

Synchronous bilateral Wilms' tumor in the adolescent and adult

Report of the fifth case and review of the world literature

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Abstract. Bilateral Wilms' tumor in the adolescent and adult is extremely rare, with only four previous cases reported. Theories as to the etiology of this entity and a review of the demographics, diagnosis, staging, and treatment of Wilms' tumor with emphasis on bilateral disease and the older patient are presented. Current approaches to the patient with an atypical presentation of Wilms' tumor can result in excellent results similar to those seen with the more typical presentation.

Key words: Bilateral Wilms' tumor – Wilms' tumor in the adult – Nephroblastomatosis

Introduction

Wilms' tumor is one of the most common intra-abdominal malignancies of childhood, accounting for approximately 6% of intra-abdominal cancers presenting before the age of 15 years. The dramatic improvement in survival with this tumor over the past 25 years has been seen with few other malignancies. While the approach to the majority of patients with Wilms' tumor has become fairly well defined, some cases present with unusual features which make placement into a specific treatment protocol difficult. Bilateral, synchronous Wilms' tumor and Wilms' tumor in the adolescent and adult population are examples of such presentations. We report an adolescent with bilateral Wilms' tumor, a combination so rare that a review of the world literature has revealed only four previously reported cases, often with incomplete documentation. A review of the

etiology, demographics, diagnosis, staging, and treatment of Wilms' tumor with emphasis on bilateral disease in the adolescent and adult patient will be presented.

Case report

Our patient was a 15-year-old white female when first referred to the University of Michigan Medical Center-Mott Children's Hospital in September 1983 for evaluation of bilateral renal masses. She had been well until March 1982 when she noted the onset of intermittent back pain. In May 1982, she developed severe left flank pain accompanied by nausea, vomiting, and pyrexia which resolved within 5 days. Over the ensuing 18 months, she had six similar acute episodes accompanied by a 7-kg weight loss. In August 1983, a left flank mass was palpable on physical examination and led to hospitalization. There was no history of trauma, hematuria, or dysuria and only occasional urinary frequency. Workup included renal ultrasound, which revealed bilateral renal masses, and Computer tomography (CT) scan confirmation of the presence of solid tumors involving both kidneys (Fig. 1). At this time, the only blood chemistry abnormality was an elevated LDH of 530 IU. Further evaluation at our institution included an intravenous pyelogram (IVP), which showed bilateral calyceal distortion (Fig. 2), and angiography, which suggested multiple hypovascular tumors originating in both kidneys (Figs. 3 and 4). On 30 August, 1983, exploratory laparotomy revealed bilateral renal tumors with no evidence of other intra-abdominal disease. The left kidney, as angiographically predicted, was nearly 100% replaced by tumor and the right side was approximately 50%–60% replaced. A left radical nephroureterectomy was performed after frozen section biopsy confirmed the diagnosis of Wilms' tumor. Final pathologic evaluation revealed multifocal Wilms' tumor in the left kidney with predominantly epithelial histology. All 30 lymph nodes in the specimen were negative for neoplasm. Tumor deposits were noted, however, in the peripelvic fat. Postoperative chest CT and bone scan were negative. She was immediately begun on a combined chemotherapy regimen of actinomycin D and vincristine, to which adriamycin was added after 1 month.

Serial CT scans showed a decrease in the size of the right renal tumor over the 3 months of treatment (Fig. 5). "Second look" laparotomy was performed on 1 December 1983 and re-

