Clinical Presentation

3

Elizabeth Mullen and Norbert Graf

Contents

E. Mullen (✉)
Harvard Medical School, Dana Farber Cancer Institute,
450 Brookline Avenue, Boston, MA 02115, USA
e-mail: elizabeth_mullen@dfci.harvard.edu

N. Graf
Department of Pediatric Oncology and Hematology,
Saarland University, Campus Homburg,
Building 9, 66421, Homburg, Germany
e-mail: norbert.graf@uniklinikum-saarland.de

Abstract

The classic clinical presentation of children with Wilms tumor (WT) overlaps with many aspects of the general presentation of abdominal mass in children. However, specific details of the history, physical exam and laboratory evaluation can raise the suspicion of WT even prior to imaging or surgical procedures. Other renal tumors, such as rhabdoid tumor of the kidney (RTK), congenital mesoblastic nephroma (CMN), clear cell sarcoma of the kidney (CCSK), and renal cell carcinoma (RCC), also have particular presenting characteristics that can steer the clinician towards the consideration of those diagnoses.

This chapter will largely address the presentation of children with WT, as the leading renal tumor in children, but will also give brief attention to these less common renal tumors of childhood. We will review both common and uncommon presentations of Wilms tumor through discussion of an evaluation for a child suspected to have either an abdominal mass or a renal tumor. We will review the basic elements of evaluation which should be performed, including history, thorough physical exam, and initial laboratory and radiologic evaluation.

3.1 Introduction

Renal tumors account for approximately 7 % of childhood cancer in both North America and Europe. Within renal tumors, Wilms tumor (WT)

K. Pritchard-Jones, J.S. Dome (eds.), *Renal Tumors of Childhood: Biology and Therapy*, Pediatric Oncology,
DOI 10.1007/978-3-662-44003-2_3, © Springer-Verlag Berlin Heidelberg 2014

is by far the most commonly occurring tumor, accounting for approximately 95 % of renal tumors (Pastore et al. 2006).

In the majority of children diagnosed with Wilms tumor, clinical presentation overlaps with the general presentation of abdominal mass in children. Specific details of the history, physical exam, and laboratory evaluation, however, can raise the suspicion of Wilms tumor even prior to imaging or surgical procedures. Other renal tumors, such as rhabdoid tumor of the kidney (RTK), congenital mesoblastic nephroma (CMN), clear cell sarcoma of the kidney (CCSK), and renal cell carcinoma (RCC) each also have particular presenting characteristics that can steer the clinician towards the consideration of those diagnosis.

This chapter will largely address the presentation of children with WT, as the leading renal tumor in children, but will also give brief attention to the less common renal tumors of childhood. We will review both common and uncommon presentations of Wilms tumor through discussion of an evaluation for a child suspected to have either an abdominal mass or a renal tumor. We will review the basic elements of evaluation which should be performed, including history, thorough physical exam, and initial laboratory and radiologic evaluation.

As there is overlap of topics in the discussion of the clinical presentation of children with renal tumors that are discussed in much greater depth in other chapters of this book, specifically chapters on WT Genetics, Imaging, Surgery, Pathology, and Non-Wilms Tumors, the reader is also referred to those chapters for additional detail.

3.2 Presentation

The classic presentation of a child with a Wilms tumor (WT) is of an asymptomatic palpable mass in the abdomen (Fig. 3.1). In most cases, this mass is found by parents who are convinced that it was not there a day before. Asymptomatic children also frequently present to their primary care doctor in a well child visit, where an incidental abdominal mass is appreciated. Complaints or symptoms are found in only about 20 % or less of children with new Wilms tumor (Gutjahr et al. 1990; Graf et al. 2003) (Table 3.1). Abdominal pain, abdominal distension, and symptoms of constipation are the most common complaints associated with the presentation of WT. Microscopic or gross hematuria, a typical presenting symptom on adult renal tumors, is uncommon in children, occurring in less than 20 %. It is seen most frequently in patients who have ureteral extension of Wilms tumor (Ritchey et al. 2008) Fever, flank pain, and weight gain or weight loss, are among symptoms that are seen at presentation in less than 10 % of patients. Signs and symptoms of anemia can be present in patients with internal blood loss due to tumor hemorrhage.

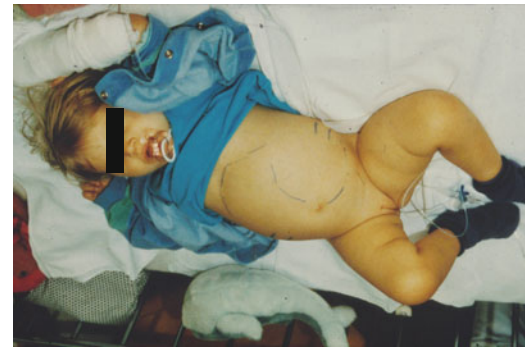

Fig. 3.1 Clinical presentation of a child with nephroblastoma with marked abdominal distension

Table 3.1 Initial symptoms in children with nephroblastoma at the time of diagnosis (Gutjahr et al. 1990; Graf et al. 2003)

Symptom	Frequency
Asymptomatic, incidental finding during regular examination	10
Incidental finding during consultation for other reasons	15
Asymptomatic mass	56
Pain	25
Hematuria	18
Fever	10
Urinary tract infection	6
Weight loss	5
Constipation	6
Enteritis	4
Vomiting	6
Others	19

3.3 History

After establishing an initial presenting complaint, a further detailed history should be obtained. History should include any family history of childhood cancer, specifics of the patient's birth, birth weight, hypoglycemia at birth, growth and development, and known physical or developmental abnormalities.

