Wilms' Tumor

73

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73.1 Introduction

The Wilms' tumor (WT) is an embryonal tumor of renal origin, but extrarenal localization may rarely occur. The first description of a kidney tumor as myoma sarcomatodes is from Eberth in 1872. In 1898, Birch-Hirschfeld classified a similar kidney tumor as embryonal adenosarcoma. In 1899, Wilms reviewed the literature and added seven more cases with the clinical picture of the tumor that now bears his name, or nephroblastoma. It is the most common kidney tumor, the second common solid tumor after neuroblastoma, and represents 6–10% of all childhood cancer cases. The incidence varies between 1 per 50.000 to 1 per 200.000 neonates. It is more common in the US with 10.9 per million than in China with 2.5 per million. Most cases are diagnosed around the age of 3 years (range 1–5 years). Males and females are affected equally. Ninety-two to ninety-five percent of the WT occur in only one kidney and are unilateral. Anomalies associated with WT are the WAGR syndrome (aniridia, genitourinary anomalies, mental retardation), the Denis-Drash syndrome (intersex, nephropathy), the Beckwith-Wiedemann syndrome (exomphalos, macroglossia, viscero-megaly), and hemihypertrophy. Patients with bilateral tumor or other associated anomalies are diagnosed significantly earlier. About 2% of patients have a positive family history with one relative who also suffered from a WT. The association with other anomalies as well as the occurrence in families suggest that altered genes are involved in the tumor pathogenesis. Several genetic loci are involved. The two more important genes are the WT 1 and WT 2 suppressor gene on chromosome 11, but additional loci have been described on several other chromosomes, so far.

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73.2 Pathology

The tumor compromises most parts of the kidney and may invade the urinary collecting system, the renal vein, or the surrounding tissues. The section shows partly solid, partly cystic regions with hemorrhagic areas (Fig. 73.1). If the WT occupies only one pole there exists a clear demarcation line to the normal kidney. The origin of the tumor is the metanephrogenic blastema; thus the histology mimics the development of a normal kidney, showing the three tissue components: blastema, tubules, and stroma (favorable histology) (Fig. 73.2). The proportions of these cell elements may be different from one tumor to the other. However, each component can exhibit focal or diffuse anaplastic cell elements (unfavorable histology), which are indicators for a poor outcome (Fig. 73.3). In 25–40% of WT patients, additional abnormal cell clusters can be found within normal parts of the kidney, the so-called *nephrogenic rests* (NR). They consist of foci of persisting blastemic cells, which are situated either intralobar or perilobar (Fig. 73.4). NR are common in neonatal kidneys and are either transformed into normal kidney tissue or into WT cell elements. Rarely both kidneys consist of diffuse nephrogenic rests—a pathology that is called *nephroblastomatosis*.

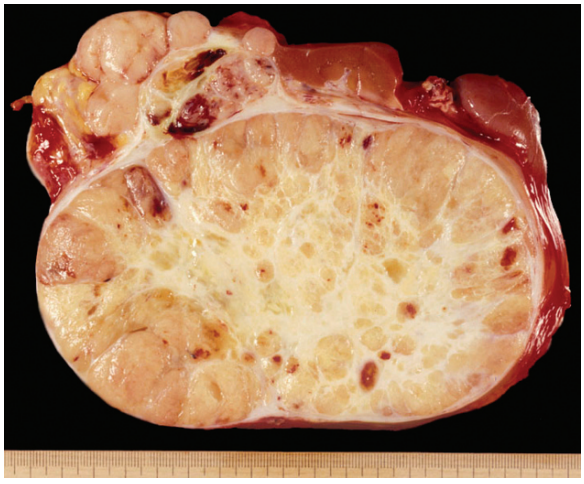

Fig. 73.1 Typical appearance of the tumor consisting of solid and cystic parts as well as hemorrhagic regions

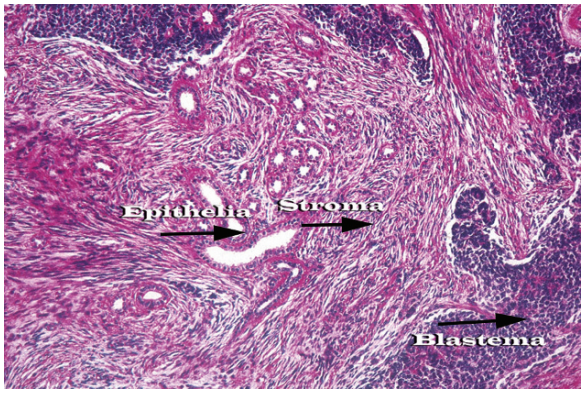

Fig. 73.2 Medium-power microscopic view of a typical Wilms Tumor with elements of tubules, blastema, and spindel cells

73.3 Clinical Presentation and Diagnosis

Most children present with an asymptomatic but rapidly growing abdominal mass. About 30% of patients suffer from abdominal pain, malaise, and weight loss.

