Wilms' Tumor in Children: An Overview

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Abstract
Wilms' tumor is the most frequently occurring renal tumor in children and is one of the most treatment-responsive tumors. A tumor-suppressor gene and other genetic abnormalities have been implicated in its etiology. In addition, patients with several congenital anomalies, such as Beckwith-Wiedemann syndrome, WAGR syndrome, and Denys-Drash syndrome, have an increased risk of Wilms' tumor. Previously, a three-drug chemotherapy regimen with surgery and radiotherapy was used with patients in all stages. Now, patients with early-stage Wilms' tumor are treated with a two-drug regimen without radiotherapy, whereas those in advanced stages still receive the three-drug regimen and radiotherapy. Two large collaborative groups – the National Wilms' Tumor Study Group (NWTS) in the United States and the International Society of Pediatric Oncology (SIOP) in Europe – are involved in Wilms' tumor management, which differs in some aspects. Multimodality treatment has been used successfully, and in Europe preoperative strategies are used as well. As the survival rate has now reached 90%, the primary objectives of the physician are to perform nephron-sparing surgery in selected cases and to reduce the dosage and duration of chemotherapy and radiotherapy in appropriate cases. Other renal tumors occur rarely, but have also been treated successfully in the last decade.

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Introduction

Renal tumors are the fifth most common tumor in children [1], and Wilms' tumor is the most frequently occurring renal tumor in children. The incidence, type, growth rate, and response to treatment of renal tumors in children differ from adult renal cancers. Renal tumors in adults are most likely carcinomas, whereas in children they are of embryonic origin and thus grow rapidly. Renal cell carcinomas, sarcomas, and other tumors of the kidney are extremely rare in children. The other difference from adult tumors is that childhood renal tumors have a better response to treatment.

This article reviews the histopathology, genetics, and changing treatment strategies of Wilms' tumor. It reports the results of our center, as well as those of two large collaborative groups: the National Wilms' Tumor Study Group (NWTS; from North America) and the International Society of Pediatric Oncology (SIOP; from Europe).

Wilms' Tumor

Wilms' tumor was first reported by Rance in 1814, and it received its name from Max Wilms, a surgeon who identified nephroblastoma as a mixture of three tissues [2, 3]. Multimodal treatment was first used in treating this tumor, and because it has achieved the best results of any tumor group it has become a treatment model for other tumors. With this successful treatment strategy

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and the creation of cooperative groups in North America and Europe, the survival rate improved from 30 to 90% between 1930 and 2000.

Epidemiology

Childhood cancers constitute between 0.5 and 1% of all cancers. In the USA, the incidence of Wilms' tumor is 7.6 cases per million under 15 years of age [4], and about 500 new cases occur annually. Wilms' tumor represents 5.9% of all childhood malignant tumors [5]. There is a minor racial difference in the incidence of Wilms' tumors. The Asian population has about half the incidence rate of Western countries, and its rate in the black population is 2.5 times higher [6, 7]. The incidence of Wilms' tumor in other countries is similar to that in the USA. In Turkey, childhood renal tumors represent 7.1% of all childhood tumors [8]. The population-based incidence rate in a part of Italy was 4.5% for Wilms' tumor [9].

Wilms' tumor is seen mostly in children between the ages of 1 and 5 years, and the peak age is 3. Although adult patients with Wilms' tumor have been reported, it is extremely rare in people older than 15 years of age [10]. The male-female ratio is near 1, ranging from 0.8 to 0.95 in various studies.

Wilms' Tumor Genetics

Two frequent genetic abnormalities in Wilms' tumor are the WT1 and WT2 gene deletions:

WT1. The first identified gene in Wilms' tumor, WT1, is responsible for genitourinary development. It is a tumor-suppressor gene located on 11p13 that is expressed in the kidney, gonads, spleen, and mesothelium. It encodes four zinc finger transcriptional factors that have regulatory functions on cell growth, differentiation, and apoptosis. Normal WT1 gene expression is necessary for the maturation of the blastemal cells, and reduced WT1 expression is associated with the stromal predominant Wilms' tumor. Lee and Haber [11] report on the functions of the WT1 gene and its association with connective tissue growth factor and vitamin D receptors. Its deletion has been shown in WAGR and Denys-Drash syndrome [12, 13].

WT2. This gene is located on 11p15 and is found in Beckwith-Wiedemann syndrome [14]. Some functions of this gene are related to insulin-like growth factor 2 (IGF-2), which encodes embryonal growth factor.