Wilms tumor has been reported in association with more than 50 different syndromes (Scott et al. 2006a). Conclusive evidence of an increased risk exists in only a minority of these conditions (Scott et al. 2006b). About 12 % of patients with a WT have an underlying syndrome (Fig. 3.2). These syndromes can be divided in overgrowth syndromes and others. One third of the syndromes affect the urogenital system and in 15 % a hemihypertrophy can be diagnosed. All other syndromes or malformations are rare including aniridia, Denys–Drash syndrome, and Beckwith–Wiedemann syndrome (Coppes et al. 1994; Graf et al. 2003). A summary of the different malformations and syndromes is given in Table 3.2. Familial WTs do occur in about 2 % of patients (Ruteshouser and Huff 2004).

History should also include any known preexisting medical conditions that might increase the child's risk of treatment morbidity. History of cardiac defect, past pulmonary issues, and history of bleeding disorders in patient or family should be identified.

3.4 Physical Exam

Physical exam should take into consideration the general appearance of the child, as well close attention to vital signs.

Increased respiratory rate, increased work of breathing, and decreased oxygen saturation can indicate pulmonary or pleural spread of disease. Increased work of breathing can also occur from elevation of the diaphragm from the underlying abdominal mass. Occasionally, accompanying peritoneal fluid can also add to abdominal distension. The degree of abdominal distension can be extreme on occasion to the extent of precipitating respiratory failure (Fig. 3.3). A small percentage of patients (4.3 % in a small series of patients at St Jude's Hospital) present with pleural effusion (Corey et al. 2004). Pleural effusions can be sympathetic or malignant and should be tapped when feasible if results will change therapy. Presence of pleural effusion at diagnosis has not been correlated with worse prognosis.

Patients that have spontaneous tumor rupture with contained loss of blood can present with signs and symptoms consistent with acute anemia (Ramsay et al. 1977). Usually this is accompanied

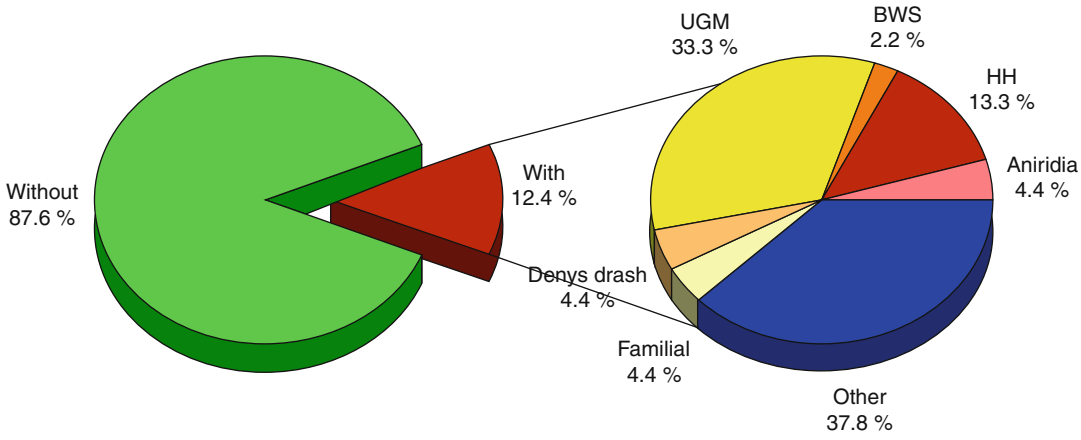

Fig. 3.2 Proportion of children with Wilms Tumor and malformations or syndromes treated in Germany in the prospective study and trials SIOP 9 and SIOP 93-01. (*UGM* urogenital malformations, *BWS* Beckwith–Wiedemann syndrome, *HH* Hemihypertrophy, *Denys–Drash* Denys–Drash syndrome)

Table 3.2 Malformations and syndromes in children with Wilms tumor (Bürger et al. 1986; Cowell et al. 1989; Gronskov et al. 2001; Rump et al. 2005; Scott et al. 2006a, b)

Syndrome Link to OMIM[a]	Characteristics	Gene	Risk [%]	Incidence [%]	
				SIOP	NWTSG/COG
Overgrowth syndromes					
Hemihypertrophy http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=235000	Hemihypertrophy	11p15 WT2	3–5	3.13	2.47
Beckwith–Wiedemann **EMG** syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=130650	**E**xomphalos **M**acroglossia **G**igantismus	11p15.5 WT2, IGF2, H19	10–20 %	<1	
Sotos syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=117550	Rapid growth, acromegalic features; nonprogressive cerebral disorder with mental retardation	5q35 *NSD1*		<1	
Simpson–Golabi–Behmel syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=312870	Postnatal overgrowth Coarse facies Congenital heart defects other congenital abnormalities	Xq26 *GPC3*		<1	
Klippel–Trenaunay syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=149000	Cutaneous hemangiomata Hypertrophy of the related bones and soft tissues	5q13.3 VG5Q		<1	
Perlman syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=267000	Renal hamartomas Nephroblastomatosis Fetal gigantismus	?		<1	
Other syndromes					
Aniridia http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=106210	Aniridia	11p13 PAX6	30 %	<1	0.84
WAGR http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=194072	**W**ilms tumor **A**niridia **G**enitourinary anomalies Mental **R**etardation	11p13 WT1		<1	
Denys–Drash http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=194080	Nephropathy Wilms tumor Genital anomalies	11p13 WT1	30 %	<1	