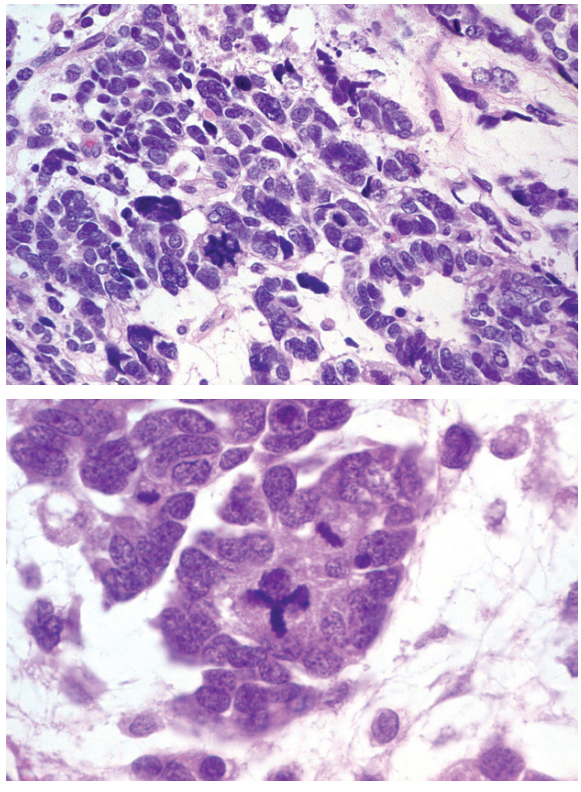

Fig. 73.3 High-power microscopic view of an anaplastic part of a Wilms Tumor with polymorphic cell nuclei and atypical cell mitosis

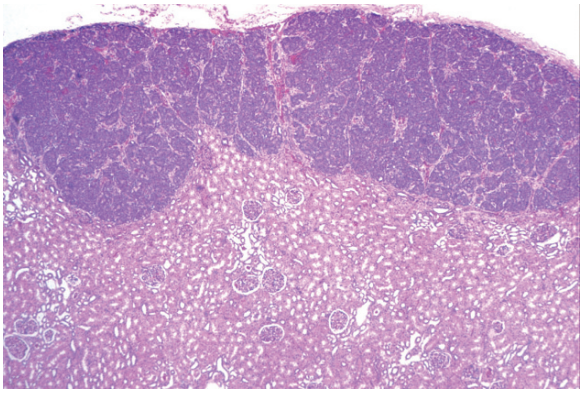

Fig. 73.4 Medium-power microscopic view of perilobar nephrogenic rest consisting of mesonephric blastema cells within normal kidney tissue

Some patients may show additionally a leftsided varicocele (occlusion of the renal vein by tumor invasion) or a symptomatic hydrocele. Ten percent of patients suffer from hematuria, mostly microscopic, when the tumor invades the urinary collecting system.

The availability of ultrasound in the private practice of GP and pediatricians today allows early diagnosis of WT and referral to the pediatric centre. The ultrasound study documents the position, size and volume of the tumor, the intravascular extension, metastatic involvement of regional lymph nodes and the liver, and the examination of the contralateral kidney. Furthermore, regular ultrasound investigations during preoperative chemotherapy allow weekly measurement of tumor volume, thereby indicating whether the tumor responds immediately to the therapy or not. The abundant availability of ultrasound today allows regular screening in patients with associated anomalies and increased risk for WT. Recommended screening intervals are two times a year.

The abdominal CT scan with contrast administration shows in detail the location of the tumor in the kidney, whether it extends into the surrounding tissues and the metastatic involvement of regional or distant lymph nodes. A chest X-ray is obtained to evaluate for the presence of pulmonary metastases. When the chest X- ray is negative, we order an additional CT scan for more precise evaluation of small pulmonary metastases, which has a significant impact on the tumor staging. To perform an MRI is optional, but it may provide additional information to confirm the diagnosis by imaging methods alone, thereby excluding different kidney pathologies. Differential diagnosis includes benign diseases such as hydronephrosis or a cystic kidney disease and malignancies such as clear cell sarcoma or rhabdoid tumor of the kidney.