Other Genetic Abnormalities. In addition to IGF-2, H19 and p57^{Kip2} are overexpressed or mutated in some patients with Wilms' tumor. p57^{Kip2} encodes cyclin-de-

pendent kinase inhibitors and is a putative tumor suppressor [15, 16].

The p53 tumor suppressor gene has been found in 75% of patients with anaplastic histology [17]. This gene regulates cell proliferation and induces apoptosis.

β-Catenin is a cellular adhesion molecule that promotes overexpression of the c-myc and cyclin D1. β-Catenin mutation has been detected in 15% of patients with Wilms' tumor [18]. There is a strong correlation between reduced expression of the WT1 gene and β-catenin mutation.

Familial Wilms' tumor has been found in 1–2% of Wilms' tumor cases [19]. Although this tumor does have the WT1 gene, some familial tumors have linkage in the 17q, and this locus has been named FWT1. Some such tumors have demonstrated a 19q anomaly, which has been described as FWT2 [15].

Other chromosomal abnormalities, such as loss of heterozygosity (LOH) of 16q, 1p, and 7p, have been identified [20]. This defect has been associated with poor prognosis, relapses, and death and has resulted in a poor outcome in patients with favorable histology Wilms' tumor. In a recent report, a 9-year-old boy with trisomy 18 had Wilms' tumor [21]. In this case, LOH was demonstrated at isochromosome 7q and heterozygosity of 16q was found in addition to trisomy 18.

Associated Congenital Abnormalities

Wilms' tumor has been associated with several congenital abnormalities. Children with genitourinary anomalies, such as horseshoe kidney, renal dysplasia, bilateral cystic renal disease, cryptoorchidism, hypospadias, aniridia, and hemihypertrophy, have a higher incidence of Wilms' tumor [22]. In addition, it is a component of the syndromes described below.

Beckwith-Wiedemann Syndrome. This syndrome is associated with macroglossia, visceromegaly, omphalocele, and gigantism. About 4–5% of patients with this syndrome have Wilms' tumor as well [23]. Although the incidence of bilateral disease has increased, the prognosis is still excellent [23]. The molecular defect is on chromosome 11p15.5 [14]. It is not clear if this defect is the same as is found on the WT2 gene. IGF-2 abnormalities are related to this gene and may be responsible for the development of Wilms' tumor and the Beckwith-Wiedemann syndrome.

WAGR Syndrome. The components of this syndrome are Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation. Cardiopulmonary problems, head anomalies, neurobehavioral disorders, musculo-

skeletal defects, and metabolic problems have also been reported [12]. The 11p13 chromosomal deletion has been identified. The Wilms' tumor risk is 30% in this syndrome. In a review of 54 patients with WAGR syndrome, 31 had Wilms' tumor and 53 had aniridia [12].

Denys-Drash Syndrome. Male pseudo hermaphroditism, glomerulonephritis, and Wilms' tumor are part of this syndrome. There is also an association with a defect on the WT1 gene [13].

Perlman Syndrome. This syndrome can be associated with Wilms' tumor and includes macrosomia, islet cell hyperplasia, renal hamartomas, and an atypical face shape [24].

Histopathology

There are two subclassifications in Wilms' tumor [25–28]:

(1) *Classical nephroblastoma:* Classical nephroblastoma includes blastemal, epithelial, and stromal components. Sometimes one or two components are predominant, and sometimes they are equally apportioned. The latter type of tumor is classified as a mixed-type or triphasic Wilms' tumor.

(2) *Anaplastic Wilms' tumor:* If the tumor cells contain multipolar mitotic figures, hyperchromasia with enlarged cells, or nuclei that are three times larger than in adjacent cells, it is classified as an anaplastic Wilms' tumor. This type of tumor constitutes 4–8% of all cases. It may have a diffuse or focal form; this classification has prognostic importance, as patients with focal anaplasia should be treated with less intensive protocols than those with diffuse anaplasia. Previously, a tumor was classified as focal anaplasia if anaplastic cells were encountered in fewer than 10% of microscopic fields. This description was revised by Faria et al. [29] in 1996, as follows: In focal anaplasia, anaplastic changes are confined to circumscribed regions within the primary tumor and are surrounded by non-anaplastic tissue. Diffuse anaplasia has the following characteristics: it is found in an extrarenal site, the random biopsy specimen reveals unequivocal anaplasia, the tumor is coupled with extreme nuclear unrest, and there is nuclear atypia elsewhere in the tumor [29].