GUM http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=137357	Genitourinary malformations	11p13 GUD		4.41	4.61
Mosaic variegated aneuploidy syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=257300	Constitutional losses or gains of whole chromosomes	15q15 BUB1B	>20 %	?	
Li–Fraumeni syndrome http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=151623	Inherited cancer syndrome	17p13 p53		<1	
Neurofibromatosis I Morbus Recklinghausen http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=162200	Cafe-au-lait spots fibromatous tumors of the skin	17q11.2 NF1		<1	

[a]Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

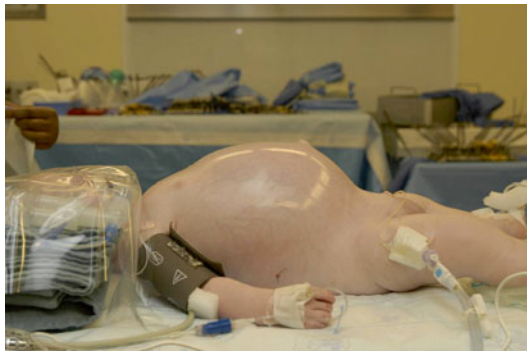

Fig. 3.3 Child with a renal mass, presenting with massive abdominal distension, leading to respiratory failure

by marked abdominal pain and distension, as well as pallor and tachycardia. Volume and blood product resuscitation should be initiated rapidly in this situation.

Hypertension can be a presenting sign, and may be asymptomatic, or accompanied by complaint of headache or pain. Consideration of a renal cause, including possibility of renal tumor should be included on the differential diagnosis of any young child with noted hypertension. Hypertension associated with renal tumors has been shown to be caused by an increase in renin activity (Maas et al. 2007). Sometimes blood pressure is difficult to control especially in children receiving preoperative chemotherapy. In the retrospective study of Maas et al., in at least a subset of patients, ACE inhibitors may be a good therapeutic option. After tumor nephrectomy, the blood pressure returns to normal values without any medication in nearly all of these children.

There are many specific physical exam findings that can heighten the suspicion of a diagnosis of a Wilms tumor in a child with abdominal mass. After initial vital signs, the examination of the abdomen should include the size and location of mass, presence of contralateral mass, clinical ascites, and observation of whether the mass moves with respiration. Tenderness to palpation raises the concern for the possibility of tumor rupture and hemorrhage with subsequent peritoneal irritation. There is a historic teaching to avoid deep palpation in patients with WT because of the concern of causing tumor rupture.

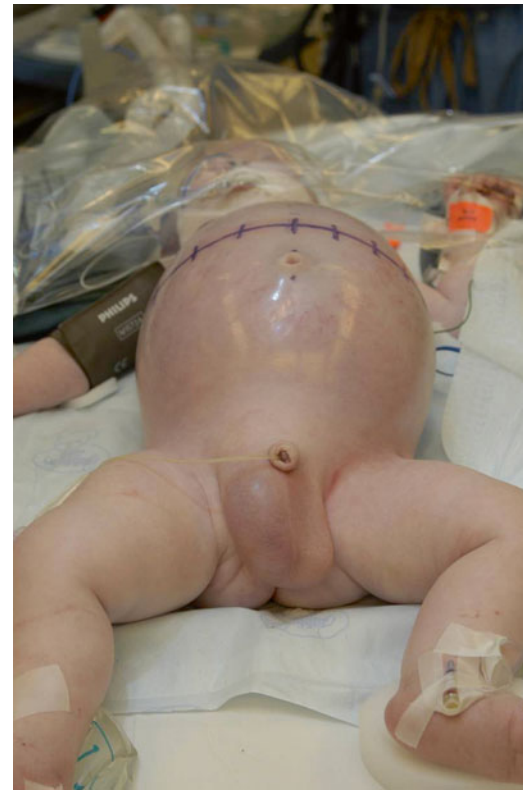

Fig. 3.4 Physical exam can also reveal presence of hydroceles or varicoceles, related to compression of the mass

On exam, mass associated with WT usually does not cross the midline, or move with respiration, which can help differentiate from a mass associated with neuroblastoma. Increased respiratory rate, observation of increased work of breathing, and/or absence of breath sounds as indicators of pulmonary spread of disease are important factors in deciding the risk of anesthesia for the patient, both for imaging or any surgical procedure.

Genital urinary abnormalities can be seen in several of the syndromes associated with increased risk of WT and should be carefully documented. The presence of hernias, hydroceles, or varicoceles (Fig. 3.4) may be related to compression of vascular and vital structures affected by the mass. Ureteral prolapse of WT observed on physical exam has also been reported in a small number of patients (Ritchey et al. 2008).

