

## Current Therapy for Wilms' Tumor

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**Key Words.** Pediatric cancer • Wilms' tumor • Nephroblastoma • Therapy • SIOP • NWTs

### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the clinical and biological prognostic factors for Wilms' tumor.
2. Discuss the different treatment strategies and staging systems adopted in North America and Europe.
3. Explain the challenges and treatment approaches for anaplastic, bilateral, and recurrent Wilms' tumor.

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### ABSTRACT

Wilms' tumor was the first solid malignancy in which the value of adjuvant chemotherapy was established. Multimodality treatment has resulted in a significant improvement in outcome from approximately 30% in the 1930s to more than 85% in the modern era. Although the National Wilms' Tumor Study Group and the International Society of Pediatric Oncology differ philosophically regarding the merits of preoperative chemotherapy, outcomes of patients treated with either

up-front nephrectomy or preoperative chemotherapy have been excellent. The goal of current clinical trials is to reduce therapy for children with low-risk tumors, thereby avoiding acute and long-term toxicities. At the same time, current clinical trials seek to augment therapy for patients with high-risk Wilms' tumor, including those with bilateral, anaplastic, and recurrent favorable histology tumors. *The Oncologist* 2005;10:815-826

### INTRODUCTION

In June 1877, at the General Infirmary at Leeds, England, Dr. Thomas Jessop (1837-1903) performed the first successful nephrectomy on a 2-year-old child with hematuria and a large malignant process arising from the left kidney [1]. It was not until 1899 that the surgeon Max Wilms (1867-1918) described seven children suffering from nephroblastoma in a monograph on "mixed tumors" [2]. It is now recognized that nephroblastoma, or Wilms' tumor, is the most common renal malignancy of childhood. Developments in surgical techniques in the 20th

century improved the prognosis for this previously lethal malignancy. However, it was the discovery of the tumor's radiosensitivity and the introduction of active chemotherapy agents that drastically improved survival rates. Today, with an overall survival (OS) rate of 90%, new treatment protocols are shifting their primary objective from maximizing cure to maximizing cure with minimal treatment-related toxicities. In this review, we discuss the advances of Wilms' tumor therapy and current treatment strategies in North America and Europe.

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## PROGNOSTIC FACTORS

Treatment regimens for Wilms' tumor are selected based on an individual's risk of recurrence, which is defined by clinical, histological, and biological prognostic factors. In this section, we describe the main prognostic indicators for Wilms' tumor. These indicators will provide a backdrop for our discussion of treatment strategies.

### Tumor Stage

Staging criteria for Wilms' tumor are based exclusively on the anatomic extent of the tumor, without consideration of genetic, biologic, or molecular markers [3]. Two major staging systems are currently used: a prechemotherapy/up-front, surgery-based system developed by the National Wilms' Tumor Study Group (NWTSG) and a postchemotherapy-based system developed by the International Society of Pediatric Oncology (SIOP) (Table 1). Both staging

systems have proven valuable in predicting outcomes. It is important to recognize, however, that the difference in surgical timing confounds stage-for-stage comparisons between the two systems.

### Histology

Histologic characteristics are the most powerful prognostic indicators for Wilms' tumor. A retrospective study of pathology samples from the first National Wilms' Tumor Study (NWTSG-1) showed that anaplasia (irregular mitotic figures, large nuclear size, and hyperchromasia) is associated with adverse outcome [4]. Anaplasia may be diffuse or focal; focal anaplasia portends a prognosis between that of tumors without anaplasia (a so-called "favorable" or "standard" histologic feature) and that of tumors with diffuse anaplasia [5, 6]. Clear-cell sarcoma of the kidney and malignant rhabdoid tumor of the kidney, initially believed

**Table 1.** Staging systems for renal tumors [3, 13]

Stage	NWTSG (before chemotherapy)	SIOP (after chemotherapy)
I	<ul style="list-style-type: none"> <li>(a) Tumor is limited to the kidney and completely excised</li> <li>(b) The tumor was not ruptured before or during removal</li> <li>(c) The vessels of the renal sinus are not involved beyond 2 mm</li> <li>(d) There is no residual tumor apparent beyond the margins of excision</li> </ul>	<ul style="list-style-type: none"> <li>(a) Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected (resection margins "clear")</li> <li>(b) The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls)</li> <li>(c) The vessels of the renal sinus are not involved</li> <li>(d) Intrarenal vessel involvement may be present</li> </ul>
II	<ul style="list-style-type: none"> <li>(a) Tumor extends beyond the kidney but is completely excised</li> <li>(b) No residual tumor is apparent at or beyond the margins of excision</li> <li>(c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor</li> </ul> <p><i>Although tumor biopsy or local spillage confined to the flank were considered stage II by NWTSG in the past, such events will be considered stage III in upcoming COG studies.</i></p>	<ul style="list-style-type: none"> <li>(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")</li> <li>(b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected</li> <li>(c) The tumor infiltrates adjacent organs or vena cava but is completely resected</li> </ul>
III	<p>Residual tumor confined to the abdomen:</p> <ul style="list-style-type: none"> <li>(a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor</li> <li>(b) Diffuse peritoneal contamination by the tumor</li> <li>(c) Implants are found on the peritoneal surfaces</li> <li>(d) Tumor extends beyond the surgical margins either microscopically or grossly</li> <li>(e) Tumor is not completely resectable because of local infiltration into vital structures</li> </ul>	<ul style="list-style-type: none"> <li>(a) Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains postoperatively)</li> <li>(b) Any abdominal lymph nodes are involved</li> <li>(c) Tumor rupture before or intraoperatively (irrespective of other criteria for staging)</li> <li>(d) The tumor has penetrated through the peritoneal surface</li> <li>(e) Tumor thrombi present at resection margins of vessels or ureter, trans-sected or removed piecemeal by surgeon</li> <li>(f) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery</li> </ul> <p><i>Regional lymph node involvement was considered stage II in the previous SIOP staging system.</i></p>
IV	<p>Presence of hematogenous metastases or metastases to distant lymph nodes</p>	<p>Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region</p>
V	<p>Bilateral renal involvement at the time of initial diagnosis</p>	<p>Bilateral renal tumors at diagnosis</p>

Abbreviations: COG, Children's Oncology Group; NWTSG, National Wilms' Tumor Study Group; SIOP, International Society of Pediatric Oncology.

to belong to the “unfavorable histology” family of Wilms’ tumors, are now considered distinct tumor types and will not be discussed further [7–10].