This classification of focal and diffuse anaplasia has been used in the NWTS (from North America); the other large-scale collaborative group, the SIOP (from Europe), stratifies risk groups according to histopathologic structures. SIOP has analyzed risk for two groups: those pa-

Table 1. Revised SIOP working classification of renal tumors of childhood [30]

A. For pretreated cases
  a. Low-risk tumors
      Mesoblastic nephroma
      Cystic partially differentiated nephroblastoma
      Completely necrotic nephroblastoma
  b. Intermediate-risk tumors
      Nephroblastoma-epithelial type
      Nephroblastoma-stromal type
      Nephroblastoma-mixed type
      Nephroblastoma-regressive type
      Nephroblastoma-focal anaplasia
  c. High-risk tumors
      Nephroblastoma-blastemal type
      Nephroblastoma-diffuse anaplasia
      Clear cell sarcoma of the kidney
      Rhabdoid tumor of the kidney

B. For primary nephrectomy cases
  a. Low-risk tumors
      Mesoblastic nephroma
      Cystic partially differentiated nephroblastoma
  b. Intermediate-risk tumors
      Non-anaplastic nephroblastoma and its variants
      Nephroblastoma-focal anaplasia
  c. High-risk tumors
      Nephroblastoma-diffuse anaplasia
      Clear cell sarcoma of the kidney
      Rhabdoid tumor of the kidney

tients who have been pretreated and those receiving primary nephrectomy. For pretreated patients, those in the low-risk group had complete necrosis and cystic nephroblastoma; focal anaplasia and other classic nephroblastoma except blastemal type characterized the intermediate-risk group. The high-risk group had blastemal-type, diffuse anaplasia and other variants of Wilms' tumor, such as clear cell sarcoma and rhabdoid tumor. Low-risk patients with primary nephrectomy had the same characteristics as low-risk pretreated patients. Intermediate-risk patients had all variants of classic Wilms' tumor, including the blastemal type, as well as focal anaplasia. High-risk group patients with primary nephrectomy had diffuse anaplasia, rhabdoid tumor of the kidney, and clear cell sarcoma of the kidney. Table 1 shows SIOP risk groups according to histopathology [30].

Tumor classification should determine the choice of treatment protocols. Anaplastic tumors, except for those in stage 1, should be treated with more intensive protocols than mixed-type tumors [31].

Table 2. Staging system for Wilms' tumor

Stage	NWTS	SIOP
I	Tumor is limited to kidney Totally excised There is no tumoral involvement in surgical margin The vessels of renal sinus are not involved There is no tumoral rupture before or during removal	Tumor is limited to kidney No tumor cells at the surgical margin The vessels of renal sinus are not involved Intrarenal vessels may be involved
II	Tumor is outside the kidney Totally removed Local spillage and intrarenal vessels could be involved	Tumor extends outside of the kidney Totally resected but capsule, adjacent tissues, renal sinus and renal vessels can be involved
III	Intra-abdominal tumor Renal hilus, abdominal lymph nodes are involved Diffuse spillage Peritoneal involvement Thrombus in vena cava	Incomplete resection Intra-abdominal lymph node involvement but renal hilus lymph node positivity makes it stage II Ureteral, peritoneal, and caval involvement Preoperative or perioperative biopsy or rupture Peritoneal metastases
IV	Hematogeneous or distant lymph node metastases	Hematogeneous and extra-abdominal lymph node metastases
V	Bilateral renal tumors	Bilateral renal tumors

Nephrogenic Rests. The nephrogenic rest is the precursor lesion of the Wilms' tumor, which sometimes can be mixed with malignancies and include blastemal, stromal, and embryonal nephroblastic tissue. It can be found in the opposite or the same foci in the affected kidney. If located peripherally, it is classified as a perilobar nephrogenic rest; if located deep in the renal lobe, it is an intralobar nephrogenic rest. Nephrogenic rests can regress or stay dormant [26].

Clinical Presentation
Most patients present with the complaint of abdominal mass. The tumor is often detected by a caregiver while bathing the child. 30% of patients have hematuria, and 25% have hypertension [32, 33]. In addition, patients can suffer from malaise, fever, weight loss, anorexia, or a combination of those symptoms. Varicocele due to compression of the tumor to the spermatic cord can be seen. Some hormones, such as erythropoietin and ACTH, can be secreted in Wilms' tumor. In addition, hypercalcemia and hemorrhagic conditions caused by reduced von Willebrand factor are associated with Wilms' tumor [33]. Physicians also should be alert for other associated findings, such as hemihypertrophy, aniridia, and genitourinary malformations.

