Current Issues in the Diagnosis and Management of Wilms' Tumor

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Significant advances have been made in the treatment of children with Wilms' tumor. Whereas 50 years ago overall survival was less than 10%, current survival estimates approach 90%. This progress has been made

Introduction

Major advances have occurred over the last 50 years in the treatment of children with Wilms' tumor. These advances, made possible by the joint efforts of pediatric oncologists, surgeons, pathologists, radiation oncologists, and support personnel, have led to a dramatic improvement in survival, which currently approaches 90%.

Despite this progress, however, several controversies relating to the diagnosis and management of this intriguing childhood neoplasm remain unresolved. This article explores these controversial issues. As background to the discussion, a brief overview of the epidemiology, etiology, histology, diagnosis, and treatment of this tumor will be presented.

Overview

Wilms' tumor is the most common intra-abdominal tumor of childhood, affecting approximately 1 child per 10,000 worldwide.[1] The disease has no sex predilection, and the median age at presentation is approximately 3.5 years. Patients with bilateral tumors have been reported to present at a younger age.[2,3]

Specific congenital anomalies have been associated with Wilms' tumor; these include hemihypertrophy, aniridia, and genitourinary abnormalities. The WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformation, and mental retardation) and the Denys-Drash syndrome (intersexual disorders, nephropathy, and Wilms' tumor) have been linked to a deletion and point mutation, respectively, within chromosome 11p13 (WT1 gene). The Beckwith-Wiedemann syndrome (macroglossia, organomegaly, hemihypertrophy, and omphalocoele) has been linked to the 11p15 locus (WT2 gene) and is thought to result from overexpression of a gene that is normally expressed by one of the paternal alleles. The incidences of Wilms' tumor in the WAGR, Denys Drash, and Beckwith-Wiedemann syndromes have been reported to be more than 30%, more than 90%, and less than 5%, respectively.[4]

Knudson and Strong have proposed a two-hit hypothesis model to explain the earlier age of onset and bilateral presentation in children with a familial history of Wilms' tumor.[5] In this hypothesis, a tumor develops from two mutational events—the first may be prezygotic or postzygotic and the second is always postzygotic. If the first mutation is prezygotic, the tumor would be heritable and may present as multiple tumors, following a Poisson distribution. Wilms' tumor development, however, still depends on a second postzygotic mutation. In contrast, if the first mutation is postzygotic, the tumor is nonhereditary and single.

Wilms' tumor is thought to arise from nephrogenic rests, persistent embryonal remnants in the kidney. The presence of multiple nephrogenic rests (nephroblastomatosis), especially when intralobar, places the child at increased risk for Wilms' tumor formation in the contralateral kidney.[6]

The classic histologic pattern for Wilms' tumor is triphasic, consisting of epithelial, blastemal, and stromal elements. Most neoplasms have a good prognosis and are classified as favorable histology. Unfavorable histologies include focal or diffuse anaplasia and clear cell sarcoma of the kidney. The results of the third National Wilms' Tumor Study (NWTS 3) indicate a survival rate approaching 90% for patients with a favorable histology tumor and 55% to 75% for most patients with anaplasia or clear cell sarcoma. The staging system devised by the NWTS is summarized in Table 1.[7]
The most common presentation is an asymptomatic abdominal mass. Hematuria, hypertension, malaise, and abdominal pain have also been documented. Several paraneoplastic syndromes have been reported; these include erythrocytosis, hypercalcemia, Cushing's syndrome, and acquired von Willebrand's disease.[8]

Ultrasound has replaced the IV pyelogram (IVP) in the work-up of a patient with an abdominal mass. Unlike the IVP, ultrasound does not expose the patient to radiation. Furthermore, ultrasound can aid in determining whether the mass originates from the kidney, the status of the contralateral kidney, and the presence of a tumor thrombus in the renal vein or inferior vena cava. Abdominal CT can provide detailed information regarding enlarged lymph nodes, tumor thrombi, the contralateral kidney, and the relationship of the tumor to adjacent organs. Liver involvement or invasion identified on the CT scan usually turns out to be nonexistent at surgical exploration.[9]. A chest x-ray, preferably in four projections (posteroanterior, lateral, and two oblique views), is mandatory for determining whether a child has stage IV disease.

