported in literature searching common electronic databases including PubMed and Google Scholar for case reports, case series, original article, and review articles searched with keywords "extrarenal," "Wilms' tumor," "nephroblastoma," and their synonyms with abstract/full article in English (Table 35.1) [29–114]. The keywords used were

Table 35.1 The list of cases of extrarenal Wilms' tumor identified on systematic review and their details

Author	Year	M/F	Age	ERWT location	Stage	Treatment	Follow-up
Moyson et al. [1]	1961	F	3	Mediastinal	II	Surgery + ChT	NA
Bhajkar et al. [29]	1964	M	2	Retroperitoneal	II	Surgery + ChT	NA
Edelstein et al. [30]	1965	M	3	Retroperitoneal	II	Surgery + ChT	2
Wu et al. [31]	1971	F	7	Pelvic	IV	Surgery + ChT + XRT	1
Thompson et al. [32]	1973	M	3	Inguinal	IV	Surgery + ChT + XRT	0.5
Thompson et al. [32]	1973	F	4	Inguinal	III	Surgery + ChT + XRT	2
Akhtar et al. [34]	1977	M	0.2	Inguinal	II	Surgery + ChT	1.5
Gaikwad et al. [33]	1977	M	0.2	Retroperitoneal	II	Surgery	0.5
Madanat et al. [35]	1978	M	0.3	Inguinal	NA	Surgery + ChT	2
Madanat et al. [35]	1978	F	9	Mediastinal	II	Surgery + ChT + XRT	3
Aterman et al. [36]	1979	F	5	Retroperitoneal	NA	Surgery + ChT + XRT	0.7
McCauley et al. [37]	1979	F	4	Retroperitoneal	NA	Surgery + ChT + XRT	4
Fried et al. [40]	1980	M	3	Retroperitoneal	NA	Surgery + ChT	NA
Johnson et al. [39]	1980	F	1	Retroperitoneal	NA	Surgery + ChT	1
Orlowski et al. [16]	1980	M	3.5	Paratesticular	II	Surgery	11
Taylor et al. [38]	1980	M	0.5	Inguinal	NA	Surgery + ChT + XRT	0.5
Bittencourt et al. [42]	1981	F	14	Female genital organs	III	Surgery + ChT + XRT	5.5
Ho et al. [41]	1981	M	1.2	Paratesticular	I	Surgery	1
Adam et al. [44]	1983	M	10	Retroperitoneal	NA	Surgery	NA
Meng et al. [43]	1983	M	3	Retroperitoneal	I	Surgery	1
Fernbach et al. [45]	1984	F	2	Spinal and paraspinal	NA	Surgery + ChT + XRT	1
Lüchtrath et al. [46]	1984	F	1.2	Inguinal	NA	Surgery + ChT	1.3
Bell et al. [47]	1985	F	13	Female genital organs	I	Surgery	9.5
Koretz et al. [48]	1987	F	36	Retroperitoneal	NA	Surgery	NA
Fukutomi et al. [51]	1988	M	49	Retroperitoneal	NA	Surgery	NA
Lai et al. [49]	1988	F	3	Inguinal	II	Surgery + ChT	1.5
Sahin et al. [50]	1988	F	56	Female genital organs	NA	Surgery + ChT + XRT	9
Broecker et al. [53]	1989	F	2	Retroperitoneal	IV	Surgery + ChT	1.3
Broecker et al. [53]	1989	F	2	Retroperitoneal	II	Surgery + ChT + XRT	7
Broecker et al. [53]	1989	F	0.9	Pelvic	II	Surgery + ChT	1
Fernandes et al. [52]	1989	M	6	Retroperitoneal	III	Surgery + ChT + XRT	6
Fernandes et al. [52]	1989	M	6	Retroperitoneal	II	Surgery + ChT + XRT	7
Fernandes et al. [52]	1989	F	2	Retroperitoneal	II	Surgery + ChT	5

Fernandes et al. [52]	1989	F	2	Retroperitoneal	II	Surgery + ChT	1
Narasimharao et al. [54]	1989	F	NA	Retroperitoneal	NA	Surgery + ChT	1
Wakely Jr et al. [55]	1989	F	4	Female genital organs	II	Surgery + ChT + XRT	6
Wakely Jr et al. [55]	1989	F	1.5	Retroperitoneal	II	Surgery + ChT + XRT	6
Mirkin et al. [56]	1990	F	4	Spinal and paraspinal	NA	Surgery + ChT + XRT	2.7
O'Dowd et al. [57]	1990	F	20	Female genital organs	NA	Surgery	NA
Strand et al. [58]	1990	M	12	Inguinal	III	Surgery + ChT	NA
Coppes et al. [25]	1991	F	0.3	Inguinal	III	Surgery + ChT	0.75
Simha et al. [59]	1991	F	3	Inguinal	III	Surgery + ChT + XRT	NA
Andrews et al. [5]	1992	F	NA	Pelvic	II	Surgery + ChT	0.7
Andrews et al. [5]	1992	M	NA	Retroperitoneal	II	Surgery + ChT	0.7
Andrews et al. [5]	1992	F	NA	Spinal and paraspinal	II	Surgery + ChT	1.4
Andrews et al. [5]	1992	M	NA	Retroperitoneal	II	Surgery + ChT	2
Andrews et al. [5]	1992	M	NA	Retroperitoneal	IV	Surgery + ChT + XRT	2
Andrews et al. [5]	1992	F	NA	Retroperitoneal	I	Surgery + ChT	3
Andrews et al. [5]	1992	F	NA	Spinal and paraspinal	III	Surgery + ChT + XRT	4
Andrews et al. [5]	1992	F	NA	Spinal and paraspinal	II	Surgery + ChT	6.5
Sarode et al. [60]	1992	M	2	Retroperitoneal	NA	Surgery + ChT	NA
Comerci et al. [61]	1993	F	22	Female genital organs	NA	Surgery	2
Rasheed et al. [62]	1993	F	4	Retroperitoneal	III	Surgery + ChT + XRT	2
Rasheed et al. [62]	1993	M	3	Retroperitoneal	III	Surgery + ChT + XRT	7
Suzuki et al. [63]	1993	M	2	Retroperitoneal	II	Surgery + ChT	NA
Gillis et al. [64]	1994	M	30	Paratesticular	NA	Surgery	2.1
Fahner et al. [65]	1995	F	2.5	Spinal and paraspinal	II	Surgery + ChT	1
Gursoy et al [4]	1995	F	48	Female genital organs	III	Surgery + ChT + XRT	0.75
Arkovitz et al. [67]	1996	M	3.5	Inguinal	III	Surgery + ChT + XRT	NA
Mount et al. [66]	1996	F	5	Retroperitoneal	NA	Surgery + ChT	2
Song et al. [68]	1997	M	2	Retroperitoneal	NA	Surgery	NA
Benatar et al. [69]	1998	F	11	Female genital organs	II	Surgery + ChT	NA
Kapur et al. [7]	1998	F	NA	Retroperitoneal	NA	Surgery + ChT	0.7
Kapur et al. [7]	1998	F	NA	Retroperitoneal	NA	Surgery + ChT	3
Abrahams et al. [72]	1999	F	0.9	Spinal and paraspinal	NA	Surgery + ChT + XRT	4
Iraniha et al. [14]	1999	F	12	Female genital organs	II	Surgery + ChT	1

(continued)

Table 35.1 (continued)

Author	Year	M/F	Age	ERWT location	Stage	Treatment	Follow-up
Jiscoot et al. [70]	1999	F	77	Female genital organs	NA	Surgery + ChT + XRT	0.5
Massarelli et al. [71]	1999	F	2	Female genital organs	III	Surgery + XRT	2.5
Babin et al. [74]	2000	F	13	Female genital organs	III	Surgery + ChT + XRT	5
Govender et al. [76]	2000	M	4	Spinal and paraspinal	III	Surgery + XRT	NA
Issac et al. [73]	2000	F	21	Female genital organs	NA	Surgery + ChT	0.5
Pereira et al. [75]	2000	F	3.5	Female genital organs	NA	Surgery + ChT	6.5
Arda et al. [77]	2001	F	5	Spinal and paraspinal	III	Surgery + ChT + XRT	NA
Muc et al. [78]	2001	F	42	Female genital organs	NA	Surgery	NA
Deshpande et al. [80]	2002	M	1	Spinal and paraspinal	NA	Surgery + ChT + XRT	NA
Oner et al. [79]	2002	F	3.5	Female genital organs	II	Surgery + ChT	7
Cojean et al. [82]	2003	M	0.2	Retroperitoneal	III	Surgery + ChT	NA
Watanabe et al. [83]	2003	F	67	Retroperitoneal	NA	NA	NA
Yunus et al. [81]	2003	M	NA	Spinal and paraspinal	NA	Surgery + ChT	1.8
Sharma et al. [84]	2004	F	3	Spinal and paraspinal	NA	Surgery + ChT	0.3
Apozanski et al. [12]	2005	M	17	Spinal and paraspinal	III	Surgery + ChT + XRT	1
McAlpine et al. [85]	2005	F	44	Female genital organs	NA	Surgery + ChT	1
Sastri et al. [18]	2006	M	0.8	Spinal and paraspinal	NA	Surgery + ChT + XRT	4
Sastri et al. [18]	2006	F	15	Retroperitoneal	NA	Surgery + ChT + XRT	5
Sastri et al. [18]	2006	M	2	Spinal and paraspinal	NA	Surgery + ChT + XRT	5
Houben et al. [86]	2007	F	2	Retroperitoneal	I	Surgery + ChT	1
Houben et al. [86]	2007	M	3	Retroperitoneal	IV	Surgery + ChT	4
Ramchandra et al. [87]	2007	M	4	Retroperitoneal	III	Surgery + ChT + XRT	1
Ramchandra et al. [87]	2007	F	3	Retroperitoneal	II	Surgery + ChT + XRT	1.3
Ratnam et al. [88]	2007	F	21	Retroperitoneal	NA	Surgery + ChT + XRT	2
Cooke et al. [6]	2009	M	1.2	Inguinal	II	Surgery	2
Garcia-Galvis et al. [90]	2009	F	62	Female genital organs	NA	Surgery + ChT + XRT	1.2
Jia et al. [91]	2009	F	3	Pelvic	III	Surgery	NA
Kadota et al. [92]	2009	F	52	Retroperitoneal	NA	Surgery	NA
Leblebici et al. [93]	2009	F	16	Female genital organs	NA	CT	NA
Ngan et al. [89]	2009	F	6	Retroperitoneal	II	Surgery	1
Taguchi et al. [95]	2010	F	2	Retroperitoneal	I	Surgery + ChT	2
Zhang et al. [94]	2010	M	0.7	Urinary bladder	NA	Surgery + ChT	1

Jeong et al. [96]	2011	M	9	Inguinal	III	Surgery + ChT + XRT	NA
Armanda et al. [2]	2012	F	0.1	Spinal and paraspinal	I	Surgery + ChT	2
Chowhan et al. [100]	2012	M	1.3	Retroperitoneal	II	Surgery + ChT	NA
Hiradfar et al. [97]	2012	F	9	Inguinal	II	Surgery + ChT	3
Li et al. [98]	2012	F	2	Pelvic	III	Surgery + ChT + XRT	3
Marwah et al. [101]	2012	F	1.2	Retroperitoneal	II	Surgery + ChT	NA
Yamamoto et al. [99]	2012	M	NA	Paratesticular	NA	Surgery	3
Baskaran [102]	2013	M	3	Retroperitoneal	II	Surgery	NA
Morandi et al. [21]	2013	M	3	Paratesticular	I	Surgery	2
Rojas et al. [103]	2013	M	2	Spinal and paraspinal	II	Surgery + ChT	NA
Al-Nsoor et al. [22]	2014	F	1.7	Retroperitoneal	II	Surgery	NA
Goel et al. [104]	2014	NA	NA	Retroperitoneal	NA	Surgery	NA
Wu et al. [11]	2014	M	1.5	Inguinal	II	Surgery	0.5
Wu et al. [11]	2014	M	0.8	Retroperitoneal	II	Surgery	0.5
Kumar et al. [105]	2015	F	7	Retroperitoneal	NA	Surgery	0.8
Thakkar et al [3]	2015	F	5	Retroperitoneal	III	Surgery + ChT + XRT	5
Itoshima et al. [106]	2016	M	4	Retroperitoneal	III	Surgery + ChT + XRT	3
Park et al. [107]	2016	F	4	Inguinal	IV	Surgery + ChT + XRT	4
Cao et al. [108]	2017	F	60	Female genital organs	NA	Surgery + ChT	1.5
Igbaseimokumo et al. [28]	2017	F	0.1	Spinal and paraspinal	NA	Surgery + ChT	2.5
Tang et al. [109]	2017	M	2	Retroperitoneal	NA	NA	NA
Tang et al. [109]	2017	F	2	Mesenteric	NA	NA	NA
Tang et al. [109]	2017	F	2	Pelvic	NA	NA	NA
Petit et al. [111]	2018	F	3	Retroperitoneal	IV	Surgery + ChT	2
Pinto et al. [112]	2018	F	33	Female genital organs	NA	Surgery	NA
Turashvili et al. [110]	2018	F	16	Female genital organs	NA	Surgery + ChT + XRT	0.5
Groth et al. [113]	2019	M	0.7	Paratesticular	NA	Surgery + ChT + XRT	1.3
Ismy et al. [114]	2019	M	1	Urinary bladder	NA	Surgery	NA
Sindhu et al [13]	2019	M	6	Urinary bladder	III	Surgery + ChT + XRT	1

Table 35.2 The distribution of available information about ERWT cases reported in the literature between 1961 and 2019 on extensive search [29–114]

Review criteria	Value
No. of the published reports	103
No. of cases	127
Male/female ratio	49:77
Median age	3 (range, 1 month to 77 years)
Location	
Retroperitoneal	53 (42.42%)
Female genital	22 (18.18%)
Inguinal	16 (12.12%)
Spinal and paraspinal	18 (13.63%)
Paratesticular	6 (4.54%)
Pelvic	6 (4.54%)
Mediastinal	2 (1.51%)
Urinary bladder	3 (2.27%)
Mesenteric	1 (0.75%)
Stage (n = 75, 52 not available)	
Stage 1	8 (10.66%)
Stage 2	36 (48%)
Stage 3	24 (32%)
Stage 4	7 (9.33%)
Treatment given (n = 123, 4 not available)	
Surgery	27 (21.95%)
Surgery + ChT	49 (39.83%)
Surgery + ChT + XRT	44 (35.77%)
Surgery + XRT	2 (1.62%)
ChT	1 (0.81%)
Median follow-up (35 not available)	2 years
Mean follow-up (35 not available)	2.61 years

extrarenal, Wilms' tumor, nephroblastoma, children, and adults. All cases, which fulfilled the criteria of ERWT definition, were included, and those which were reported as teratoid or rhabdoid Wilms' tumors were excluded. Between 1961 and 2019, the systematic search revealed 103 published studies and 127 cases reported so far to the best of our search (Table 35.2). ERWT was found to be more common in females (60.62%) with a median age of 3 years, and 96 (75.59%) cases reported in children <18 years and 17 (13.38%) in adults. The most common location was retroperitoneally followed by the female genitalia and inguinal and spinal/paraspinal regions with less than 14% cases reported in unusual areas. The stage was reported in only 57.57% and stage II was most common. The most commonly adopted mode of treatment was surgery, which was possible in almost all patients, followed by ChT ± XRT. The follow-up was not available in 27% patients; mean follow-up in the rest was <2 years. The mortality data, EFS, and OS were poorly reported.

In our unpublished experience, authors have seen three cases of ERWT over a period of 18 years. All three were young males (<3 years of age), and the ERWT were found in the retroperitoneal location. Two cases were stage I and were treated with surgery + ChT, while one case was stage II, which involved ureter resulting in hydronephrosis (Figs. 35.1 and 35.2). Although the mass was separate from the kidney (which was normal on imaging), radical nephrectomy along with excision of the tumor was necessitated because of ureteral involvement; surgery was followed by ChT (Fig. 35.3). EFS of 2 years were noted in three patients.

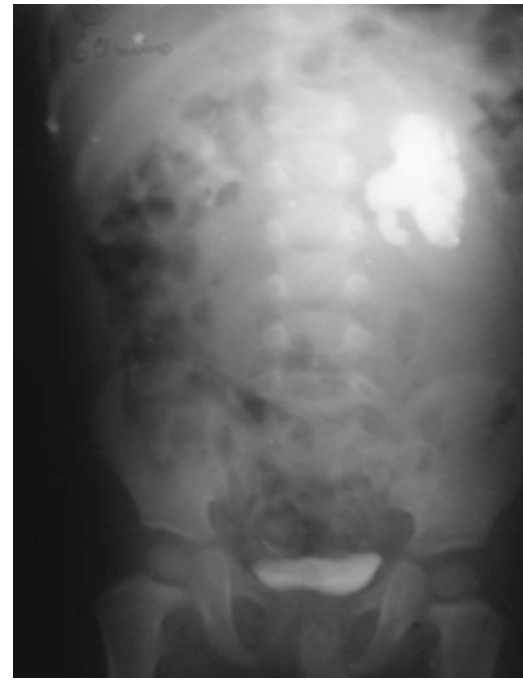

Fig. 35.1 Intravenous urography showing upper ureteral obstruction due to tumor encasement and normal architecture pelvicalyceal system of the kidney suggestive of an extrarenal tumor

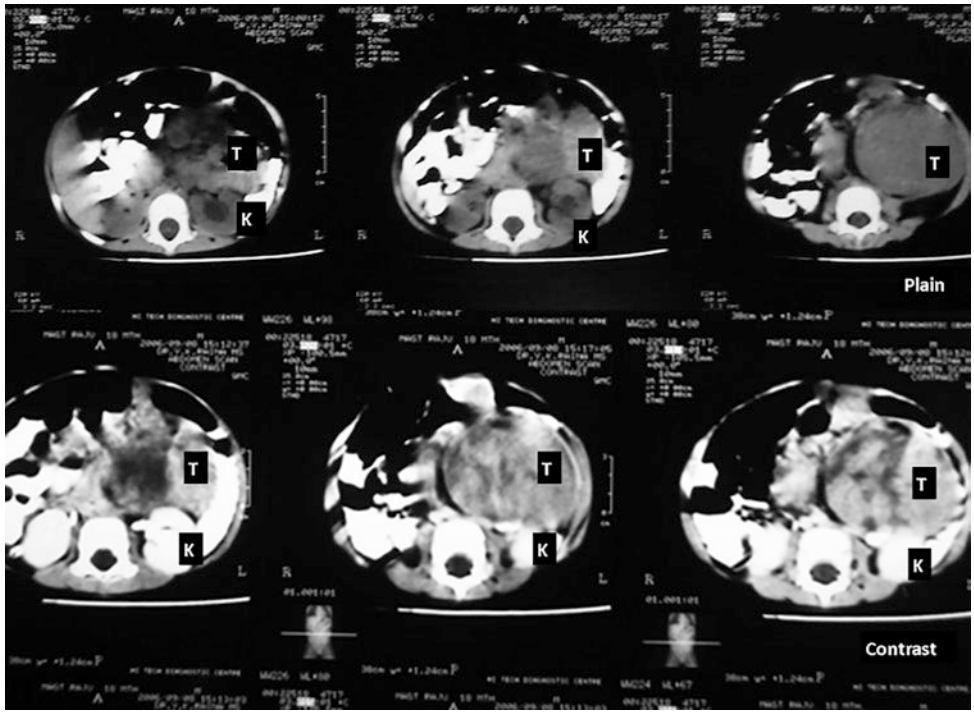

Fig. 35.2 Computed tomography (plain and contrast) showing a retroperitoneal mass separate from the kidney with ureteral encasement and hydronephrosis, which was confirmed to be extrarenal on surgery (*K* kidney, *T* tumor)

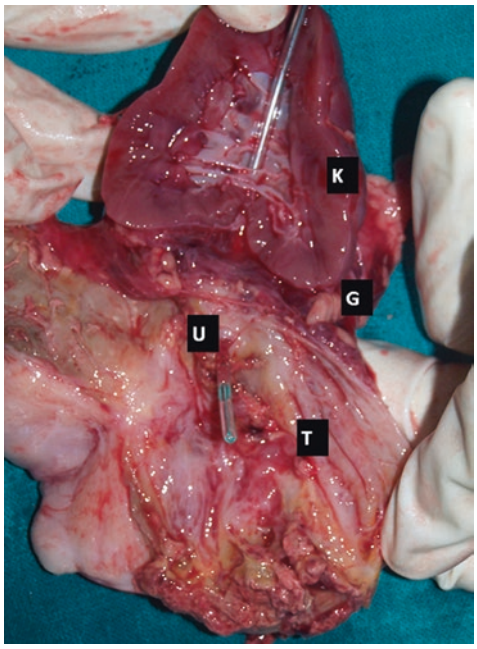

Fig. 35.3 Excised specimen showing extrarenal tumor with intact Gerota's fascia all around and invasion of the ureter by the extrarenal tumor (*K* kidney, *G* Gerota's fascia, *U* ureter encasement by the tumor, *T* tumor)

35.9 Conclusions

The diagnosis of ERWT is by exclusion of the presence of a primary tumor in the kidney. Tumor in the supernumerary kidney and a teratoid WT should be excluded by a careful imaging and pathological examination. Staging and treatment of ERWT follows NWTS-5 protocol, and the prognosis is reasonably good as they present in early stage. However, there is a need to centralize the cases in the registry to develop better understanding of its behavior.

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Complications of Treatment

36

Sushmita N. Bhatnagar

36.1 Introduction

Like in every condition/disease, there is a risk of complications, in the same way the management of Wilms' tumor (WT) also has complications. Different modalities have their shortcomings either on an immediate basis or on long-term basis, and the knowledge of these is extremely essential for identifying and treating these complications adequately and appropriately.

As in the treatment of WT, risk stratification is an important aspect; similarly, risk assessment of development of complications on therapy has been ascertained for appropriate measures in the prevention and care of the complications should they occur. The criteria for risk assessment are summarized in Fig. 36.1.