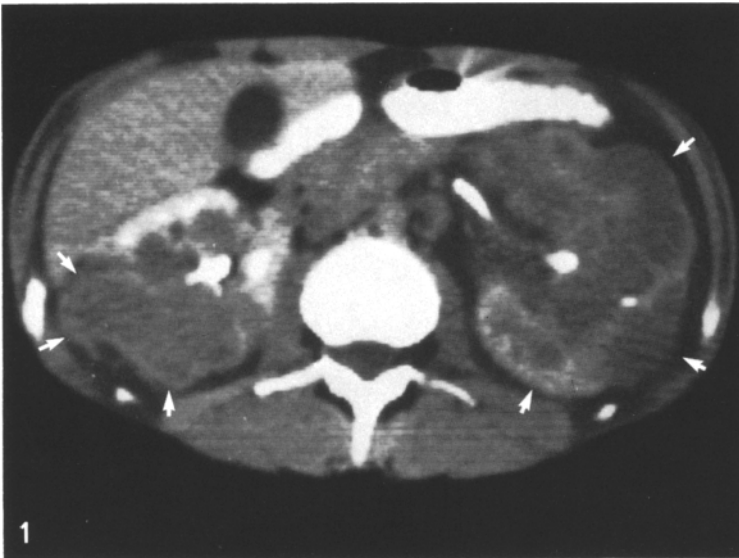


Fig. 1. CT scan demonstrating bilateral renal neoplasms

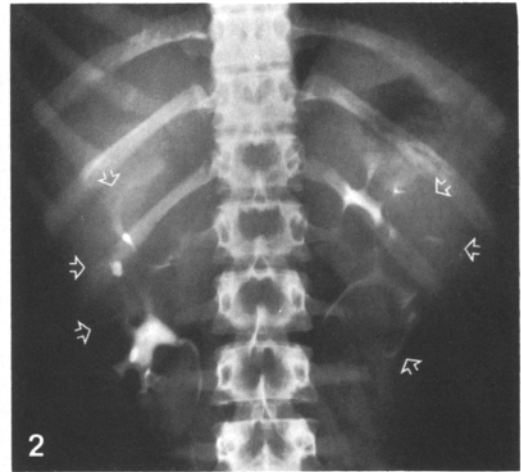


Fig. 2. IVP Shows calyceal distortion bilaterally due to intrarenal neoplasm

vealed what appeared grossly to be a right renal upper pole "scar" with cystic changes throughout the remaining kidney. Partial nephrectomy was performed with removal of all gross tumor; pathologic evaluation of the specimen revealed both necrotic and viable Wilms' tumor in the upper pole mass. Biopsies from the remaining renal parenchyma showed the diagnosis of nephroblastomatosis. Postoperatively, the three-drug chemotherapy regimen was resumed. At no time did the patient develop renal insufficiency.

In May 1984, 9 months following her original operation, she developed recurrent right flank pain. Abdominal CT scan revealed right hepatic lobar and T10 vertebral metastases. Radiation to the lower thoracic spine was initiated and 2400 rads were administered. She was next treated with "lethal"-dose Melphalan followed by autologous bone marrow transplantation, which was complicated by an immune thrombocytopenia responsive to danazol and vincristine. CT scan in February 1985 showed sclerosis of the bony metastasis and enlargement

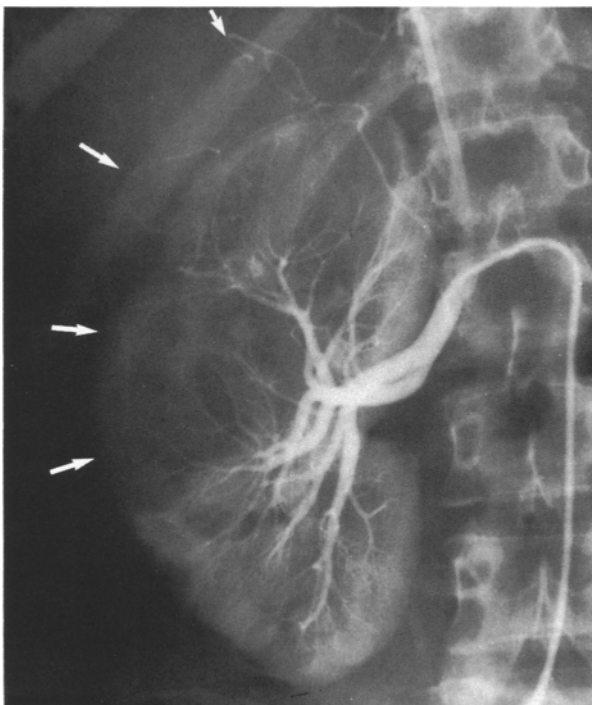


Fig. 3. Renal arteriogram (right) at presentation demonstrating involvement of upper two-thirds of right kidney