Treatment of a child with Wilms' tumor involves a radical or modified radical nephrectomy. A stage is assigned to the patient based on pathologic findings and imaging studies. The results of three National Wilms' Tumor Studies (NWTS 1-3) have provided guidance for further management.[7,10,11] In patients with stage I or II, favorable histology tumors and those with stage I, anaplastic histology, postoperative radiation is unnecessary if dactinomycin (Cosmegan) and vincristine are given in combination. The NWTS 2 showed that the duration of dactinomycin and vincristine can be restricted to 10 weeks.

For patients with stage III or IV, favorable histology lesions, the addition of doxorubicin has been shown to improve outcome. For stage III, favorable histology disease, the administration of fractionated radiation therapy at a dose of 1,000 cGy to the flank or abdomen is as effective as 2,000 cGy. Patients with tumors classified as stage IV, favorable histology who have at least stage III local disease receive the same radiation dose to the flank or abdomen as do those with stage III, favorable histology lesions.

The most common site of hematogenous metastases is the lungs. For patients with lung metastases, whole-lung radiation therapy is employed and is given in a fractionated fashion to a dose of 1,200 cGy. For stage II-IV anaplastic tumors and all clear cell sarcomas, the renal bed or abdomen is at risk for local recurrence, and radiation therapy is given to reduce this risk. Overall survival at 4 years ranges from 97% for patients with stage I, favorable histology disease to 54% for those with stage II-IV, anaplastic disease (Table 2). Despite the phenomenal improvement in the prognosis of patients with Wilms' tumor, various aspects of the diagnosis and management of this neoplasm remain controversial. These unresolved issues include the extent of surgery, the role of chemotherapy as an adjuvant and as treatment for recurrence, the optimal dose and timing of radiation therapy, and the approach to managing bilateral tumors.

**Surgical Management**

Using a transverse supraumbilical incision, the abdomen is explored with attention to possible metastasis in the peritoneal cavity. The opposite kidney is visually inspected, and all surfaces are palpated for any lesions. Any suspicious nodules are biopsied. The involved kidney is then handled carefully to avoid tumor rupture and upstaging of the patient, which would require more extensive therapy. The kidney and hilar structures are removed en bloc along with a generous segment of the ureter. The renal vein and inferior vena cava are palpated to detect tumor thrombi prior to vessel ligation. The liver and para-aortic nodes are inspected, and gross nodules or enlarged nodes are biopsied. A random biopsy of the para-aortic nodes is performed if the lymph nodes appear normal. In some patients, the tumor is found to be extensive, compromising vital structures. These tumors are biopsied and treated with chemotherapy and/or radiation therapy, which reduces the tumor burden and allows for subsequent resection. In NWTS 3, the use of preoperative treatment facilitated surgical resection in 93% of initially unresectable patients.[12]

**Should the Contralateral Kidney Be Explored?**

Whether the contralateral kidney should be explored surgically is the subject of controversy. This procedure involves opening Gerota's fascia so that the surgeon can inspect and palpate the contralateral kidney. The finding of a contralateral tumor significantly changes patient management, as will be discussed below. Some have argued that exploration of the contralateral kidney adds to possible surgical morbidity and unnecessarily prolongs anesthesia duration, and have suggested that advances in diagnostic imaging obviate the need for this exploration. Table 3 summarizes current data on the pro-portion of patients with bilateral Wilms' tumor detected by preoperative imaging.
In NWTS 2 and 3, approximately one third of patients with bilateral tumors were not detected preoperatively by IVP or CT.[2] Based on these findings, the NWTS surgical committee recommended careful exploration of the contralateral kidney in patients suspected to have Wilms' tumor in order to rule out bilateral involvement.[13]

Recent studies by Koo et al and Goleta Dy et al have challenged this approach.[14,15] Concern has been raised over the potential morbidity caused by handling and mobilizing the opposite kidney, the longer incision, and complete mobilization of the contralateral colon. In both series, all bilateral tumors were diagnosed pre-operatively. In the report by Koo et al, patients had one or more of the following examinations: IVP, ultrasound, CT, and MRI. In Goleta Dy's report, all bilateral tumors were detected by ultrasound and/or CT.