The therapist could be the pediatric oncologist, the surgeon, or the pediatric radiotherapist. The skill and expertise, the selection of protocol, and thorough/appropriate evaluation for the primary site of the tumor as well as for distant metastases are extremely important for proper staging and risk stratification. This is a crucial first step for appropriate therapy failing which the risk of complications increases manifold. For children who have large size tumors, those involving bilateral kidneys, those infiltrating into the vessels, and those showing metastatic spread to the lungs or other organs have a higher risk of developing complications during treatment. Also,

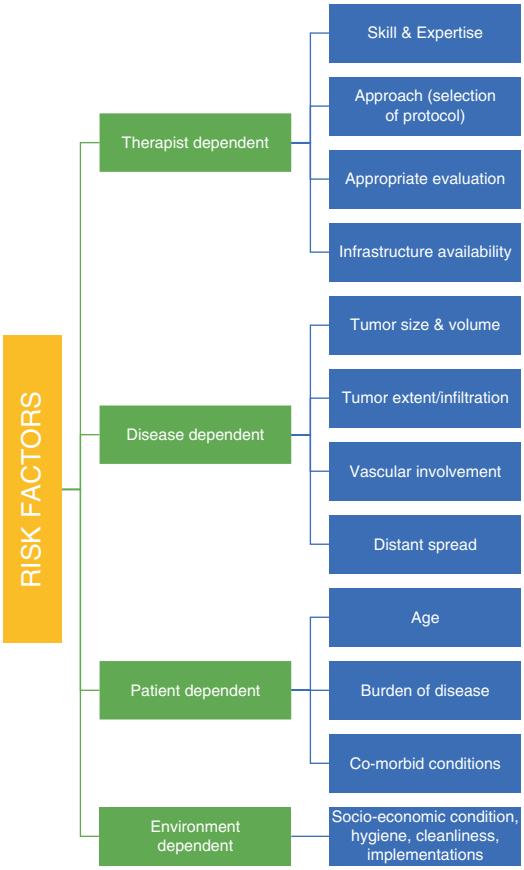

Fig. 36.1 Risk assessment for development of complications

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malnourished children having nutritional anemia, those with tumor induced hypertension, those with concomitant infections such as tuberculosis or HIV, those with associated congenital anomalies or syndrome, have a risk of complications higher than those without the co-morbid conditions. Control of the comorbid conditions as and when feasible must be done to reduce the complications during therapy. Dindo et al. [1] have elaborately described an objective classification system, the Clavien-Dindo classification, which has been used by other researchers as well for analyzing the outcomes as well as to predict the surgical complications [2]. The several complications of surgery, chemotherapy (ChT), ports and lines, and radiation therapy (XRT) are discussed herewith and categorized into two categories as follows:

(a) During treatment—immediate complications.
(b) After treatment—early (up to 5 years), intermediate (5–10 years) and delayed complications (late effects) after 10 years of completion of treatment.

36.2 Complications of ChT

The risk and incidence of ChT-related complications are dependent on many factors, most importantly the drugs used, their dosages, and the length of treatment. The type of drugs used in different protocols and in different stages has already been discussed elsewhere; hence, the general and specific complications related to the drugs will be described here.

36.2.1 Complications During ChT: Immediate Complications

The common complications of ChT for WT are similar to most of the chemotherapeutic drugs and differ in intensity from one child to another. These complications are loss of appetite, nausea/vomiting, stomatitis, diarrhea/constipation, fatigue/lethargy, alopecia in majority of children, weight loss, neutropenic infections presenting as fever, and bleeding from multiple sites as well as into the tumor due to thrombocytopenia and/or coagulopathy. Tumor lysis syndrome, though rare, is a metabolic emergency and can occur in WT with drastic consequences if not recognized and treated.

Neutropenic infections, with or without fever, are a cause of grave concern and deserve a specific mention as regards diagnosis and management. These infectious complications during the ChT cycles occur to single or multiple factors such as breach in skin or mucous membrane/s, myelosuppression, immunocompromised state and/or breach in hygiene, cleanliness, and diet. Leucopenia with an absolute neutrophil count (ANC) <500 cells/mm^3 escalates the risk of infection manifold and subsequently hikes the morbidity as well as risk of mortality [3]. Prevention is the key to shrink the incidence of morbidity and mortality; nevertheless, early identification, hospitalization, and prompt initiation of broad-spectrum antimicrobials (while awaiting culture reports) are fruitful. In severe neutropenic infections, administration of granulocyte colony stimulating factor (G-CSF) could be lifesaving. Clinical practice guidelines have been updated in 2017 regarding empiric management of febrile neutropenia in children with cancer [4].

The ChT drugs used for the treatment of WT are vincristine (VCR), actinomycin-D (AMD), doxorubicin (DOX), cyclophosphamide (CTX), etoposide (ETOP), and carboplatin (CARB) depending on the stage of the disease. Each of these drugs has specific complications/toxicities which are tabulated as under in Table 36.1.

36.2.2 Complications of ChT: After Treatment

With the delight of achieving cure in >90% of children with WT also comes the anguish of complications after completion of treatment, the late effects. Many of the complications of chemotherapeutic drugs are transient and wear off after completion of treatment. However, some of the complications remain permanent affecting the

Table 36.1 Complications/toxicities of chemotherapeutic agents used for treatment of WT [5]

Name of the chemotherapeutic agent	Major complication/toxicity	Others	Specific issues
Vincristine	Neurological: Peripheral neuropathy, paresthesia, sensory loss, loss of deep tendon reflexes	• Renal: Uric acid nephropathy • Reproductive: Aspermia, amenorrhea • GI: Nausea, vomiting, constipation, paralytic ileus • Bone marrow: Myelosuppression	• Extravasation due to improper peripheral IV line causes severe cellulitis • Intrathecal administration is lethal
Dactinomycin	Hepatobiliary: Hepatitis, deranged liver function tests, hepatomegaly, hepatic veno-occlusive disease/ hepatopathy/sinusoidal obstruction syndrome, hepatic failure leading to death	• Renal: Renal impairment, renal failure • GI: Similar+ dysphagia • Bone marrow: Myelosuppression • General: Severe mucocutaneous reactions • Radiation along with this drug leads to severe toxicity	• Risk of second malignancies higher • Myelosuppression could be fatal • Veno-occlusive disease could be fatal • During radiation, dose of this drug must be reduced by 50%, within 2 months of radiation
Cyclophosphamide	Urinary: Hemorrhagic cystitis—Hematuria	• Pulmonary: Interstitial pulmonary fibrosis could be irreversible and fatal • Cardiac: Acute heart failure, subclinical decreases in LVEF	• Risk of second malignancies • Risk of infertility
Doxorubicin	Cardiac: Cardiomyopathy, congestive cardia failure, Acute left ventricular failure	• Myelosuppression severe • GI: Similar	• Extravasation results in severe local tissue injury and necrosis which requires wide excision/ skin grafting • Higher risk of second malignancies such as AML and MDS (myelodysplastic syndrome) • Tumor lysis syndrome
Etoposide	Hematologic: Severe leucopenia, thrombocytopenia, severe myelosuppression, bleeding from multiple sites	• GI: Similar • Alopecia • Hepatic toxicity • Hypersensitivity • Orthostatic hypotension	• Risk of infertility • Second malignancies- leukemia • Acute renal failure with high doses
Carboplatin[a]	Ototoxicity	• GI: Similar • CNS: Central neurotoxicity • Hepatic: Liver toxicity, jaundice • Peripheral neuropathy • Magnesium loss Hematologic: • Severe leucopenia, neutropenia, thrombocytopenia, myelosuppression	• Allergic reactions may occur within minutes of carboplatin administration

[a]Complications are worse if cisplatin is used instead

quality of life of the child with WT. Following completion of therapy, there are instances where more than one modality of treatment has caused the complication and thus it becomes difficult to assess the exact cause of the complication. A valuable means of studying the late effects in children with WT is provided by the Childhood Cancer Survivor Study (CCSS) of St. Jude Hospital [6]. COG has provided guidelines for **l**ong-**t**erm **f**ollow-**u**p (LTFU) patients, and the resource guide is available online for healthcare professionals.

The late effects of ChT-induced permanent toxicities are discussed organ-wise in this section.

1. Renal dysfunction [7]

   The assessment of renal dysfunction/toxicity is done by regular assessment of renal function tests, serum Ca+, Mg+, PO_4, serum electrolytes, urine routine, and BP monitoring.

   (a) *Reduction in glomerular filtration rate* (GFR) occurs with platinum drugs—cisplatin (CIS) and CARB, of which CARB is less nephrotoxic and remains permanently only in a minority of patients. This is usually detected after detection of raised creatinine levels as the renal function tests are done regularly for all patients on LTFU.

   (b) *Hypertension* (BP above 95th percentile on at least three occasions) occurs in children treated with nephrotoxic drugs such as CIS, CARB, and ifosfamide (IFO) (used in ICE therapy for recurrence). Other risk factor for development of hypertension is XRT to the abdomen. The overall incidence of WT survivor (WTS) developing hypertension is variable across studies and is roughly 20–40% [8, 9].

   (c) *Proximal tubular dysfunction* is caused by ifosfamide, and it leads to progressive renal insufficiency in up to 50% of patients. Proximal tubulopathy could lead to Fanconi syndrome (characterized by urinary excretion of glucose, amino acids, phosphate, bicarbonate, and other solutes) in 5% of patients [10].

   (d) *Proteinuria* > 2+ protein in the urine should warrant further investigations and assessment of degree of renal dysfunction.

   (e) *Magnesium wasting tubulopathy* occurs with cisplatin in practically all the patients. It could be mild and undetected, but severe tubulopathy leads to hypomagnesemia, hypocalcemia, and/or hypokalemia. Severity of this toxicity increases when cisplatin is used in combination with IFO.

   (f) *Renal failure* could be acute or chronic and irreversible leading to end-stage renal disease (ESRD) requiring renal transplantation [11].

   Late effects of potentially nephrotoxic ChT were systematically reviewed by Kooijmans et al. in the Cochrane database across 52 studies, in which 4499 of 13,327 participants were evaluated by renal function tests to find prevalence of adverse renal effects to be highly variable between 0 and 84% [12]. This variation could be multifactorial and is present for all categories of renal toxicities which also indicates that there is a need to have an adequate study design to be able to assess the long-term effects in a standardized manner.

2. Genital/reproductive system dysfunction

   The ChT agents such as CTX and ETOP are implicated in causing infertility in both males and females. Other reproductive system dysfunctions are delayed puberty, precocious puberty, menstrual irregularities, and pregnancy-related issues such as spontaneous abortions, fetal growth disturbances, and preterm labor [13].

3. Cardiac toxicity

   Cardiac dysfunction secondary to ChT drugs such as anthracyclines (DOX) is due to myocytic toxicity leading to decreased myocardial mass and myofibril dysfunction [14].

The complications that arise due to these include cardiomyopathies and congestive cardiac failure [15].

The various abnormalities which can occur are as follows:

(a) Systolic dysfunction.
(b) Diastolic dysfunction (impaired left ventricular filling, delayed relaxation) leads to left atrial and pulmonary wedge pressure causing pulmonary congestion [16].
(c) Decreased left ventricular ejection fraction.
(d) Valvular dysfunction.

4. Second malignancies

According to a large international cohort study carried out by Breslow et al. between 1960 and 2004, 195 patients were found to have developed second malignancies of which 174 were solid tumors and 28 leukemias. Solid tumors occurring at sites such as in the lip/oral cavity/pharynx/parotid, digestive tract, retroperitoneum, respiratory tract, bones/joints/cartilage (osteosarcoma/chondrosarcoma, Ewing's sarcoma), skin (melanoma), peripheral autonomic nervous system, breast, thyroid and endocrine glands, lymph nodes (Hodgkin's and Burkitt's lymphoma), urinary tract, eyes, and brain were found. The risk of leukemia is highest approximately in the first 5 years after completion of treatment of WT, while the solid tumors occur 10 years and later [17].

36.3 Complications of Ports/Lines

For the treatment of low-risk WT, most therapists agree that port placement is not mandatory. Some centers, however, place ports/lines for all patients receiving ChT. For advanced disease, central venous access is definitely the best option as these children frequently require intravenous antibiotics, transfusions of blood/blood products, total parenteral nutrition (TPN), surgical intervention, etc. The placement of central venous catheters also aids in improved participation of the child in the treatment and thus creates a harmonious environment for both the caregiver and the family. Nevertheless, the complications of all the different types of ports/lines must be well versed to the caregivers before the port/line is selected and placed. The selection criteria are also an important aspect of reducing the incidence of complications, and the factors to be taken into account are age of the patient, burden of disease, duration of use, details of utilization, expertise of the team, feasibility of care post-insertion, as well as the cost/affordability of the parents.

The complications of each type of central venous catheters such as the completely implantable catheters (portacath), tunneled exteriorized catheters (lines—Hickman/Broviac), and PICC (peripherally inserted central catheter) can be categorized into four categories as in Fig. 36.2.

The specific complications under each category have been tabulated as in Table 36.2. The incidences of these complications are variable across studies and occur in up to 40% of children in whom CVCs have been inserted [18]. The incidence of complications of PICC lines varies from 17% to 50% across different centers [19]. Most of the studies have shown higher incidence of noninfective complications. Several factors are directly associated with increased incidence of complications such as lesser age and poor general condition of the child, procedural expertise in insertion as well as care of the CVC, type of the device used, site of insertion – upper versus lower parts of the body (not applicable to portacath), duration of use, and type of infusions used [20–23]. Most of the complications of the CVCs have to be managed by removal of the CVC, except when the complications are mild and can be managed conservatively.

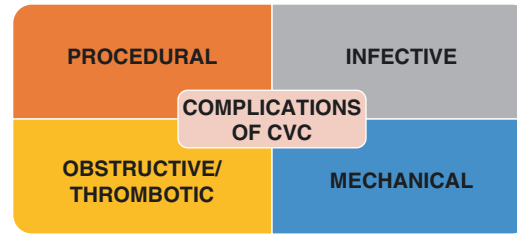

Fig. 36.2 Categorization of complications of CVCs

Table 36.2 Complications of CVCs

Category of complications	Complications	
	PICC line	Tunneled exterior catheters and portacath
Procedural	Edema	Hematoma
	Improper placement	Bleeding
Minor to major	Vein rupture (discrepancy in size of PICC line and the vein)	Malposition
	Venous dissection	Venous dissection
	Extravascular infusion	Arrhythmias (related to improper placement of tip of catheter)
	Inability to advance to the desired length due to valves, spasm, tortuosity	Pneumothorax
	Subcutaneous extravasation	Hydrothorax
		Hemothorax
		Hemomediastinum
		Cardiac tamponade
		Injury to thoracic duct—Chylothorax
		Air embolism
		Arterial puncture
		Arteriovenous fistula
		Ligation of vein (in open technique)
		Nerve injury—Brachial plexus, phrenic nerve,
		Guidewire knotting, fracturing
Infective	Localized catheter site infection	Localized/catheter site infection/port pocket seroma/cellulitis/abscess
Mild Moderate Severe	Systemic infection	Systemic bloodstream infection – CLABSI (central line-associated bloodstream infection)
		Endocarditis
		Bone or joint infections (localized or distant)
		Severe sepsis with multi-organ failure and death
Thrombotic/ obstructive Partial Total	Venous thrombosis	Venous thrombosis
	Venous stenosis	Venous stenosis
	Device occlusion	Device occlusion
Mechanical	Disconnection	Disconnection
	Fracture with migration	Fracture with migration
Partial	Dislocation	Dislocation
Total	Kinking of catheter	Thinning of the skin over the port/skin necrosis
	Accidental removal/dislodgement	
	Extrinsic obstruction due to compression	
	Leakage	

36.4 Complications of Peripheral Lines

Many centers select the option of using peripheral lines for ChT especially for low-risk WT. The complications with peripheral lines are mainly extravasation into subcutaneous tissues. Injury to the tissues can range from mild and localized to extensive and severe. Recognition of extravasation and prompt action to control the damage is of utmost importance to prevent considerable damage requiring surgical intervention/permanent disability/disfigurement. Different ChT agents activate variable tissue responses based which they have been classified into vesicants, irritants and non-vesicants based on the potential to cause tissue injury, of which vesicants cause the maximum tissue damage.

Table 36.3 Clinical features and management of extravasation injury [24, 25]

Grades	Clinical features	Management
Grade 1	Pain, difficulty in flushing cannula, no/minimal swelling	Disconnect infusion, remove cannula, limb elevation, local analgesic ointment+/−
Grade 2	Pain, difficulty in flushing cannula, swelling +, redness +	Disconnect infusion, remove cannula, limb elevation, local analgesic/soothing/antibiotic ointment+/−
Grade 3	Pain, difficulty in flushing cannula, swelling ++, redness + skin blanching +, prolonged capillary refill time (CRT)	Disconnect infusion, **leave cannula in situ till review by pediatric oncologist/team is done,** local treatment such as irrigation with normal saline or saline and hyaluronidase, systemic analgesics and anti-inflammatories, prophylactic antibiotics, nonocclusive dressing, limb elevation
Grade 4	Pain, swelling +++, redness at periphery+, skin blanching ++, involved area cold, prolonged capillary refill time (CRT) > 4secs, decreased/absent pulsations, blistering+/−, skin breakdown/ necrosis	Disconnect infusion, **leave cannula in situ till review by pediatric oncologist/team is done**, local treatment such as irrigation with normal saline or saline and hyaluronidase, systemic analgesics and anti-inflammatories, prophylactic antibiotics, nonocclusive dressing, limb elevation, surgical intervention—Desloughing/necrosectomy/release of compartment, etc. as required

As soon as ChT is commenced through a peripheral cannula, initial assessment must be conducted every hour if continuous drip form is being used. For bolus infusion, the site of cannulation should be assessed every 8 h and/or before and after giving the bolus injection. The clinical features and management of the grades of extravasation injury are tabulated as in Table 36.3.

Local treatment must begin within one hour of extravasation to minimize the damage, especially with the vesicant ChT drugs. Before giving irrigation, the affected area should be infiltrated with 1% lignocaine subcutaneously in four quadrants. About 10–20 mL saline should be injected in the edematous area at multiple sites and about 5 mL through the cannula if it is not removed. Remove all the edema and infiltrated saline by massaging in the direction of the puncture marks. Hyaluronidase should be injected at multiple sites of about 0.2 mL/site of 1000 units/mL which has to be followed by saline irrigation.

Surgical intervention is based on the extent of extravasation injury such as multiple incisions, desloughing, necrosectomy, and later skin grafting and required only in Grade 3 and 4 injury. Multiple incisions with instillation of saline and/or hyaluronidase into the affected area is known as Gault technique [26].

To prevent medicolegal implications of ChT extravasation, it is imperative to explain to the parents/caretaker in detail all the issues of ChT as well as the type of line used, whether central or peripheral.

36.5 Complications of Surgical Intervention

Over the years, with advancement of science and technology, the rate of surgical complications has decreased significantly though it still remains high in children with advanced disease. As discussed in Fig. 36.1, there are many risk factors of surgical complications. Several risk factors related to the tumor such as tumor size, displacement of great vessels, and contralateral extension can be defined preoperatively in today's times with imaging and complications prevented [27]. Thorough patient evaluation is necessary to identify comorbid conditions which the child may be suffering from which will not only increase the risk of the treatment of WT but can also lead to higher mortality rates during therapy. However, with newer modalities and approaches to surgical management, there are unique complications reported which need to be borne in mind before proceeding with the decision-making of the surgical procedure, not to mention the existence of adequate expertise in performing the procedures.

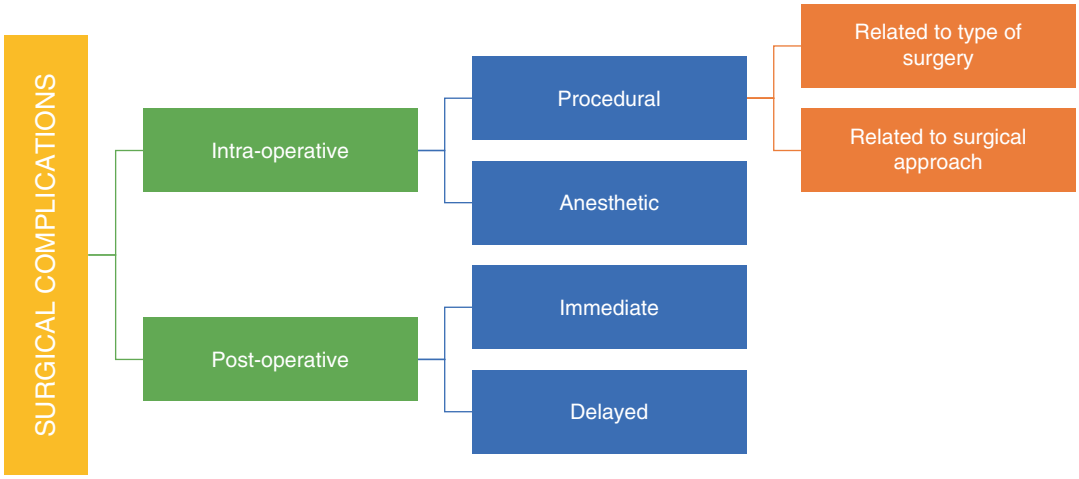

Fig. 36.3 Surgical complications

Along with surgical complications, those related to anesthesia also need to be considered. Thus, the complications shall be discussed under the flowing headings as mentioned in Fig. 36.3.

36.6 Intraoperative Complications

The most commonly used surgical procedure for excision of WT is open radical nephroureterectomy (RN). The complications of RN include:

1. Extensive hemorrhage

   Bleeding during surgery could occur from the vessels feeding the tumor, from the tumor itself either within the capsule due to handling or due to tumor rupture, from the tumor bed, from the renal pedicle, from the liver surface or parenchyma, or from the surrounding major arteries and veins such as the aorta and inferior vena cava (IVC). The incidence of bleeding varies from one center to another, from about 2% to >15%, and could be dependent on the treatment protocol utilized and/or surgical expertise [28, 29].
2. Intraoperative spillage

   Intraoperative spillage (IOS) could be intracapsular or intraperitoneal. Spill within the peritoneal cavity could be minor (soilage/contamination as occurs in needle or instrument injury) or major (fragmentation of the tumor in more than one piece). The incidence of IOS depends on the protocol used for treatment. As evidenced and verified by many researchers, the incidence of IOS is much less with SIOP protocol due to reduction in the size as well as vascularity of the tumor following upfront ChT. On the contrary, upfront surgery as per the COG protocol has been demonstrated to have much higher incidence of IOS. As per SIOP-5 study, the spillage rate was 6% in stage II and III patients [30]. As per NWTS-4 study, in a similar cohort of patients, the spillage rate was found to be 20% [31]. UKCCLG reported similar rates of intraoperative tumor spillage of about 3% for ChT pretreated patients [32].
3. Major vascular injury

   Damage to the IVC, aorta, and contralateral renal pedicle can occur with large as well as infiltrating tumors. Extensive hemorrhage is one problem, the other being cardiovascular decompensation of the child on table, which could be detrimental. Identification of vascular structures, hooking them with a vascular sling after achieving a clear identifiable plane, is essential before clamping, ligating, and dividing the vessels. Also, the vascular clamps

also should be ready before the surgery is commenced. The incidence of major vascular injury differs between institutes; nevertheless, it is approximately 1–2% [33, 34].

4. Injury to surrounding viscera

   The right- and left-sided tumors have different anatomy in terms of surrounding viscera. For the right-sided tumors, injury can occur to the liver, diaphragm, duodenum, and ascending colon, while on the left side, the major injuries reported are to the pancreas and spleen apart from bowel, the incidence being around 2%. Partial colectomy and distal pancreatectomy have been reported [2].

5. Anesthesia complications

   The specific anesthesia-related complications occur with increased length of surgery, thermoregulation, appropriate management of third space losses, intraoperative fluid and electrolyte management, adequate volume and timely blood replacement with extensive hemorrhage, IVC clamping/hooking/compression/tenting during dissection of tumor pedicle causing major shifts in venous return and cardiac output, and hypertension during tumor dissection [35, 36].

   The incidence of complications increases manifold with increase in complexity of the tumor such as intravascular invasion of tumor into the IVC, hepatic veins, heart, and those with associated renal anomalies such as the horseshoe kidney [37]. The use of cardiopulmonary bypass (CPB) for the extraction of the intravascular tumor thrombus could lead to additional complications related to the bypass such as cardiovascular, pulmonary, hematologic, renal, and neurologic [38].