73.4 Therapy

The mainstay of therapy is the radical surgical excision of the tumor and additional metastases. The international protocols include detailed recommendations for diagnosis, controls, and chemotherapeutic regimen in WT patients.

The basis of the therapy is the clinical Staging in regard to the tumor extent and the histological Grading (favorable or unfavorable histology). The National Wilm's Tumor Study Group (NWTS) and the International Society for Paediatric Oncology (SIOP-Societé Internationale pour Oncolgie Paediatrique) use a similar staging system:

Stage I: Tumor limited to the kidney and completely resected. No tumor rupture.

Stage II: Tumor extends beyond the kidney but is completely resected; regional extension of the tumor, vessel infiltration, tumor biopsy, or local spillage.

The SIOP protocol differentiates between Stage IIa—no lymph nodes involved—and Stage IIb—regional (hilar) lymph nodes involved.

Stage III: Residual nonhematogenous tumor, involvement of paraaortic or paracaval lymph nodes, diffuse spillage, peritoneal implants, local infiltration of vital structures.

Stage IV: Distant metastases.

Stage V: Bilateral tumor.

The study protocols of the NWTS and the SIOP are significantly different in that regard that SIOP includes preoperative chemotherapy—biopsy is only optional—and the NWTS protocol recommends primary surgery and biopsy if primary resection is not feasible or recommended (Table 73.1). The benefit of primary chemotherapy consists of a significant shrinkage of the tumor, evidenced by weekly ultrasound controls, and as a result a reduced incidence of intraoperative rupture

Table 73.1 Differences between the SIOP protocol and the protocol of the NWTS-Group

NWTS	SIOP
• Tumor nephrectomy or biopsy • Postoperative chemo-(radio-)therapy	• Chemotherapy, biopsy optional • Secondary tumor nephrectomy • Postoperative chemo-(radio-)therapy
Disadvantages	
• Tumor rupture and spillage • More complications • Extensive resection • Increased mortality	• Diagnostic error • Downstaging • Downgrading

Table 73.2 Advantages and disadvantages of the protocols of SIOP and NWTS

- Downstaging
  - Less stage III (less radiation)
  - More stage I and II
  - More relapses in stage II
  - Therefore adriamycin is included in all stage II (late heart failure)
- Complications → 9.8% vs. 6.8%
- Tumor rupture and spillage 15.3% vs. 2,2%
  - Stage III → more radiation therapy
  - Less relapse-free survival but same overall survival

with diffuse spilling. The preoperative chemotherapy results in a downstaging of the tumor. This effect after chemotherapy may raise doubts in regard to Stage II, because it might have been in reality a stage III. Therefore, within the SIOP protocol, Stage II patients receive additionally antracyclin to adjust for this problem. The WT trial in the UK recommends preoperative chemotherapy also, but includes percutaneous biopsy to obtain histological confirmation. This procedure has the risk of tumor leakage along the needle tract leading to recurrences within the biopsy tract.

Radiotherapy of the tumor region is recommended for Stage III; therefore, tumor spillage during surgery should be avoided at all costs. Lung radiation can be omitted if pulmonary metastases disappear under chemotherapy or when they have been resected successfully. However, pulmonary radiation is inevitable if additional pulmonary metastases reappear.

One of the criticisms in regard to the SIOP protocol was the uncertainty of diagnosis without a preoperative biopsy. The SIOP arguments are that imaging methods today are so excellent that misdiagnosis is extremely rare. In SIOP-9, only 2% of patients received preoperative chemotherapy inappropriately for nonmalignant processes and 3% had other malignant diseases. However, neither dactinomycin nor vincristine is associated with much short-term toxicity, and no long-term complications have been identified so far. Furthermore, biopsy is recommended if the tumor does not significantly respond to chemotherapy with a shrinking volume within 1 or 2 weeks. The disadvantage of the NWTS protocol is caused by the fact that the surgical procedure for the usually very large tumor is more difficult. Thus, surgical complication rates are higher (9.8% vs. 6.8%) although not significant, but tumor rupture occurs significantly more often (15.3% vs. 2.2%). As a consequence, the number of Stage III patients with the additional need for local radiation is significantly higher (30.4% vs. 14.2) (Table 73.2).