Of the more commonly employed preoperative examinations, CT has identified more bilateral tumors than IVP or ultrasound. In the NWTS 4 report by Ritchey et al, 96% of involved kidneys were detected by CT.[16] Likewise, at St. Jude 97% of patients with bilateral Wilms' tumor were identified preoperatively by CT scanning.[17]

Does the morbidity from exploration of the contralateral kidney warrant elimination of this added procedure? In an NWTS 3 report of 1,910 children, 19.8% had some form of surgical complication, but none of these complications was attributable to contralateral kidney exploration.[18] Likewise, in the study by Koo et al, 52 patients underwent contralateral kidney exploration without added morbidity.

Furthermore, the argument that exploration of the contralateral kidney necessitates a longer incision also is questionable. Patients who undergo surgery for Wilms' tumor almost always require a long incision to avoid rupture or spillage from a large tumor.

Finally, it should be noted that those who argue against performing contralateral kidney exploration have made their recommendations based on a combined total of 12 children with bilateral tumors. This contrasts with the more favorable experiences with this procedure in the 322 children from the NWTS and St. Jude. At present, therefore, formal inspection and palpation of the contralateral kidney are still necessary.

Can Partial Nephrectomy Be Used for Unilateral Tumors?

Concern has been raised regarding the potential for significant long-term renal dysfunction in patients with Wilms' tumor who have undergone unilateral nephrectomy.[19,20] Focal segmental glomerulosclerosis has been reported in patients with a unilateral kidney after nephrectomy for nephroblastoma.[21,22] The mechanisms of renal failure or dysfunction may include radiation nephritis, chemotherapy-related nephrotoxicity, and hyperfiltration of remaining nephrons secondary to removal of a significant amount of renal tissue.[23] Theoretically, biopsy of the tumor, followed by chemotherapy and subsequent partial nephrectomy after tumor shrinkage, should preserve renal tissue and result in less morbidity for the patient.

Several authors have addressed the role of renal-sparing procedures in children with Wilms' tumors. At the Hospital for Sick Children in Toronto, 37 patients with a histologic diagnosis of Wilms' tumor after percutaneous biopsy were treated with a 4- to 6-week course of combination chemotherapy. Nine patients (four with a unilateral tumor and five with bilateral disease) underwent partial nephrectomy; of these, two patients had an intra-abdominal recurrence 18 months and 24 months, respectively, after partial nephrectomy.[24] After preoperative chemotherapy, only 4 (13.3%) of 30 patients with unilateral tumors were amenable to partial nephrectomy.

The abdominal CT scans of 43 children with nonmetastatic unilateral Wilms' tumor at St. Jude Children's Research Hospital were reviewed retrospectively. Criteria for partial nephrectomy included tumor involving only one pole and less than one-third of the kidney, a functioning kidney, no invasion of the collecting system or renal vein, and clear margins between the tumor, kidney, and surrounding structures. Preoperative CT scans met these criteria in only 2 (4.7%) of 43 cases.[25] In a report by the Austrian/Hungarian Wilms’ Tumor Study, 3 of 21 patients with a stage I Wilms’ tumor underwent partial nephrectomy after preoperative chemotherapy, allowing renal preservation. Selection criteria for renal preservation included tumor involving only one pole, without collecting system or renal vein involvement; less than 25% residual tumor at week 4 after preoperative chemotherapy; normal excretion of tumor-involved kidney; more than 50% remaining renal parenchyma to be preserved after partial nephrectomy; and absence of Wilms' tumor nodules. These three patients remain disease-free 26 to 60 months after partial nephrectomy.[26]

Other authors also have advocated partial nephrectomy for unilateral Wilms' tumor.[27] In a report by Ritchey et al from NWTS 1-4, 55 children developed renal failure after undergoing treatment for Wilms' tumor. Patients who had a nephrectomy for a unilateral Wilms' tumor and had a normal contralateral kidney had a .25% incidence of renal failure. The authors concluded that...
parenchymal-sparing procedures, such as partial nephrectomy, may not benefit this subset of patients because of their low risk of renal failure. They also concluded that children with bilateral Wilms' tumor or tumor in a solitary kidney should be considered for renal parenchymal-sparing operations because of their significant risk of renal dysfunction.\[28\]

In summary, partial nephrectomy, either before or after chemotherapy, remains experimental for unilateral Wilms' tumor. Additional trials are needed to determine the role of partial nephrectomy in a disease for which cure rates approach 90% and the risk of renal failure is lesas than 1%. Because of the small numbers of patients who may be amenable to partial nephrectomy, it may be impossible to conduct such trials.