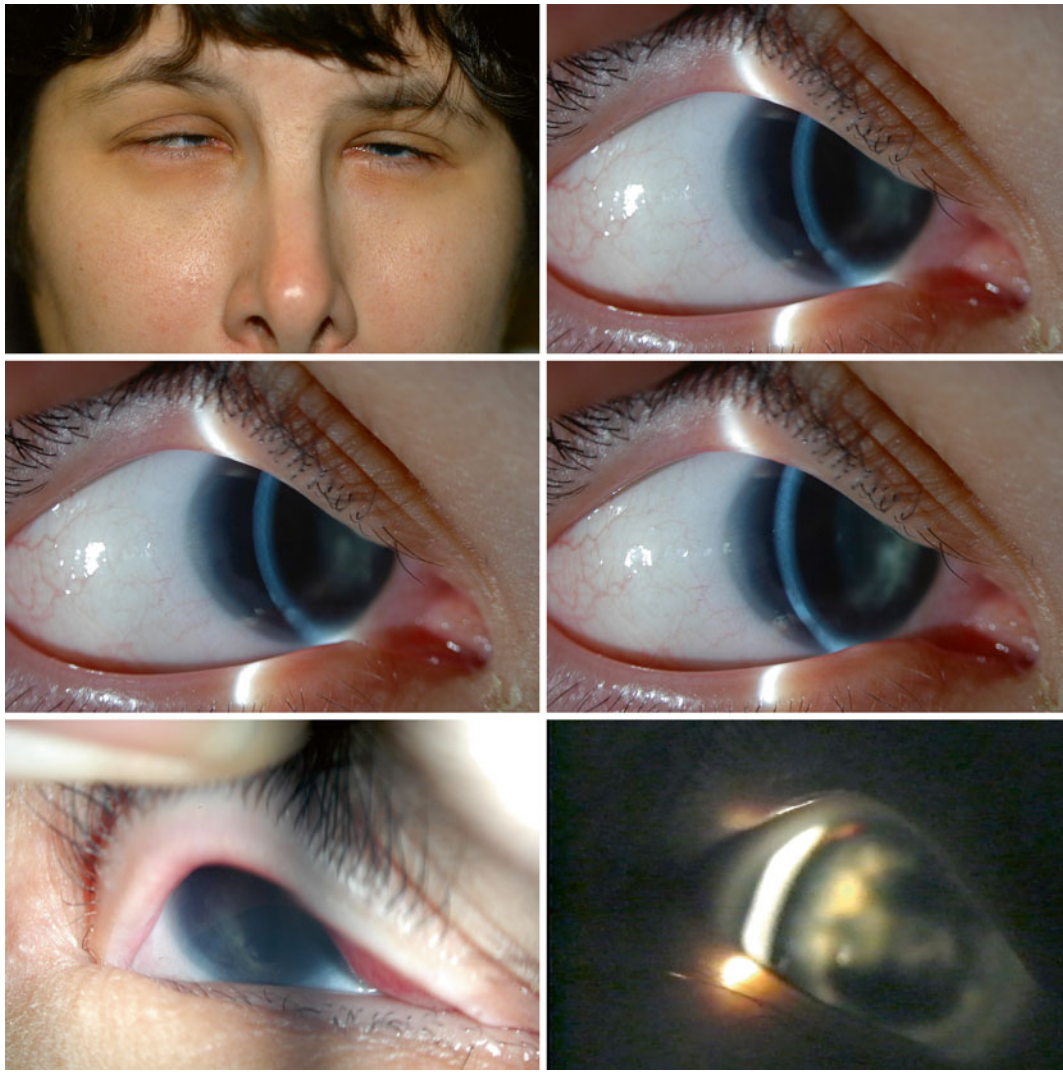

Fig. 3.5 Aniridia on exam of adolescent

An extremity exam, including extremity measurements, should be done, to investigate the possibility of subtle hemihypertrophy. An ophthalmologic finding of aniridia in a patient would markedly increase the chance of a finding of Wilms tumor (Fig. 3.5).

3.5 Laboratory Evaluation

Initial assessment of patient with suspected renal mass should include a complete blood count with differential, with special attention to the hematocrit. Renal function should be assessed through a full panel of electrolytes, including magnesium, phosphorous, and calcium, as well as blood urea nitrogen (BUN) and creatinine (Cr.). It is rare for a patient with a renal tumor to present with renal failure, but compression from mass effect can lead to ureteral compression, more often in patients with bilateral disease. These patients often have expected severe hypertension. Ca has been observed to be markedly elevated in some infants with renal tumors (Bayindir et al. 2009; Amar et al. 2001; Glick 2004). Most commonly, these patients are found

to have congenital mesoblastic nephroma or rhabdoid tumor. The hypercalcemia associated with these tumors can be clinically significant and require careful medical management. The underlying cause though is most likely to be from increased secretion of parathyroid hormone. The calcium levels usually improve after surgical resection of the tumor, but can persist for some time and can require medical and pharmaceutical management.

A clotting screen should be performed in every child with a nephroblastoma, including a PT and PTT. Very rarely, a coagulopathy caused by an acquired von Willebrand syndrome (AVWS) is diagnosed during routine laboratory tests (Coppes et al. 1992; Leung et al. 2004). These children do need vWF concentrate or fresh frozen plasma prior to and after surgical procedures (Hickman line insertion, tumor nephrectomy or biopsy). After tumor nephrectomy, the AVWS is always resolved.

A complete urinalysis should be performed. Although uncommon in children with renal tumors relative to adults presenting with renal tumors, hematuria can be the only presenting sign of a renal tumor. This suggests invasion of the tumor into the renal pelvis or less commonly ureter (Senthilnathan et al. 2004) Depending on the location of the tumor in relation to the renal sinus, even a very small tumor unable to be palpated on exam can produce hematuria.

In children presenting with fever, coincident urinary tract infection (UTI) should be ruled out with urine culture, as obstruction can contribute to increased incidence of UTI at diagnosis.