36.7 Postoperative Complications

With adequate pre-operative and intra-operative care, the post-operative complications can be prevented/minimized, except in advanced disease when the inherent disease itself causes complications during treatment, such as large tumor size exceeding 10 cm, tumor thrombus extension occurs into the IVC beyond the hepatic veins, bilateral WT, etc. Nevertheless, certain complications occur in spite of all the precautions and preparations, which are mentioned below.

1. Surgical site infection

   Approximately 2% of children develop surgical site infection (SSI) postoperatively, the incidence being higher in debilitated patients [39]. The surgical site infection could be mild with superficial gape or severe resulting in burst abdomen. Appropriate wound care principles have to be applied based on the severity of SSI.

2. Intestinal obstruction

   Many studies have reported intestinal obstruction as the most common postoperative complication of surgery of WT, the overall incidence being around 5% [27]. Adhesive bowel obstruction and intussusception are the etiological factors of intestinal obstruction in the majority.

3. Bleeding from operative site

   Bleeding can occur from the tumor bed, from the pedicle due to slippage of ligature, or due to severe sepsis and disseminated intravascular coagulation (DIC). Identification of the causative factor is crucial to the management of bleeding, which could lead to sudden mortality postoperatively.

4. Enterocutaneous fistulae

   Fistula/e could develop with inadvertent and unrecognized injury to the surrounding bowel during the surgery, which increases the morbidity as well as risk of mortality.

36.8 Complications Following Nephron Sparing Surgery (NSS)

Partial nephrectomy/nephron sparing surgery (NSS), done either in a unilateral small tumor or bilateral WT, deserves an exclusive comment even though there isn't enough data available as yet to have statistically significant parameters.

Intraoperatively, the complications which occur frequently are excessive blood loss, incom-

plete excision leading to macroscopic or microscopic residual tumor influencing recurrence of the tumor, and increased need for stenting the pelvicalyceal system [40].

Postoperative complications include prolonged urine leak (often managed with stenting), transient renal insufficiency especially with bilateral NSS, severe infection/sepsis (related to prolonged surgery and immunocompromised status of the child), and local recurrence (due to inadequate excision necessitating upgrading the treatment protocols) [41–44].

36.9 Complications Following Laparoscopic/Robotic Nephrectomy

Patient selection is a very important step when laparoscopic surgery is planned and for carefully selected patients; in experienced hands, there is comparable incidence of complications [44]. Similar observations have been made for robotic/robotic-assisted laparoscopic nephrectomy [45]. On comparing the complication rates of open versus laparoscopic RN, it was noted that there were fewer complications in laparoscopic approach and this approach had additional benefits of faster recovery, lesser amount of painkillers, no intestinal obstruction, no increased incidence of intraoperative tumor spill, etc. [46] Nonetheless, experience and expertise with laparoscopic/robotic surgery are the prerequisites to avoid intraoperative and postoperative complications.

36.10 Complications of Radiation Therapy

Radiation therapy (XRT) has been utilized since the 1940s as a routine for the treatment of WT soon after surgery to improve the survival rates, even before the innovation of chemotherapeutic drugs [47, 48]. The modes and techniques of radiation therapy have evolved from telecobalt machines to linear accelerators with many more precise techniques to define just the tumor and spare the normal tissues. The indications as well as modalities of XRT in WT have already been discussed elsewhere.

Table 36.4 Factors affecting the rate and frequency of complications of XRT

S no	Risk factor	Details
1	Age of the child	Younger the age, higher the risk and incidence of complications
2	Site of radiation	• Flank • Whole abdomen irradiation (WAI) • Whole lung irradiation (WLI) • Other metastatic sites
3	Type of XRT	• Photon beam RT • Proton beam RT • Stereotactic body RT
4	Volume to radiation to neighboring organs	• In flank • In abdomen • In chest
5	Duration of XRT	Dependent on the stage and malignancy grade of the disease

The rate and frequency of complications of radiation therapy are dependent on the following factors as listed in Table 36.4.

The complications of XRT can be categorized into:

(a) During therapy.
(b) After completion of therapy (delayed complications).

36.10.1 Complications During XRT

During the twentieth century, XRT commenced with radium and then cobalt followed by photon beam linear accelerator. The incidence of acute complications is comparatively much higher with these traditional techniques. With the advent of advanced techniques such as volumetric modulated arc therapy (VMAT) [49, 50], conformal radiation therapy (3D-CRT), and image modulated radiation therapy (IMRT) in the twenty-first century, the complications have minimized even when whole abdominal irradiation (WAI) has been used. XRT complications include:

1. Varying degrees of skin effects over the irradiated site from mild erythema to sunburn-like

changes to severe radiation dermatitis with localized hair loss.
2. Fatigue and lethargy, usually mild to moderate and occurring regardless of the site of RT.
3. Radiation enteritis causing nausea/vomiting, diarrhea, anorexia, pain in the abdomen, abdominal cramps, etc.
4. Right flank XRT as well as WAI has been found to cause deranged liver function tests that are usually transient, severe thrombocytopenia, and acute liver failure that presents as hepatosplenomegaly, jaundice, and ascites. Rarely, left flank XRT can also lead to liver toxicity with the traditional methods of XRT. The liver toxicity occurring either during therapy or after completion of therapy is known as radiation-**i**nduced liver disease (RILD). There are no clear-cut incidences documented as these children are treated with multi-modality approach and receive supportive therapies such as blood/blood product transfusions, and to ascertain the exact cause and mechanism of RILD is still to be studied.
5. Radiation nephritis occurs in the residual kidney in cases of NSS or contralateral kidney in ipsilateral nephrectomy due to XRT to the abdomen, if kidney sparing techniques are not applied.
6. Myelosuppression leading to decreased blood cell counts occurs with larger dose of radiation or to a larger surface area covered. Monitoring with complete blood count becomes essential for such children.
7. Pulmonary irradiation can cause chest pain/discomfort, cough, dysphagia, breathlessness, pericarditis, and skin changes over the chest.

36.10.2 Complications After XRT

While the acute complications during XRT are not many and have low frequency with advanced XRT delivery systems available these days, those complications occurring over long term after completion of XRT are far too many which have come to light after being studied from the year 1960 onward [17, 51]. In view of the high proportion of long-term complications, there is constant ongoing research to tone down the therapies with the objective to decrease the morbidity and late effects of therapy.

The complications of XRT after completion of therapy are discussed herewith organ-wise.

1. Liver Abnormalities

   Typically, the RILD occurs many months after completion of RT. Hepatic fibrosis, veno-occlusive disease that is radiation dose dependent, manifest as early or late complication. The COG studied the hepatobiliary late effects of XRT in abdominal tumors such as WT, neuroblastoma, and hepatoblastoma and evaluated that the risk of injury to the liver is dependent on radiation dose, volume of the liver, and prior liver compromise and in those in whom dactinomycin and doxorubicin have been used collaterally [52]. The NWTS evaluated the occurrence of portal hypertension in WT and indicated that there is a strong association between higher liver radiation doses and portal hypertension in such patients [53]. Lung irradiations also cause RILD, and those children who receive both abdominal and lung XRT are at the highest risk of developing RILD in the long term. Toxicity could also occur with left flank XRT, though the incidence is one-fourth as compared to those receiving right flank XRT [54]. Non-cirrhotic portal hypertension with splenomegaly and esophageal varices, a rare complication, is also a possibility over long term [55].
2. Pancreatic Dysfunction

   Diabetes mellitus resulting from pancreatic dysfunction due to WAI is a permanent and overwhelming complication [56].
3. Renal Dysfunction

   Radiation nephropathy occurs due to impairment of renal function following radiation therapy and may be acute (3–12 months post-therapy) or chronic (many years later). Clinically, radiation nephropathy can be assessed by hypertension, proteinuria, anemia and renal failure.

   The ipsilateral kidney in partial nephrectomy or contralateral kidney with total abdominal XRT has always been affected with conventional approaches. Several studies

have been done to assess the residual kidney damage which ranges from subclinical glomerular and tubular damage to renal insufficiency leading to ESRD and has been found to be due to combination of factors related to both ChT and XRT [57]. The syndromic WT patients exhibit a much higher incidence of ESRD [11, 58]. As studied by the COG, renal impairment and associated hypertension occur in most survivors, though the severity is dependent on the risk factors [9]. XRT dose of more than 20Gy results in significant nephropathy [59].

4. Musculoskeletal Effects

   Major musculoskeletal abnormalities were reported in the earlier phase of XRT due to multiple factors. Growing bones in children are highly sensitive to ionizing radiation. In WAI, exposure of vertebral bodies resulted in shortening of the vertebral body height, eventually resulting in short stature, scoliosis/kyphosis, or both. With advancement in pediatric radiotherapeutic equipment, the rate of complications seems to have decreased. The several deformities occurring with XRT (rate and frequency of deformities dependent on factors as elaborated in Table 36.3) are hypoplastic ribs, hypoplastic ilium, osteochondromas, thoracic dysplasia, vertebral column abnormalities such as kyphosis and scoliosis (10–70%), vertebral body asymmetry, epiphyseal closure, end plate irregularities, growth arrest lines, and anterior beaking [60].

5. Reproductive Organ Complications

   The reproductive organs in both males and females are affected by XRT, especially with WAI. Convincing evidence exists in literature regarding fertility and pregnancy issues in the survivors. The complications could range from mild to severe and in females could lead to ovarian failure, uterine fibrosis causing infertility and spontaneous abortions, intrauterine fetal growth arrest, preterm delivery, low birth weight, etc. in those who conceived. Long-term follow-up study undertaken by NWTS regarding pregnancy outcomes after treatment of WT reported that fetal malposition, preterm labor, as well as hypertension during pregnancy were increased. The babies born of these female survivors were more likely to have birth weight of less than 2500 g, while the male counterparts had increased possibility of congenital anomalies in their offsprings [61]. Outcomes in the future in terms of late effects still need to be studied after toxicity minimizing therapeutic adjustments being done in the present.

6. Second Malignant Neoplasms (SMN)

   The risk of developing a second malignant neoplasm after years of XRT has been well reported and documented in several studies. These malignancies, known as radiation-induced second malignancies (RISM), most frequently occur within the radiation field (about 75%) [60, 62] but can also occur at distant sites, the exact mechanism of which is unknown, such as bone tumors, soft-tissue sarcomas, leukemias, lymphomas, myelodysplastic syndrome (MDS), breast cancers, gastrointestinal tumors, melanomas, etc.; the overall risk could be four times higher than in the normal population. With modified therapeutic protocols to reduce the late effects of therapy, there could be decrease in the incidence of RISM, except leukemias which seem to be expanding [17, 63].

   The cumulative incidence of SMNs estimated by Lee et al. [63] was 0.6% at 10 years, 1.6% at 20 years, and 3.8% at 30 years following diagnosis of WT. The latent period for development of second malignancies was found to be highly variable from 1 year to 35 years, the median being 12.5 years. Several risk factors for occurrence of second malignancies were studied, and it was found that except the older age (about 10–12 years) of child at diagnosis, no other factor contributed to occurrence of SMN. There was no conclusive evidence that radiation was definitely associated with SMN or RISM according to Lee et al. The cumulative incidence of SMNs as per published data is represented in Table 36.5.

Table 36.5 Published data regarding SMN following diagnosis of WT

Year	Group/center/author	Incidence of SMN				Types of SMN
		10 years	20 years	30 years	40 years	
1983	Dana Farber cancer institute and Boston Children's hospital [64]	Not studied			18%	Cancers (37%) Benign tumors (53%) Borderline neoplasms (10%)
1988	NWTS [65]	1%				
1997	SIOP [66]	0.65%	None reported after 10 years			AML (25%) Bone tumors (37.5%) CNS PNET (25%) Histiocytic lymphoma (12.5%)
2008	British childhood cancer survivor study [67]	0.8%	2.6%	7%	12.8%	Soft-tissue sarcomas Adenocarcinoma Bone tumors Renal cell carcinoma Breast cancer Miscellaneous malignancies
2010	International collaborative study (north American, British, Nordic) [17]	–	0.5%	2.4%	6.7%	GI organs (17.8%) Bones/joints/cartilage (11.5%) Breast cancer (13.2%) Eye, brain, CNS (9.7%) Leukemias (16%) Thyroid and endocrine (10.3%) Others
2011	St. Jude Children's Hospital [68]	0.3%	1.5%	3.9%		Soft-tissue sarcomas (18%) Breast cancer (15%) Bone tumors (12%) Others—Adenocarcinoma (12%), melanoma (9%), thyroid (9%), ALL (6%), medulloblastoma (3%), renal cell carcinoma (3%)
2014	NWTS [69]			4.5%	15%	Breast cancer
2016	Lee et al. [63]	0.6%	1.6%	3.8%		Connective tissue/bone (29%) Thyroid carcinoma (15%) Nervous system (15%) Leukemias (12%) GI system (12%) Breast carcinoma (9%) Renal system (6%) GU system (3%)

7. Cardiac and Pulmonary Complications

Metastatic WT with localized or bilateral lung involvement receives XRT in the form of localized therapy or whole lung irradiation (WLI). Survivors are thus at high risk for both pulmonary and cardiac long-term effects such as decrease in total lung capacity, decrease in vital capacity by up to 70%, pulmonary fibrosis, interstitial pneumonia, cardiac toxicities such as valvular dysfunction, congestive cardiac disease, heart failure, etc. [70]. In addition, concomitant XRT to the chest and abdomen leads to high radiation dosages that increase the risk of toxicities [71].

The National Wilms Tumor long-term follow-up study analyzed the pulmonary effects of XRT and submitted that the cumulative incidence of lung toxicity of irradiated survivors was approximately 5% as compared to 0.5% in nonirradiated counterparts [72]. Protection of the thyroid gland during lung XRT is an essential step as it has been noticed that unprotected thyroid during WLI results in thyroid abnormalities especially hypothyroidism [73].

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37 Post-Therapy Surveillance of Wilms' Tumor Survivors

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37.1 Introduction

Wilms' tumor (WT) which is the most common renal tumor in children has a recurrence rate of 15–20% [1]. The treatment of children with WT does neither end at removal of the tumor nor with chemotherapy (ChT) or radiation therapy (XRT); it is a continuous process that extends beyond his/her adulthood. Children with WT are at increased risk of developing certain late secondary effects and are associated with chronic health disorders. Cardiomyopathy and congestive heart failure due to anthracyclines and XRT have been known since the inception of therapy, but significant morbidity has been reduced due to careful modification in the current regimens [2]. Survivors of WT are at substantially higher risk of mortality between the third and fifth decade from diagnosis. Approximately three-fourths of such deaths are due to either subsequent primary neoplasm or cardiac disease [3]. This makes the need for the long-term follow-up all the more necessary. The development of end-stage renal disease (ESRD) in unilateral disease is very low but slightly increased in the bilateral disease group [4, 5]. Second malignant neoplasm (SMN), although rare, should be a concern, and screening to pick them up should be our priority. Planned surveillance by imaging modality has enabled to identify more than two-thirds of relapses in asymptomatic children with WT [6]. Planned surveillance imaging identified 70% of the relapses with the following distribution of modalities: ultrasonography (USG) (32%), chest X-ray (CXR) (31%), computerized tomography (CT) (33%), and magnetic resonance imaging (MRI) (4%) [6].

37.2 Role of Surveillance and Allied Controversies

The goal of scheduled interval diagnostic imaging is to detect the relapse before the development of any signs and symptoms [7]. Surveillance strategy is based on the assumption that it will help in early detection of recurrence and thus will improve the salvage rate and help in minimizing the intensity of the therapy and its associated adverse effects [7]. However, little information is available regarding the costs, benefits, and risks involved with the different surveillance strategy

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[8]. The surveillance risks include ionizing radiation, need for sedation, intravenous cannulation, and frequent follow-up visits leading to psychological distress for the families and child [9, 10]. The intensive surveillance strategy also puts financial burden on the family and has implications over the education of the child and the job of the parents.

Few studies have also tried to determine the beneficial effect of the routine surveillance imaging on the salvage rate of the relapsed patients. Many such studies did not find any difference in salvage rate between the patients detected by imaging or clinically [8].

Another controversy is regarding the optimal imaging to detect the relapse early. The CT scan does detect the smaller size (1–2 cm) lesions that are not detected by CXR/USG. However, the prognosis gets affected only when the relapsed lesion is more than 2 cm in size [6]. The CXR/USG has been found to have enough sensitivity to detect the lesion before the tumor burden has any adverse impact on the outcome. The advantages offered by CXR/USG over the CT include less ionizing radiation, no need for sedation/intravenous cannulation, less cost, and optimal sensitivity. The high sensitivity of CT may lead to high false positivity that needs to be resolved by further evaluation posing unnecessary risk and burden on child and family [6].

Recommendations for post-therapy imaging surveillance followed worldwide are based on the guidelines proposed by the Children's Oncology Group (COG) and Societe Internationale D'oncologie Pediatrique (SIOP). These guidelines were originally proposed for the research purpose but are widely followed as surveillance protocol [6].

37.2.1 Post-Therapy Follow-Up

The surveillance for relapse detection and toxicity surveillance should start right after nephrectomy as about 15% of the patients with WT relapse after treatment [1]. Most of the relapse occur within 2 years after surgery, and only occasionally relapse occurs 5 years after nephrectomy [1]. Surveillance plays a major role in the management of recurrences and the long-term successful outcome. Surveillance involves history, physical examination, and imaging during the follow-up visits.

Since children with WT have overall survival (OS) rates greater than 90%, follow-up imaging after therapy treatment should be minimally invasive. The OS for patients with recurrent WT (RWT) favorable histology (FH) is around 50%; it is very important to identify and treat them early [7]. In addition, all childhood cancer survivors should undergo annual physical examination incorporating anthropometric measurements, nutritional status, and overall health [11].

The common site of relapse in WT are the lungs, which account for 50–60%, and the abdomen with 30%, while other sites (bone or brain) are involved in approximately 15% of cases [9].

37.2.2 Healthcare Records

Maintaining and organizing the personal record of the child's medical information will be of immense help to the healthcare professional for the long-term follow-up. In the long run when the child enters adulthood, the document about a brief history of the diagnosis, treatments, medications, follow-up, do's and don'ts, any near-death incidents, or complications will be very useful, as a transition back to the family physician or another healthcare professional [12].

37.3 COG Surveillance Protocol

COG recommends chest CT and abdominal CT/MRI for the first 2–3 years, based on disease stage and histology and later chest radiographs and abdominal ultrasonography [13] (Table 37.1). Contrast-enhanced CT and MRI are better than USG in the identification of small tumors (1–2 cm), nephrogenic rests (NR), and nephroblastomatosis (NB) [14].

Table 37.1 COG recommendations for post-therapy CT surveillance imaging in WT [13]

Disease group	Imaging	Frequency
Very low risk stage I	CT chest	End of therapy, then every 2 months × 3, then every 3 months × 4
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy, then every 2 months × 3, then every 3 months × 4, then change to US
Low and standard risk stage I–III	CT chest	End of therapy, then every 6 months to 3 years
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy, then every 6 months to 3 years
Higher risk favorable histology	CT chest	End of therapy then every 3 months × 8
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy then every 3 months × 8, then change to US

There are studies that have tried to evaluate the need of routine pelvic surveillance imaging and have shown that omitting pelvic CT from the routine off-therapy surveillance imaging can save up to 40% of the effective dose of radiation without having any adverse impact on detection of recurrence [15, 16].

COG provides long-term follow-up guidelines for childhood cancer survivors, and these help prepare survivors who are reaching early adulthood to successfully manage their own healthcare. Third to fifth decade from diagnosis, survivors of WT are at a substantially increased risk of mortality, and 75% of such deaths were attributed to subsequent primary neoplasms and cardiac diseases [3]. Patients who have received XRT are at significantly higher risk [3].

37.3.1 Blood and Other Investigations for Long-Term Follow-Up of Organ-Systems at Risk and Assessment of Overall Well-Being

Following nephrectomy, physical examination including measurement of weight, height, and body mass index (BMI) and testicular examination for hydrocele should be done annually [11]. Blood urea and serum electrolytes should be asked for at the time of entry into the long-term follow-up and should be repeated as clinically indicated. Serum creatinine, estimated glomerular filtration rate (eGFR) calculation, and urinary proteinuria (microalbuminuria) should be tested annually [11].

The National Wilms' Tumor Study (NWTS) report estimated that unilateral WT patients had a 20-year cumulative incidence of ESRD of 1.3%; it was 15% for BWT [17]. However, patients with associated Denys-Drash syndrome (DDS) (75%), WAGR syndrome (36–90%), cryptorchidism, and hypospadias (7%) have significant risk of ESRD [18]. Thus, lifelong nephrological follow-up for renal function must be provided to the patients with high propensity for ESRD (syndromic patients and bilateral tumors) [19].

Renal transplant for children with bilateral WT with ESRD is usually delayed until 1 to 2 years have passed without any evidence of malignancy because majority of tumors recur within 2 years of diagnosis [20]. For children with WT and DDS who proceeded to renal transplantation, the clinical outcomes are comparable to children with other ailments, with no graft failures because of recurrence. Children with WT and DDS have a good outcome following renal transplantation although the numbers of studies are few [20].

37.3.2 Early Screening for Infertility

Puberty, hormonal regulation, fertility, and sexual function are impaired with the use of alkylating ChT and XRT to the central nervous system and ovaries. The long-time female survivors may have an increased risk of miscarriage, premature delivery, small for age infants, and premature menopause [21, 22]. Gonads of postpubertal girls are more sensitive to XRT than prepubertal girls. XRT dose as low as 5 Gy and 10 Gy can affect ovarian function in post- and prepubertal girls, respectively [23]. Infertility causes mental strain impairing quality of life and also can lead to mild post-traumatic stress disorder. All girls with abdominal XRT should be considered at high risk for pregnancy complications and should be managed at appropriate referral for the fertility and obstetric care [24].

37.3.3 Hearing Tests

Hearing tests must be performed for patients who receive carboplatin, and children aged 6 or older should be screened with a pure tone audiogram, but very young kids can be tested using auditory brainstem response (ABR). Those who have hearing impairment are screened yearly till 6 years of age and then every 2 years till 12 years of age, and then frequency can be decreased to once every 5 years [11].

37.3.4 Cardiac Function

Anthracycline ChT affects the functioning of the heart if dosage of ≥250 mg/m^2 is administered at the time treatment, echocardiography (ECHO) is recommended every 2-year follow-up, and problems may also result from XRT to the heart or surrounding organs and tissues. If XRT dose is <15 Gy or none, no need for ECHO but if the dose is ≥15–<35 Gy, screening ECHO is required every 5 years. Screening ECHO should be done every 2 years if the radiation dose is >35 Gy [11].

37.3.5 Screening for Colon Cancer

This should start 10 years after XRT or by age 35 (whichever is later). Microscopic examination of stool should be done to look for occult blood [11].

37.3.6 Thyroid Tests

Thyroid testing is required if the patient has received XRT to the head or brain for brain metastasis. In such patients, physical thyroid examination and thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels should be done annually. Female survivors at risk for thyroid problems should be treated for hypothyroidism before becoming pregnant. Thyroid USG should be done every 3 years to screen for thyroid nodules and masses [11].