**Pulmonary Metastases**

**Is Chest CT Better Than Chest X-Ray for Detection?**

As mentioned above, the lungs are the most common site of hematogenous spread in Wilms' tumor. Hence, the detection of pulmonary metastases is essential in the management of a child with nephroblastoma, as this finding will alter therapy. The NWTS currently recommends a chest x-ray, preferably in four views, for the diagnosis of pulmonary metastases.\[29\] Cohen and colleagues have previously reported that chest CT is more sensitive than a chest radiograph for the detection of lung nodules.\[30\]

However, the results of some studies have raised the question, what proportion of patients with pulmonary nodules on chest CT scan that were not detected by chest radiograph truly have lung metastases? For example, in a study by Chang et al, 38 (55%) of 69 lesions on CT scan not identified on chest x-ray proved to be benign or could not be identified at thoracotomy.\[31\] Furthermore, multiple causes for benign pulmonary nodules in children with Wilms' tumor have been cited previously; these include atelectasis, round pneumonia, pseudotumor, Histoplasma capsulatum, hamartoma, and intrapulmonary lymph node.\[32-34\]

**How to Manage Patients With Positive Chest CT Scans?**

Another question that needs to be addressed is whether more intensive therapy improves the outcome of patients with a negative chest x-ray and positive CT scan. The NWTS addressed this issue in a report by Green et al. In their retrospective study of 27 patients with a pulmonary metastasis detected only by chest CT, 18 were treated as if they had stage IV disease; ie, they received three drugs (dactinomycin, vincristine, and doxorubicin) plus whole-lung irradiation. The other patients were treated based on the local abdominal stage, ignoring the thoracic CT findings. The two groups did not differ significantly with regard to 4-year event-free survival (88.1% vs. 88.9%) or overall survival (94.0% vs. 88.0%).\[35\]

In contrast, in a prospective study by Wilimas et al at St. Jude Children's Research Hospital, 11 patients had pulmonary lesions detected by CT but not detected by chest radiograph. The patients were treated based on abdominal findings, ignoring chest CT findings. Of the 11 children, 4 (36%) relapsed. This relapse rate was higher than that in a control population (20%), but the difference was not statistically significant.\[36\]

Clearly, both studies have limitations.\[37\] In the study by Green et al, the patients were evaluated retrospectively; 32 patients had lung nodules on CT with negative chest radiographs, but 5 children were excluded during analysis because of unknown or unfavorable histology. Only reports were reviewed; none of the radiographs was studied. In addition, a number of CT scans were done after abdominal surgery, making atelectasis a likely explanation for the CT-detected pulmonary nodules. Finally, the authors did not address what happened to the nodules after treatment or no treatment. In the study by Wilimas et al, the small number of patients precludes the findings from reaching statistical significance. Also, the patients with negative chest x-ray and positive CT were compared to a group of patients whose characteristics were not reported.

Thus, further studies are needed to determine whether children with negative chest radiographs should have thoracic CT. Patients with positive chest x-rays do not need chest CT, as this would not alter therapy. In patients who have a negative chest x-ray and positive chest CT, a biopsy of the lesion(s) should be performed before administering more intensive therapy (whole-lung radiation therapy with or without doxorubicin).

Whole-lung irradiation in combination with chemotherapy is not without associated morbidity. In 153 stage IV patients treated with whole-lung irradiation and combination chemotherapy (dactinomycin, vincristine, and doxorubicin, with or without cyclophosphamide [Cytoxan, Neosar]), interstitial pneumonitis of unknown etiology occurred in 15 patients (9.8%). The pneumonitis was presumed to be related to whole-lung irradiation and the administration of dactinomycin or doxorubicin. Only 4
A study by Macklis and colleagues found a 93% incidence of musculoskeletal and soft tissue growth abnormalities in patients treated with whole-lung irradiation after more than 10 years of follow-up.[39]

A study from the International Society of Pediatric Oncology (SIOP) suggested that whole-lung irradiation may not be necessary for successful therapy of patients with stage IV, favorable histology Wilms' tumor if the metastases completely respond to chemotherapy.[40] If such is the case, the controversy surrounding the detection of pulmonary nodules on chest CT after a negative chest x-ray may be moot.