Urinary b-fibroblastic growth factor (b-FGF) has been shown to be elevated in some children with WT, but is currently not a clinically useful test, as it is not a specific or constant finding (Sköldenberg et al. 2001).

Intra-tumoral hemorrhage may occur, resulting sometimes in an emergency situation with a rapid abdominal enlargement and profound and symptomatic anemia. In such a situation, emergent surgery is required. In most of these children, presurgical tumor rupture occurs. This can be a rupture into the abdominal cavity but also to the retroperitoneal space. Sometimes the bleeding into the tumor is compressed by the tumor capsule without a rupture. Only then preoperative chemotherapy might be possible to apply, but one should be aware that shrinkage of the tumor releases the pressure of the intratumoral vessels resulting in a second bleeding. Such children need to stay in the hospital to handle a possible emergency situation. Surgeons should always be involved in such a decision process.

3.6 Imaging Evaluation

If a renal tumor is suspected, either by finding of a mass or unexplained hematuria, hypertension, or other concerning findings, diagnostic imaging should be obtained promptly. Initial radiologic evaluation should be aimed at identifying the presence and origin of the tumor. Once a tumor is confirmed, imaging should be aimed at assessing important staging factors, such as possible rupture, metastatic spread to local lymph nodes or other organs, (primarily liver and lung,) presence of bilateral kidney lesions, and involvement of renal veins as well as the inferior vena cava (IVC). Abdominal and chest radiographs can often identify presence of primary and metastatic disease; however, a thorough diagnostic evaluation should include additional imaging techniques. Although some patients present with massive pulmonary metastasis (Fig. 3.6), computed tomography (CT) scan of the chest is more sensitive for the detection of small, but clinically

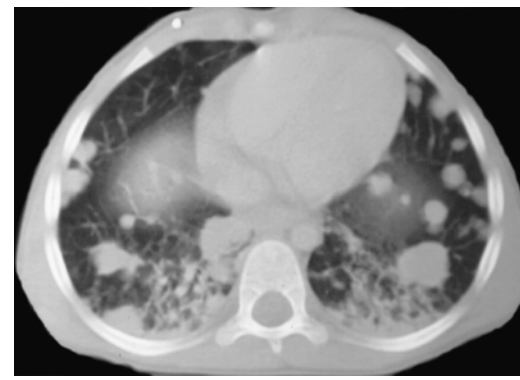

Fig. 3.6 Lung metastasis in a child with Wilms tumor

important pulmonary metastatic lesions (Cohen 2008). Detection of CXR negative but CT positive lesions has been shown to be important to the staging and appropriate therapeutic assignment of patients (Owens 2002).

Abdominal ultrasound provides much valuable information about origin of mass, presence of bilateral lesions, and vascular involvement. It is important to identify patients that present with involvement of tumor thrombus in the renal veins and IVC (Fig. 3.7). This can complicate the risk of upfront surgery, particularly if the tumor thrombus extends through the hepatic portion of the IVC. It can also increase the risk of mortality for the patient. An extension of the tumor and a related thrombus may involve the inferior vena cava and can grow into the right atrium. This is a potential cause of death due to massive cardiac insufficiency. Pulmonary emboli can occur, mandating hospitalization during initial diagnostic and therapeutic period. Immediate surgery is not routinely recommended; as such thrombi can often be successfully managed with initial chemotherapy. In many situations, with good chemotherapy response, the thrombus will shrink and facilitate further surgical procedures. In other cases, surgery has to be done under cardiopulmonary bypass.

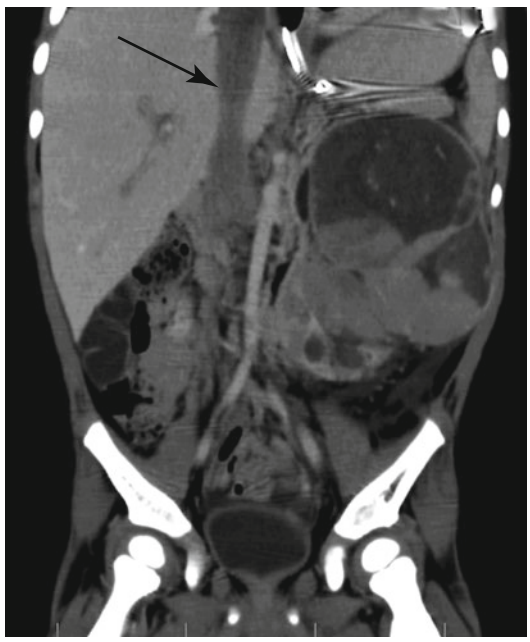

Fig. 3.7 V. cava thrombus in a child with Wilms tumor. The *arrow* indicates the V. cava thrombus

Magnetic resonance imaging (MRI) has been increasingly employed in the initial diagnostic evaluation of renal tumors, but its use is still being studied. It may be useful for more detailed characterization of vessel involvement and for establishing the presence of nephrogenic rests versus tumor.

3.7 Histologic Diagnosis

The use of preoperative chemotherapy versus upfront nephrectomy and the discussion of the merits and flaws of various biopsy techniques are covered in depth in other chapters in this text and will not be discussed here.

3.7.1 Characteristics of Patients as Regards to Stage and Histology at Diagnosis

NWTS V registered 2,596 patients with WT (Dome et al. 2006). Patients were staged according to NWTS staging system (Table 3.3). Although there was central review of pathology and imaging, it was not real time, and assignment of histological type and stage was entered by the local institution.