37.3.7 Breast Screening

Women survivors who have received chest XRT for lung/bone metastasis during childhood have an increased risk of developing breast cancer at a much younger age (usually 30 to 40 years old). Early screening for breast cancer in females should be a part of the follow-up schedule. Monthly breast self-examination is also recommended. Annual physical breast examination by healthcare provider should be done starting at puberty until the age of 25 and then every 6 months thereafter. Mammogram and breast MRI are initiated at age 25 years or 8 years after chest radiation and should be repeated every year [3, 11, 25].

Psychosocial assessment of the cancer survivor is recommended with attention to the education and vocational program. These patients should also be evaluated for social withdrawal annually. Routine discussions should be held to reduce the lifestyle risk factors like obesity, smoking, lack of exercise, etc. [26]

37.4 SIOP Surveillance Protocol

SIOP 2001 and the new SIOP-RTSG (Renal Tumor Study Group) Umbrella protocol recommend chest radiographs and an abdominal ultrasound to detect recurrence (Table 37.2). The Indian Council of Medical Research (ICMR) has adapted the long-term guidelines from the SIOP RTSG 2001 protocol [27].

37.4.1 Surveillance Program of SIOP-RTSG Umbrella Protocol 2016

SIOP-RTSG Umbrella protocol mentions little more elaborate surveillance program for relatively longer periods of follow-up. The off-therapy physical examination (including blood pressure measurements), the diagnostics to detect a relapse, and the toxicity diagnostics and surveillance and their frequencies are mentioned in Table 37.3 [29].

37.5 UKCCLG Surveillance Protocol

The United Kingdom Children's Cancer and Leukemia Group (UKCCLG) guidelines are similar to those of Umbrella protocol [30]. UKCCLG recommends liaison with local pediatric nephrologists at the end of treatment and with the geneticists for the patients with underlying predisposition, malformations, and/or bilateral disease. UKCCLG endorses the recommendations of the International Late Effects of Childhood Cancer Guideline Harmonization Group for the surveillance of breast cancer and cardiac toxicity (Table 37.4) [25, 31].

Table 37.2 Recommendations for long-term follow-up as per SIOP-2001 [28]

	Investigation	Frequency after completing therapy
Patients with nonmetastatic disease at diagnosis	Blood pressure	Every visit
	Serum creatinine	6 months × 8
	Chest X-ray	1st year: Every 3 months Second year: Every 3 months Third year: Every 6 months
	Abdominal USG	End of treatment 1 and 5 years after stopping therapy
	Echocardiography	According to institutional policy
Patients with nephrogenic rest[a]	Abdominal USG	3 months × 8 6 months × 6 Yearly × 5
Metastatic patients in CR after stopping therapy	Chest X-ray	1st year: Every 2 months Second year: Every 2 months Third year: Every 6 months
	Serum creatinine	6 months × 8
Irradiated patients	X-ray bony structures, Spine+/− pelvis	Yearly to full growth and then every 5 years
Bilateral tumors	Chest X-ray and USG abdomen	1st year: Every 2 months Second year: Every 2 months Third year: Every 3 months Fourth year: Every 3 months
	Serum creatinine and proteinuria	5th–tenth year: Every 4 months Every 6 months
Partial nephrectomy	Abdominal USG	3 months × 8 6 months × 6 Yearly × 5

[a]Following CR to treatment, maintenance therapy of vincristine and actinomycin D every 28 days is given for 1 year

Table 37.3 Surveillance program suggested in SIOP-RTSG 2016 Umbrella protocol [29]

	Frequency after completing therapy
Physical examination	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months Fifth year: Every 6 months After 5 years: Once a year
Investigations	
Diagnostics to detect a relapse	
Chest X-ray AP or PA and lateral view	1st year: Every 3 months[a] Second year: Every 3 months[a] Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
Abdominal USG	1st year: Every 3–4 months Second year: Every 3–4 months Third year: Every 4 months Fourth year: Every 6 months Fifth year: Every 6 months After 5 years: Once a year
Toxicity diagnostics and surveillance	
Urine (glucose, albumin, β-microglobulin, calcium, phosphate, magnesium, erythrocyte)	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
24-h urine collection	In case of albuminuria
Blood (full blood count, urea, creatinine, Ca++, PO^{4-}, Mg++, albumin, ALAT, ASAT, bilirubin, TSH)	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
ECG/echocardiography	After anthracyclines, lung irradiation and in case of high blood pressure
24-h blood pressure	In case of high pressure
Lung function	After lung irradiation once a year
Endocrinology	In case of disorders, contact pediatric endocrinologist
Audiometry	Once after carboplatin, in case of pathological result, refer to ENT specialist
Neuropsychological testing	In case of syndromes with potential retardation (e.g., WAGR)

[a]In case of stage IV disease: X-ray or CT of the lung every 2 months depending on the local standards

37.6 Differences Between Various Collaborative Groups' Post-Therapy Surveillance Protocols

The most important difference between COG and all other guidelines is the imaging method used for the surveillance. The COG group recommends use of chest and abdominal CT to detect any local or distant relapse. In comparison, all other protocols recommend the long-term follow-up using CXR and USG abdomen. The CT scan is a more sensitive screening test than CXR/USG and can detect smaller lesions. However, the need for sedation, intravenous contrast, and exposure to ionizing radiation are well known disadvantages of CT scan. Various studies failed to document any advantage of CT over

Table 37.4 CCLG guidelines for follow-up of renal tumors [30]

	Frequency after completing therapy
Physical examination including BP measurement	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Optional
Investigations	
Diagnostics to detect a relapse[a]	
Chest X-ray AP or PA and lateral view	1st year: Every 2–3 months[b] Second year: Every 3 months Third year: Every 3 months
Abdominal USG	1st year: Every 2–3 months[b] Second year: Every 3 months 3rd–seventh year: Every 3 month (or clinical examination in compliant patient) if patient was <12 month at initial diagnosis of Wilms' tumor, nephrogenic rests found in nephrectomy specimen, initial bilateral tumors, partial nephrectomy
Toxicity diagnostics and surveillance	
Urine dipstick	1st year: Every 3 months[b] Second year: Every 3 months[b] Third year: Every 6 months Fourth year: Every 6 months After 4 years: Once a year
GFR and 24-h urine collection	In case of proteinuria, nephrocalcinosis, hypertension, and decreased kidney function[c]
Blood: Full blood count, urea, creatinine, cystatin C, Ca++, phosphate, Mg++, albumin, ALAT/ASAT, bilirubin, and blood gas	1st year: Every 3 months Second year: Every 6 months Third year: Every 6 months Fourth year: Every 6 months Fifth year: Once a year
ECG/echocardiography	Long-term follow-up should be done according to local policy
Lung function	
Endocrinology	
Audiometry	

[a]Relapse surveillance should start right after nephrectomy as a significant proportion of the relapses occur during post-operative treatment
[b]High-risk histology (stage III, IV, and V) and intermediate risk histology (stage IV) have a significantly higher risk of relapse the first year after nephrectomy and should have USS/X-ray every second month
[c]Referral to a local pediatric nephrologist

USG as screening test. In addition, the high sensitivity of CT may lead to high false positivity that needs to be resolved by further evaluation posing unnecessary risk and burden on child and family [6].

There are some subtle differences in the recommendations by various groups for the surveillance of other organ-systems at risk also, e.g., breast cancer screening and cardiomyopathy surveillance (Table 37.5) [25, 31].

37.7 Challenges in Resource Challenged Nations

Besides many other challenges, abandonment of adjuvant treatment and lack of post-therapy surveillance are major concerns in resource challenged nations. Infectious complications are a significant contributor to the treatment-related mortality [32]. The early detection of recurrence will help in minimizing adverse sequelae of more

Table 37.5 Breast cancer screening and cardiomyopathy surveillance [25, 31]

		COG	CCLG	Concordance
Breast cancer surveillance	Age of initiating surveillance	25 years	25 years	Yes
	Frequency of surveillance	Every year	Every year	Yes
	When to stop surveillance	No age limit	No age limit	Yes
	Screening test			
	Clinical breast examination, mammography, and breast MRI	Yes	Yes	Yes
	Age at initiation of screening			
	Clinical breast examination	Puberty	Age 25 years and at least 10 years after chest radiation	No
	Mammography	Age 25 years or 8 years after chest radiation	Age 30 years	No
	Breast MRI	Age 25 years or 8 years after chest radiation	Age 25 years	No
	Surveillance frequency			
	Clinical breast examination	Every year from puberty to 25 years of age and then every 6 months	Regularly	No
	Mammography	Every year	Every year (age 30–50 years) and then every 3 years	No
	Breast MRI	Every year	Every year (age 25–29 years) Or age 25–50 years if dense breast tissue	No
Cardiomyopathy surveillance	*Screening test*			
	Echocardiography	Yes	Yes	Yes
	Radionuclide angiography	Yes	No	No
	Surveillance begins at	≥2 years after treatment or ≥5 years after diagnosis (whichever is first)	1–3 months after treatment	No
	Screening frequency	Every 1–5 years	Every 3–5 years	No
	Duration of screening	Lifelong	Not stated	No
	If any abnormality on screening test	Refer to cardiologist	Refer to cardiologist	Yes

intensive adjuvant therapy and decrease cost and resources. The surveillance protocol should be cost-effective and must keep the radiation risk and family inconvenience in account. The expense per test for screening, total number of tests required, population under surveillance, and cost of investigating false positive screening can unnecessarily burden already strained health resources in poor countries. Surveillance imaging regimens that include only CXR and USG cost less than half to the regimens that include CT scans [6]. Mullen et al. have shown that CT has no advantage over USG as a surveillance tool for unilateral favorable histology (FH) WT. Elimination of CT scans from surveillance programs for this cohort of patients is unlikely to

impact survival; in fact, it would result in significant decrease in radiation exposure and expenditure [6]. As most of the recurrences occur within 2 years after treatment, surveillance beyond 2 years is being questioned and needs to be thoroughly evaluated especially in resource challenged nations.

37.8 Palliative and Near End of Life Care

Most of medical schools do not teach about the terminal care and death in pediatric population. This is a very complex issue and involves the caregivers, parents, sibling, society/community, religion, etc.

There are many challenges to providing a decent pediatric palliative care (PPC), including controlling the disease, shifting to end of life care, financial restrictions, and acceptance of death [33]. Symptom control (fever, dyspnea, easy fatigability, anorexia, nausea/vomiting) and the overall well-being of children with advanced disease are a challenge in itself, and the primary objective is to ease their suffering. A multidisciplinary support team should promptly try to communicate between parents and caregivers about the quality of medical care for children who are dying of cancer. The terminal care includes many aspects of symptom management. Adequate pain management is one of the most important aspects, but it must include adequate symptomatic relief to other symptoms like nausea/vomiting, constipation, fever, respiratory distress, etc. Most of the parents in the poor socioeconomic countries are working to earn a living. They would like to take care of their children at home [34]. In such scenario, the primary physician and nearby primary healthcare centers (supported by government) should be communicated and facilitated by educating them about the management of various acute events like acute pain, febrile neutropenia, etc. The availability of oral morphine and other pain medications should be ensured. In addition, it is equally important to identify and arrange the social support (philanthropic) for food, travel, stay, expensive medication, etc. Most of the studies admit the importance of at least one meaningful contact of health providers with the bereaved families. This contact may be in any form such as a call, email, or letter and should comprise of making an effort to remember the child. All grieving families should be provided bereavement support from the psychosocial team, including psychoeducation [33, 34].

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Prognosis and Outcomes

38

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38.1 Introduction

Clinical outcome in Wilms' tumor (WT) has progressively improved. The credit for this certainly goes to ongoing National Wilms Tumor Study Group (NWTSG)/Children Oncology Group (COG) and International Society of Pediatric Oncology (SIOP) trials, which have identified a variety of novel factors affecting prognosis other than staging. With the incorporation of multimodality therapy, the 4-year overall survival (OS) for low-risk (LR) WT is reported at 98.4% [1]. However, despite this success, a subset of high-risk (HR) WT continues to elude the researchers and treating physicians. Whereas favorable histology (FH) has 4-year OS of 99% to 86%, OS in unfavorable histology (UH) continues in ranges from 78% to 28% depending on the stage [2]. These HR WT carry poor clinical prognosis with high recurrence rates, and therefore, survival rates are low worldwide.

Aggressive chemotherapy (ChT) and radiation therapy (XRT) in HR WT or those with relapsed tumors have their own set of complications affecting outcomes adversely. The results of these therapies are comparable to conventional ChT but with low survival. There is therefore urgent need to think beyond the multimodal approach of surgery, ChT, and XRT to improve prognosis in this subset of patients.

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38.2 Prognostic Factors

As mentioned previously, additional prognostic factors have been incorporated as a result of international trial studies. These factors aid in the risk stratification scheme, thereby providing treatment with precision. There are a lot of future potentials as further success may be achieved through novel markers to refine risk stratification.

Although both SIOP and National Wilms Tumor Study Group (NWTSG)/COG approach provide excellent overall outcomes, all prognostic factors are not adaptable in both approaches. One prognostic factor that is predictive of outcome in NWTSG/COG may not be having the same value in SIOP. This is because the approach to clinical management is distinct. COG permits immediate histological diagnosis, accurate staging, and lymph node (LN) status without alteration in staging post nephrectomy. In SIOP instead, because of preoperative ChT, fewer patients have LN involvement detection. Response to ChT may be assessed by reduction in tumor volume. Response is also assessed by histological changes following ChT. These factors, viz., staging, histology, reduction in tumor volume, and initial responsiveness to ChT, are utilized for risk stratification in SIOP [3].

As WT appears to have a spectrum with a subset of very low-risk (VLR) WT at one end and HR WT or diffuse anaplastic histology (AH) tumor at another, a special mention for the subset of VLR WT seems imperative to define a

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class of tumor where the prognosis is reported as excellent. These are defined as stage I, FH WT with weight less than 550 g, and age at diagnosis less than 2 years. Studies regarding the need for post-nephrectomy ChT or observation and chances of relapse in VLR WT have been conducted. AREN0532 study enrolled such 116 patients who didn't receive ChT with a median follow-up of 80 months. Tumors were analyzed for 1p and 16q loss, 1q gain, and 11p15 imprinting. Relapse was seen in 12 patients. Results showed that 11p15 methylation status was associated with relapse. Loss of heterozygosity (LOH) was 20% and loss of imprinting (LOI) was 25%. So, most of these patients can be safely managed with observation alone, but there is a need to incorporate biomarkers along with clinical features for observation strategy [4].

Recently, tumor-associated macrophages (TAMs) have been known to predict the prognosis in WT; presence of high-density M2-type macrophages was pointer to higher tumor stage and shorter OS [5].

Important prognostic factors that contribute to high recurrence and mortality include:

1. Tumor stage.
2. Tumor histology.
3. Tumor weight (COG), tumor volume (SIOP).
4. Age > 2 years.
5. Molecular and genetic markers (LOH 16q,1p and 1q gain).

38.2.1 Tumor Stage

While details of COG and SIOP staging have been mentioned elsewhere, it is well known that since the beginning, the tumor stage is considered a prognostic factor for WT. It is an established factor to have prognostic importance or to assign treatment regimens since the first NWTS study in 1969. Higher stages (III to V) are linked with poorer prognosis due to extensive disease as compared to lower stages (I and II) (Table 38.1) [6]. Ehrlich et al. advocated stratifying stage III subgroup patients into risk appropriate treatment groups after evaluating patients enrolled on NWTS-5. According to this study, among patients with local stage III disease, the LN involvement and microscopic residual disease combination were associated with 8-year event-free survival (EFS) of 71% and OS of 86%. This was lower to results with LN involvement alone (8-year EFS and OS of 82% and 91%, respectively), the microscopic residual disease only (8-year EFS and OS of 84% and 94%), and neither LN involvement nor microscopic residual disease (8-year EFS and OS, 90% and 95%, respectively) [7]. SIOP 93–01 estimated 5-year OS for stage I and IV were 97% and 82%, respectively [3, 8].

38.2.2 Tumor Histology

In COG protocol, histological assessment is done before the administration of chemotherapy, and tumor is categorized based on:

(a) Focal anaplasia.
(b) Diffuse anaplasia (DA).
(c) No anaplasia/Favorable histology (FH).

In SIOP, following ChT, the tumor is histologically classified as low, intermediate, and high risk based on the degree of necrosis and balance of cell types (blastemal, epithelial, and stromal). Those with DA and/or blastemal-type tumor are HR categories.

In COG, patients showing FH WT stage I or II disease without LOH experienced EFS of more than 85% and OS of more than 99% [9]. A comparison of outcome in FH WT and those with diffuse anaplasia revealed significant difference in NWTS-5. Four-year OS for stage I/II FH and III/IV FH were 98% and 92%, respectively. For those with diffuse anaplasia in stage I/II, stage III, and stage IV, it was 83%, 65%, and 35% respectively. For bilateral tumors with diffuse anaplasia, 4-year OS was adjudged as 55% [10].

38.2.2.1 Anaplastic Histology

Five to 10% of WT demonstrate AH. AH is established by the presence of atypical cells, polyploid mitotic figures, large nuclear size, and hyperchromatic nucleoli [11]. In a NWTSG

Table 38.1 Stagewise survival rates for WT children as reported in NWTS/COG (AREN0321, AREN0532, and AREN0533)

Stage	NWTS/COG study protocols	Reported survival (%)
I and II	Primary surgical resection followed by 19 weeks of VCR and AMD	*Surgery alone* [31] 5-year EFS 84%
VLR WT (age < 2 years, FH, tumor <550 g)	May be managed by resection alone [4, 31]	*Surgery, adjuvant ChT* 5-year EFS 97% 4-year EFS 90%; no deaths
Stage I and II with LOH at 1p and 16q	± DOX	4-year EFS 75% improved to 4-year EFS 84% with addition of DOX [3]
Anaplastic WT	Flank XRT	4-year EFS 33–70% depending on stage [10]
Stage III	Primary surgical resection followed by 25 weeks of VCR, AMD, DOX, and XRT based on LN involvement or peritoneal contamination	4-year EFS 66%
Stage III FH with LOH 16q and 1p	Addition of CTX and ETOP; regimen M [34]	4-year EFS 91%
Stage IV	Primary surgical resection followed by 25 weeks triple drug or intensive therapy. Regimen M in LOH evidence XRT if metastasis persisted	Resolution of lung metastasis OS 95% (6-week triple drug regimen) [35] *Without WLI* 4-year EFS 78% *With WLI*[a] 4-year EFS 85% ***C**ombined radiation with regimen M* 4-year EFS 88%
Stage V	[b]6-week triple drug regimen → NSS→postoperative ChT depends on histology and presence of tumor in LN or peritoneal cavity	*Depending on Stage II to IV* 4-year EFS 83% to 33%

VLR WT very low-risk Wilms' tumor, *DOX* doxorubicin, *VCR* vincristine, *AMD* actinomycin-D, *CTX* Cyclophosphamide, *ETOP* Etoposide, *XRT* radiotherapy, *ChT* chemotherapy, *LN* lymph node, *LOH* loss of heterozygosity; *OS* overall survival, *EFS* event free survival, *NSS* nephron-sparing surgery, *WT* wilms' tumor, *WLI* whole lung irradiation, *FH* fovarable histology

[a]A previous NWTS/COG study figure

[b]Similar in SIOP

study, a multivariate analysis of 632 patients not having metastasis at the time of diagnosis, it was concluded that anaplasia is associated with a high risk of mortality, metastases, and recurrences [11]. DA, fortunately less common, is associated with more than 60% of deaths. It is the most important predictor for shorter survival at the time of diagnosis. As in COG, in SIOP too, DA is considered the most important negative predictor of outcome. Percentage of viable cells in the tumor and the cell type in viable component after administration of neoadjuvant ChT also contribute to prognostic information in revised SIOP histological classification [12].

38.2.2.2 Blastemal Histology

Blastemal-type WT has been reclassified by SIOP as a HR histological subgroup in WT in 2002 [13]. This histological subtype fortunately contributed only 10% in SIOP 93–01 cohort but was responsible for one-third of events. This morphology is therefore a strong prognostic factor associated with adverse outcome, if seen in patients who received preoperative ChT. The risk of relapses also appears to be high in patients with blastemal-type histology as compared to other histological subtypes in the non-anaplastic tumor [14].

The benefit of knowledge of histological subgroup was seen in SIOP 2001 study as patients

with blastemal histology received extra ChT, which increased 5-year EFS of 67% in SIOP 93–01 to 80% in SIOP 2001 for all stages of localized disease [3]. The addition of doxorubicin (DOX) Nto vincristine (VCR) and actinomycin-D (AMD) also showed an increase in EFS in blastemal-type WT. Post-ChT histological classification also permitted reduced therapy in some subgroups. OS was comparable in patients with VCR and AMD, with or without DOX in stage II or III intermediate-risk WT [15].

38.2.3 Tumor Weight (COG) and Volume (SIOP)

As discussed above, a subgroup of patients with tumor weight below 550gm along with age below 2 years and FH have excellent prognosis in COG studies. In risk stratification scheme, this subset of patients was observed, while those in similar age group but with tumor weight equal to or above 550gm were subjected to EE4A (VCR-AMD) for 18 weeks) [3].

Tumor volume as a prognostic factor is valuable in SIOP experience. It was used as a prognostic factor in the German Society of Pediatric Oncology and Hematology (GPOH) institutions. In SIOP93–01 and 2001, a cutoff volume of 500 mL in intermediate-risk subgroup showed a distinctive difference in the outcome of the non-epithelial, non-stromal types of intermediate-risk WT. Five-year OS and EFS were 95% and 88% for smaller tumors as compared to 90% and 76%, respectively, for larger tumors [3]. This difference led to more intensification of therapy in patients with tumor greater than 500 mL.

38.2.4 Age

In COG studies, higher age was associated with higher recurrence rates and hence poorer outcome. This was possibly due to fact that anaplasia was rarely seen in below 1-year age group. Now, with improved therapeutic options, the impact of age as a prognostic factor is reduced. Impact of age as prognostic factor is well defined in VLR WT as mentioned above. Children with age less than 24 months generally have a lower relapse and better prognosis than the older children. A study showed that 20% of infants had an incidental diagnosis of WT; this subset of infants had a relatively smaller-sized nonmetastatic tumors and higher rate of malformations than infants of the matching age group having symptoms. It was also noted that oncological outcomes such as 5-year EFS rate in infants (under 1 year of age) of 96% were much better than 80% EFS rates in children aged 1–2 years ($P = 0.018$) [16]. Age is not used in SIOP trials for risk stratification.

Adult patients with WT have higher treatment-related toxicity than their younger counterparts, though the survival rates are comparable with children having the same stage and histology.

38.2.5 Molecular and Genetic Markers

38.2.5.1 Loss of Heterozygosity

One of the important goals of NWTS-5 was to prospectively estimate the prognostic importance of LOH at chromosomes 1p and 16q and 1q gain. Coexisting LOH for chromosomes 1p and 16q observed in approximately 5% of FH WT was seen to be significantly associated with an increased relative risk (RR) of relapse and death [17]. For patients with stage I/II disease, the RR of relapse and death were 2.9 ($p = 0.001$) and 4.3 ($p = 0.01$) individually. Among the cases with stage III/IV, the RR of relapse and mortality were 2.4 ($p = 0.01$) and 2.7 ($p = 0.04$), respectively.