Classic Wilms’ tumor is composed of three cell types—blastemal, stromal, and epithelial—which can be present in various proportions. Also present are heterologous epithelial or stromal components, which include mucinous or squamous epithelium, skeletal muscle, cartilage, osteoid tissue, and fat [11]. Histologic classification defined by the NWTSG and SIOP studies differs because the SIOP protocols use preoperative chemotherapy. Hence, the SIOP histologic classification reflects chemotherapy-induced changes, including “regressive” changes or cell differentiation. Whereas the NWTSG classifies Wilms’ tumors based on the presence or absence of anaplasia, the revised SIOP histologic classification divides Wilms’ tumors into three risk groups: (a) low risk (completely necrotic nephroblastoma or cystic partially differentiated nephroblastoma), (b) intermediate risk (regressive, epithelial, stromal, mixed, or focal anaplastic nephroblastoma), and (c) high risk (blastemal or diffuse anaplastic nephroblastoma) [12, 13].

### Patient Age

Cooperative group studies have shown that increasing patient age is associated with increased risk of recurrence in nonmetastatic Wilms’ tumor [14–17]. A subgroup with an outstanding prognosis are patients less than 2 years of age with small (<550 g) stage I favorable histology tumors [18–20]. At the other end of the age spectrum, adults with Wilms’ tumor were previously found to have relatively unfavorable outcomes compared with their pediatric counterparts, with an event-free survival (EFS) rate of 20%–30% [21]. More recent studies, however, have indicated that the survival rate for adult Wilms’ tumor is similar to that for pediatric Wilms’ tumor, although toxicity of treatment is greater in adults [22, 23].

### Biological Prognostic Factors

Several biological factors have recently been identified that may supplement stage and histology in assigning risk. One such factor is loss of heterozygosity (LOH) at chromosomes 1p and 16q. Studies in the 1990s showed that children with LOH at 16q had greater risks of relapse and mortality than did children without this change [24–26]. A similar finding applied to LOH at chromosome 1p [24, 25]. To corroborate these findings, the fifth National Wilms’ Tumor Study (NWTSG-5) prospectively analyzed LOH in primary Wilms’ tumors. Tumor-specific LOH for both chromosomes 1p and 16q, identified in approximately 5% of patients with favorable histology Wilms’ tumor, was shown to correlate with a significantly increased risk of relapse and death [27].

Future Children’s Oncology Group (COG) clinical studies will augment therapy for patients with favorable histology Wilms’ tumor and LOH at 1p and 16q. Other promising prognostic markers are an increase in gene copy number or expression at chromosome 1q [28, 29] and telomerase expression level [30, 31]. Gene expression profiling also shows promise to identify new prognostic factors [32–34].

### TREATMENT OF WILMS’ TUMOR WITH FAVORABLE HISTOLOGIC FEATURES

Several cooperative groups and individual institutions have made important contributions to the optimization of Wilms’ tumor therapy. Because the NWTSG and SIOP studies have included the largest number of patients, this review focuses on their findings. Since the NWTSG and SIOP nephroblastoma studies began more than three decades ago, there has been a philosophical difference of opinions about the administration of preoperative chemotherapy. The NWTSG and its successor, the COG, advocate up-front resection of the primary tumor before chemotherapy is given. In contrast, SIOP recommends the administration of chemotherapy for 4 weeks before surgery. Both treatment approaches yield excellent clinical outcomes (Table 2), yet a fertile debate continues about the relative merits of each approach [35].

### The NWTSG Experience

In the NWTSG and upcoming COG studies, primary surgical resection of the tumor is the initial treatment of most children. A transabdominal, transperitoneal incision is recommended to permit inspection of sites of involvement and to facilitate biopsy of suspicious sites [36]. An NWTSG review of surgical factors that predict recurrence demonstrated that failure to sample the lymph nodes was an adverse prognostic feature, even in comparison with documented tumor invasion of the lymph nodes. Presumably, a subset of patients who did not undergo lymph node sampling was undertreated [37]. One of the main challenges for surgeons is to avoid tumor spillage, which increases the risk of local abdominal relapse and subsequent poor outcome [37]. Surgical complications observed in the fourth National Wilms’ Tumor Study (NWTSG-4) were bowel obstruction (5.1%), extensive hemorrhage and wound infection (1.9% each), extensive vascular injuries (1.4%), and injuries to other visceral organs (1%) [38]. Risk factors for surgical complications included intravascular extension into the inferior vena cava, the atrium, or both; a flank or paramedian surgical approach; and a tumor diameter greater than 10 cm. Interestingly, nephrectomy performed by a general surgeon carried a higher risk of complications (odds ratio, 9.0; 95% confidence interval, 1.3–65;  $p =$

**Table 2.** Summary of patient outcomes from recently reported large studies of Wilms' tumor with favorable or standard histologic characteristics<sup>a</sup>

Study	Stage	RFS/EFS (%)	OS (%)	Reference
NWTS-3	I	16-year 92.5	16-year 97.6	[92]
	II	89.6	92.9	
	III	80.4	86.2	
	IV	76.5	79.5	
NWTS-4	I	94.9 (2-year)	98.7 (2-year)	[93, 94]
	II	83.6 (8-year)	93.8 (8-year)	
	III	88.9 (8-year)	93.0 (8-year)	
	IV	80.6 (2-year)	89.5 (2-year)	
NWTS-5	I (age < 24 months, tumor weight < 550 g)	2-year 86.5	2-year 100	[19]
SIOP-9	I	2-year 88	2-year 93	[95]
	II N0	85	88	
	II N1 and III	71	85	
SIOP93-01	I	5-year 88.3	5-year 97.0	[12]
UKW2/UKW3	I	4-year 86.5	4-year 94.7	[17, 96]
	II	82	91	
	III	82	84	
	IV	70	75	
	V	70	78	

<sup>a</sup>When treatments are randomized, results from the protocol-recommended treatment arm are listed.

Abbreviations: EFS: event-free survival; N0, no lymph node involvement; N1, lymph node involvement; NWTS, National Wilms' Tumor Study; OS: overall survival; RFS: relapse-free survival; SIOP, International Society of Pediatric Oncology; UKW, United Kingdom Children's Cancer Study Group Wilms' tumor trial.

.03) than that performed by a pediatric surgeon (reference group; odds ratio, 1.0) or a pediatric urologist (odds ratio, 0.7; 95% confidence interval, 0.3–1.8).

A study of the feasibility of partial nephrectomy in treating nonmetastatic, unilateral Wilms' tumors found that only 4.7% of patients would be eligible for this procedure [39, 40]. Partial nephrectomy was allowed only if the tumor involved one pole and less than one third of the kidney, if the patient had a functioning kidney, if the collecting system or renal vein had no tumor involvement, and if clear margins existed between the tumor and surrounding structures. Because the rate of renal failure in patients with unilateral Wilms' tumor is less than 1% [41], kidney-sparing resection is not generally recommended.

Nephrectomy without adjuvant therapy was suggested to be adequate treatment for a subset of patients with highly favorable clinical features in the 1970s [42]. Retrospective review of NWTS-4 found that age at diagnosis less than 24 months and tumor weight less than 550 g were correlated with the absence of relapse-associated variables previously described in patients with stage I favorable histology tumors [43, 44]. Based on these findings, NWTS-5 prospectively treated 75 children younger than 24 months with small (<550 g) stage I favorable his-

tology tumors with nephrectomy only. The study closed early according to predefined stopping rules because the risk of relapse at 2 years was 13.5%; however, all patients were successfully salvaged with standard therapy [19]. In light of the high OS rate achieved, the COG is planning a study to re-evaluate the benefit of nephrectomy-only in this selected group of patients.