**Chemotherapy**

**Do All Patients Need Adjuvant Therapy?**

Is there a subset of patients who do not require adjuvant treatment after nephrectomy? It should be reiterated that the NWTS 2 found that adjuvant radiation was not necessary in patients with stage I, favorable histology tumors provided that they receive a combination of dactinomycin and vincristine.

In a pilot study from the Dana-Farber Cancer Institute and Children's Hospital in Boston, eight patients less than 24 months of age with stage I (Cassady) Wilms' tumor underwent nephrectomy and no further therapy.[41] The study was based on a 1973 report by Cassady, which showed an excellent outcome in patients with unilateral, nonmetastatic, small (total tumor and kidney specimen weight, less than 550 g) tumors with a favorable histologic pattern.[42] In the pilot study, the event-free survival rate was 88% and overall survival rate was 100% at a mean follow-up of 5 years. The only recurrence developed in the contralateral kidney of one boy. This child is alive and disease-free after treatment for a metachronous bilateral Wilms' tumor.

In an effort to identify a subset of patients with stage I, favorable histology tumors who may need less therapy, Weeks et al studied 24 patients with stage I, favorable histology lesions in NWTS 3 who relapsed and compared them with 48 control subjects who had not relapsed for at least 2 years after diagnosis. Specific attention was made to document any invasion of tumor capsule, presence of an "inflammatory pseudocapsule," renal sinus invasion, and tumor in intrarenal vessels. Among the NWTS 3 patients, no relapses occurred when all four variables were absent. One or more of these features were present in 100% of relapsed cases, as compared with 46% of controls.[43] This study suggests that future trials should focus on patients who have stage I, favorable histology tumors without adverse clinical and/or histologic factors. Such trials should aim to determine whether adjuvant chemotherapy can be eliminated in this select group of patients.

**How Should Recurrent Disease Be Treated?**

Another controversy focuses on what treatment approach should be used in patients with recurrences. In the NWTS 2 and 3, the 3-year post-relapse survival rate for children with recurrent Wilms' tumor was 30%. A post-relapse survival rate more than 40% was seen in certain subgroups of patients; these included children who had a solitary pulmonary recurrence, those who had a recurrence in the abdomen when radiotherapy was not previously given, those who were originally stage I, those who were initially treated only with dactinomycin and vincristine, and those whose disease recurred 12 months or more after diagnosis. Patients who relapsed were treated with combination chemotherapy, with or without radiation therapy and/or surgery, at the discretion of the investigator. The chemotherapeutic agents employed in the vast majority of cases were dactinomycin, vincristine, doxorubicin, and cyclophosphamide. Thus, treatment for relapse consisted primarily of conventional therapies that had often been used as part of initial therapy.[44] In another series from Wilimas et al, 20% of 156 patients with stage I-IV Wilms' tumor relapsed. Only time to relapse had a significant influence on survival. In three of eight surviving patients, surgery alone was performed and was curative. However, most relapses occurred at multiple sites, and failure of salvage therapy was primarily due to the ineffectiveness of chemotherapy.[45]

A recent study from the same group advocated the use of ifosfamide, carboplatin, and etoposide (ICE) chemotherapy in relapsed Wilms' tumor. Four of five patients treated with ICE responded, and this combination had no significant adverse effects on the remaining kidney.[46] In a report from the United Kingdom Children's Cancer Study Group (WTI) Study, 71 of 321 children relapsed after initial therapy for Wilms' tumor. In general, treatment of relapse included early surgical resection of operable disease and adjuvant chemotherapy. Local recurrence at previously nonirradiated sites was treated with radiation therapy at a dose of 3,500 to 4,000 cGy. Second-line chemotherapy varied and included single agents and combinations of ifosfamide, etoposide (VePesid) or teniposide (Vumon), cisplatin (Platinol) or carboplatin.
Garaventa et al reported on 25 relapsed patients treated with high-dose chemotherapy followed by autologous bone marrow transplantation. Only one of eight children who had measurable disease at transplantation survived, as opposed to 8 of 17 who were in complete remission.[48] Clearly, salvage rates after relapse are dismal, with the majority of children dying from recurrent disease. At present, there is no "standard" chemotherapy or treatment approach for recurrent disease. Optimal chemotherapy still needs to be defined.