38.2.5.2 Gene Expression Profiles

The WT1 alteration and 11p15 LOH or loss of imprinting (LOI) are thought to make distinct pathogenetic mechanisms for the growth and/or progression of WT; yet these events are not necessarily independent given the proximity of the 11p13 and 11p15 loci. In a study conducted by Perlman et al., all patients with WT1 mutations also had 11p15 LOH, yet 11p15 LOH was identified without WT1 mutations in a proportion of patients. Accordingly, 11p15 is apparently an added sensitive prognostic indicator [18].

Chromosome 1q gain is one of the most frequent cytogenetic findings in WT, seen in approximately 30% of WT cases [19]. Data gathered through the NWTS-5 clinical trial was used to evaluate the prognostic importance of 1q gain in FH WT. Among all stages, 8-year EFS and OS for patients with 1q gain were 77% and 88%, respectively. For cases without 1q gain, 8-year EFS and OS were 90% and 96%, respectively. But, no significant variation in particular histologic predominance based on presence or absence of 1q gain was observed [20].

TP53 gene mutations in WT are associated with high risk for relapse and fatal outcome [21]. Whereas FH WT practically never carries TP53 mutations, approximately 75% of AH WT does so. It shows that TP53 mutation may lead to the development of AH and provide predictive pointer toward aggressive disease [20, 22]. TP53 mutations are found in at least 90% of fatal cases of AH WT, more so in the presence of diffuse anaplasia. Importantly, even among non-anaplastic fatal tumors, 26% had TP53 changes; so, the mere presence of TP53 gene mutations cannot be taken as diagnostic of AH WT.

Some contemporary molecular profiling has demonstrated significant associations linking AH and loss of 4q and 14q [19]. Distinct candidate genes involved in WT pathogenesis at these latter loci have not been recognized yet, and the importance of these genomic alterations remains unknown.

As mentioned above in the discussion of VLR WT, 11p15 methylation analysis may be used as a biological prognostic marker in patients who do not require postoperative ChT. Patients may be divided into three categories, viz., retention of imprinting (ROI), LOI, or LOH. There was a significant relapse in LOH at 11p15 [18].

MYCN gene has frequently been reported in WT as well as other embryonal tumors, and its overexpression due to P44L mutation in WT has been recognized as an inherent prognostic feature as its connection with poorer relapse-free and overall survival is independent of histology [23]. Further details of molecular markers are mentioned elsewhere in this book.

38.3 Prognosis in Special Population

38.3.1 Children with Bilateral Wilms' Tumor

Approximately 1% of children with unilateral Wilms' tumor (uWT) develop metachronous lesions. End-stage renal disease (ESRD) in metachronous bilateral Wilms' tumors (BWT) with diffuse anaplasia is quite high. High risk of recurrence with BWT results in relatively poor prognosis as compared to uWT. The addition of renal failure also creates a difference in the quality of life.

To conserve renal function, nephron-sparing surgery (NSS) is an acceptable norm. But it may bring an extended risk of relapse, which should be controlled by other approaches such as ChT and XRT [24]. However, it continues to be a challenge, to adjust between preserving renal function and preventing recurrence, emphasizing the need for further prospective studies. These patients are at high risk of renal impairment leading to ESRD, especially if they also receive RT.

In 81 children with synchronous BWT who received radiation therapy as part of their treatment in NWTSG study, almost one-third of patients had raised serum creatinine; 18 patients had moderate renal insufficiency, and 10 had severe renal insufficiency with estimated GFR < 60 mL/min/1.73 m^2 [25].

38.3.2 Children with Lung Metastasis

In COG AREN0533, "rapid complete responders" (RCR), considered as those with complete radiological disappearance of lung metastasis after DD4A regimen or whose residual nodule is negative for tumor at 6-week reevaluation, were continued with DD4A without whole lung irradiation (WLI). This study perceived superior OS after omission of primary WLI in patients with complete response (CR) [26]. Similarly, patients who did not have complete resolution of nodules were labeled as "slow, incomplete responders" (SIR). EFS was significantly increased, with the excellent OS, in patients with

stage IV FH WT and SIR using four cycles of cyclophosphamide/etoposide in addition to DD4A drugs in this study.

In SIOP 93–01 trial, 5-year EFS and OS were 73% and 88%, respectively. Survival was better in stage IV patients with complete response to pre-nephrectomy 6-week ChT and those who underwent metastasectomy, compared to those with incomplete response who had only 48% survival [27].

38.3.3 Children with Recurrence

Recurrence occurs in about 15% of FH WT and nearly 50% of AH WT [27]. So, UH is a significant prognostic factor associated with recurrence. Apart from histology, stage and presence of certain molecular markers like LOH contribute to relapse significantly in certain patients, even with FH. The majority of recurrences are seen in the lung and within 2 years of therapy.

In recurrence, prognostic factors that are associated with better response to salvage therapy and therefore better outcome include:

1. Late recurrence more than 12 months after initial diagnosis.
2. Initial FH.
3. Lower stage at initial diagnosis.
4. Complete resection with no gross residual disease.
5. No XRT.
6. Initial treatment with VCR and AMD (Table 38.2).

Table 38.2 Showing post-relapse comparative survival after initial regimen [36, 37]

Treatment regimen	Post-relapse survival
Initial therapy VA *Salvage therapy* (CTX, DOX, and XRT)	OS 82%, 4-year EFS 71%
Initial therapy VAD, XRT *Salvage therapy* (CTX, CARB along with surgery, and XRT)	OS 48%, 4-year EFS 42%

VA vincristine-actinomycin-D, *VAD* vincristine-actinomycin-D-doxorubicin, *CTX* cyclophosphamide, *CARB* carboplatin, *XRT* radiotherapy, *OS* overall survival, *EFS* event free survival

As believed earlier, regarding increased risk of local recurrence in patients with stage III disease, a study had shown that initial needle biopsy was not clearly associated with increased risk of local recurrence in abdominal cavity [28].

After initial diagnosis of WT, around 1% of children develop metachronous lesion, and 90% of them show relapse in initial 2 years. Presence of persistent metanephric cell foci (nephrogenic rests) contributes to recurrence in the contralateral kidney.

Children who develop recurrence have post-relapse 4-year survival of 50–80%. Among them, the OS and 4-year EFS are lower in children who had initially received more intensive regimen (Table 38.3).

38.3.4 Children with Syndromic WT

Although syndromic WT is mentioned in detail elsewhere, it is imperative to mention here that these subsets of children behave differently in terms of increased mortality due to a variety of reasons. In around 10% of cases, WT occurs as a component of multiple malformation syndromes like WAGR, Beckwith-Wiedemann syndrome (BWS), or Denys-Drash syndrome (DDS). In a case series of 64 patients with WAGR syndrome and FH, 7% had bilateral disease and 50% developed chronic kidney disease after 20-year follow-up. Four patients in this study developed ESRD, requiring a transplant [29]. These patients, therefore, require aggressive renal surveillance with ultrasound. Diffuse mesangial sclerosis in DDS also gradually proceeds to nephrotic syndrome and renal failure. Higher mortality was reported in BWS earlier. But it improved progressively due to better tumor recognition and treatment. Prognosis is now favorable after childhood [30].

38.4 Survival Outcomes

OS has progressively increased from 20% in the 1960s to 90% in both SIOP and COG groups. Five-year OS rate approaches approximately 98% in children with VLRWT [31].

Table 38.3 Showing brief outcome in high- (HIC), upper middle-income (UMIC), lower middle-income (LMIC), and low-income (LIC) countries reported in different studies [33]

Author	Country	Period	*N*	M:F	Mean age at diagnosis (year)	Stage at diagnosis	Survival		Limiting factors for care
							EFS	OS	
Offer et al. [33]	England HIC	1968–2012	178	0.8–1	3	I–II—43% II–IV—34% V 7%	–	1 year 88% 5 years 76% 10 years 76%	Delayed asymptomatic diagnosis
Verma and Kumar [38]	India LMIC	2005–2014	108	4:1	2.5	I—21% II—30% III—35% IV—10% V—4%	5 years 73%	5 years 74%	Malnutrition Drug shortage Poor supportive care Lack of surgical expertise
Guruprasad et al. [39]	India LMIC	2003–2010	61	0.9:1	3.3	I—28% II—16% III—38% IV—15% V—3%	5 years 83%	5 years 85%	Loss of follow-up Late presentation
Seyed-Ahadi et al. [40]	Iran UMIC	1992–2002	55	1.2:1	3.8	I—33% II—16% III—38% IV—9% V—2%	4 years 71%	4 years 86%	Late presentation, associated anomalies
Visser et al. [41]	South Africa UMIC	1983–2007	98	0.8:1	3.8	I—37% II—18% III—24% IV—21%	–	76.5%	Malnutrition
Sangkhathat et al. [42]	Thailand UMIC	1996–2007	34	1.3:1	2.1	I—38% II—12% III—38% IV—6%	4 years 53%	4 years 65%	Late presentation Poor treatment compliance Finances
Abudidris et al. [43]	Sudan LMIC	1999–2007	37	0.9:1	4.1	I—3% II—19% III—68% IV—11%	–	11%	Finances Loss to follow-up Late presentation Lack of education
Libes et al. [44]	Kenya LIC	2008–2011	136	–	–	–	–	2 years 36%	Drug shortage Lack of education

HIC high income country, *LMIC* low-middle income country, *LIC* low income country

Table 38.4 Outcomes of WT according to the histology, stage, and the income status of the country

		LMIC		HIC					
		5 years	5 years	4 years		8 years [49]		10 years [50]	
Histology	Stage	EFS %	OS %	EFS %	OS %	EFS %	OS %	EFS %	OS %
FH	I	92.3 [45]	92.6 [48]	85.4 [47]	96.87 [47]	92	97	91.2	100
	II	83.3 [45]	92.0 [48]	90.23 [47]	100 [47]	83	94	91.4	97.1
	III	94.4 [45]	69.2 [48]	84.34 [47]	97.96 [47]	88	93	82.8	88.6
	IV	80 [45]	47.1 [48]	76.5 [47]	94.1 [47]	76	82	65.6	77.9
	V	50 [45]	50.0 [48]	83.18 [47]	97.7 [47]	74	89	71.8	80.8
UH	I	87.8 [46]	100 [46]	68.4 [10]	78.9 [10]	88	88	75.0[a]	72.9[a]
	II	40 [46]	100 [46]	82.6 [10]	81.5 [10]	52	58		
	III	57.1 [46]	71.4 [46]	64.7 [10]	66.7 [10]	47	52		
	IV	80[b] 60[c]	–	33.3 [10]	33.3 [10]	36	36		
	V	–	–	25.1 [10]	41.6 [10]	40	45		

HIC high income country, *LMIC* low-middle income country, *FH* favorable histology, *UH* unfavorable histology, *EFS* event free survival, *OS* overall survival

[a]Anaplastic histology EFS, OS

[b](I–IV) Focal anaplasia [45]

[c](II–IV) Diffuse anaplasia [45]

The outcome of uWT in SIOP 2001 treated according to histological subtypes showed that while OS was above 90% in low to intermediate risk, it was only 75% in high-risk tumors after 5 years. The dismal outcome was seen in high-risk metastatic WT with 2-year OS of 33% [3].

From 1969 to 1995, 6185 patients were enrolled in a COG study, and OS was 84% through 2002 [32]. Major cause of deaths among these children included tumor related in 86%, therapy related in 9%, unrelated to disease in 5%, and unknown in 1% [32]. Ninety-one percent of deaths occurred in the first 5 years of diagnosis and were due to primary tumor. Late deaths were attributed almost equally to therapy and tumor related [32].

Survival after diagnosis and treatment is better in most high-income countries (HIC). Low- and middle-income countries (LMIC) prevail to struggle with WT detection and treatment. Overall survival varied from 70% to 97% in HIC, 61% to 94% in upper middle-income countries, 0% to 85% in lower middle-income countries, and 25% to 53% in low-income countries [33]. Delay in diagnosis, shortage of available treatment, and poor follow-up contributed to the large variations in outcomes. In comparison with HIC, in studies from LMIC, data regarding stagewise 5-year EFS and OS along with histology as parameter are relatively deficient (Tables 38.3 and 38.4).

38.5 Summary and Conclusions

Tumor stage, tumor histology, molecular and genetic markers like LOH at chromosome 16q and 1p, and presence of TP53 are therefore important prognostic factors in the management that contribute to overall outcome in WT. Poorer prognosis is associated with anaplastic histology in stage II to IV tumors, which are the most important predictors of outcome in children. Diffuse anaplasia is worse than focal. The blastemal subtype is associated with adverse outcomes. Other poor prognostic factors affecting outcome include higher stage of the tumor at the time of diagnosis, age older than 2 years, higher positive lymph node density, and large tumor size. Identification of these poor prognostic factors at the beginning of treatment is imperative for physicians to aid in utilizing available therapeutic options and also for evidence-based counseling about overall survival. Future studies in group trials shall possibly reveal more markers for unresponsive tumors.

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Non-Wilms' Renal Tumors

39

Archana Puri, Kiran Mishra, and Rama Anand

39.1 Congenital Mesoblastic Nephroma

39.1.1 Incidence and Epidemiology

CMN or "Bolande's tumor" despite its rarity is still one of the most common congenital tumors [1]. The term CMN was coined by Bolande in 1967 to emphasize its congenital nature and predominant mesenchymal component in its histology [1]. It is the most common solid renal tumor of neonates and infants younger than 6 months. Although it accounts for less than 5% of all pediatric renal tumors, 67% of all renal tumors in infants younger than 6 months are CMN [2]. Its estimated incidence is 1:500,000 infants [3]. The median age at diagnosis for CMN in most series is 2 months, with up to 80% of all cases reported in the first month of life and up to 90% in infants younger than 1 year with only few sporadic reports in older children and adults. It shows sex predilection with a male/female ratio of 1.5:1 [1, 2].

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39.1.2 Clinical Presentation

It often presents as an incidentally diagnosed asymptomatic abdominal mass, noted either since birth or soon after birth. This abdominal mass may even get detected prenatally usually in association with maternal polyhydramnios; CMN is the most common renal tumor that is diagnosed on antenatal ultrasonography (USG). Perinatal presentations are often associated with premature labor; rarely however they may present with hydrops fetalis, congestive heart failure (due to hypertension, or arteriovenous shunting), or tumor rupture causing hemoperitoneum and shock. Rare postnatal presentations may include metabolic disturbances with hypercalcemia, nephrocalcinosis, and syndrome of increased renin secretion. Although hypercalcemia can occur in 1–2% of renal tumors of childhood, it is most commonly reported with malignant rhabdoid tumor of the kidney (MRTK) and rarely in CMN [4]. It is a paraneoplastic phenomenon due to ectopic production of parathormone and prostaglandin E2, manifesting with nonspecific symptoms such as anorexia, vomiting, floppiness, and constipation. However, severe hypercalcemia (>15 mg%) can present with severe abdominal pain, persistent vomiting, extreme weakness, severe dehydration, rapid deterioration of renal function, coma, and death [4]. Serum calcium levels in such conditions can act as a biochemical tumor marker, with normalization of calcium levels after complete tumor resection.

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Increased renin secretion can either occur from the tumor or be because of local ischemia produced by compression of normal glomeruli by tumor, and it often manifests as hypertension [5].

39.1.3 Radiological Diagnosis

Pathognomonic ultrasonographic (USG) features of CMN are of a small round tumor with indistinct margins and characteristic hypoechoic rim around the tumor. Further diagnostic clarity is provided by contrast enhanced computerized tomography (CECT), which often shows solid-cystic tumor with indistinct demarcation from the normal kidney with **double-rim sign** (tumor appears having two boundaries). The double-rim sign correlates with hypoechoic ring on Doppler USG [2]. It is hypothesized and often confirmed on histological examination that hypoechoic ring is caused by slow blood flow in dilated blood vessels and entrapped nephrons at the tumor periphery. Another characteristic radiological finding of CMN is the presence of **intra-tumor pelvis**, signifying that part of the pelvis is encapsulated by the tumor [2]. Although it may be difficult to differentiate CMN from WT radiologically, it is worthwhile to note that CMN tends to infiltrate the kidney, encapsulating the pelvis rather than forming a pseudocapsule as noted in WT (Fig. 39.1).

39.1.4 Pathology

At gross examination, CMN appears to be an infiltrative mass with ill-defined margins and no capsule. On cut section, it is predominately solid with whorled, firm, yellow surface with rubbery consistency (Fig. 39.2). Histologically, they have uniform spindle-shaped cells arranged in bundles with trapping of normal tubules and glomeruli at the periphery of the tumor. Early age of onset and infiltrative growth pattern of CMN with entrapment of tubules and glomeruli rather than the formation of tubular structures help to differentiate

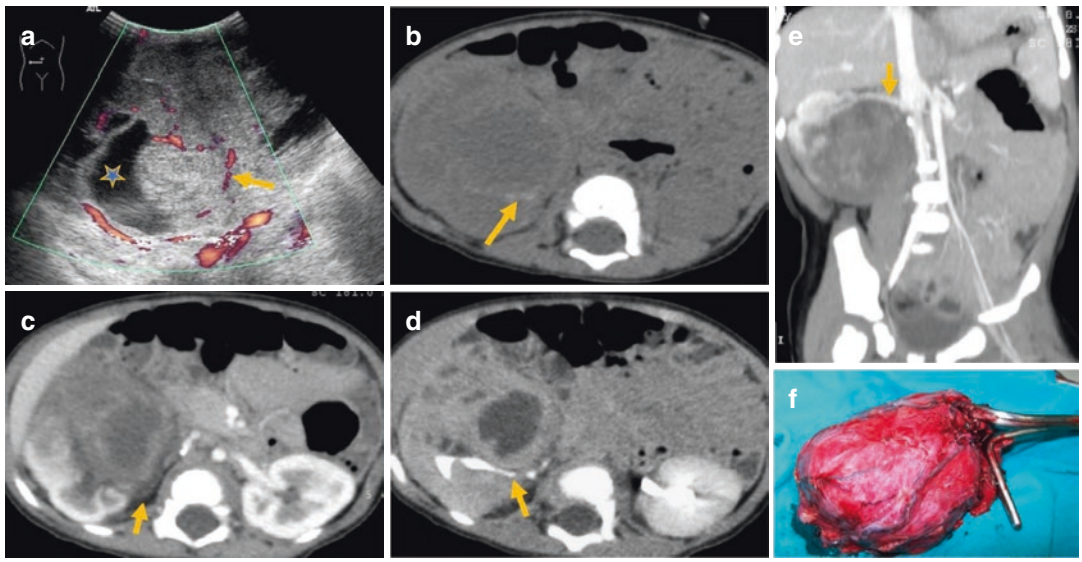

Fig. 39.1 Nine-month-old boy with right lumbar mass noted since 1 month. (**a**) Axial color Doppler image shows a large, heterogeneous mass with anechoic areas due to necrosis (*); solid area shows some peripheral and internal vascularity (arrow); (**b**) Non-contrast CT scan shows a hypodense mass with areas of hemorrhage (arrow); (**c**) CECT shows mildly enhancing mass arising from medial aspect of the lower pole of the right kidney showing non-enhancing necrotic areas, indistinct demarcation from the normal kidney, double-rim sign, and involvement of the renal sinus; (**d**) delayed phase image shows calyceal distortion by the mass and intra-tumor pelvis (arrow); (**e**) coronal section shows the mass displacing the inferior vena cava (IVC) and right renal artery (arrow) without evidence of invasion or encasement; (**f**) photograph of resected tumor—histopathology revealed cellular variant of CMN

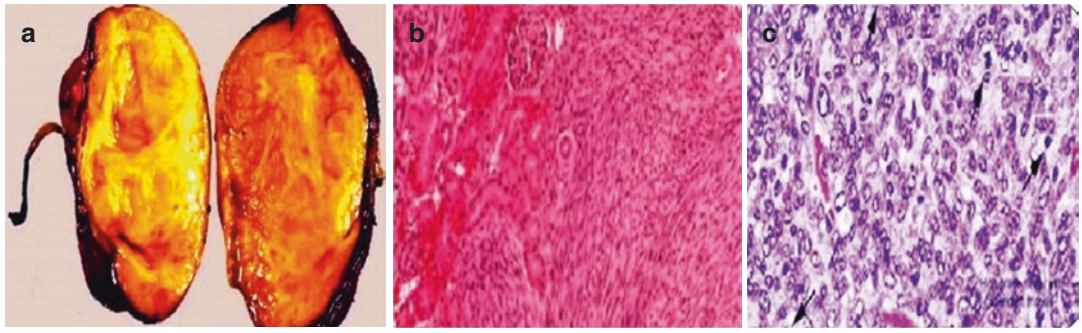

Fig. 39.2 (**a**) Gross specimen showing large unencapsulated large renal tumor with firm yellowish-white whorled cut surface suggestive of CMN. (**b**) Classic CMN showing intersecting bundles of spindle cell pushing through into the kidney substance with low grade nuclei with very few mitoses. (**c**) Cellular CMN with polygonal and spindle cells with high mitotic rate (black arrow)

it from WT. Fine needle aspiration cytology (FNAC) in CMN, unlike WT, is usually hypocellular and is composed of cohesive clusters of spindle cells with round to oval nuclei with fine chromatin and indistinct nucleoli [6]. Blastemal component is conspicuously absent. Thus, on FNAC, WT treated with preoperative chemotherapy or WT with stromal predominance forms close differentials for CMN.

There are three histological subtypes or variants of CMN based on cellularity and mitosis, namely, classical (24%), atypical or cellular (66%), and mixed (10%) (Fig. 39.2). Atypical or cellular variant is also called as malignant mesenchymal nephroma of the kidney and is characterized by aneuploidy and high mitotic index (8–30 mitoses per 10 high power fields) and exhibits cystic degeneration, intra-tumoral hemorrhage, and necrosis [1, 2, 7]. Classical variant morphologically resembles infantile fibromatosis of the renal sinus, and cellular variant is identical to infantile fibrosarcoma. Cytogenetic and molecular studies have documented chromosomal changes especially trisomy 11 and translocation **t(12:15) (p13; q25) with ETV6 NTRKS gene fusion** in most cases of cellular CMN, as is also noted in infantile fibrosarcoma [1, 8]. While CMN exhibits strong immunoreactivity for vimentin, fibronectin, and actin, it shows only focal or weak desmin positivity [1]. It is worthwhile to mention that cellular variant has a delayed age at presentation (121 ± 236 days versus 6.6 ± 7.4 days for classical variant). Imaging findings may also assist to predict the likely pathological variant. Presence of foci of hemorrhage and degenerative cystic, necrotic changes in the tumor on imaging are more consistent with the cellular histology, while classical variety is characterized by the presence of hypoechoic rim and a large solid component in the tumor. Presence of extrarenal extension of tumor in adjacent surroundings is also consistent with cellular histology [7].

39.1.5 Management

Although previously, all primary renal tumors diagnosed prior to 6 months of age were considered benign CMN and were treated with upfront radical nephroureterectomy (RN) alone ensuring no spillage, tumor-free margins, and lymph node sampling, a lot of rethinking had occurred recently for infants more than 3 months of age [9]. It was observed that likelihood of renal tumor being benign decreases drastically after 3 months and there may be a need to consider cellular or mixed variant of CMN or even an alternate diagnosis of WT in them [7]. The infiltrative nature of CMN with its tendency to extend into hilar and perirenal soft tissue excludes partial nephrectomy as a surgical option for these infants [10]. Unlike WT, adjuvant postoperative ChT may be required in few situations in CMN such as incomplete exci-

sion and positive tumor margins (PTMs) and with cellular or mixed histology, particularly in those who are more than 3 months of age [1, 2].