The NWTSG has recommended preoperative chemotherapy under certain circumstances, including the occurrence of Wilms' tumor in a solitary kidney, bilateral Wilms' tumor, tumor in a horseshoe kidney, tumor thrombus in the inferior vena cava above the level of the hepatic veins, and respiratory distress resulting from the presence of extensive metastatic tumor [45].

The role of chemotherapy in treating Wilms' tumors is undisputed. The activity of dactinomycin and vincristine against Wilms' tumor was shown in the 1950s and 1960s, and these drugs have served as the cornerstone of Wilms' tumor therapy ever since [46, 47]. Doxorubicin was added to the Wilms' tumor treatment armamentarium in the 1970s [48]. Through successive NWTS trials, the combination, length, and mode of administration of these three drugs have been refined to optimize survival rates while minimizing acute and long-term toxicities. Radiation therapy,

although still an important component of Wilms' tumor therapy, is restricted to treatment of stage III or IV disease. The conclusions drawn from each of the five NWTSG trials are summarized in Table 3.

Although most of the treatment results from NWTSG-5 have not yet been reported, we believe that the NWTSG-5 treatment approach provides a reasonable standard of care for Wilms' tumor with favorable histologic features (Table 4).

### The SIOP Experience

The SIOP strategy of giving preoperative chemotherapy is based on the premise that preoperative therapy reduces the risk of tumor rupture during surgery, thereby reducing the likelihood of local and distant recurrence. A succession of SIOP studies, beginning in 1971, determined the optimal preoperative therapy regimen for patients with renal tumors. The main results of past trials are summarized in Table 5. (The treatment regimens for the most recently completed study, SIOP 93-01, are shown in Table 4.)

The paradigm of maximizing cure while minimizing toxicity is being evaluated in the ongoing SIOP-2001 protocol, in which postoperative chemotherapy is tailored according to histologic features, as defined by a new classification system [12, 13]. Another aim of the study is to

decrease late cardiac toxicity in patients with stage II or III and histologically intermediate-risk disease. These patients are randomly assigned treatment with or without doxorubicin, which is known to cause late cardiac toxicity [12, 49].

### Pros and Cons of the NWTSG and SIOP Approaches

The NWTSG and SIOP approaches to Wilms' tumor treatment each have distinct advantages and disadvantages. The primary strength of the NWTSG approach is that up-front resection allows an accurate assessment of histologic diagnosis and tumor extent. Most patients treated on SIOP Wilms' tumor studies do not undergo tumor biopsy before starting therapy. On SIOP 93-01, approximately 5% of lesions in patients treated with chemotherapy were ultimately shown not to be Wilms' tumor and included 1.8% that were benign [12]. A research benefit of removing the tumor before chemotherapy is that it enables the collection of untreated tumor for biology studies and provides an unadulterated view of the tumor's molecular biology. The primary strength of the SIOP approach is that preoperative chemotherapy usually reduces the tumor volume, thereby decreasing the likelihood of spillage and "downstaging" the tumor [11]. As a result, fewer patients received local

**Table 3.** Primary conclusions from NWTSG studies of Wilms' tumor with favorable histologic features

Study	Stage/group	Chemotherapy	Radiation therapy
NWTSG-1 [97] (1969–1973)	I	–	Unnecessary for children < 2 years (when treated with chemotherapy)
	II and III	Vincristine and dactinomycin combination better than either drug alone	–
NWTSG-2 [92] (1974–1978)	I	6 months of vincristine and dactinomycin sufficient	Unnecessary
	II, III, and IV	Addition of doxorubicin increased RFS rate	–
NWTSG-3 [92] (1979–1986)	I	11 weeks of vincristine and dactinomycin sufficient	–
	II	Doxorubicin unnecessary	Unnecessary
	III	Doxorubicin necessary	With 1,000-cGy abdominal irradiation
		Doxorubicin unnecessary	With 2,000-cGy abdominal irradiation
	IV	No benefit to the addition of cyclophosphamide	–
NWTSG-4 [93, 98] (1986–1994)	I–IV	"Pulse-intensive" chemotherapy as effective, less toxic, and less expensive	–
	II, III, and IV	6 months of chemotherapy sufficient	–
NWTSG-5 (1995–2001)	I	Without chemotherapy, 2-year OS rate remained 100% but RFS rate was 86% – arm closed	–
	All stages	Loss of heterozygosity at chromosomes 1p AND 16q is an adverse prognostic indicator	

Abbreviations: NWTSG, National Wilms' Tumor Study; NWTSG, National Wilms' Tumor Study Group; OS, overall survival; RFS, relapse-free survival.

**Table 4.** Treatment regimens for Wilms' tumor with favorable or standard histologic features from recently completed NWTSG and SIOP studies [12, 59, 99, 100]

Stage <sup>a</sup>	NWTSG-5		SIOP 93-01		Radiation therapy
	Chemotherapy	Radiation therapy	Chemotherapy		
			Preoperative	Postoperative	
I	VA × 18 weeks	–	VA × 4 weeks	VA × 4 weeks <sup>b</sup>	–
II	VA × 18 weeks	–	VA × 4 weeks	VDA × 27 weeks	Node-negative: none Node-positive: 15 Gy
III	VDA × 24 weeks	10.8 Gy	VA × 4 weeks	VDA × 27 weeks	15 Gy
IV	VDA × 24 weeks	12 Gy lung (if lung metastasis)  10.8 Gy flank (if local stage III)	VDA × 6 weeks	CR after 9 weeks: VDA × 27 weeks  No CR after 9 weeks: ICED × 34 weeks	None if lung lesions disappear by week 9, otherwise 12 Gy

<sup>a</sup>Note that the NWTSG stage is determined before surgical resection and the SIOP stage after resection; the staging systems are not equivalent.

<sup>b</sup>Patients were randomly assigned to receive postoperative VA for 4 or 18 weeks. Treatment with VA was no less effective for 4 weeks than for 18 weeks.

Abbreviations: A, dactinomycin; C, carboplatin; CR, complete remission; D, doxorubicin; E, etoposide; I, ifosfamide; NWTSG, National Wilms' Tumor Study; NWTSG, National Wilms' Tumor Study Group; SIOP, International Society of Pediatric Oncology; V, vincristine.