Imaging Studies
Calyceal distortion with renal displacement is the characteristic finding for Wilms' tumor. Before the ultra-sonography (USG) and tomography era, direct radiograph and intravenous urography were used widely. USG and contrast-enhanced tomography (CT) of the abdomen are more effective diagnostic techniques in the staging and follow-up of patients [34–38], as they can detect tumor size, invasion, and tumoral involvement of the lymph nodes. Doppler USG shows vena cava invasion, which is important for determining the preoperative treatment strategy. USG or CT shows other parenchymal organ metastasis, such as to the liver, but not whether subpleural or parenchymal nodules are true metastatic nodules or are related to infections or postoperative changes. However, that question is not relevant to prognosis. Because the presence or absence of lung nodules does not affect the treatment plan in the early stages, a lung CT is not necessary [39]. The survival of the patients with metastasis from the right kidney is worse than the survival of those with metastasis from the left kidney [40].

Staging
Two large groups are involved in Wilms' tumor management: the NWTS (from North America) and the SIOP (from Europe). They use similar staging systems with only minor differences. SIOP gives preoperative chemotherapy and then does staging after preoperative treatment and surgery. The NWTS group treats patients with surgery at the time of diagnosis, and then they are staged. The staging system of these two groups is shown in table 2 [30, 41].

Treatment

Multimodality treatment has been used to treat Wilms' tumor successfully. Its components are described below.

Surgery

Surgery is the cornerstone of treatment. Transperitoneal approaches are used [42], as the flank incision is not suitable for Wilms' tumor. All abdominal organs, lymphadenopathies, and the opposite kidney should be investigated carefully. Ligation of both the renal artery and vein is preferable before performing radical nephrectomy. Surgeons must take care to prevent tumor spillage, which has a negative effect on prognosis [43]. Wilms' tumor is an encapsulated tumor, and as much as possible, it should be removed with no capsular perforation. In SIOP studies, surgery is performed after 1 month of chemotherapy treatment.

The UKCCSG (United Kingdom Children Cancer Study Group) has examined the accuracy of percutaneous needle biopsy for initial diagnosis and found that 4% of the samples were not diagnostic but that 85% of the samples confirmed the diagnosis of Wilms' tumor. The authors therefore recommend needle biopsy at the time of diagnosis. Patients in this large series had minimal complications and no increased risk of local recurrence or upstaging [44].

Another study looked at the results of nephron-sparing surgery in stage I patients who had 50% of the kidney preservable [45]. They suggested that this technique should be used in selective cases. The role of nephron-sparing surgery in other types of patients has not yet been clarified [46].

Chemotherapy

NWTS: The NWTS group has investigated five protocols [47–49]. In NWTS 1 (1969–73) the vincristine + dactinomycin combination was more effective than either drug alone in stage II and III patients [50]. NWTS 2 was conducted between 1974 and 1978. It found that a treatment duration of either 6 or 15 months was equally effective in stage I patients, and, after these results were published, treatment duration in protocols was shortened. Addition of adriamycin to the chemotherapy protocols improved the survival rate in patients with Wilms' tumor [49].

In NWTS 3, stage I patients were treated successfully with a two-drug regimen for 10 weeks [51]. For stage II patients, there was no significant difference in outcome between the RT or no RT arms, nor between the arm without adriamycin. Stage IV patients received no benefit from the addition of cyclophosphamide to the three-drug regimen. Different radiotherapy doses (1,000 vs. 2,000 cGy) also had no effect on survival. After this report, most treatment centers decreased the radiotherapy doses they used to treat Wilms' tumor. NWTS 4 also demonstrated that pulse-intensive actinomycin-D (single injection of 45 μg/kg) was as potent as the long-term injection dose (15 μg/kg/day for 5 days) [52]. The addition of adriamycin had a strong effect on survival in patients with stage III in NWTS 3–4 studies [53].

NWTS 5 investigated whether stage I patients actually benefited from chemotherapy. Without chemotherapy, the 2-year overall survival was 100%, but relapse-free survival was 86%. Therefore, this arm has been closed. LOH at chromosome 1 and 16q has been shown to be a poor prognostic factor in this study [20].