Overall recurrence rate for CMN is 5%, but with cellular histology, it rises to 10–20%. Cellular variant of CMN is associated with even distant metastasis to the lungs and brain and an unacceptably high mortality of 57% in this group of patients [10]. Recurrence usually occurs within 1 year after surgical resection. Recurrence rate increases with invasion of renal sinus and vascular invasion and in stage III tumors. Surgery remains the mainstay of treatment even for recurrent or metastatic disease. Adjuvant ChT with vincristine (VCR) alone or in combination with actinomycin-D (AMD) and cyclophosphamide (CTX) is the usual first-line ChT for recurrent or metastatic disease [10]. It is postulated ETV6 NTRKS gene fusion not only renders them chemosensitive but also provides a possibility of targeted therapy in children with cellular CMN with recurrent or metastatic disease. Targeted therapy with larotrectinib, crizotinib, and entrectinib is under trial and may hold promise in refractory cases of cellular CMN [10].

Overall prognosis of CMN is favorable, but stringent follow-up is mandatory for a minimum of 18 months after surgical excision in all patients with CMN [10]. Event-free survival (EFS) and overall survival (OS) of even cellular CMN is 85% and 90%, respectively.

39.2 Malignant Rhabdoid Tumor of the Kidney

39.2.1 Incidence and Epidemiology

MRTK is a rare but highly aggressive renal neoplasm and accounts for 2% of pediatric renal tumors [11]. Originally, it was thought to represent the monophasic sarcomatoid variant of WT [11]. However, later in 1981, it was identified as a separate entity probably arising from primitive cells involved in the formation of renal medulla [12, 13]. Its frequent association with primary and metastatic central nervous system (CNS) tumors subsequently leads to speculations of its probable neuroectodermal origin [12]. Moreover, it can occur in extrarenal locations including the liver, soft tissues, lung, skin, heart, and brain, suggesting its origin from a non-organ-specific mesenchymal cell. It derives its name from its histological appearance, which resembles rhabdomyosarcoma (RMS), but undoubtedly it is not of myogenic origin and does not show any skeletal muscle markers on immunohistochemistry (IHC). The median age at presentation for MRTK is 11 months (range: 0 to 4.5 years), and it is extremely rare beyond 5 years of age [14, 15]. Age at diagnosis is a significant prognostic factor for survival in children with MRTK; infants have a dismal prognosis as compared to older children.

39.2.2 Clinical Presentation

It often presents as a unilateral abdominal mass with almost equal probability to occur on either side and is bilateral in 4% of patients [13]. Although a definitive diagnosis of MRTK is often made on histopathology, **presence of large renal tumor in a young infant, especially when associated with hematuria, hypercalcemia, and diffuse hematogeneous and lymphatic spread, suggests a diagnosis of MRTK** [13]. Hematuria (both gross and microscopic) is seen more frequently with MRTK as compared to a WT due to its more central origin from the renal medulla leading to early invasion of the renal pelvis. Gross and microscopic hematuria was reported more frequently (59% and 76%, respectively) in children with MRTK as compared to children with WT (18% and 24%, respectively) [13]. Similarly, fever was noted in 45% of children with MRTK as compared with 22% with WT. While 71% of patients with MRTK had more advanced stage at presentation (stage III: 44%; stage IV: 27%), 67% of children with WT had stage I (41%) and stage II (26%) disease [13]. Presence of hypercalcemia (with serum calcium of more than 10.5 mg%) is quite characteristic of MRTK and is seen in nearly one-fourth of cases [13]. The association of MRTK with synchronous and metachronous primary and secondary intracranial malignancy

is well-documented. The primary brain tumors tend to occur in midline commonly in the posterior fossa and include medulloblastoma, ependymoma, primitive neuroectodermal tumors, and cerebellar and brainstem astrocytoma [11]. They may also extend into the inferior vena cava and renal vein.

39.2.3 Radiological Diagnosis

Although imaging findings of MRTK are indistinguishable from WT, there are some telltale signs that may provide subtle hints to diagnose RTK (Fig. 39.3). USG usually shows a large lobulated mass with heterogeneous echogenicity, which may have intravascular extension into the renal vein or inferior vena cava (IVC). **Presence of a large (5–12 cm), lobular, central, intrarenal mass, with ill-defined margins (57%) in a young child, extending beyond the renal medulla into the renal sinus and renal pelvis, is quite characteristic of MRTK** [11, 14]. Another classical radiological sign of MRTK is perilobular calcification that is noted in 45% of cases as compared to egg shell calcification seen in less than 10% of children with WT. [12, 14] Agrons et al. found peripheral crescent of fluid attenuation, representing subcapsular hematoma or tumor necrosis, in 71% of children with MRTK. However, this is not pathognomonic of MRTK as it is seen in 12% of other more common pediatric renal neoplasms [11].

39.2.4 Pathology

Grossly, the tumors are unencapsulated and often have extensive areas of hemorrhage and necrosis. Both primary and metastatic MRTK comprise of sheets of monomorphic tumor cells with abundant eosinophilic cytoplasm and large eccentric nuclei with prominent **owl eye** nucleoli and have pathognomonic **intracytoplasmic pink inclusions adjacent to areas surrounding necrosis** (Fig. 39.4). On ultrastructural examination, it shows similarity to RMS with plenty of eosinophilic cytoplasm containing filamentous inclusions, which shows positive immunoreactivity to vimentin and focal cytokeratin, but not of actin or myosin as seen in tumors of myogenic origin [12]. Although no IHC staining is considered pathognomonic of MRTK, genetic abnormalities leading to inactivation of the **Hsnf5/INI-1tumor suppressor gene on chromosome 22** is considered quite characteristic of both renal and extrarenal rhabdoid tumors [8]. It is noteworthy that for all other renal tumors except MRTK, IHC staining for integrase interactor 1 **(INI-1)** shows nuclear positivity [8].

39.2.5 Management

RN and LN sampling were combined with alternating cycles of carboplatin and etoposide with cyclophosphamide for 24 weeks and radiotherapy (XRT) for all stages of MRTK earlier [16].

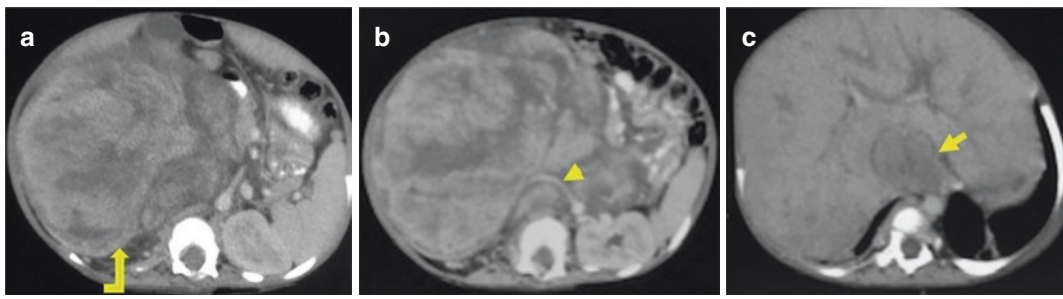

Fig. 39.3 Fifteen-month-old female child presented with right-sided renal mass and hematuria since 1 year of age. CECT scan axial images (**a**, **b**) show a large lobulated solid well-circumscribed mass replacing the right kidney. Mass shows marked necrosis and is involving the renal hilum, with extension into the right renal vein and IVC. The right renal artery is displaced anteriorly (arrowhead) by the dilated IVC filled with tumor thrombus. (**c**) Large suprahepatic IVC thrombus (arrow) is seen

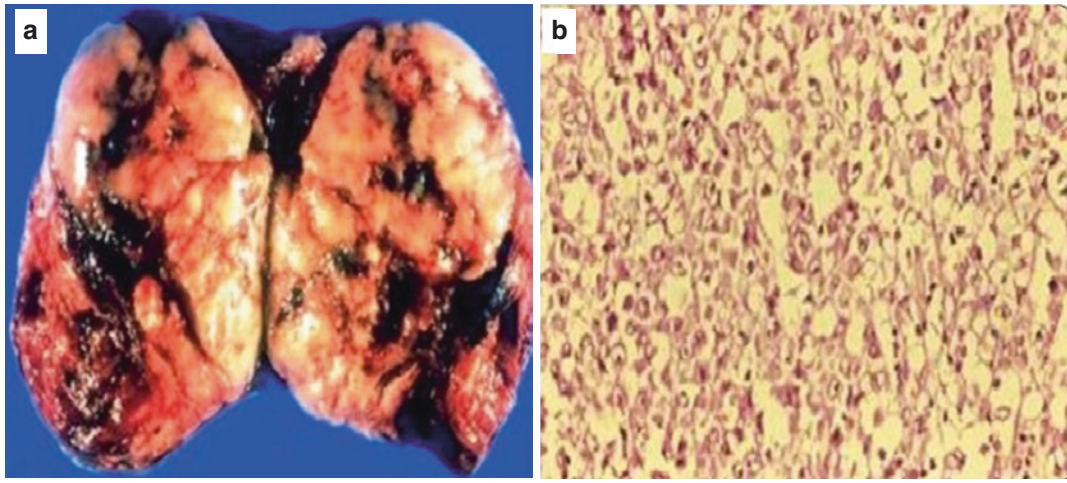

Fig. 39.4 (**a**) Gross specimen of a child with RTK. Cut surface shows large areas of necrosis and hemorrhage. (**b**) Light microscopy (4×) showing sheets of monotonous cells with prominent nucleoli

Table 39.1 Dosage and duration of UH-1 and UH-2

Drugs	Cumulative doses mg/m^2 UH-1	Cumulative doses mg/m^2 UH-2
Cyclophosphamide	14,800	14,800
Carboplatin	3000	3000
Etoposide	2000	2000
Doxorubicin	225	225
Vincristine	**22.5**	**31.5**
Irinotecan	**0**	**60**
Duration (weeks)	**28**	**40**

The current Children's Oncology Group (COG) protocol, ARENO321, recommends intensive ChT with alternating cycles of CTX, carboplatin (CARB), and etoposide (ETOP) alternating with VCR, DOX, and CTX and higher doses of XRT to flanks (20 Gy) for MRTK [17]. In the current COG study trial, children with stage I and II MRTK are treated by revised UH-1 ChT protocol for 28 weeks, while those with stage III and IV would receive vincristine and irinotecan "window" followed by revised UH-2 ChT for 40 weeks [17]. The salient differences between revised UH-1 and UH-2 are as shown in Table 39.1.

MRTK carried a dismal prognosis with overall mortality of 80% at 12–18 months follow-up [16]. An OS of 23.2% at 4-year follow-up was noted in NWTS trial [16]. Moreover, infants less than 6 months of age had worse prognosis than those who were older than 2 years at presentation with 4-year survival being 8.8% and 41.6%, respectively [16]. Even after complete tumor resection with tumor-free margin and negative lymph node (LN) status, only 50% survived with conventional ChT used for WT. [16] Results of current COG protocol, ARENO321, are still awaited.

39.3 Clear-Cell Sarcoma of the Kidney

39.3.1 Incidence and Epidemiology

CSSK is the second most common primary pediatric renal malignancy after WT, accounting for 5% of all renal tumors in childhood [18, 19]. Its diverse histological patterns often

mimic other renal tumors and result in misdiagnosis in 27–50% of patients with CCSK [18, 20]. Historically, it was considered as an unfavorable variant of WT till 1970, when it was identified as a distinct clinicopathological entity [19]. Alike WT, it typically presents in 2–3 years of age with mean age at presentation being 36 months [19, 20]. However**, its more aggressive biological behavior, tendency for late relapses and recurrences, propensity for skeletal and brain metastasis, absence of familial associations and syndromes, and absence of associated nephroblastomatosis are quite unlike WT** [21]. While Marsden et al. termed it as the "bone metastasizing tumor of childhood," Beckwith and Palmer called it "clear-cell sarcoma" based on its histological appearance [19]. Although occasional reports of in utero presentation, in adults as late as 58 years are available, it is extremely rare in first 6 months of life and in adults [19]. Unlike WT, it shows male preponderance of 2:1 and barely occurs bilaterally with only handful of case reports [22].

39.3.2 Clinical Presentation

It is similar to WT with abdominal mass, distension, and hematuria. Other constitutional symptoms like fever, vomiting, anorexia, bony pain, and hypertension can also occur, warranting differentiation from neuroblastoma (NB). CCSK mostly presents with locally advanced disease (stage II: 33%; stage III: 34%), with stage I (27%), stage IV (6%), and bilateral tumors (stage V) being extremely uncommon with few anecdotal reports [18]. LNs are the most frequent site of metastases (51%), followed by bone (13%), lung (10%), and liver (9%). Unlike WT, vascular extension into the renal vein and IVC is unknown in CCSK with only few case reports [23]. It is worthwhile to know that not all renal tumors with vascular thrombosis are WT and an alternate histological diagnosis like CCSK needs to be considered if the tumor and thrombus are not responding to conventional ChT [23]. Vascular thrombus in CCSK is often nonadherent to vessel wall and can be excised [23]. However, sometimes it may require extensive procedures even amounting to cardiopulmonary bypass (CPB) [23]. **Other pathognomonic characteristic of CCSK is its propensity for late relapses in 20–30% of children with CCSK, often occurring at a median time interval of 24 months (range: 5 months to 8 years after completion of treatment**) [18, 19, 21].

Although 30% of relapses occur more than 3 years after diagnosis, it may even occur as late as 10 years, emphasizing the need for long-term follow-up. Conventionally, the bone was the most common site of relapse in CCSK, followed by the lungs, brain, retroperitoneum, and liver. However, with the recent use of intensive ChT protocols, the brain being a safe sanctuary for tumor cells has surpassed the bone as the most common site of CCSK recurrences. Thus, recent recommendations suggest inclusion of drugs with CNS penetration such as ifosfamide in the ChT protocols and emphasize the need for regular brain imaging during follow-up visits [18]. Thus, CCSK is often a diagnosis of exclusion, and its possibility should be entertained if the intrarenal mass is not responding to conventional ChT of Wilms' tumor (WT) [24].

39.3.3 Radiological Diagnosis

Imaging features of CCSK are common to other renal neoplasm. USG usually shows inhomogeneous pattern of soft tissue echoes and well-defined echo-free areas corresponding to tumor necrosis. On CECT, tumors are usually unilateral having well-demarcated soft tissue component with interspersed necrotic areas and calcification in 25% of cases (Fig. 39.5). Clinically, apparent bone and brain metastasis may be absent at the time of initial diagnosis. However, bone scans and brain imaging form an integral part of initial evaluation and follow-up of children with CCSK [25].

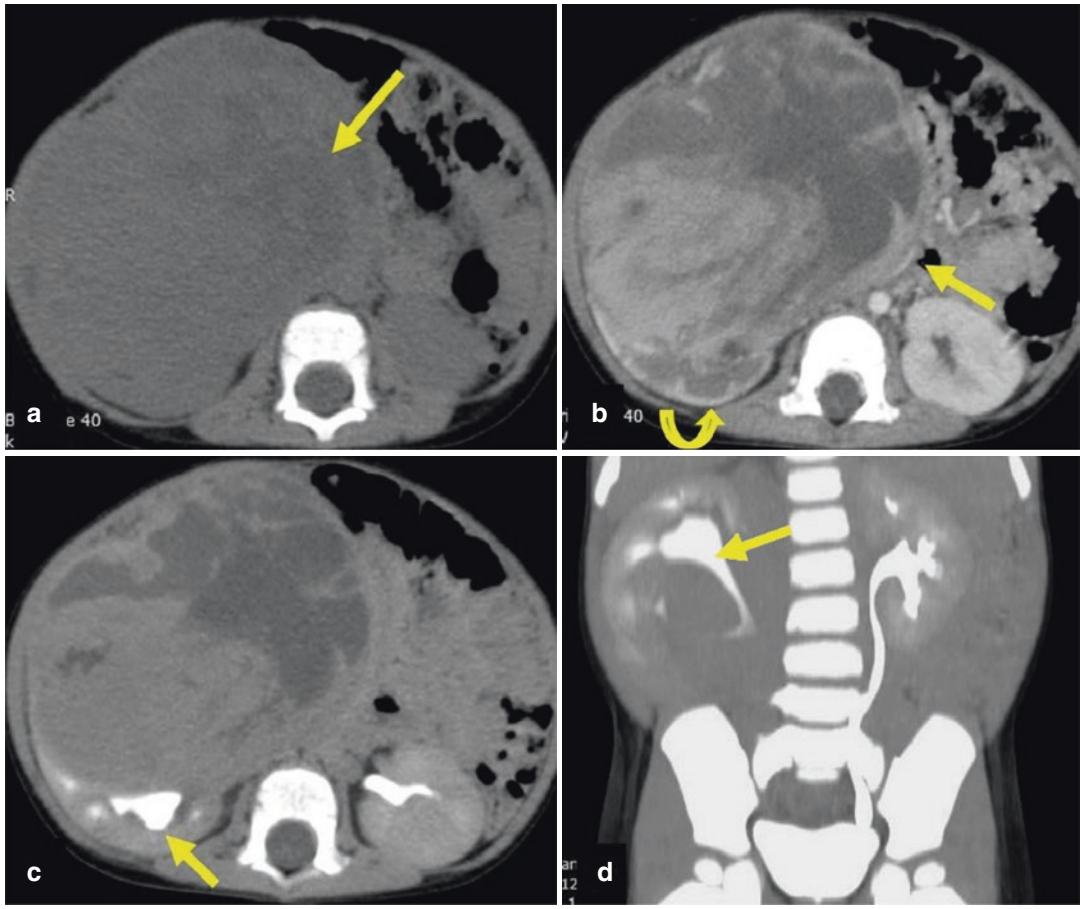

Fig. 39.5 CT scan of a 1.5-year-old child clinically suspected of WT. (**a**) NCCT axial image shows a large solid mass in the right renal fossa with necrotic areas (arrow), with no calcification or hemorrhage. (**b**) CECT axial image reveals a large, heterogeneously enhancing mass arising from lower pole of the right kidney replacing most of the kidney and causing leftward displacement of IVC (arrow) and bowel loops. Mass shows extensive necrosis and enhances less than adjacent renal tissue (elbow arrow). Delayed scans (**c**) axial and (**d**) 3D coronal reformatted image show upward displacement of renal the pelvis (arrow). Histopathology was consistent with CSSK. Bone scan of the child done postsurgery was normal

39.3.4 Pathology

Histopathological diagnosis of CCSK is quite challenging due to diverse histological patterns and mimics other pediatric renal neoplasms. **The useful dictum is that if multiple patterns coexist within the same renal tumor, then one should entertain the diagnosis of CCSK** [21]. On gross examination, it is usually a large, unicentric, well-circumscribed tumor with well-defined margins (Fig. 39.6). On cut section, it has soft tan-gray color and produces abundant mucinous material that imparts a glistening look to it. Cyst, hemorrhage, and necrosis may be present. Errors in histological diagnosis do occur in 27–50% of children with CCSK due to diverse histological patterns [18]. Different patterns may coexist within the same tumor in different proportions. The most common pattern found in CCSK is the classic pattern which may occur diffusely or at least focally in 90% of tumors. It comprises of sheets of cells that are separated by delicate fibrovascular septa with pathognomonic **chicken wire appearance**. The cells contain clear cytoplasm, monotonous round "**Orphan Annie"** nuclei with fine chromatin and indistinct nucleoli (Fig. 39.6).

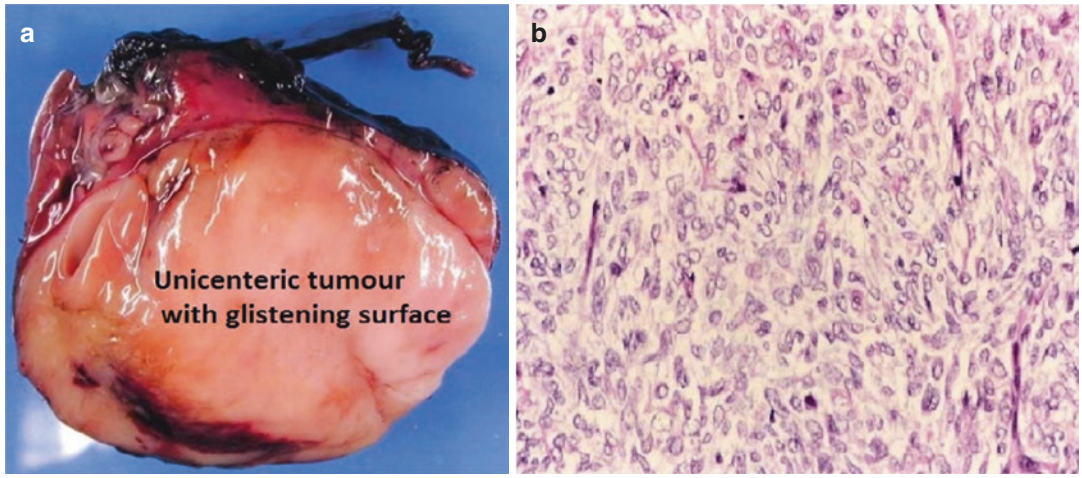

Fig. 39.6 (**a**) Gross specimen of CCSK showing unicentric, well-circumscribed mass with well-defined edges and glistening cut surface. (**b**) Photomicrograph of classical pattern of CCSK showing sheets of cells with "Orphan Annie" nuclei with intervening arborizing septa

The classic pattern closely mimics the blastemal component of WT. Entrapped renal tubules may be visible at the periphery of the tumor creating diagnostic confusion with epithelial component of WT. The interspersed matrix is composed of mucopolysaccharides which contribute to clear-cell appearance [18–21].

Alterations in the cord cell and septal morphology result in a variety of histological patterns in CCSK, namely, myxoid, sclerosing, cellular, epithelioid, spindle, palisading, and anaplastic. Myxoid pattern is observed in 50% of specimens. It is characterized by presence of extracellular myxoid material which comprises of hyaluronic acid and is stained by Alcian blue stain. Sclerosing pattern is seen in one-third of cases (35%) and has acellular deposition of collagen that may get hyalinized to give it an osteoid appearance. Cellular pattern (26%) mimics closely primitive neuroectodermal renal tumors and blastemal component of WT. Palisading and spindle morphology may be confused with cellular variant of CMN. However, CCSK lacks characteristic t(12;15) translocation of CMN [18–21]. FNAC may be needed in children with advanced CCSK who require preoperative ChT. **Varying proportion of cells with clear cytoplasm, septa with arborizing vasculature, and relevant IHC staining may clinch the diagnosis of CCSK** [19].