**Table 5.** Primary conclusions of SIOP studies of Wilms' tumor with favorable histologic features

Study	Stage	Therapy
SIOP-1 [101, 102] (1971–1974)	I, II, or III	There was no difference in survival rate between the preoperative radiation therapy and immediate surgery groups. Significantly fewer tumor ruptures occurred in the pretreated group, and the recurrence-free survival rate was lower for patients who experienced intraoperative rupture.
SIOP-2 [101] (1974–1976)	I, II, or III	Study confirmed that patients who receive preoperative radiation therapy with dactinomycin are less likely to experience tumor ruptures than are those who undergo immediate surgery. Six months of postoperative treatment was as effective as 15 months in terms of event-free and overall survival rates.
SIOP-5 [3, 103] (1977–1979)	I, II, or III	Preoperative chemotherapy with vincristine and dactinomycin was as effective as radiation therapy with actinomycin-D in preventing tumor rupture.
SIOP-6 [104] (1980–1986)	I II	Treatment with vincristine and dactinomycin was as effective for 17 weeks as for 38 weeks in terms of event-free and overall survival rates. Patients with negative lymph nodes who were assigned to receive no radiation therapy had a higher recurrence rate.
SIOP-9 [95] (1987–1993)	I, II, or III II	Preoperative vincristine and dactinomycin was as effective for 4 weeks as for 8 weeks in terms of stage distribution and tumor shrinkage. For patients with negative lymph nodes, the rate of relapse was reduced by treatment with epirubicin without radiation therapy.
SIOP 93-01 [12] (1993–2000)	I	Reduction of postoperative chemotherapy (for intermediate-risk and anaplastic Wilms' tumor) to four doses of vincristine and one dose of dactinomycin was not less effective than standard postoperative chemotherapy.

Abbreviation: SIOP, International Society of Pediatric Oncology.

irradiation on SIOP-9 than on NWTSG-5, although slightly more of the SIOP-9 patients received anthracycline [35]. A second advantage of preoperative chemotherapy is that response to treatment may provide a valuable prognostic indicator [50, 51]. In the absence of a clear choice between up-front nephrectomy and preoperative chemotherapy, it is reasonable to base the timing of resection on factors such as tumor size, the patient's clinical condition, and the experience of the surgeon.

Another difference between the NWTSG and SIOP studies is in the management of lung metastases. In the most recent NWTSG studies, computerized tomographic (CT) scan and chest x-ray were performed to determine the presence of lung metastases. If the two imaging modalities yielded discordant results (usually in the form of "CT-only" nodules), the disease stage was ultimately designated by the treating physician. Any patient deemed to have lung metastases was given whole-lung irradiation. The 2-year

relapse-free survival estimate for patients with stage IV disease treated on NWTS-4 was 81% [52]. In the SIOP studies, only chest x-ray was used to evaluate lung metastasis. If lung metastases completely disappeared with chemotherapy (or were completely resected), patients did not receive lung irradiation. With this approach, SIOP reported a 4-year EFS rate of 83% [53]. In contrast, the first Wilms' tumor study by the United Kingdom Children's Cancer Study Group reported a survival rate of only 65% when radiation therapy was not given to patients with lung metastases [54]. This finding raises the question about the role of lung irradiation. Future COG trials will assess the necessity of lung irradiation for patients whose tumors have favorable biological and histological features and show rapid response to chemotherapy.

### TREATMENT OF ANAPLASTIC WILMS' TUMOR

The first trial to place anaplastic Wilms' tumor into a distinct treatment group was the third National Wilms' Tumor Study (NWTS-3) (1979–1986). On this study and on NWTS-4 (1986–1994), patients received vincristine, dactinomycin, and doxorubicin for 15 months and were randomly assigned to receive or not receive cyclophosphamide [6]. Patients with stage II–IV diffuse anaplastic disease had a 4-year relapse-free survival estimate of 27% when treated without cyclophosphamide and 55% when treated with cyclophosphamide ( $p = .02$ ) [6]. On the basis of these results, NWTS-5 incorporated cyclophosphamide into the treatment plan for patients with stage II, III, or IV diffuse anaplasia. Such patients received abdominal irradiation and a novel chemotherapy regimen consisting of vincristine, doxorubicin, and cyclophosphamide alternating with cyclophosphamide and etoposide. Patients with stage II–IV focal anaplasia were treated with abdominal irradiation, vincristine, doxorubicin, and dactinomycin. The 4-year EFS estimates for patients with diffuse and focal anaplasia were 55.1% and 74.9%, respectively. Four-year EFS estimates for patients with stage II ( $n = 28$ ), III ( $n = 51$ ), and IV ( $n = 16$ ) anaplasia who had undergone immediate nephrectomy were 82.1%, 68.3%, and 37.5%, respectively. OS estimates were similar to EFS estimates [55].

On NWTS-5, patients with stage I diffuse or focal anaplastic Wilms' tumor were treated with vincristine and dactinomycin because earlier studies had shown good outcomes for this group [56]. However, preliminary analysis yielded unexpectedly low 4-year EFS and OS estimates of 69.5% and 82.6%, respectively [55]. Hence, future COG studies will add doxorubicin and irradiation to the therapeutic regimen for these patients.

### TREATMENT OF BILATERAL WILMS' TUMOR

Synchronous bilateral Wilms' tumors account for only 6% of all Wilms' tumors but they pose the special challenge

of establishing local tumor control while preserving renal function. The management of bilateral Wilms' tumor has evolved from primary surgical extirpation to kidney-preserving resection after preoperative chemotherapy. Preoperative chemotherapy often results in significant reduction in tumor size, thereby facilitating subsequent renal salvage. Extended follow-up of patients with bilateral Wilms' tumor who were enrolled on NWTS-2 and -3 showed no difference in survival rates between those treated initially with surgical resection and those treated with biopsy and preoperative chemotherapy [57]. On NWTS-4, the risk of local recurrence for patients who underwent kidney-sparing resection was 8.2% [58]. The NWTS-5 recommendation for the management of bilateral Wilms' tumor includes initial biopsy and local staging followed by chemotherapy (according to abdominal stage and histologic features) and second-look surgery at week 5 [59]. If needed, additional chemotherapy or radiation therapy is given, but definitive surgery is recommended within 12 weeks of diagnosis to limit the risk of chemoresistant clonal expansion [3]. Failure of bilateral Wilms' tumor to respond to preoperative chemotherapy is often due not to anaplasia but to persistence of mature elements with a skeletal muscle component. In patients with anaplastic tumors, complete surgical excision is warranted, and in such cases the NWTSG favors tumor resection with a margin of renal tissue rather than enucleation. Long-term survival rates for patients with synchronous bilateral Wilms' tumors are approximately 70%–80% [57, 60, 61].

Metachronous bilateral Wilms' tumor accounts for approximately 2% of all Wilms' tumors. The NWTSG has reported lower survival rates for patients with metachronous rather than synchronous bilateral tumors [62, 63]. A literature review by Paulino et al. showed that the OS rate for patients with metachronous bilateral Wilms' tumor was 49.1% at 5 years and 47.2% at 10 years, and a second tumor developed at a median interval of 23.1 months [64]. Children in whom a contralateral tumor developed more than 18 months after the initial diagnosis had a better OS rate than did those in whom it developed less than 18 months after diagnosis (10-year OS rate, 55.2% versus 39.6%). Children younger than 12 months who have perilobar nephrogenic rests are at markedly increased risk of contralateral disease and require frequent and regular surveillance for several years [65].