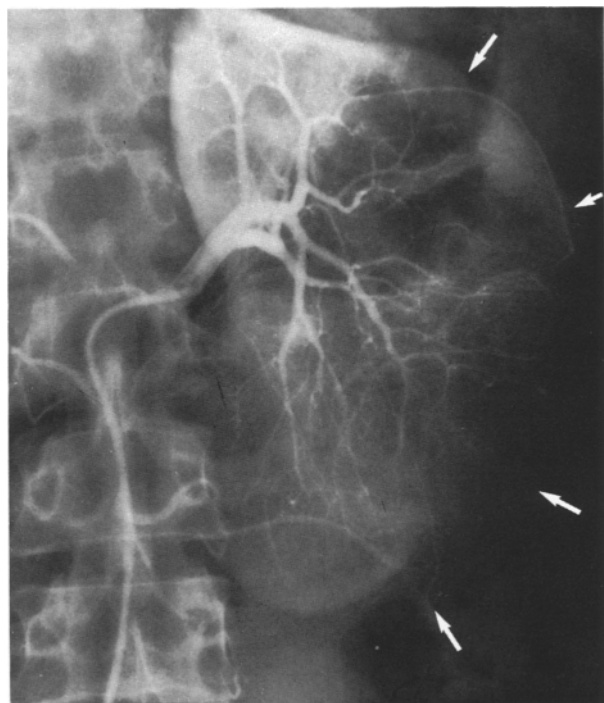


Fig. 4. Renal arteriogram (left) at presentation demonstrating near-total involvement by neoplasm



Fig. 5. Postoperative CT scan following left radical nephrectomy and combination chemotherapy demonstrating marked regression of right renal neoplasm

of the hepatic mass. The metastatic nature of the latter was confirmed by percutaneous biopsy and, as it represented the only evident focus of disease, right hepatic lobectomy was performed on 8 February 1985. The patient was undergoing a gradual recovery when she again developed severe thrombocytopenia refractory to all management and expired in March 1985, 19 months after her initial diagnosis.

Review of previous case reports

Four cases of bilateral Wilms' tumor in the adolescent or adult, defined here as patients older than 12 years, have been previously reported in the world literature. Details of these cases are often obscure due to the historical nature of the reports or the need to translate from a foreign language. We have included all those cases for which reasonable data was available.

Case 1. Battendorf [4], in a 1970 report translated from the German literature, described a 59-year-old female who presented with right pulmonary hilar prominence, dizziness, right hemiparesis, microscopic hematuria, and proteinuria. She was presumed to have lung cancer with central nervous system metastatic disease and became comatose and died without further therapy. At post-mortem examination, bilateral upper pole renal masses were detected which proved histologically to be Wilms' tumor with "glomerular differentiation". This was accompanied by renal venous and inferior vena caval thromboses and tumor involvement of hilar nodes. In addition, there were cerebral metastases accompanied by signs of increased intracranial pressure.

Case 2. This case is included in the report of a series of 1,351 cases of Wilms' tumor by Klaproth et al. [28] from 1959, which included 45 cases from the Cleveland Clinic diagnosed and treated between 1921 and 1953. A 29-year-old female was first treated in 1943, at age 17 years, with radiation therapy for a right renal neoplasm described as "spindle cell sarcoma arising from the nerve and smooth muscle". She was seen again in 1956 at the Cleveland Clinic for evaluation of hypertension. An IVP at that time revealed a right renal neoplasm and she underwent exploratory laparotomy with nephrectomy for a tumor pathologically identified as Wilms' tumor. She suffered a number of postoperative complications related in part to her previous radiation therapy and died 5 months after surgery. Postmortem examination revealed that the remaining kidney was almost completely replaced by neoplasm, again histologically Wilms' tumor. This case is included to ensure completeness, recognizing that these findings could represent metastasis to the remaining kidney as well as asynchronous neoplasia.

Case 3. Knudson et al. [29] reviewed 97 cases of Wilms' tumor from the M. D. Anderson Hospital between 1944 and 1970. In this report, a notation is made of bilateral Wilms' tumor in a patient over 12 years of age. No further details are available.

Case 4. Tsunoda et al. [44], in 1969, reviewed the Japanese literature and reported 19 cases of bilateral Wilms' tumor. The author cited a report by

Fugita [21] of an 18-year-old female with synchronous bilateral Wilms' tumor who was diagnosed in 1928 and treated with a right nephrectomy but expired, presumably of her disease. No further details are available.

Discussion

Demographics

The incidence of Wilms' tumor has been noted to be remarkably stable and without geographic preference occurring at a rate of approximately 7.8 per million children under 15 years of age [14]. It ranks fifth in frequency among the solid tumors of childhood behind CNS tumors, lymphoma, neuroblastoma, and soft tissue sarcoma [40]. While 95% of cases are diagnosed before age 10, with a peak incidence at age 3, cases have been documented in the fetus and in adults up to the age of 80 years.

The incidence of Wilms' tumor in adults is difficult to determine, although there appears to be a peak in the 4th decade. Recent reviews [3, 27] have noted close to 200 cases of Wilms' tumor in adults and adolescents over 12 years of age, but authors report that in many of these cases the diagnosis is questionable. Kilton [27] reviewed 35 cases of adult Wilms' tumor in 1980 that in his opinion were the only cases in the world literature with adequate documentation.