Recent advances in IHC and molecular genetics had helped immensely in making the precise diagnosis of CCSK. It shows positivity to nonspecific IHC markers like nerve growth factor, vimentin, and Cyclin D1 and is conspicuously negative for WT1, desmin, and cytokeratin. Recently, diffuse strong nuclear positivity **with BCL-6 coreceptor antibody (BCOR)** had provided a sensitive and specific marker for diagnosing CCSK [21]. The two specific genetic events associated with CCSK and of diagnostic significance are recurrent BCOR intrarenal tandem duplication (seen in 70% of CCSK patients) and chromosomal translocation t (10;17) (q22;p13) resulting in fusion of **YWHAE gene with NUTM2B or NUTM2E gene** (observed in 12% of CCSK patients) [21]. Triphasic WT is usually not confused with CCSK. Diagnostic dilemmas arising between blastemal component of WT and CCSK are resorted by strong nuclear positivity of Cyclin D1 in CCSK and its negativity in WT. Similarly, WT1 is positive in WT and negative in CCSK [18, 21].

39.3.5 Management

Over the years, the management of CCSK has evolved and is currently based on risk stratification of the disease. Some landmark recommendations, over the past few decades, that have improved the survival in CCSK include [19, 20]:

(a) Addition of DOX to VCR and AMD.
(b) Addition of CTX to the adjuvant ChT protocol.
(c) Acknowledging brain relapses in CCSK and considering drugs with CNS penetration like ifosfamide (IFO).
(d) Risk stratification of CCSK with treatment of stage I disease with three drugs (VCR, AMD, and CTX) and no postoperative flank XRT in comparison with four-drug protocol (VCR, AMD, CTX, and ETOP) for stage II–IV disease with XRT.

39.3.6 NWTS/COG Protocol

Prior to NWTS-5 (1995–2002), children with CCSK were treated similar to WT. NWTS-5 advocated that all patients diagnosed with CCSK irrespective of the stage undergo primary surgery (radical nephroureterectomy), if possible safely, followed by postoperative ChT (Regimen I) and XRT (10.8 Gy) for 24 weeks [20]. Regimen I included vincristine, doxorubicin, and cyclophosphamide alternating with cyclophosphamide and etoposide. Five-year EFS and OS of 79% and 89%, respectively, were reported with relapse rate of 19% [20]. **AREN0321** (2006–2013) is the current COG protocol recommended for all high-risk pediatric renal tumors including CCSK. Primary surgery (RN with LN sampling) may be done in resectable tumors; otherwise, neoadjuvant ChT may be given for 6 weeks [20]. Postoperative adjuvant ChT for stage I–III is ETOP-CTX-VCR-DOX (ECVD); for stage IV, CARB is added to the ECVD (ECVDC). Postoperative XRT (10.8 Gy) is administered in stage II–IV. Results of this trial are still awaited [20].

39.3.7 SIOP Protocol

During the period 2001–2016, preoperative ChT, AMD, and VCR for stages I to III and AMD, VCR, and DOX (AVD) for stage IV were recommended for 4–8 weeks. This was followed by surgery and postoperative adjuvant ChT for 36 weeks (AVD for stage I and DOX, ETOP, CTX, and CARB for stages II–IV). XRT 25.2 Gy was administered postoperatively in case of stage II and III. Five-year EFS and OS of 78% and 86%, respectively, and relapse rate of 15% were reported [20]. The recently recommended **Umbrella protocol i**s similar to the previous SIOP protocol as far as preoperative ChT is concerned. However, all patients irrespective of the stage receive ETOP, CARB, IFO, CTX, and DOX **(ECICD)** along with 10.8 Gy flank XRT in stage II–III [20]. Results of this trial are also still awaited [20].

39.4 Renal Cell Carcinoma

39.4.1 Incidence and Epidemiology

Pediatric renal cell carcinoma (RCC) poses a unique therapeutic challenge not only due to its rarity but also because of its limited understanding. Majority of inferences on pediatric RCC are drawn either based on small case series or by extrapolating data from adult RCC guidelines. The natural history of pediatric RCC clearly shows its distinct clinical and biological behavior, which is indeed different from adult RCC. It constitutes 2–5% of all pediatric renal neoplasms, and overall only 0.5–2% of all RCC occurs in less than 21 years of age [8, 22, 26]. Mean age at presentation in most series varies from 9 to 15 years (median: 9 years) with no sex predilection [8, 22, 26]. Probability of having a RCC increases with age, and in the second decade of life, WT and RCC have equal chance of occurrence [26, 27]. **RCC should be suspected in a child with renal tumor who presents beyond 5 years of age** [8]. It appears to arise from the epithelium of proximal renal tubules. Furthermore, RCC can

occur as a second malignancy in children after treatment of NB, acute lymphoblastic leukemia, supratentorial PNET, acute non-myelocytic leukemia, and cardiac leiomyosarcoma and after exposure to CTX and topoisomerase inhibitors [28]. Exposure to asbestos, tanning, smoking, obesity, and analgesic overuse are known predisposing factors for adult RCC; however, their association with pediatric RCC is not well-established [27].

39.4.2 Clinical Presentation

Unlike adult RCC, which often presents with metastatic disease, or with paraneoplastic phenomenon (like fever, hypertension, weight loss, hepatic dysfunction, polycythaemia, gynecomastia, and hypercalcemia), pediatric RCC usually presents with one or the other symptoms or signs related to primary tumor (mass, flank or abdominal pain, and hematuria) [8, 27]. Paraneoplastic phenomenon is infrequent in children (5–6%), except an occasional report where it was noted in 31% [27]. Metastasis at presentation to the lung, bone, liver, and brain is identified in 20% of children with RCC [8]. The classic **Grawitz triad** of pain, lump, and hematuria is evident in only 9% of children with RCC [29]. Incidental diagnosis on renal imaging occurs in 50–66% of adult RCC patients, while it is 12–25% in pediatric RCC [8, 30]. Bilateral presentations are rare and are associated with underlying conditions like von Hippel-Lindau disease and tuberous sclerosis [22].

39.4.3 Radiological Diagnosis

RCC presents as solid intrarenal mass with no pathognomonic imaging findings to differentiate it from WT. However, **it is more vascularized and calcification is more common in RCC as compared to WT (25% versus 9%)** (Fig. 39.7) [8]. LN metastases are common and occur even with small primary tumors (<7 cm) [26]. Sensitivity of imaging findings to detect LN metastases in RCC remains low at 57.1%, and imaging alone is not sufficient to rule out nodal involvement in pediatric RCC [26]. It is noteworthy that nearly one-third of the LNs more than 1 cm in size on imaging had positive disease on pathology [26]. Therefore, irrespective of imaging findings, routine LN sampling at surgery is mandatory in pediatric RCC to avoid incomplete staging and better disease control [26].

39.4.4 Pathology

On gross pathological examination, pediatric RCC are smaller in size and have golden yellow appearance as compared with fleshy appearance in WT [8]. Traditionally, RCC exhibits various histological subtypes, namely, conventional or clear-cell carcinoma and papillary. Adult RCC usually have clear-cell, non-papillary histology with translocation or terminal deletion of chromosome 3 at 3p13 [28]. This cytogenetic abnormality at 3p is seldom observed in pediatric RCC, who have translocation involving X chromosome at Xp 11.2 resulting in fusion of TFE3 gene and less commonly TFEB gene at 6p21 to a variety of targets in 24–70% of patients, often labeled as **translocation morphology** [28]. Fusion targets of TFE3 include PRCC, ASPL, PSF, and CLTC [28]. Children with translocation morphology have indolent disease with good outcome and may be amenable to targeted therapy by tyrosine kinase inhibitor in the near future [28, 30]. Translocation morphology is present in 46.7% of pediatric RCC, followed by papillary (16.7%) (Fig. 39.8) [26].

The salient clinical, imaging, and biological differences of pediatric RCC from WT and adult RCC are as shown in Table 39.2 [27, 28].

39.4.5 Management

Surgery is the mainstay of treatment and results in cure if tumor is localized and completely resected. They are ChT and XRT resistant. Most of the children with localized RCC undergo radical nephrectomy with LN sampling [26]. Although debate on LN dissection in RCC con-

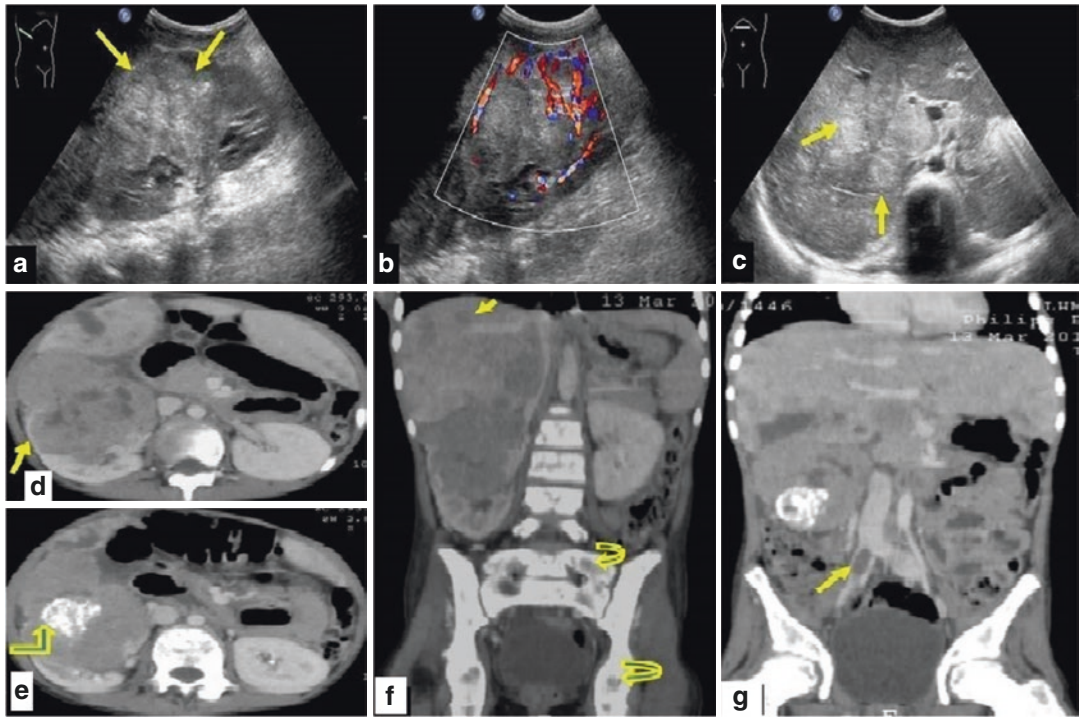

Fig. 39.7 RCC in a 12-year-old male with right flank mass since 5 months. (**a**, **b**) USG gray scale and color Doppler images show a large heterogeneous, hyperechoic lobulated mass with peripheral and internal vascularity arising from interpolar region of the right kidney. (**c**) USG image of the liver shows multiple variable size hyperechoic metastases (arrows). CECT (**d**, **e**) axial images show heterogeneously enhancing mass arising from interpolar region of the right kidney, forming positive beak sign with renal parenchyma (arrow). Mass contains areas of necrosis and coarse, chunky calcification (bent arrow). Coronal multiplanar reformation (MPR) images show (**f**) multiple liver (arrow) and skeletal metastases (curved arrows). (**g**) Non-enhancing hypodense thrombus in the right common iliac vein (arrow)

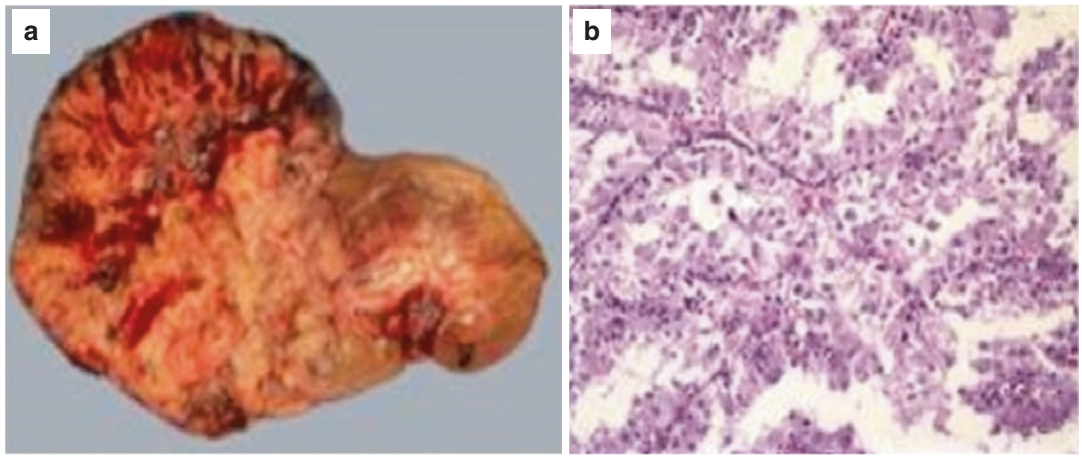

Fig. 39.8 (**a**) Gross morphology of a case of translocation Xp11.2 RCC. (**b**) Light microscopy (4×) showing papillary structure with fibrovascular stalk. Cells have abundant cytoplasm with centrally placed nuclei

Table 39.2 Clinical, imaging, and biological differences of adult RCC, pediatric RCC, and WT

Features	Adult RCC	Pediatric RCC	WT
Mean age (years)	50–60	9–15	2–3
Sex (M:F)	2:1	1:1	1:1
Presentation			
Asymptomatic (%)	50–66	12–36	–
Abdominal lump (%)	32	9–64	90
Hematuria (%)	65	30–50	10
Paraneoplastic syndrome	Frequent	5–6%	Rare
Hypertension (%)	20	5	20
Bilateral (%)	1	10	5
Calcification on imaging (%)	5	24	5–10
Histology	Mixed, clear cell	Translocation, papillary	Triphasic, biphasic, monophasic
IHC	3p translocation	TEF3	WT1, WT2

tinues, recent evidence supports mandatory LN sampling in all pediatric RCC [26]. For left-sided RCC, hilar, paraaortic, and ipsilateral common iliac nodes and for right-sided RCC, hilar, inter aortocaval, retrocaval, and ipsilateral common iliac nodes should be sampled [28]. Nephron sparing surgery (NSS) was resorted to in 15% of pediatric RCC with lower tumor stage [26]. However, their role is not well-established in the management of pediatric RCC. For advanced metastatic disease with unresectable RCC, the management options are limited. Immunotherapy with interferon and interleukin (IL_2), tyrosine kinase inhibitors like sunitinib, rapamycin, and platinum-based ChT may be tried in these children [22]. The 5-year OS of pediatric RCC is better than adult RCC (60% and 40%, respectively) [27]. Pediatric RCC with stage I–III have 100% and stage IV have less than 10% 5-year survival [27].

39.5 Intrarenal Neuroblastoma

Intrarenal neuroblastoma (IRNB) are rare, aggressive renal neoplasm, which may mimic clinical and imaging features of WT. Their biological behavior and prognosis is however very different from WT. They usually arise from adrenal nests located within the renal tissue or from the intrarenal sympathetic ganglia and need to be differentiated from secondary intrarenal invasion by a malignant suprarenal mass [31, 32]. Unlike WT, they occur in younger age group (11–40 months) with occasional reports in older children [32]. They are usually associated with constitutional symptoms like fever, weight loss, anemia, and bony pains. The renal mass is usually indistinguishable from that of WT, though it often crosses midline. **An important clinical clue to their diagnosis is the presence of associated hypertension in nearly 66–100% of children with IRNB as compared to 20% in WT and 27% in extrarenal NB** [33]. Catecholamine release from the tumor and compression of renal artery by the tumor with secondary renin angiotensin system activation lead to hypertension. Majority of them (80%) may present with metastases to the bone, bone marrow, and lymph nodes [32, 33]. Although their imaging findings mimic WT, presence of vascular encasement, massive retroperitoneal lymphadenopathy, and intrarenal speckled, multifocal, ringlike calcification is seen more frequently in IRNB (40–67%) as compared to WT (13%) [32–34]. Thus, the possibility of IRNB should always be kept in a child presenting with a renal mass presenting with hypertension, multifocal intrarenal calcification, and evidence of vascular encasement on imaging (Fig. 39.9). Assessment of urinary catecholamine levels, MIBG scans, and bone marrow aspiration may clinch the diagnosis in such patients. Management consists of cisplatin-, adriamycin-, and cyclophosphamide-based ChT with RN with adrenalectomy.

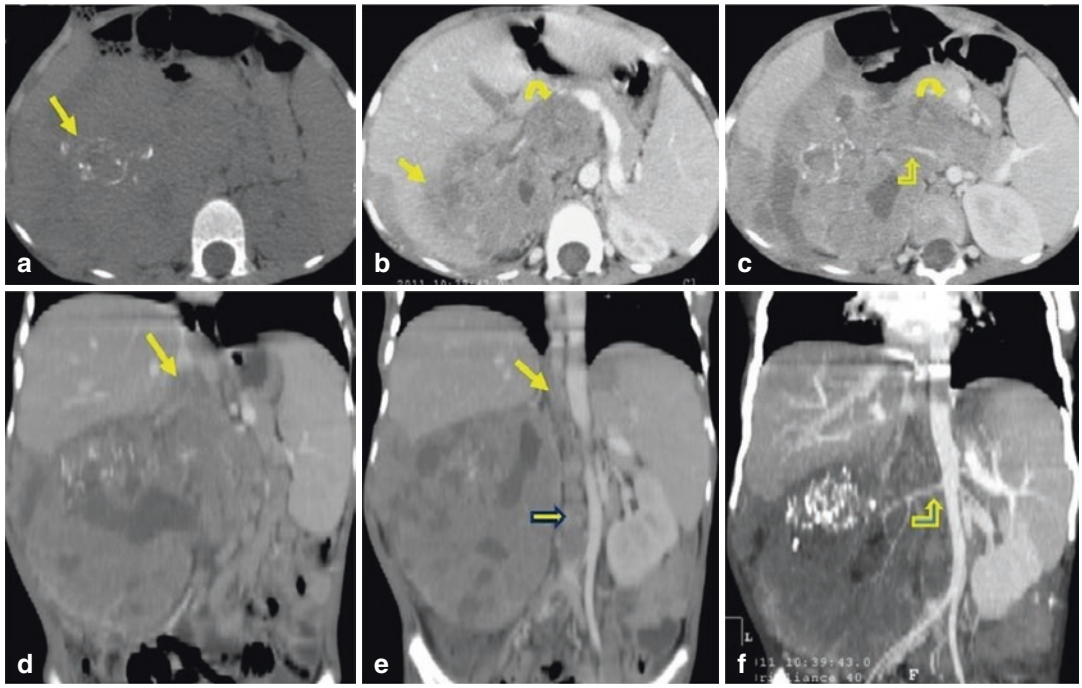

Fig. 39.9 IRNB in a 6-year-old male child with abdominal distension and malaise. CT scan axial images NCCT (**a**) show a mass in the right renal fossa with calcification (arrow); CECT (**b**, **c**) show right renal mass with calcification, adjacent liver infiltration (arrow), encasement of the right renal artery (bent arrow), thrombosis of the right renal vein, and IVC (curved arrow) with extension into the left renal vein. Coronal MPR images (**d**, **e**) show malignant tumor thrombus in IVC (arrow) and retroperitoneal lymphadenopathy (block arrow). Coronal maximum intensity projection (MIP) (**f**) shows right renal artery encasement (bent arrow) by the mass. Based on imaging features, diagnosis of WT was suggested. However, histopathology showed small round cells in a fibrillary background suggestive of NB. Urinary vanillylmandelic acid (VMA) was raised

39.6 Primitive Neuroectodermal Tumor (PNET) or Renal Ewing's Tumor

They arise from neural crest cells and neuroectoderm and are usually located in the paraspinal area and ribs and rarely from the skin, soft tissues, kidney, and retroperitoneum [35]. Unlike osseous Ewing's sarcoma, which occurs at a median age of 15 years, renal Ewing's tumor occurs in adolescents or young adults [35]. **It is primarily a histological diagnosis** with nonspecific clinical presentation. One-third of the patients have metastasis and vascular thrombus at presentation [36]. It is composed of primitive round blue cells with high nuclear cytoplasmic ratio and **perivascular pseudo-rosette formation** (Fig. 39.10). IHC staining and molecular studies play a key role in establishing the accurate diagnosis. A panel of IHC markers including CD99, NSE, WT1, LCA, FL-1, cytokeratin, desmin, myogen, and chromogranin are usually required to ensure precise diagnosis [37]. **While renal PNET are positive for CD99, NSE, and FL-1, they are negative for the rest of the IHC markers.** They also exhibit translocation t (11;22) (q24; q12) with fusion of EWS-FIL-6 gene [37]. They require multimodal therapy including induction ChT with VCR, IFO, DOX, and ETOP **(VIDE)** for six courses followed by local control by RN and consolidation ChT with VCR, AMD, and IFO (VAI) for standard-risk patients and VAI plus high dose busulfan and melphalan for high-risk patients [37]. Local XRT

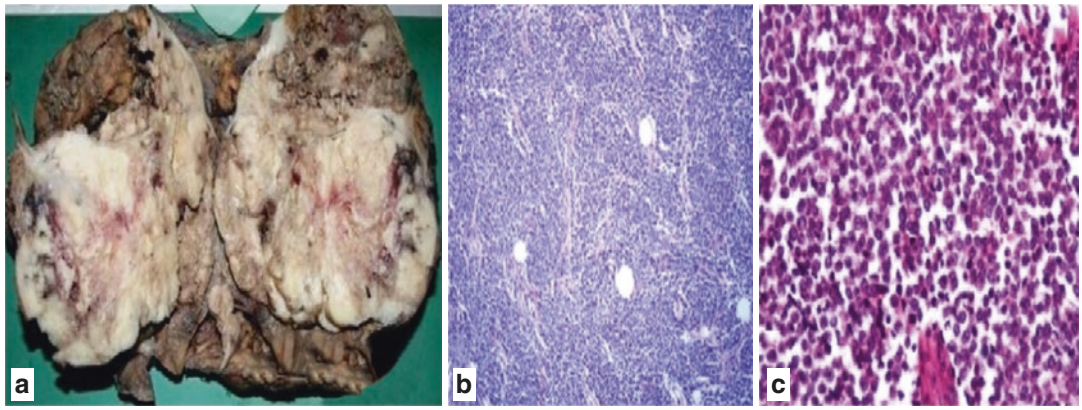

Fig. 39.10 (**a**) Gross examination showing a friable, grayish white, lobulated mass (15 × 13 × 7 cm), with multiple foci of hemorrhage and necrosis replacing most of the kidney. (**b**) Tumor composed of monotonous sheets of round cells divided by fibrovascular septae. (**c**) Focal areas of pseudo-rosette

may be administered for incomplete resection or with PTMs. Five-year OS is dismal (45–55%) [37].

39.7 Renal Lymphoma

Renal involvement in lymphoma usually occurs due to systemic spread of non-Hodgkin's lymphoma (Burkitt's subtype) manifesting as multiple or solitary metastatic nodules or infiltrates in kidney [38]. Primary renal lymphoma (PRL) is extremely rare and is thought to arise from mucosa associated lymphoid tissue [39]. Specific diagnostic criteria laid down for diagnosing PRL emphasize on absence of other nodal or extranodal involvement. PRL usually presents with renal enlargement which may be bilateral in 10–20% of patients [39]. It may even present with renal failure and hypertension [38]. Multiple bilateral renal masses on imaging as seen in renal lymphoma are also noted in WT, cystic renal tumors, angiomyofibroma, metastatic disease, acute myeloid leukemia, and fungal infection [39]. **Although renal lymphoma does not have any characteristic imaging finding, retroperitoneal lymphadenopathy with involvement of the liver and spleen may suggest its diagnosis**. They are classically described as homogeneous masses, but they may have heterogeneous attenuation as shown in Fig. 39.11.