### TREATMENT OF RECURRENT WILMS' TUMOR

Before the mid-1980s, the long-term survival rate after recurrence of Wilms' tumor barely reached 30% [66–70]. During this era, salvage therapy consisted of vincristine, dactinomycin, doxorubicin, radiation therapy, or surgery. Often, salvage therapy was identical to the primary therapy. In recent years, cyclophosphamide, ifosfamide, cisplatin, carboplatin, and etoposide were shown to be active against Wilms' tumor [71–

**Table 6.** High-dose chemotherapy with stem cell rescue for relapsed, refractory Wilms' tumor

Preparative regimen	Total patients	EFS	OS	Reference
Melphalan/vincristine/carmustin, or busulfan	25	34% at 40 months <sup>a</sup>	–	[105]
Melphalan/etoposide/carboplatin	8	–	75% at 2 years	[106]
Melphalan/etoposide/carboplatin	29	50% at 3 years	–	[107]
Melphalan/etoposide/carboplatin	23	48.2% at 58 months	60.9% at 58 months	[108]
Thiotepa/cyclophosphamide/carboplatin; carboplatin/etoposide/cyclophosphamide	13	60% at 4 years	73% at 4 years	[109]

<sup>a</sup>Disease-free survival rather than event-free survival reported in this study.  
Abbreviations: EFS, event-free survival; OS, overall survival.

83], and multiagent regimens containing these drugs, most notably the ICE combination (ifosfamide, carboplatin, and etoposide), have significantly improved postrelapse survival rates to the 50%–60% range [71, 84, 85]. Favorable prognostic factors after relapse include favorable histologic features, relapse occurring more than 12 months after the initial diagnosis, low stage (I or II) of primary disease, initial treatment with vincristine and dactinomycin only, few pulmonary nodules, and no previous irradiation of the tumor bed [67, 84]. Studies of relapsed Wilms' tumor performed at St. Jude Children's Research Hospital indicated that patients who undergo complete resection of the recurrent tumor have a greater chance of survival than do patients who undergo only a partial resection or no surgery at all [69, 84]. It is unclear whether surgical resection was therapeutic or whether the patients who underwent surgery had a lower disease burden. Another study from the NWTSG showed that although therapeutic resection of pulmonary nodules does not improve outcome, it may have a role in histological confirmation of recurrence [86].

An unresolved question regarding the treatment of recurrent Wilms' tumor is the benefit of high-dose therapy with autologous stem cell rescue. Several groups have reported promising salvage rates resulting from the use of either single or tandem stem cell transplants (Table 6). It is unclear, however, whether outcomes of high-dose therapy are superior to those obtained with modern, multiagent chemotherapy regimens [71, 84, 85]. A large randomized study will be required to answer this question.

### FUTURE DIRECTIONS

Although survival rates after recurrence of Wilms' tumor have improved since the 1980s, at least 40% of patients remain without cure on current treatment regimens. Novel agents and treatment strategies are needed to improve clinical outcomes for this group. One of the promising new cytotoxic agents for treating Wilms' tumor is the camptothecin analogue topotecan. Preclinical xenograft studies (Dome, unpublished observations) and a phase I clinical trial have demonstrated that topotecan has significant antitumor activ-

ity when given daily for 5 days on two consecutive weeks [87]. A multi-institutional phase II study of topotecan is ongoing. Topotecan also has shown antitumor activity against Wilms' tumor when used in combination with cyclophosphamide [81, 88]. Another promising class of agents consists of anti-angiogenesis agents, including molecules that target the vascular endothelial growth factor (VEGF) pathway. Xenograft models have shown that such agents can inhibit growth of Wilms' tumor [89], prevent metastatic spread [90], or even induce tumor regression [91]. The anti-VEGF antibody bevacizumab is undergoing phase I testing in pediatric patients.

### SUMMARY

The treatment of Wilms' tumor is one of the great success stories in oncology. Modern treatment regimens yield OS rates of 90%, and this success has precipitated a shift in emphasis to reducing toxicity. Although North America and Europe have different philosophies on preoperative chemotherapy, the overriding message is that most patients with Wilms' tumor survive long term, regardless of the sequence of therapeutic interventions. In spite of this success, there remain patients for whom current treatment is suboptimal, including those with anaplastic, bilateral, or recurrent disease with favorable histologic features. These "problematic" groups account for about 25% of patients who have Wilms' tumor, and this high proportion underscores the need for a continued effort to develop novel treatment approaches.

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### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