The overwhelming majority of patients (2,315 of 2,596) had favorable histology WT. Slightly less than one third were under 2 years of age, 1/3 were between ages 2 and 3, and 38 % were over age 4. 82 % of these patients had localized disease (stages 1–III), 13.1 % had metastatic (stage IV) disease, and 5.6 % had bilateral disease.

The incidence of focal anaplasia (FA) and diffuse anaplasia (DA) was much lower and demonstrated different clinical characteristics than the group of FH WT patients. There was a marked increase incidence in female over male patients (FA 74.6 % female, DA 64.9 %). Patients tended to present at older ages, less than 10 % were under age 2, in FA the majority (52.5 %) were between ages 2 and 3, and in DA almost 60 %

Table 3.3 NWTS staging

Stage I
(a) Tumor limited to the kidney and completely excised
(b) The tumor was not ruptured before or during removal
(c) The vessels of the renal sinus are not involved beyond 2 mm
(d) No residual tumor apparent beyond the margins of excision
Stage II
(a) Tumor extends beyond the kidney but is completely excised
(b) No residual tumor is apparent at or beyond the margins of excision
(c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor
Stage III Residual tumor confined to the abdomen:
(a) Regional lymph nodes in the renal hilum, the periaortic chains, or beyond shown to contain tumor
(b) Diffuse peritoneal contamination by the tumor
(c) Peritoneal tumor implants
(d) Tumor extends beyond the surgical margins either microscopically or grossly
(e) Tumor is not completely resectable because of local infiltration into vital structures
Stage IV Presence of hematogenous metastases or metastases to distant lymph nodes
Stage V Bilateral renal involvement at the time of initial diagnosis

Table 3.4 Revised SIOP (after chemotherapy) staging

I	(a) Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, and the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface and is completely resected (resection margins "clear") (b) The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls) (c) The vessels of the renal sinus are not involved (d) Intrarenal vessel involvement may be present
II	(a) The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear") (b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected (c) The tumor infiltrates adjacent organs or vena cava but is completely resected
III	(a) Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains postoperatively) (b) Any abdominal lymph nodes are involved (c) Tumor rupture before or intraoperatively (irrespective of other criteria for staging) (d) The tumor has penetrated through the peritoneal surface (e) Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon (f) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery
IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V	Bilateral renal tumors at diagnosis

were greater than 4. There was also a higher percentage of metastatic and bilateral disease in both FA and DA groups (FA 25.4 % stage IV, 18.6 % stage V, DA 18.9 % stage IV, 10.8 % stage V).

The NWTS patients are grouped through different staging systems in SIOP and UK protocols (Table 3.4); however, it is still possible to compare the number of patients that present with metastatic and bilateral disease.

European data on overall characteristics of children with WT supports similar rates of metastatic disease found at presentation.

Thirteen percent of patients will be diagnosed with metastatic disease at presentation (Pastore et al. 2006). These children are older with a median age of 5.2 years compared to 3.4 years in localized tumors and they present with larger tumors of more than 600 ml as median tumor volume compared to 400 ml in localized tumors.

More than 60 % of these patients have isolated metastases to the lung and more than 10 % to the liver. Extra-regional lymph node involvement occurs in less than 10 % of patients with metastatic disease. Metastases to bone and brain are uncommon. In case of bone metastasis, diagnosis of clear cell sarcoma of the kidney (CCSK) is more likely. If metastatic disease occurs in infants with a renal tumor, a rhabdoid tumor of the kidney should be considered, for metastases are very unlikely in WTs in this age group.

3.8 Prenatal Diagnosis

Prenatal diagnoses of nephroblastoma are described (Siemer et al. 2004). Such tumors are found during regular ultrasound screens in pregnancy. Interdisciplinary workout between gynecologists, pediatric surgeons, neonatologists, and pediatric oncologist is needed to provide the best treatment for such a child in terms of prolonging pregnancy, way of delivery, and optimal time for surgical removal of the tumor. A sectio Caesarea is always recommended. In most cases, histology shows a mesoblastic nephroma.

3.9 Diagnosis in Patients with Associated Syndromes and Malformations

Patients with syndromes known to have an associated increased risk of developing WT usually undergo routine interval surveillance screening, most often by ultrasound. Therefore, patients with syndromes may present asymptomatically and with lower stage disease. A higher incidence of synchronous and metachronous bilateral WT is associated with many of these syndromes.

3.10 Early Diagnosis: Children Diagnosed on Routine Surveillance

In Germany in about 10 % of patients, an early diagnosis of WT is made during routine scheduled pediatric well-child care, by exam on an asymptomatic child (Gutjahr et al. 1990). Another 15 % of patients are diagnosed during a consultation for other reasons without tumor-related symptoms (Graf et al. 2003). This results in 25 % of children being asymptomatic at the time of diagnosis in Germany.