Bilateral involvement was first reported by Rance [42] in 1814: a case which represents the earliest description of Wilms' tumor. Recent reviews place the frequency of bilaterality at between 1%–12% of all cases, with most larger series estimating the rate at approximately 5% [6, 10]. Two-thirds of bilateral cases present synchronously; the remainder are typically diagnosed from 2 years to as long as 19 years after the initial tumor. Synchronous, bilateral disease tends to present at a younger age than does unilateral disease (30 months vs 45 months) [7, 10, 29].

There is an increased incidence of congenital anomalies in patients with Wilms' tumor. Specifically, these include hemihypertrophy, aniridia, and various genitourinary anomalies [37]. This frequency of congenital anomalies may be up to ten times higher in cases of bilateral Wilms' tumor, especially with regard to hemihypertrophy and hypospadias [10].

Etiology

Because of its histologic resemblance to embryonic renal tissue (classically with epithelial, blastemal, and stromal elements), it is speculated that

Wilms' tumor is associated with nephroblastomatosis, which represents the persistence of immature renal tissue beyond the time of completion of nephrogenesis (36 weeks) [33]. The pathology literature is often confusing and describes a number of histologic variants of nephroblastomatosis which could be associated with Wilms' tumor, including nodular renal blastema, sclerosing metanephric hamartomas, Wilms' tumorlets, and glomerular immaturity with sclerosis [8]. Examination of multiple sections of kidneys with Wilms' tumor has shown nephroblastomatosis in a significant percentage of cases, leading to the belief that this represents a precursor lesion [8, 33]. In these studies, all cases of bilateral tumor showed evidence of nephroblastomatosis, supporting the hypothesis that this multicentric abnormality may be particularly important in the occurrence of multifocal neoplasia. This finding further supports the view that bilateral Wilms' tumor represents multiple primary tumors rather than metastasis from the contralateral kidney.

Another area of great interest related to the origin of Wilms' tumor is that of genetic heritability. Through analysis of familial cases of Wilms' tumor as well as cases of unilateral, bilateral, and multifocal neoplasm, a theory of heritability of this entity has been developed and widely accepted [30]. This theory is based on a two-step mutational model and predicts that hereditary cases may account for 20%–38% of Wilms' tumor cases [29]. The theory proposes that non-hereditary cases result from two somatic (postzygotic) mutations in a cell, yielding a single unifocal tumor. In the heritable case, the first mutation is in the germinal cell line which is prezygotic and, therefore, affects all cells in the patient. A single additional postzygotic mutation in the target tissue would then be necessary for manifestation of the tumor. From such a model, one would expect a younger age of presentation for patients with inherited tumors as well as an increased frequency of bilateral as well as multifocal unilateral tumors among the patients with this heritable form. Nephroblastomatosis may represent the phenotypic expression of the proposed first mutation.

There are several lines of evidence from clinical reviews supporting such a theory. First, the average age of presentation has been shown to be lower in bilateral and familial cases [29], although a more recent study [10] has not substantiated this in familial cases. Second, there is an increased prevalence of associated anomalies with well demonstrated heritability in Wilms' tumor patients. Finally, a specific chromosomal abnormality, de-

letion of the p13 band of chromosome II, has been identified in a number of Wilms' patients, particularly in association with aniridia [40]. The bulk of the evidence supports the theory of heritability as autosomal dominant with incomplete penetrance, with bilaterality expected in 15% of heritable cases. That bilaterality in the older patient is markedly unique is predicted by these theories.

Diagnosis

The most common presenting symptoms in the patient with Wilms' tumor are abdominal mass, pain, hematuria, fever, and hypertension [40]. While a mass lesion is the most frequent finding in the typical pediatric patient (90%), in adults abdominal pain is the most frequent complaint (60%) followed by abdominal mass (48%) and hematuria (36%) [27]. In as many as 42% of adult patients, the symptoms have been present for greater than 1 year prior to diagnosis [27]. Hematuria and hypertension have been noted to be more frequent in cases of bilateral disease [2].