## REFERENCES

- 1 Willetts IE. Jessop and the Wilms' tumor. *J Pediatr Surg* 2003;38:1496–1498.
- 2 Wilms M. Die Mischgeschwülste der Niere. Georgi A, ed. Leipzig, Germany:1899.
- 3 Kalapurakal JA, Dome JS, Perlman EJ et al. Management of Wilms' tumour: current practice and future goals. *Lancet Oncol* 2004;5:37–46.
- 4 Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms' tumors: results from the First National Wilms' Tumor Study. *Cancer* 1978;41:1937–1948.
- 5 Faria P, Beckwith JB, Mishra K et al. Focal versus diffuse anaplasia in Wilms' tumor—new definitions with prognostic significance: a report from the National Wilms' Tumor Study Group. *Am J Surg Pathol* 1996;20:909–920.
- 6 Green DM, Beckwith JB, Breslow NE et al. Treatment of children with stages II to IV anaplastic Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1994;12:2126–2131.
- 7 Green DM, Breslow NE, Beckwith JB et al. Treatment of children with clear-cell sarcoma of the kidney: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1994;12:2132–2137.
- 8 Haas JE, Palmer NF, Weinberg AG et al. Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. *Hum Pathol* 1981;12:646–657.
- 9 Haas JE, Bonadio JF, Beckwith JB. Clear cell sarcoma of the kidney with emphasis on ultrastructural studies. *Cancer* 1984;54:2978–2987.
- 10 Weeks DA, Beckwith JB, Mierau GW et al. Rhabdoid tumor of kidney. A report of 111 cases from the National Wilms' Tumor Study Pathology Center. *Am J Surg Pathol* 1989;13:439–458.
- 11 Beckwith JB. Wilms' tumor and other renal tumors of childhood: a selective review from the National Wilms' Tumor Study Pathology Center. *Hum Pathol* 1983;14:481–492.
- 12 de Kraker J, Graf N, van Tinteren H et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. *Lancet* 2004;364:1229–1235.
- 13 Vujanic GM, Sandstedt B, Harms D et al. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol* 2002;38:79–82.
- 14 Breslow N, Churchill G, Beckwith JB et al. Prognosis for Wilms' tumor patients with nonmetastatic disease at diagnosis—results of the second National Wilms' Tumor Study. *J Clin Oncol* 1985;3:521–531.
- 15 Breslow N, Sharples K, Beckwith JB et al. Prognostic factors in nonmetastatic, favorable histology Wilms' tumor. Results of the Third National Wilms' Tumor Study. *Cancer* 1991;68:2345–2353.
- 16 Breslow NE, Palmer NF, Hill LR et al. Wilms' tumor: prognostic factors for patients without metastases at diagnosis: results of the National Wilms' Tumor Study. *Cancer* 1978;41:1577–1589.
- 17 Pritchard-Jones K, Kelsey A, Vujanic G et al. Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumor treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilms' Tumor Working Group. *J Clin Oncol* 2003;21:3269–3275.
- 18 Green DM, Breslow NE, Beckwith JB et al. Treatment outcomes in patients less than 2 years of age with small, stage I, favorable-histology Wilms' tumors: a report from the National Wilms' Tumor Study. *J Clin Oncol* 1993;11:91–95.
- 19 Green DM, Breslow NE, Beckwith JB et al. Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 2001;19:3719–3724.
- 20 Larsen E, Perez-Atayde A, Green DM et al. Surgery only for the treatment of patients with stage I (Cassady) Wilms' tumor. *Cancer* 1990;66:264–266.
- 21 Byrd RL, Evans AE, D'Angio GJ. Adult Wilms' tumor: effect of combined therapy on survival. *J Urol* 1982;127:648–651.
- 22 Arrigo S, Beckwith JB, Sharples K et al. Better survival after combined modality care for adults with Wilms' tumor. A report from the National Wilms' Tumor Study. *Cancer* 1990;66:827–830.
- 23 Reinhard H, Aliani S, Ruebe C et al. Wilms' tumor in adults: results of the Society of Pediatric Oncology (SIOP) 93-01/Society for Pediatric Oncology and Hematology (GPOH) Study. *J Clin Oncol* 2004;22:4500–4506.
- 24 Grundy P, Telzerow P, Moksness J et al. Clinicopathologic correlates of loss of heterozygosity in Wilms' tumor: a preliminary analysis. *Med Pediatr Oncol* 1996;27:429–433.
- 25 Grundy PE, Telzerow PE, Breslow N et al. Loss of heterozygosity for chromosomes 16q and 1p in Wilms' tumors predicts an adverse outcome. *Cancer Res* 1994;54:2331–2333.
- 26 Grundy RG, Pritchard J, Scambler P et al. Loss of heterozygosity on chromosome 16 in sporadic Wilms' tumour. *Br J Cancer* 1998;78:1181–1187.
- 27 Grundy PE, Breslow N, Li S et al. Loss of Heterozygosity for Chromosomes 1p and 16q is an Adverse Prognostic Factor in Favorable Histology Wilms' Tumor. A Report from the National Wilms' Tumor Study Group. *J Clin Oncol* 2005;23:7312–7321.
- 28 Hing S, Lu YJ, Summersgill B et al. Gain of 1q is associated with adverse outcome in favorable histology Wilms' tumors. *Am J Pathol* 2001;158:393–398.
- 29 Lu YJ, Hing S, Williams R et al. Chromosome 1q expression profiling and relapse in Wilms' tumour. *Lancet* 2002;360:385–386.
- 30 Dome JS, Bockhold CA, Li SM et al. High telomerase RNA expression is an adverse prognostic factor for favorable histology Wilms' tumor. *J Clin Oncol* 2005 Sept 19 (epub ahead of print).
- 31 Dome JS, Chung S, Bergemann T et al. High telomerase reverse transcriptase (hTERT) messenger RNA level correlates with tumor recurrence in patients with favorable histology Wilms' tumor. *Cancer Res* 1999;59:4301–4307.
- 32 Williams RD, Hing SN, Greer BT et al. Prognostic classification of relapsing favorable histology Wilms' tumor using cDNA microarray expression profiling and support vector machines. *Genes Chromosomes Cancer* 2004;41:65–79.
- 33 Li W, Kessler P, Yeger H et al. A gene expression signature for relapse of primary Wilms' tumors. *Cancer Res* 2005;65:2592–2601.
- 34 Takahashi M, Yang XJ, Lavery TT et al. Gene expression profiling of favorable histology Wilms' tumors and its correlation with clinical features. *Cancer Res* 2002;62:6598–6605.
- 35 D'Angio GJ. Pre- or post-operative treatment for Wilms' tumor? Who, what, when, where, how, why—and which. *Med Pediatr Oncol* 2003;41:545–549.
- 36 Ladd WE. Embryoma of the kidney (Wilms' tumor). *Ann Surg* 1938;108:885–902.
- 37 Shamberger RC, Guthrie KA, Ritchey ML et al. Surgery-related factors and local recurrence of Wilms' tumor in National Wilms' Tumor Study 4. *Ann Surg* 1999;229:292–297.