Renal failure in lymphoma is multifactorial and can be due to vascular or ureteric obstruction by the engulfing renal mass or by enlarged retroperitoneal LNs and rarely due to tumor associated glomerulopathy [38]. Renal failure is often aggravated by induction ChT with rapid breakdown of tumor cells leading to hyperuricemia (>8 mg %), hyperphosphatemia (≥6.5 mg%), hyperkalemia (>6 mg%), uremia, and hypocalcemia (<7 mg%) [40]. These metabolic derangements, collectively termed as **tumor lysis syndrome**, occur due to massive destruction of tumor cells with release of nucleic acids, electrolytes, and cytokines in systemic circulation. It poses a medical emergency with risk of cardiac arrhythmia, renal failure, seizures, coma, and sudden death [40]. Management usually involves prophylactic intravenous hydration, electrolyte correction, use of hypouricemic agents like allopurinol and rasburicase, and dialysis if required [40]. Management of renal lymphoma is usually medical with use of drugs like VCR, prednisolone, CTX, L-asparaginase, and cytosine arabinoside as in NHL [38].

39.8 Angiomyolipoma

Angiomyolipoma (AML) is an extremely rare benign mesenchymal renal tumor constituting less than 0.3% of all renal tumors [41]. It was

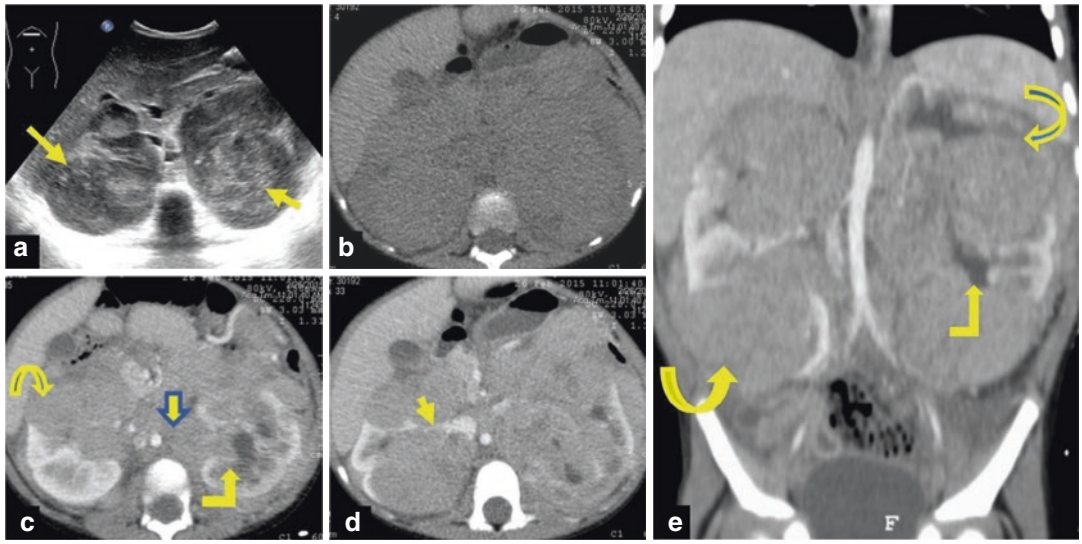

Fig. 39.11 Bilateral primary renal Burkitt's lymphoma in a 4-year-old male child with on and off fever, abdominal pain, and distension. USG abdomen transverse view (**a**) shows bilateral enlarged kidneys with multiple hypoechoic and hyperechoic lesions and loss of corticomedullary differentiation. Axial NCCT (**b**) and CECT (**c**, **d**, **e**) scan images show multiple large ill-defined round to oval heterogeneously enhancing lesions (curved arrows) in bilateral renal parenchyma distorting the renal contour, encasing renal vessels (arrow), splaying and encasement renal pelvis, and calyces (bent arrow). Enlarged preaortic and paraaortic LNs are seen (block arrow)

initially considered to be hamartoma consisting of mature adipose tissue, dysmorphic blood vessels, and smooth muscles; later, however, it was evident that it arises from perivascular epithelioid cells and was designated as PECOMA [41, 42]. Majority of AML (80%) occur sporadically in adult females, without associated genetic syndromes, and are diagnosed incidentally on imaging studies [41, 42]. However, remaining 20% of them have associated tuberous sclerosis (TSC) or lymphangioleiomyomatosis (LAM). TSC is an autosomal dominant disease characterized by subependymal nodules and astrocytoma manifesting as epilepsy, neurocognitive impairment, and autism and may be associated with hypomelanotic macular skin lesions, facial angiofibroma, and ungal fibroma [41]. LAM is a rare condition where there is smooth muscle infiltration into the small airways and alveoli leading to degenerative changes and respiratory failure [42]. Unlike sporadic AML, which are usually unilateral, those with TSC occur at early age, within the first decade of life, and are often large, multifocal, and bilateral [41, 42]. **Therefore, in all newly diagnosed cases of pediatric AML, it is mandatory to have a formal work-up for TSC, and genetic counseling is advisable**. Surprisingly, however, there are numerous reports of non-TSC, sporadic AML in children as young as 13 months of age presenting as unilateral tender, renal masses associated with a history of trivial trauma, acute flank pain, hematuria, and hypertension being often mistaken as WT or RCC [43, 44]. Retroperitoneal hematoma (**Wunderlich syndrome**) and hemorrhagic shock due to tumor rupture are some of the other rare life-threatening presentations of AML [42].

The pathognomonic distinguishing feature of AML from other renal neoplasms is the presence of fat in the lesion as shown in Fig. 39.12 [41–44]. Tissue attenuation values of <−10 Hounsfield unit (HU) on NCCT are suggestive of fat [42]. A subset of **fat-poor** or **minimal-fat AML** (4–5%) pose a diagnostic dilemma and need to be differentiated from RCC [44]. Although presence of peritumoral collateral blood vessels, calcification, and claw-sign are suggestive of RCC, but in equivocal cases, further clarity on diagnosis may be provided by either "chemical shift MRI" or percutaneous biopsy [42, 44]. Histologically,

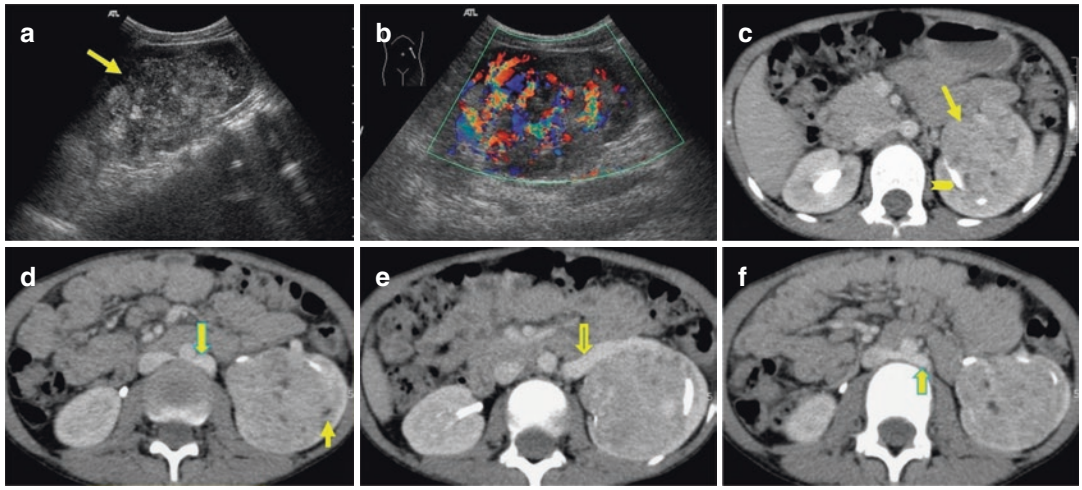

Fig. 39.12 Eight-year-old male child, a known case of tuberous sclerosis, presented with left flank pain and renal mass. USG abdomen (**a**, **b**) shows a heteroechoic left renal mass with non-shadowing echogenic areas (fatty elements) and marked internal vascularity. CECT scan images (**c**) show heterogeneously enhancing left renal mass (arrow) distorting the calyces (arrowhead). (**d**) Mass shows multiple small hypodense foci (small arrow) of fat attenuation and retroaortic course of left renal vein (block arrow). (**e**, **f**) A dilated venous channel (block arrows) was extending from the mass, with retroaortic course, draining into IVC

there are two main types of AML, a classical type and an epithelioid variant; both show **positive immunostaining with HMB 45.** Most of AML are benign and have nominal risk of malignancy with vascular invasion and perirenal extension. LN metastases are reported with large tumors (>7 cm) of epithelioid histology [41, 42].

Management is usually conservative with annual USG surveillance if the tumor is small (<4 cm). Surgical resection may be required in large tumors (>4 cm) especially if they are symptomatic and are prone to rupture as suggested by associated aneurysm >5 mm [41]. Any suspicion of malignancy and inability to have regular follow-up also warrant surgical resection. NSS is advocated in children with low nephrometric scoring or in setting of TSC with bilateral renal involvement [41, 45]. Predominately exophytic masses and polar distribution, at least 7 mm or more away from renal sinus and pelvicalyceal system, have low nephrometric scores and are thus more amenable for partial nephrectomy [45]. Selective arterial embolization (SAE) with gelatin microspheres and absolute alcohol, cryoablation, and radiofrequency ablation (RFA) are some of the novel treatment options for AML with a success rate of 60–89% [41]. In bulky, unresectable tumors and in those with limited renal reserve, mTOR inhibitors like sirolimus, rapamycin, and more recently everolimus have been used with 30% response in 80% of cases [41].

39.9 Renal Cystic Tumors

Renal cystic tumors may present with a wide spectrum of lesions ranging from cystic nephroma and cystic partially differentiated nephroblastoma (CPDN) to cystic variant of WT. Cystic nephroma (CN) is a benign lesion, usually presenting as a multilocular cyst in a child. CN is an uncommon tumor with incidence of <1%. It has bimodal age group of presentation, first peak is seen in <4 years of age with male predominance, and the second peak is seen in adults with female predominance [46, 47]. CPDN, considered as a favorable histology variant of WT, is seen in <2 years of age with male/female ratio of 2:1 [48]. Both CN and CPDN can present with abdominal mass and rarely hematuria [49].

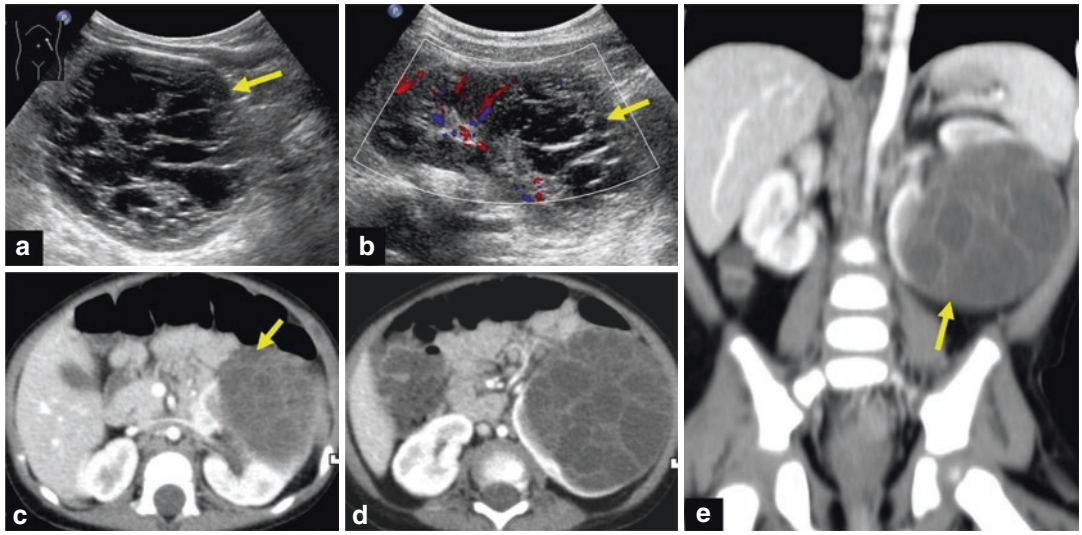

Fig. 39.13 Multilocular CN in a 14-year-girl with nontender left renal lump. USG gray scale and color Doppler images (**a**, **b**) show a well-encapsulated, avascular multilocular cystic mass in the left kidney. CECT images axial (**c**, **d**) and coronal MPR (**e**) show a well-circumscribed multicystic left renal mass with mildly enhancing thin internal septae separating the variable-sized cysts. Mass is arising from interpolar region and lower pole of the left kidney and does not show any septal calcification or enhancing soft tissue

It usually presents as a unilateral, well-encapsulated, solitary multilocular lesion, comprising of multiple noncommunicating cyst of varying sizes (Fig. 39.13); cysts neither communicate with each other nor with pelvis. They may present with flank pain, abdominal mass, urinary tract infection, hypertension, or hematuria. Cysts in multilocular CN are lined by cuboidal epithelium, and the septa are composed of fibrous tissue, in which well-differentiated tubules may be present [50]. The surrounding renal parenchyma may be compressed. While in CPDN, the septa contain blastemal cells with or without epithelial and stromal cell types. Thus, CN and CPDN lack solid component and have similar imaging findings. The distinction between the two is done by histological examination of resected specimen. On the contrary, cystic WT has solid component besides the cyst and has distinct differentiating features on radiology and histology. Both CN and stage I CPDN are managed by nephrectomy alone. Postoperative adjuvant ChT, as in WT, may be needed in higher stages of CPDN [50]. Both CN and CPDN have excellent prognosis with complete surgical excision [46, 48].

39.10 Ossifying Renal Tumor of Infancy

Ossifying renal tumor of infancy is a rare benign tumor arising from papillary region of renal medulla and extends into the collecting system. It occurs in infants with age ranging from 6 days to 14 months. It commonly presents with hematuria and mimics staghorn calculus due to its ossification. On imaging, it usually presents with hydronephrosis with a filling defect in the collecting system [15].

39.11 Metanephric Stromal Tumors

Metanephric neoplasms may sometimes mimic WT. They are rare benign tumors of the kidney and have a wide spectrum ranging from pure epi-

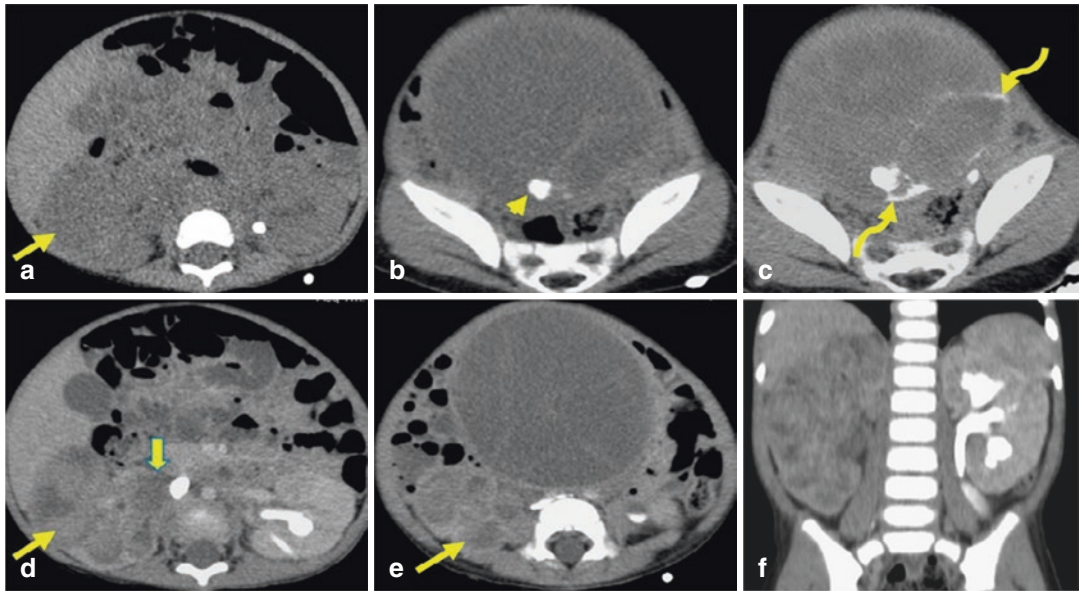

Fig. 39.14 Metanephric stromal tumor in a 2-year-old male child who presented with progressively increasing abdominal distension. NCCT axial images (**a**, **b**) show a hypodense right renal mass (arrow) and a mass with calcification (arrowhead) filling the urinary bladder, causing its distension. CECT axial images. (**c**) Streaks of contrast (curved arrow) seen in urinary bladder, with heterogenous enhancement of the mass. (**d**, **e**) Heterogeneously enhancing mass involving the renal medulla, pelvicalyceal system causing marked parenchymal thinning. Mass is extending into the renal pelvis and ureter (block arrow). Corticomedullary differentiation is preserved in the left kidney. (**f**) Coronal MPR shows mild hydronephrosis and dilated upper ureter secondary to obstruction by the mass. Percutaneous nephrostomy tube is seen in situ in the left renal pelvis

thelial metanephric adenoma to pure stromal variety (metanephric stromal tumors). Metanephric adenofibroma lies in the middle of the spectrum and has both epithelial and stromal components and is easily misdiagnosed as biphasic WT [51]. It is, however, important to differentiate them from WT as surgery is the mainstay of their treatment and they often do not require ChT and XRT [52]. Figure 39.14 displays the imaging findings of metanephric stromal tumor in a patient who had undergone nephroureterectomy.

In conclusion, the most common NWRT in infants include CMN and RTK, whereas RCC predominates in adolescence. CCSK has similar age distribution as WT. Other rare malignant NWRT includes lymphoma, PNET, and IRN. Multilocular CN, CPDN, and AML are some of the common nonmalignant pediatric renal tumors. The diagnosis of NWRT should always be entertained in children less than 6 months and more than 6 years of age, especially when they present with advanced disease and metastasis to the brain, bones, or lungs at a very young age. Imaging features of unencapsulated tumor with retroperitoneal extension to psoas muscle, large extrarenal mass, vascular encasement, large retroperitoneal lymphadenopathy, and abundant calcification in a presumed renal mass should also raise a suspicion of NWRT. As the management and prognosis of these tumors are variable and differ significantly from WT, it is warranted that a histological confirmation should be done at the outset. Use of IHC and molecular genetics has not only reduced the diagnostic uncertainties but has also helped in risk stratification of these tumors. A brief synopsis of NWRT is shown in Table 39.3.

Table 39.3 Synopsis of pediatric NWRT (salient clinical, imaging, and pathological clues to diagnosis)

Tumor	Median age	Diagnostic clues (clinical + imaging)	Pathology/IHC cytogenetics	Treatment/outcomes
CMN	2 months	– Renal lump in neonates, <3 months – Hypercalcemia – Ill-defined edges – Double-rim sign – Intra-tumor pelvis	Classical, cellular, mixed Positive IHC: Vimentin, Actin Trisomy 11 Translocation (t12:15)(p13;q25) ETV6 NTRKS gene fusion	RN with LN sampling Adjuvant treatment: – Incomplete excision – Cellular/mixed histology – Tumor margin positive – Age > 3 months 5-year OS >95%
MRTK	11 months (<4.5 years)	– Large renal lump <1 year – Presentation with advanced disease + metastasis (brain/bone) – Hematuria – Hypercalcemia – Central renal mass, ill-defined edges, into renal sinus+ pelvis – Lobular architecture – Linear calcification	– Monomorphic cells + large nucleus + owl eye nucleoli – Pathognomonic Intracytoplasmic pink Inclusions – INI-1 negative	If resectable- RN+ LN sampling + ChT+ XRT If unresectable—Neoadjuvant ChT for 6 weeks Current COG: Alternating cycle of CARBO, CYCLO, ETOPO (CCE) with VCR, DOX, CYCLO (VDC). (UH-1, UH-2) + XRT in all stages Dismal prognosis
CCSK	36 months	– Aggressive behavior – Presentation as locally advanced disease – Unresponsive to conventional CT of WT – Tendency for skeletal + brain metastases – Late relapse and recurrences – Rarely bilateral – Vascular involvement rare	Multiple patterns in the same tumor – Abundant myxoid material—gives it glistening cut surface – Characteristic Chicken Wire appearance + Orphan Annie nuclei – IHC- cyclin D1+, WT1 negative, BCL6 positive – Translocation of t(10:17)(q22;p13) with fusion of YWHAE gene with NUTM2B	– If resectable, RN+ LN sampling + ChT + XRT (except stage I) – If unresectable, neoadjuvant ChT for 6 weeks Current COG: (Regimen I) ECVD− stage I–III ECVD+ carboplatin—Stage IV XRT− stage II–IV (local + metastasis) 5-year OS—79–89% Relapse rate—19%
RCC	9–15 years	– Suspect RCC in a child with renal mass > 5 years of age – Paraneoplastic 5–6% – More vascularized mass + calcification	– Translocation pathology on Xp.12 – Papillary IHC: TFE3	– RN+ LN sampling – Metastatic: Interferon, IL2, tyrosinase inhibitor like rapamycin, sunitinib 5-year survival: Stage I–III: 100% Stage IV: 10%
IRNB	11–40 months	Suspect in a child with renal mass + hypertension + calcification	Confirmation with urinary catecholamine MIBG Bone marrow	As neuroblastoma

Table 39.3 (continued)

Tumor	Median age	Diagnostic clues (clinical + imaging)	Pathology/IHC cytogenetics	Treatment/outcomes
PNET	Adolescence	Nonspecific	Perivascular pseudo-rosette formation IHC: CD99 +, FL-1 +	Induction ChT (VIDE), local control, postoperative adjuvant ChT (VAI) 5-year OS -45–55%
PRL	Variable	Bilateral renal lumps Bilateral renal infiltrates Retroperitoneal LN Hepatosplenomegaly	As for NHL	As for NHL
AML	Variable	– Sporadic/genetic – Tuberous sclerosis needs to be ruled out – Tender renal lump after trivial trauma – Flank pain, hematuria – Fat density in lesion	Classical, epithelioid IHC: HMB +ve	Observation <4 cm Surgery: NSS >4 cm, symptomatic, prone to rupture Noncompliance to follow-up Large tumor with epithelioid histology SAE, Cryoablation mTOR inhibitors: Sirolimus, rapamycin everolimus
CN/ CPDN	<24 months	Multilocular, noncommunicating cyst	CPDN: Blastemal cells in septa CN: Fibrous septa, may have mature tubules	Surgery: RN CPDN: Relapse/II–IV may need ChT

RN radical nephrectomy, *WT* Wilms' tumor, *IRN* intrarenal neuroblastoma, *RCC* renal cell carcinoma, *CCSK,* clear-cell sarcoma, *MRTK* malignant rhabdoid tumor of the kidney, *CMN* congenital mesoblastic nephroma, *PNET* primitive neuroectodermal tumor, *PRL* primary renal lymphoma, *AML* angiomyolipoma, *CN* cystic nephroma, *CPDN* cystic partially differentiated nephroblastoma, *ChT* chemotherapy, *XRT* radiotherapy, *LN* lymph node, *OS* overall survival

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