The surgical procedure consists of a transabdominal tumornephrectomy via a large transverse incision. Whether or not the contralateral kidney must be explored during surgery is a matter of debate. We think that today's preoperative imaging methods are so excellent that this extension of the procedure is rarely necessary.

The hilum of the kidney is approached first and the vessels are ligated in order to avoid intraoperative spread of malignant cell elements through the renal vein. However, this part of the procedure is often not feasible due to the huge size of the tumor and the close connection to the vena cava or aorta. The adrenal gland may be left in place if it is not abutting the tumor. The ureter is ligated and divided as low as possible. Careful sampling of regional and distant lymph nodes is essential for correct staging. Metastatic lesions in the liver or lungs must be excised surgically if they are present after appropriate chemotherapy.

73.5 Special Problems

Tumor extension into the renal vein and vena cava presents a particular problem. The preoperative imaging examinations show the extension of the invasion accurately. Preoperative chemotherapy often reduces not only the size but also the intravascular extension of

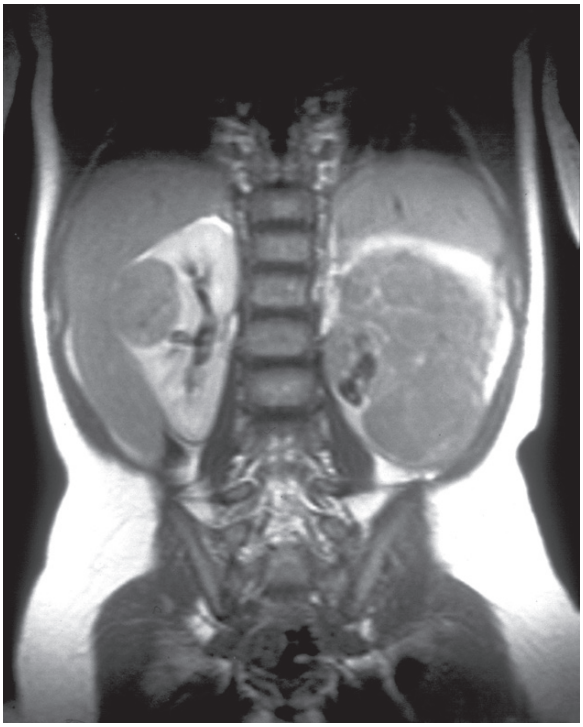

Fig. 73.5 Bilateral Wilms Tumor. In this case tumor enucleation on the right side is not a violence of the protocol

the tumor. If the tumor thrombus is located within the infradiaphragmatic vena cava it can be removed through a horizontal cavatomy after occlusion of the vein above the liver or within the pericardium. If the tumor extends beyond the diaphragm into the right atrium cardiopulmonary bypass is recommended.

The protocols agree that primary chemotherapy is necessary if a *bilateral WT* is present. Four to 6 weeks of chemotherapy result in a significant reduction of tumor size and volume and kidney-sparing surgery can be performed (Fig. 73.5). The surgical procedure should always start at the more difficult side; if a kidney-sparing surgical procedure on this side is not possible and tumornephrectomy is inevitable, the surgeon should do the best to save as much normal kidney tissue as possible on the other side, even by tumor enucleation. Some authors recommend a bench dissection of the tumor with autotransplantation of the kidneys for these difficult cases. Results in bilateral tumors are excellent and exceed 80% after 2 years. *Metachronous tumor*s occur in about 1% after therapy of unilateral WT. Partial nephrectomy is recommended after preoperative chemotherapy.

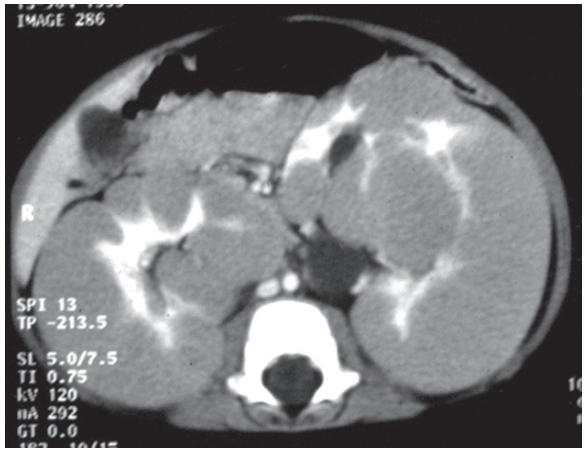

Fig. 73.6 Diffuse bilateral microscopic nephroblastomatosis. This kidney responded well to chemotherapy, but the patient developed a unilateral Wilms Tumor 2 years later, which was resected by nephron-sparing surgery

WT in horseshoe kidneys is approximately two times more common than in the general population. We recommend preoperative chemotherapy to reduce the tumor size and to allow an easier resection of the involved side.