- 38 Ritchey ML, Shamberger RC, Haase G et al. Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor Study Group. *J Am Coll Surg* 2001;192:63–68.
- 39 Wilimas JA, Magill L, Parham DM et al. Is renal salvage feasible in unilateral Wilms' tumor? Proposed computed tomographic criteria and their relation to surgicopathologic findings. *Am J Pediatr Hematol Oncol* 1990;12:164–167.
- 40 Wilimas JA, Magill L, Parham DM et al. The potential for renal salvage in nonmetastatic unilateral Wilms' tumor. *Am J Pediatr Hematol Oncol* 1991;13:342–344.
- 41 Ritchey ML, Green DM, Thomas PR et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. *Med Pediatr Oncol* 1996;26:75–80.
- 42 Green DM, Jaffe N. The role of chemotherapy in the treatment of Wilms' tumor. *Cancer* 1979;44:52–57.
- 43 Green DM, Beckwith JB, Weeks DA et al. The relationship between microstaging variables, age at diagnosis, and tumor weight of children with stage I/favorable histology Wilms' tumor. A report from the National Wilms' Tumor study. *Cancer* 1994;74:1817–1820.
- 44 Weeks DA, Beckwith JB, Luckey DW. Relapse-associated variables in stage I favorable histology Wilms' tumor. A report of the National Wilms' Tumor Study. *Cancer* 1987;60:1204–1212.
- 45 Shamberger RC. Pediatric renal tumors. *Semin Surg Oncol* 1999;16:105–120.
- 46 Farber S. Chemotherapy in the treatment of leukemia and Wilms' tumor. *JAMA* 1966;198:826–836.
- 47 Vietti TJ, Sullivan MP, Haggard ME et al. Vincristine sulfate and radiation therapy in metastatic Wilms' tumor. *Cancer* 1970;25:12–20.
- 48 D'Angio GJ, Evans A, Breslow N et al. The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer* 1981;47:2302–2311.
- 49 Green DM, Grigoriev YA, Nan B et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. *J Clin Oncol* 2001;19:1926–1934.
- 50 Boccon-Gibod L, Rey A, Sandstedt B et al. Complete necrosis induced by preoperative chemotherapy in Wilms' tumor as an indicator of low risk: report of the international society of paediatric oncology (SIOP) nephroblastoma trial and study 9. *Med Pediatr Oncol* 2000;34:183–190.
- 51 Weirich A, Leuschner I, Harms D et al. Clinical impact of histologic subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. *Ann Oncol* 2001;12:311–319.
- 52 Green DM, Breslow NE, Beckwith JB et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1998;16:3744–3751.
- 53 de Kraker J, Lemerle J, Voute PA et al. Wilms' tumor with pulmonary metastases at diagnosis: the significance of primary chemotherapy. International Society of Pediatric Oncology Nephroblastoma Trial and Study Committee. *J Clin Oncol* 1990;8:1187–1190.
- 54 Pritchard J, Imeson J, Barnes J et al. Results of the United Kingdom Children's Cancer Study Group first Wilms' Tumor Study. *J Clin Oncol* 1995;13:124–133.
- 55 Dome JS, Green DM, Cotton CA et al. Treatment of anaplastic Wilms' Tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 2005 (ASCO Annual Meeting Proceedings):8508.
- 56 Zuppan CW, Beckwith JB, Luckey DW. Anaplasia in unilateral Wilms' tumor: a report from the National Wilms' Tumor Study Pathology Center. *Hum Pathol* 1988;19:1199–1209.
- 57 Montgomery BT, Kelalis PP, Blute ML et al. Extended follow-up of bilateral Wilms' tumor: results of the National Wilms' Tumor Study. *J Urol* 1991;146:514–518.
- 58 Horwitz JR, Ritchey ML, Moksness J et al. Renal salvage procedures in patients with synchronous bilateral Wilms' tumors: a report from the National Wilms' Tumor Study Group. *J Pediatr Surg* 1996;31:1020–1025.
- 59 Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. Philadelphia/Baltimore/New York/London/Buenos Aires/Hong Kong/Sydney/Tokyo: Lippincott Williams & Wilkins, 2001.
- 60 Bishop HC, Tefft M, Evans AE et al. Survival in bilateral Wilms' tumor—review of 30 National Wilms' Tumor Study cases. *J Pediatr Surg* 1977;12:631–638.
- 61 Blute ML, Kelalis PP, Offord KP et al. Bilateral Wilms' tumor. *J Urol* 1987;138:968–973.
- 62 Coppes MJ, de Kraker J, van Dijken PJ et al. Bilateral Wilms' tumor: long-term survival and some epidemiological features. *J Clin Oncol* 1989;7:310–315.
- 63 Jones B, Hrabovsky E, Kiviat N et al. Metachronous bilateral Wilms' tumor, National Wilms' Tumor Study. *Am J Clin Oncol* 1982;5:545–550.
- 64 Paulino AC, Thakkar B, Henderson WG. Metachronous bilateral Wilms' tumor: the importance of time interval to the development of a second tumor. *Cancer* 1998;82:415–420.
- 65 Coppes MJ, Arnold M, Beckwith JB et al. Factors affecting the risk of contralateral Wilms' tumor development: a report from the National Wilms' Tumor Study Group. *Cancer* 1999;85:1616–1625.
- 66 Groot-Loonen JJ, Pinkerton CR, Morris-Jones PH et al. How curable is relapsed Wilms' tumour? The United Kingdom Children's Cancer Study Group. *Arch Dis Child* 1990;65:968–970.
- 67 Grundy P, Breslow N, Green DM et al. Prognostic factors for children with recurrent Wilms' tumor: results from the Second and Third National Wilms' Tumor Study. *J Clin Oncol* 1989;7:638–647.
- 68 Pinkerton CR, Groot-Loonen JJ, Morris-Jones PH et al. Response rates in relapsed Wilms' tumor. A need for new effective agents. *Cancer* 1991;67:567–571.
- 69 Wilimas JA, Champion J, Douglass EC et al. Relapsed Wilms' tumor. Factors affecting survival and cure. *Am J Clin Oncol* 1985;8:324–328.
- 70 Tournade MF, Lemerle J, Brunat-Mentigny M et al. Ifosfamide is an active drug in Wilms' tumor: a phase II study conducted by the French Society of Pediatric Oncology. *J Clin Oncol* 1988;6:793–796.
- 71 Abu-Ghosh AM, Krailo MD, Goldman SC et al. Ifosfamide, carboplatin and etoposide in children with poor-risk relapsed Wilms' tumor: a Children's Cancer Group report. *Ann Oncol* 2002;13:460–469.
- 72 de Camargo B, Melaragno R, Saba e Silva N et al. Phase II study of carboplatin as a single drug for relapsed Wilms' tumor: experience of the Brazilian Wilms' Tumor Study Group. *Med Pediatr Oncol* 1994;22:258–260.
- 73 Ettinger LJ, Gaynon PS, Krailo MD et al. A phase II study of carboplatin in children with recurrent or progressive solid tumors. A report from the Children's Cancer Group. *Cancer* 1994;73:1297–1301.
- 74 Kung FH, Desai SJ, Dickerman JD et al. Ifosfamide/carboplatin/etoposide (ICE) for recurrent malignant solid tumors of childhood: a Pediatric Oncology Group Phase I/II study. *J Pediatr Hematol Oncol* 1995;17:265–269.
- 75 Loss JF, Santos PP, Leone LD et al. Outcome of pediatric recurrent and refractory malignant solid tumors following ifosfamide/carboplatin/etoposide (ICE): A phase II study in a pediatric oncology centre in Brazil. *Pediatr Blood Cancer* 2004;42:139–144.