Radiotherapy

Radiotherapy is not indicated in patients with stage I-II, favorable histology or stage I, anaplastic tumors after nephrectomy. As mentioned above, in patients with stage III, favorable histology tumors, total flank or abdominal radiation therapy at a dose of 1,000 cGy is just as effective as 2,000 cGy provided that three-drug chemotherapy is employed. The addition of doxorubicin to daunomycin and vincristine seems to substitute for the second 1,000- cGy radiation dose.[49] Postoperative irradiation of the flank is commonly given to the preoperative tumor volume with a 1- to 2-cm margin. Care is taken to position the medial border of the port so that it includes the para-aortic nodes on the contralateral side while avoiding the opposite kidney. For children who have had diffuse tumor spillage, diffuse intraoperative rupture, or peritoneal implants, a whole-abdominal field is employed, extending from the dome of the diaphragm to a level below the obturator foramen. The femoral heads are shielded, and the field is allowed to extend laterally on both sides. For patients with lung metastases, a dose of 1,200 cGy in eight fractions to bilateral lungs is commonly employed.

What Is the Optimal Radiation Dose for Unfavorable Histologies?
The optimal dose for patients with anaplastic histology and clear cell sarcoma of the kidney is less clear. For stage II-III, anaplastic tumors, the NWTS 4 advocates an age-adjusted dose (Table 4).[50] For stage I-III, clear cell sarcoma, the NWTS 4 recommends a total dose of 1,080 cGy. Recent analysis of the NWTS 3 data indicate that intra-abdominal relapse rates among patients with anaplastic histology and clear cell sarcoma of the kidney do not differ in children receiving total doses 1,800 cGy or less vs those given more than 1,800 cGy.[51,52] In view of these findings, which show that higher doses of radiation do not increase local control, the present NWTS 4 age-adjusted recommended dose in anaplastic tumors may need to be modified to decrease the risk of scoliosis, muscle atrophy, and impairment in spinal growth associated with higher radiation doses.

What Is the Optimal Timing of Radiotherapy?
For children who need adjuvant radiation therapy after nephrectomy, when is the best time to initiate radiotherapy? In NWTS 1 and 2, the intra-abdominal relapse rate was significantly higher in children with an unfavorable histology tumor than in those with a favorable histology (40% vs 4%) when there was a ≥ 10-day delay from nephrectomy to the start of radiation therapy.[53] In NWTS 3, 10 of 15 patients who experienced an intra-abdominal relapse had delays of more than 10 days after surgery before the initiation of radiation therapy. Of 103 patients with stage III, favorable histology tumors who started radiotherapy 10 days or more after surgery, 10 suffered an intra-abdominal relapse, as compared with 5 of 174 patients whose radiation therapy began within 10 days.[49] Therefore, the available data indicate that radiotherapy should be initiated within 10 days after surgery.

Synchronous Bilateral Tumors

The frequency of synchronous bilateral Wilms' tumors ranges from 4% to 9% in the literature.[54,55] The management of patients with these tumors has evolved from an initial surgical approach (unilateral nephrectomy and contralateral partial nephrectomy) to bilateral biopsies followed by preoperative chemotherapy. The main reason for the change in management is to preserve more renal parenchyma and prevent renal dysfunction and failure. In an NWTS report, renal failure was found in 55 patients, 39 of whom had bilateral tumors. The incidence of renal failure in patients with bilateral tumors was 16.4% in NWTS 1 and 2, 9.9% in NWTS 3, and 3.8% in NWTS 4.[28] After bilateral renal biopsy, both tumor sites are staged, and combination chemotherapy (vincristine and actinomycin) is employed until maximum tumor regression is attained. The addition of doxorubicin, with or without radiation therapy, may be necessary for tumors that respond poorly to vincristine plus actinomycin. Second-look surgery is performed to determine whether there has
been sufficient response to chemotherapy, with or without radiation therapy, to allow for preservation of a substantial amount of normal renal tissue.