A comparison between the group of children with and without symptoms was done for children treated according SIOP 93-01 in Germany (Graf et al. 2003). During the time period between April 1994 and December 2001, 947 patients with a Wilms tumor were analyzed. 687 (72.5 %) of them did show tumor-related symptoms at the time of diagnosis (group A), whereas 260 patients (27.5 %) were diagnosed without having such symptoms (group B). Ninety seven patients of group B had no symptoms at all and were diagnosed by casual ultrasound. In 163 patients other symptoms – but not related to the tumor – did lead to the diagnosis. Twenty percent of patients in group B compared to 11.9 % in group A had an underlying syndrome. Age and tumor volume were significantly lower in group B than in group A (median age: 1.73 years versus 3.10 years, $p<0.001$; tumor volume: 222 ml versus 344 ml, $p<0.001$). Stage distribution and histology were in favor of group B. There were less patients with metastatic disease in group B (17 (6.5 %) versus 130 (18.9 %), $p<0.001$). The 5-year relapse-free survival was insignificant better for group B compared to group A (90 % versus 84 %, $p=0.0502$), whereas the overall survival was not different between both groups (91 % versus 90 %). For more detailed information, see Table 3.5. In summary, an earlier diagnosis of WT results in less treatment because of lower stages and a favorable distribution of histological subtypes (Graf et al. 2003). As a regular screening by abdominal ultrasound may contribute to an earlier diagnosis, the question of screening for Wilms tumor has to be answered.

3.10.1 Surveillance in Children with Increased Risk of Wilms Tumor

Regular surveillance in children thought to be at increased risk of Wilms tumor has become widespread in parts of Europe and North America. In the UK, a working group of clinical geneticists, pediatricians, pediatric oncologists, and radiologists was formed to formulate recommendations for Wilms tumor surveillance. These recommendations are based on available evidence from literature, current practice, and expert opinion (Scott et al. 2006a). In their summary, they state the following:

1. Surveillance should be offered to children at 5 % risk of Wilms tumor.
2. Surveillance should be offered only after review by a clinical geneticist.

Table 3.5 Patients treated in Germany according to SIOP 93-01

	all patients		patients with tumour related symptoms or unknown symptoms		patients without symptoms or with symptoms not related to the tumour	
	n	%	n	%	n	%
registered	947	100	687	72.5	260	27.5
Syndromes						
unknown	74	7.8	66	9.6	8	3.1
no	739	78.0	539	78.5	200	76.9
				p <0.05		
yes	134	14.1	82	11.9	52	20.0
Aniridia	7		2		5	
Hemihypertrophy	14		8		6	
Beckwith-Wiedemann	9		2		7	
Denys Drash	3		2		1	
Urogenital malform	41		24		17	
other	83		53		30	

Table 3.6 Molecular genetic investigations to define the risk of Wilms tumor development and indication for screening by ultrasound every 3 months (Scott et al. 2006a, b)

Phenotype	Method	Result	Screening
Aniridia	FISH for PAX6/WT1	Del(WT1)	Yes
WAGR		WT1 normal	No
Denys–Drash syndrome	WT1-Mutation	Yes	Yes
		No	No
Fanconi anemia	BRCA2	Biallelic	Yes
		Monoallelic	No
Mosaic variegated aneuploidy	Karyotype	All	Yes
	BUB1B mutation screen		
Beckwith–Wiedemann syndrome	LOI, UPD 11p15	LOI KvDMR1	No
		LOI CDKN1C	No
		All others	Yes
Simpson–Golabi–Behmel syndrome	GPC3-mutation/deletion	Male	Yes
		Female	No
Perlman syndrome	Unknown	All	Yes
Hemihypertrophy	UPD 11p15	Yes	Yes
		No	No

WAGR Wilms–aniridia–genitourinary–mental retardation, *FISH* fluorescence in situ hybridization, *LOI* loss of imprinting, *UPD* uniparental disomia

3. Surveillance should be carried out by renal ultrasonography every 3 month.
4. Surveillance should continue until 5 years in all conditions except Beckwith–Wiedemann syndrome, Simpson–Golabi–Behmel syndrome and some familial Wilms' tumor pedigrees, where it should continue until 7 years.
5. Surveillance can be undertaken at a local center, but should be carried out by someone with experience of pediatric ultrasonography.
6. Screen-detected lesions should be managed at a specialist center.

The reason to offer surveillance only after review by a clinical geneticist is obvious as there are some malformations and syndromes in which the risk of developing a Wilms tumor can be better excluded after molecular genetic testing. Table 3.6 lists the molecular genetic investigations to define the risk of Wilms tumor development and indication for screening by ultrasound

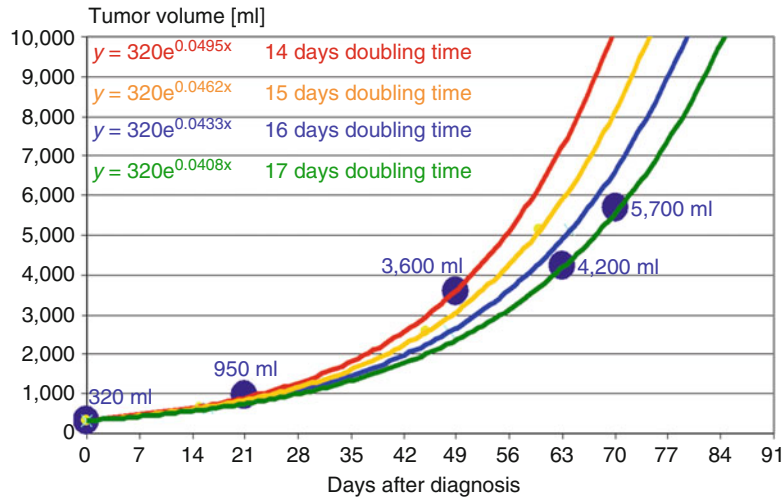

Fig. 3.8 Natural course of a Wilms tumor (Zoubek et al. 1999)

every 3 months (Scott et al. 2006a). In cases where surveillance is indicated, abdominal ultrasound should be done in 3-month intervals. Longer time intervals are not recommended as the doubling time of Wilms tumors is between 2 and 3 weeks (Zoubek et al. 1999) (Fig. 3.8).