- 76 Pein F, Pinkerton R, Tournade MF et al. Etoposide in relapsed or refractory Wilms' tumor: a phase II study by the French Society of Pediatric Oncology and the United Kingdom Children's Cancer Study Group. *J Clin Oncol* 1993;11:1478-1481.
- 77 Pein F, Tournade MF, Zucker JM et al. Etoposide and carboplatin: a highly effective combination in relapsed or refractory Wilms' tumor—a phase II study by the French Society of Pediatric Oncology. *J Clin Oncol* 1994;12:931-936.
- 78 Pinkerton CR, Pritchard J. A phase II study of ifosfamide in paediatric solid tumours. *Cancer Chemother Pharmacol* 1989;24(suppl 1):S13-S15.
- 79 Pratt CB, Horowitz ME, Meyer WH et al. Phase II trial of ifosfamide in children with malignant solid tumors. *Cancer Treat Rep* 1987;71:131-135.
- 80 Pratt CB, Douglass EC, Etcubanas E et al. Clinical studies of ifosfamide/mesna at St Jude Children's Research Hospital, 1983-1988. *Semin Oncol* 1989;16:51-55.
- 81 Saylor RL III, Stewart CF, Zamboni WC et al. Phase I study of topotecan in combination with cyclophosphamide in pediatric patients with malignant solid tumors: a Pediatric Oncology Group Study. *J Clin Oncol* 1998;16:945-952.
- 82 Schwartzman E, Scopinaro M, Angueyra N. Phase II study of ifosfamide as a single drug for relapsed paediatric patients. *Cancer Chemother Pharmacol* 1989;24(suppl 1):S11-S12.
- 83 Tournade MF. A phase II study of ifosfamide in the treatment of relapses in Wilms' tumor. *Cancer Chemother Pharmacol* 1989;24(suppl 1):S31-S33.
- 84 Dome JS, Liu T, Krasin M et al. Improved survival for patients with recurrent Wilms' tumor: the experience at St. Jude Children's Research Hospital. *J Pediatr Hematol Oncol* 2002;24:192-198.
- 85 Marina NM, Wilimas JA, Meyer WH et al. Refining therapeutic strategies for patients with resistant Wilms' tumor. *Am J Pediatr Hematol Oncol* 1994;16:296-300.
- 86 Green DM, Breslow NE, Ii Y et al. The role of surgical excision in the management of relapsed Wilms' tumor patients with pulmonary metastases: a report from the National Wilms' Tumor Study. *J Pediatr Surg* 1991;26:728-733.
- 87 Santana VM, Zamboni WC, Kirstein MN et al. A pilot study of protracted topotecan dosing using a pharmacokinetically guided dosing approach in children with solid tumors. *Clin Cancer Res* 2003;9:633-640.
- 88 Saylor RL III, Stine KC, Sullivan J et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol* 2001;19:3463-3469.
- 89 Rowe DH, Kayton ML, O'Toole KM et al. Pathological angiogenesis in a murine model of human Wilms' tumor. *J Pediatr Surg* 1999;34:676-679.
- 90 Frischer JS, Huang J, Serur A et al. Effects of potent VEGF blockade on experimental Wilms' tumor and its persisting vasculature. *Int J Oncol* 2004;25:549-553.
- 91 Huang J, Frischer JS, Serur A et al. Regression of established tumors and metastases by potent vascular endothelial growth factor blockade. *Proc Natl Acad Sci U S A* 2003;100:7785-7790.
- 92 Green DM. The treatment of stages I-IV favorable histology Wilms' tumor. *J Clin Oncol* 2004;22:1366-1372.
- 93 Green DM, Breslow NE, Beckwith JB et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1998;16:237-245.
- 94 Breslow NE, Ou SS, Beckwith JB et al. Doxorubicin for favorable histology, Stage II-III Wilms' tumor: results from the National Wilms' Tumor Studies. *Cancer* 2004;101:1072-1080.
- 95 Tournade MF, Com-Nougue C, de Kraker J et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *J Clin Oncol* 2001;19:488-500.
- 96 Mitchell C, Jones PM, Kelsey A et al. The treatment of Wilms' tumour: results of the United Kingdom Children's Cancer Study Group (UKCCSG) second Wilms' tumour study. *Br J Cancer* 2000;83:602-608.
- 97 Sutow WW, Breslow NE, Palmer NF et al. Prognosis in children with Wilms' tumor metastases prior to or following primary treatment: results from the first National Wilms' Tumor Study (NWTs-1). *Am J Clin Oncol* 1982;5:339-347.
- 98 Green DM, Breslow NE, Evans I et al. The effect of chemotherapy dose intensity on the hematological toxicity of the treatment for Wilms' tumor. A report from the National Wilms' Tumor Study. *Am J Pediatr Hematol Oncol* 1994;16:207-212.
- 99 Reinhard H, Semler O, Burger D et al. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms' Tumor. *Klin Padiatr* 2004;216:132-140.
- 100 Grundy RG, Hutton C, Middleton H et al. Outcome of patients with stage III or inoperable WT treated on the second United Kingdom WT protocol (UKWT2); a United Kingdom Children's Cancer Study Group (UKCCSG) study. *Pediatr Blood Cancer* 2004;42:311-319.
- 101 Burger D, Moorman-Voestermans CG, Mildenerger H et al. The advantages of preoperative therapy in Wilms' tumour. A summarised report on clinical trials conducted by the International Society of Paediatric Oncology (SIOP). *Z Kinderchir* 1985;40:170-175.
- 102 Lemerle J, Voute PA, Tournade MF et al. Preoperative versus postoperative radiotherapy, single versus multiple courses of actinomycin D, in the treatment of Wilms' tumor. Preliminary results of a controlled clinical trial conducted by the International Society of Paediatric Oncology (S.I.O.P.). *Cancer* 1976;38:647-654.
- 103 Lemerle J, Voute PA, Tournade MF et al. Effectiveness of preoperative chemotherapy in Wilms' tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *J Clin Oncol* 1983;1:604-609.
- 104 Tournade MF, Com-Nougue C, Voute PA et al. Results of the Sixth International Society of Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor. *J Clin Oncol* 1993;11:1014-1023.
- 105 Garaventa A, Hartmann O, Bernard JL et al. Autologous bone marrow transplantation for pediatric Wilms' tumor: the experience of the European Bone Marrow Transplantation Solid Tumor Registry. *Med Pediatr Oncol* 1994;22:11-14.
- 106 Hempel L, Kremens B, Weirich A et al. High dose consolidation with autologous stem cell rescue (ASCR) for nephroblastoma initially treated according to the SIOP 9/GPOH trial and study. *Klin Padiatr* 1996;208:186-189.
- 107 Pein F, Michon J, Valteau-Couanet D et al. High-dose melphalan, etoposide, and carboplatin followed by autologous stem-cell rescue in pediatric high-risk recurrent Wilms' tumor: a French Society of Pediatric Oncology study. *J Clin Oncol* 1998;16:3295-3301.
- 108 Kremens B, Gruhn B, Klingebiel T et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplant* 2002;30:893-898.
- 109 Campbell AD, Cohn SL, Reynolds M et al. Treatment of relapsed Wilms' tumor with high-dose therapy and autologous hematopoietic stem-cell rescue: the experience at Children's Memorial Hospital. *J Clin Oncol* 2004;22:2885-2890.

**ADDITIONAL READING**

D'Angio GJ. Pre or postoperative treatment of Wilms' tumor? Who, what, when, where, how, why—and which. *Med Pediatr Oncol* 2003;41:545–549.

de Kraker J, Pritchard-Jones K. Treatment of Wilms' tumor: an international perspective. *J Clin Oncol* 2005;23:3156–3157.

Dome JS, Coppes MJ. Recent advances in Wilms' tumor genetics. *Curr Opin Pediatr* 2002;14:5–11.

Green DM. The treatment of stages I-IV favorable histology Wilms' tumor. *J Clin Oncol* 2004;22:1366–1372.

Kalapurakal JA, Dome JS, Perlman EJ et al. Management of Wilms' tumor: current practice and future goals. *Lancet Oncol* 2004;5:37–46.