Both the NWTS and SIOP have shown excellent survival rates after biopsy, chemotherapy (with or without radiotherapy), and subsequent surgical resection. Overall 10-year survival rates range from 70% to 80%, which are comparable to figures obtained by an initial surgical approach.[3,56] Multivariate analysis of selected variables in the NWTS revealed that the presence of unfavorable histology, stage of most advanced tumor at diagnosis, and older age (more than 3 years) were adverse prognostic factors. Renal parenchymal-sparing techniques do not compromise locoregional control.[17]

Patients who have nonresponding, massive bilateral tumors undergo bilateral nephrectomy. These children eventually require dialysis and renal transplantation. In a study by Penn of 16 bilateral and 4 unilateral tumors, the incidence of recurrence or metastases was 47% in patients who received renal homografts less than 1 year after treatment of tumors, as compared with 0% in those who received grafts more than 1 year after treatment.[57] In another study by DeMaria et al, patients with bilateral tumors who had undergone renal transplantation had a significantly higher mortality than those who did not. The increased mortality was secondary to sepsis resulting from chemotherapy, radiotherapy, and immunosuppression.[58]

Hence, renal-conservation techniques should be employed before rendering a child anephric, as survival and quality of life are worse if the patient undergoes renal transplantation. Bilateral nephrectomy should be reserved for children with persistent, massive bilateral tumors that prove unresponsive to chemotherapy and radiation therapy.

**Can Resection Be Avoided After Biopsy and Chemotherapy?**

Is there a subset of patients who do not require surgical resection after initial biopsy and chemotherapy? The NWTS reported that 18 (13.8%) of 130 kidneys required no operation other than biopsy. However, the outcome of the patients is not mentioned in this report. Furthermore, all of the patients had chemotherapy, and the number who had radiation therapy is unknown.

In a report from St. Jude Children's Hospital, Paulino and colleagues noted that 23 (30.3%) of 76 kidneys were not resected after biopsy and chemotherapy; 20 of the 23 kidneys were irradiated. After chemotherapy, 7 (30.4%) of 23 kidneys had a pathologic and/or radiologic complete response (CR). In an attempt to answer whether radiation therapy is necessary after a CR to chemotherapy, the authors reviewed the local recurrence rate in the four kidneys that were irradiated and the three that were not. Local control was achieved in all four kidneys irradiated after a CR to chemotherapy; however, local control was achieved in only one of three nonirradiated kidneys. Because of the small numbers, one could not determine from this study whether radiation therapy is necessary after a CR to chemotherapy.[17]

**Metachronous Bilateral Tumors**

The incidence of metachronous bilateral Wilms' tumor ranges from 2% to 3%.[3,59] Initial reports indicated that the prognosis for the metachronous presentation was inferior to the synchronous type.[59,60] An analysis of the literature from 1950 to 1980 showed that survival of patients with sequential tumors has improved and has now become identical to that of patients with simultaneous tumors. In the SIOP experience from 1971 to 1980, the survival rates for synchronous and metachronous presentations were not significantly different (69% and 56%, respectively).

It may be that current treatment is more efficient and, hence, produces a better outcome. On the other hand, almost all patients nowadays receive dactinomycin and vincristine, with or without doxorubicin, and these agents may suppress the appearance of a metachronous tumor.

**Follow-Up**

D'Angio and colleagues established guidelines for diagnostic imaging during the follow-up period for children treated for Wilms' tumor (Table 5).[29] Because the most common site of failure is the lungs, a chest x-ray is recommended at 6 weeks and 3 months after nephrectomy and thereafter is repeated as outlined in Table 5.

Abdominal ultrasound is recommended at more frequent intervals in patients with stage III, favorable histology tumors; all clear cell sarcomas; and stage II-III, anaplastic tumors because of the higher frequency of intra-abdominal relapse in these groups than in patients with stage I-II, favorable histology tumors. Likewise, children with nephrogenic rests need more frequent abdominal ultrasound and longer follow-up than those without nephrogenic rests because of the risk of metachronous tumor.
In patients with clear cell sarcomas, a skeletal survey, bone scan, and an MRI of the brain should be performed in the follow-up period because of the tendency of these tumors to metastasize to the skeleton and brain.[61]
In all patients who have had radiation therapy, skeletal x-rays of irradiated bones should be performed yearly because of the risk of scoliosis and kyphosis. In a NWTS late effects study, scoliosis was seen in 61% of irradiated patients vs 9% of nonirradiated patients.[62]

**Conclusions**

Although many advances have been made in the treatment of Wilms' tumor, progress is still needed in the treatment of unfavorable histology and recurrent tumors. Furthermore, the role of partial nephrectomy in unilateral Wilms' tumor still needs to be defined. Likewise, future trials should be directed toward identifying children who do not require adjuvant therapy after surgical resection. With the cooperation of various disciplines, we will continue to improve current therapeutic strategies and achieve less morbidity in children with nephroblastoma.

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