Nephroblastomatosis is a diffuse mostly bilateral, microscopic, or macroscopic presence of NR in the kidneys, usually in children under 2 years of age. Microscopic nephroblastomatosis is common in children with bilateral WT, or in children younger than 1 year, or in patients with associated syndromes. Macroscopic nephroblastomatosis is characterized by significantly enlarged and lobulated kidneys (Fig. 73.6). Therapeutic regimen includes biopsy and reduced chemotherapy until the kidneys achieve the normal appearance. However, long-term regular controls are mandatory, because a unilateral or bilateral synchronous or metachronous Wilms' tumor may occur months or years later.

73.6 Nephron-Sparing Surgery

Nephron-sparing surgery is a well-established method in adult patients with unilateral renal cell carcinoma—a comparable tumor with good overall results. In contrast, renal salvage procedures in unilateral WT remain a controversial issue and tumor nephrectomy is recommended as the standard surgical procedure. On the

basis of today's excellent survival rate of more than 90% of patients, the question whether in some carefully selected cases of unilateral WT a kidney-sparing surgery could represent a valid option preserving a maximum of healthy renal tissue for the patient must be asked.

Any reduction of kidney tissue causes structural and functional hypertrophy of the remaining nephrons. While the overall function is normal, the glomerular filtration rate rises in the remaining kidney by 70%, the creatinine clearance is reduced to 75% of normal, and the systolic blood pressure increases. In young children, the minimal amount of renal tissue is about 25% of total in order to keep the glomerular filtration rate at a level greater than 50 mL/m/1.73 m^2. In adolescence, about 40% of the total is needed to avoid renal insufficiency. The risk of end-stage renal insufficiency after nephrectomy in otherwise normal patients is considered to be as low as 0.2% and 0.6%. In bilateral WT, the incidence of end-stage renal disease 20 years after treatment is between 5.4% and 12% in the literature. Unilateral nephrectomy bears the additional long-term risk of focal glomerulosclerosis caused by hyperfiltration of the remaining kidney tissue. Microalbuminuria, proteinuria, and a decreased glomerular filtration rate can be observed in adults as a long-term sequel of renal agenesis or unilateral nephrectomy. The cumulative incidence of end-stage renal disease is significantly higher in patients with Denish-Drash syndrome, Wilm's tumor aniridia syndrome, hypospadias or cryptorchidism, or other genito-urinary anomalies (Table 73.3). However, this group of patients represents only 0.75% of overall WT population.

A further argument for renal salvage procedures in unilateral WT lies in the advantage of renal tissue preservation in cases of secondary contralateral nephrectomy, i.e., due to metachronous WT or trauma. The main argument for a partial nephrectomy, however, comes from findings during the surgical procedure, when a comparable small WT is located on one pol of the kidney and a heminephrectomy could easily be performed. This finding is more often encountered when patients are treated according to the SIOP protocol with a 4-week course of chemotherapy before surgery. Significant reduction in volume, measured weekly by ultrasound reflects a favorable histology. A reduction in tumor volume to at least 50% after chemotherapy, the location of the tumor on the upper or lower pole of the kidney, Stage I (or local Stage I in a Stage VI patient), and salvage of at least half of the normal kidney are the prerequisites for a nephron-sparing strategy (Table 73.4; Fig. 73.7). These criteria have been included in the recent SIOP protocol as an option for centers that can provide the necessary surgical experience. Only occasionally a lesion will be small enough to allow partial nephrectomy without preoperative chemotherapy.

The tumor heminephrectomy needs a 10–15 min occlusion of the renal vessels. Thereafter, careful coagulation of the bleeding vessels on the cut surface and closure of the urinary collecting system by single or continuous sutures is necessary. In most cases with a small WT on one pol of the kidney, tumor resection can be easily performed including a rim of healthy renal tissue. It is important to emphasise that when the resection through normal renal tissue seems to be doubtful an intraoperative ultrasound examination is necessary to define the appropriate resection line. If this option is not available, tumor nephrectomy should be better preferred. Inadvertent opening of the tumor must be avoided strictly, since it changes the stage from I to III, which then needs additional local radiation therapy.