References

Amar AM, Tomlinson G, Green DM et al (2001) Clinical presentation of rhabdoid tumors of the kidney. J Pediatr Hematol Oncol 23:105–108

Bayindir P, Guillerman RP, Hicks MJ et al (2009) Cellular mesoblastic nephroma (infantile renal fibrosarcoma): institutional review of the clinical, diagnostic imaging, and pathologic features of a distinctive neoplasm of infancy. Pediatr Radiol 39:1066–1074

Bürger D, Feickert HJ, Mildenberger H (1986) Current status of nephroblastoma treatment. Monogr Paediatr 18:224–242

Cohen M (2008) Wilms tumor: a new method for quantification of lung metastatic tumor burden. Pediatr Radiol 38:817–818

Coppes MJ, Zandvoort SWH, Sparling CR et al (1992) Acquired von Willebrand disease in Wilms' tumor patients. J Clin Oncol 10:422–427

Coppes MJ, Haber DA, Grundy PE (1994) Genetic events in the development of Wilms' tumor. N Engl J Med 331:586–590

Corey B, Yang CH, Wilimas J, Davidoff A, Dome J (2004) Significance of pleural effusion at diagnosis of Wilms tumor. Pediatr Blood Cancer 42:145–148

Cowell JK, Wadey RB, Buckle BB, Pritchard J (1989) The aniridia Wilms' tumor association: molecular and genetic analysis of chromosome deletions on the short arm of chromosome 11. Hum Genet 82:123–126

Dome JS, Cotton CA, Perlman E et al (2006) Treatment of anaplastic Wilms' tumor: results from the fifth National Wilms Tumor Study. J Clin Oncol 24(15): 2352–2358

Glick RD, Hicks MJ, Nuchtern JG et al (2004) Renal tumors in infants less than 6 months of age. J Pediatr Surg 39:522–525

Graf N, Reinhard H, Aliani S et al (2003) Wilms tumour with or without tumour related symptoms at diagnosis. Med Pediatr Oncol 41:266 O036 (abstract)

Gronskov K, Olsen JH, Sand A, Pedersen W, Carlsen N, Bak Jylling AM, Lyngbye T, Brondum-Nielsen K, Rosenberg T (2001) Population-based risk estimates of Wilms tumor in sporadic aniridia. A comprehensive mutation screening procedure of PAX6 identifies 80% of mutations in aniridia. Hum Genet 109: 11–18

Gutjahr P, Kaatsch P, Spaar HJ et al (1990) Klinik, Therapie und Prognose bei 373 Kindern mit Wilms-Tumoren – Ergebnisse der bundesweiten Studie 1980–1988. Akt Urol 121:132–141

Leung RS, Liesner R, Brock P et al (2004) Coagulopathy as a presenting feature of Wilms tumour. Eur J Pediatr 163:369–373

Maas MH, Cransberg K, van Grotel M et al (2007) Renin-induced hypertension in Wilms tumor patients. Pediatr Blood Cancer 48:500–503

Owens CM, Veys PA, Pritchard J et al (2002) Role of chest computed tomography at diagnosis in the management of Wilms' tumor: a study by the United Kingdom Children's Cancer Study Group. J Clin Oncol 20:2768–2773

Pastore G, Znaor A, Spreafico F, Graf N et al (2006) Malignant renal tumours incidence and survival in European children (1978–1997): report from the

Automated Childhood Cancer Information System project. Eur J Cancer 42:2103–2114
Ramsay NK, Dehner LP, Coccia PF et al (1977) Acute hemorrhage into Wilms tumor: a cause of rapidly developing abdominal mass with hypertension, anemia, and fever. J Pediatr 91:763–765
Ritchey M, Daleya S, Shamberg R, Ehrlich P, Hamilton T, Haased G, Sawine R (2008) Ureteral extension in Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Pediatr Surg 43(9):1625–1629
Rump P, Zeegers MP, van Essen AJ (2005) Tumor risk in Beckwith-Wiedemann syndrome: a review and meta-analysis. Am J Med Genet A 136:95–104
Ruteshouser EC, Huff V (2004) Familial Wilms tumor. Am J Med Genet C Semin Med Genet 129C:29–34
Sköldenberg EG, Christiansson J, Sandstedt B et al (2001) Angiogenesis and angiogenic growth factors in Wilms tumor. J Urol 165:2274–2279
Scott RH, Walker L, Olsen ØE et al (2006a) Surveillance for Wilms Tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child 91:995–999
Scott RH, Stiller CA, Walker L et al (2006b) Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet 43: 705–715
Senthilnathan R, Bagdi RK, Senthilganesh K, Senthilbarathi (2004) Interesting presentations of Wilms' tumor. J Indian Assoc Pediatr Surg 9: 193–197
Siemer S, Lehmann J, Reinhard H et al (2004) Prenatal diagnosis of congenital mesoblastic nephroma associated with renal hypertension in a premature child. Int J Urol 11:50–51
Zoubek A, Slavc I, Mann G et al (1999) Natural course of a Wilms' tumour. Lancet 354:344