SIOP Studies [54, 55]: The SIOP 1 study compared the effectiveness of prenephrectomy irradiation versus immediate surgery and found that the two arms had the same overall survival rates. The SIOP 2 study found that preoperative treatment resulted in a decreased tumor rupture rate. In the SIOP 5 study, preoperative chemotherapy was substituted for preoperative radiotherapy. The SIOP 6 study showed that 17 weeks of chemotherapy treatment was as effective as 38 weeks of treatment for patients with stage I disease. Relapse risk increased in stage II lymph-node-negative patients who did not receive radiotherapy. The addition of epirubicin was planned in this group of patients. Also, radiotherapy doses were decreased from 30 to 15 Gy. The aim of the SIOP 9 protocol was to determine how the duration of preoperative chemotherapy affected survival. There was no significant difference in survival between 4 and 8 weeks of preoperative treatment [56]. SIOP 93-01 studies have aimed to reduce treatment duration. Stage I patients were treated postoperatively for 4 weeks, whereas patients in other stages received 27 weeks of postoperative treatment. In this randomized study, there was no significant difference in terms of event-free survival rates [57], although patients with progressive disease during preoperative chemotherapy had poorer survival than the others [58].

UKCCSG Protocols: This group treated patients with the postoperative chemotherapy regimen used by the NWTS group. Patients with tumors that the surgeons thought were unresectable were given preoperative chemotherapy [59–61]. In patients with stage I, vincristine alone was as effective as vincristine and actinomycin-D.

In the first study, the duration of the vincristine regimen in stage I was 6 months [59]. This duration was shortened to 10 weeks in the second study [61]. This recommendation was limited to patients younger than 4 years. The group did not recommend using single-agent vincristine in older patients. Treatment results with stage IV patients were not as good as those obtained by the NWTS group.

Other single-center or collaborative studies have been published in different centers [62–64].

Radiotherapy

In the early years, all stage I and II patients were treated with flank irradiation, and those with stage III and IV were treated with whole abdominal radiotherapy. Since 1975, patients with favorable histology stage I no longer receive radiotherapy. Stage III and IV patients and those with otherwise local stage I and II receive flank irradiation instead of whole abdomen radiotherapy. Dosages were reduced to 2,700 cGy and later to 1,000 cGy depending on the histology and stage, rather than the age of the patient [65, 66]. Whole lung irradiation of 12 Gy was generally given in patients with metastatic lung disease with post-stamp boost (or boosts) of 10 Gy whenever possible [41]. Since about 1990, patients with stage III and IV are treated with radiotherapy delivered to the tumor bed in 10-Gy dosages. Lung irradiation is used only in patients with residual or resistant disease after undergoing induction chemotherapy.

Treatment of Anaplastic Wilms' Tumor

All patients except stage I should be treated with intensive chemotherapy and radiotherapy. Vincristine + actinomycin-D + adriamycin and cyclophosphamide are used in this type of tumor [67]. In the last NWTS study, patients with stage I disease were treated with vincristine + actinomycin-D for 18 weeks and achieved good results. Patients with diffuse anaplastic stage II–IV disease were treated with vincristine + cyclophosphamide + actinomycin-D + etoposide for 24 weeks. The results in this group were unsatisfactory. The authors suggested that new drugs, such as carboplatin, should be tried in patients with anaplastic Wilms' tumor [68].

Treatment of Bilateral Wilms' Tumor

The principal treatment of bilateral Wilms' tumor is nephrectomy of the larger tumor after preoperative treatment or through immediate surgery [69, 70]. After induction chemotherapy, the smaller tumor should be removed by partial nephrectomy. Some authors suggested that limited radiotherapy could be applied. Whatever the treatment, salvage of the kidney should be the goal.

Prognosis

The prognosis of patients with Wilms' tumor is the most favorable of all solid tumors, and an 85% survival rate in all patients has been reached. The survival rate is 95% in patients in stages I and II, 75–80% in stage III patients, and 65–75% in patients with stage IV. Only 15% of patients with favorable histology have recurrent disease, compared to a rate of 50% in those with anaplastic histology. The most common sites of recurrence are the lungs, pleura, tumor bed, and the liver. Among all patients with Wilms' tumor, those with liver involvement have a poorer prognosis than those with lung metastasis [40, 71].

Future Perspectives in Wilms' Tumor

Partial nephrectomy or nephron-sparing surgery should be done in selected patients. Low-risk patients should receive fewer chemotherapeutic agents and at lower cumulative doses. Vincristine alone or no treatment should be used in these patients. Trials to further reduce radiotherapy doses or omit radiotherapy in selected cases may be undertaken.

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