The preoperative imaging studies provide only a vague hint whether renal salvage will be possible. It is our experience that only the intraoperative situs is decisive for the definite surgical approach. Moreover, some WTs that have responded well to primary

Table 73.3 Significant decreased risk of renal failure after unilateral nephrectomy in syndromic patients

	n	Renal failure—%
DDS	22	62.4
WAGR syndrome	46	38.3
Male GU anomalies	153	10.9
Bilateral disease	397	5.5
Unilateral disease	5358	1.0

Table 73.4 Nephron-sparing surgery may be performed if these criteria are fulfilled

- Local Stage I (IV)
- Tumor involving one pole
- No invasion of renal vein
- At least 50% of normal kidney tissue remaining
- Resection must be possible with tumor-free margins
- Surgeon and oncologist agree about the decision

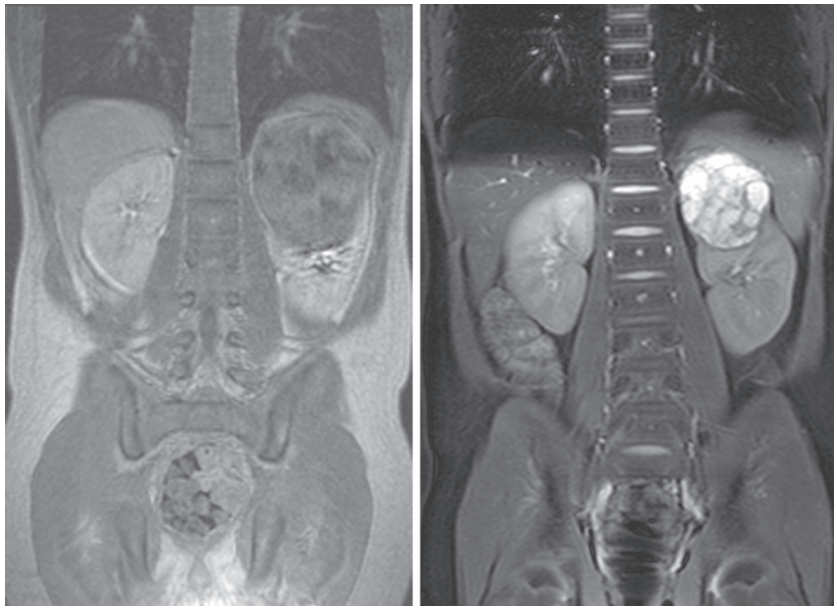

Fig. 73.7 Significant reduction of tumor volume and tumor localization on one pole of the kidney. Heminephrectomy including the tumor is easily possible and saves the other normal half of the kidney

chemotherapy but remain a large mass preoperatively and are therefore determined for tumor nephrectomy. However, during surgery they can turn out as a resectable tumor with the possibility of preservation of at least 50% of the healthy renal tissue. Thus, the final decision should be felt during the surgical procedure and in accordance with the present oncologist. In regard to the discussion in the literature about the risks or the advantages of nephron-sparing surgery in WT patients, we should consider a statement of Beckwith "…the proven efficacy of modern chemotherapy for Wilm's tumor, coupled with the power of imaging technology, provides a basis for considering more conservative management of problems that formerly would have required destruction of most or all renal function."

73.7 Prognosis

Current result in the treatment of WT is one of the most impressive success stories in pediatric oncology. While in the fifties of the last century about 50% of all patients with WT died despite the introduction of radiation, survival rates reach more than 90% now with a multimodal therapy including tumor nephrectomy in unilateral WT. Despite the differences in protocols between the NWTS and the SIOP, the overall long-term results are similar. The recent results of the SIOP study are presented in Table 73.5.

Table 73.5 5-year survival results according to the SIOP-Study 93-01

Relapse free after 4 years:	
Stage I	97%
Stage II and III	86%
Stage IV	60% (80%)
Stage V	82%
Survival with a local relapse	50%
Survival with systemic relapse	40%

Furthermore, the preliminary results of partial nephrectomy in the SIOP 93-01 study show that the relapse-free survival was not different to total nephrectomy. We conclude that modern techniques of diagnosis and treatment allow less aggressive strategies with lower morbidity and excellent cure rates.

Further Reading

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