In the past, the IVP has been the mainstay of evaluation of the patient with Wilms' tumor, typically revealing calyceal distortion and displacement, with ultrasound used frequently to confirm the renal origin and solid nature of the abdominal mass. Angiography is not used routinely in these patients, but may be useful in older patients where the diagnosis is unclear or in bilateral cases to assess the feasibility of heminephrectomy [24,

36]. CT scanning has emerged as possibly the single most useful study in the evaluation of the patient with bilateral Wilms' tumor. With contrast infusion, CT can reveal the extent of the tumor mass and renal functional status as well as vena caval patency, and can also demonstrate the presence of metastatic disease. It is of critical importance for follow-up [9]. In cases of bilaterality, it has been shown to be quite sensitive in the preoperative assessment of feasibility of partial nephrectomy [13]. In the older patient group, intraoperative biopsy is often needed to conclusively make the diagnosis; percutaneous biopsy is contraindicated where Wilms' tumor is suspected due to the risk of tumor spread, which may adversely affect prognosis.

Prior to the advent of CT, as many as 30%–50% of cases of bilateral Wilms' tumor were unsuspected prior to operation. Surgical exploration, therefore, was critical not only for treatment but also for diagnosis. Complete visual and manual inspection of the contralateral kidney via reflection of the colon and opening of Gerota's fascia was emphasized at least 25 years ago [35], and is commonly performed today to ensure proper investigation of the possibility of bilateral disease.

Classification/staging

The cooperative National Wilms' Tumor Study (NWTS) has developed the most widely used system for grouping patients based on factors of prognostic significance. From the results of the first two phases of the study, some modifications

Table 1. NWTS staging system

Stage I	Tumor limited to kidney, completely excised; capsular surface intact, no rupture, no residual tumor at margins of resection
Stage II	Tumor extends beyond the kidney but is completely excised; penetration through capsule into perinephric soft tissues; renal vessels may contain tumor; previous biopsy or local operative flank; no residual tumor at margins of resection
Stage III	Residual nonhematogenous tumor is confined to the abdomen <ol style="list-style-type: none"> any abdominal lymph nodes involved diffuse peritoneal contamination secondary to rupture or spillage peritoneal implants tumor grossly or microscopically beyond surgical margin tumor not completely resectable due to infiltration of vital structures
Stage IV	Hematogenous metastases present (lung, liver, bone, CNS)
Stage V	Bilateral renal involvement

Table 2. TNM system for Wilms' tumor staging

T-1	Tumor encapsulated; less than 550 cc; no capsular, collecting system, or major vascular invasion; complete surgical removal
T-2	Tumor exceeds one or more of above criteria but is apparently totally excised
T-3	Tumor is massive, invades other organs, and/or cannot be totally excised
N-0	No nodes involved
N-1	Hiar or para-aortic lymph nodes positive
M-0	No non-nodal metastases
M-1	Pulmonary metastases only
M-2	Hepatic, CNS, bony or other metastases

Clinical stage correlation with TNM stage

Stage I	= T ₁ N ₀ M ₀
Stage II	= T ₁ N ₁ M ₀ or T ₂ N ₁ M ₀
Stage III	= T ₃ N ₀ M ₀ or T ₃ N ₁ M ₀
Stage IV	= any T, any N, M ₁
Stage V	= any T, any N, M ₂

have been adopted to make it a true staging scheme (Table 1) [15]. In addition to the factors noted in the grouping system, separate stratification is based on histologic findings. Approximately 11% of patients exhibit anaplastic or sarcomatous elements in their tumor classifying them as "unfavorable histology". The remainder demonstrate more typical histology with varying degrees of epithelial, blastemal, or stromal differentiation and are classified as "favorable histology". The prognosis for patients with unfavorable histology is significantly worse than that for those with favorable histology. This system is applicable to patients regardless of age, although advanced age may be a negative prognostic indicator.

A TNM system has also been developed for Wilms' tumor, although it has not been employed in NWTS analyses (Tables 1 and 2) [12, 22]. The NWTS staging system places all patients with bilateral disease in group V without regard to prognostic factors that separate patients into the other groups. The TNM system, however, has been used by some to further stratify patients with bilateral disease basing their stage on the side of most significant involvement [34, 46]. Using this method in a review of 20 bilateral cases, Malcom et al. [34] showed that survival in this group is related to the same prognostic factors as in unilateral disease and suggest that survival in synchronous bilateral disease is no different than similarly staged cases of unilateral disease.

Treatment

Before 1960, treatment of Wilms' tumor was limited primarily to surgery, radiation, or both with reasonable results. Since 1960, an aggressive multimodal approach combining surgery, radiation, and chemotherapy has improved the outcome from overall survivals of approximately 30% to 80%–90% in stages I and II. The NWTS has been instrumental in defining and standardizing the optimal treatment of patients classified in groups I–IV. Surgery typically involves radical transperitoneal nephroureterectomy with thorough exploration of the abdomen, including the contralateral kidney. Care in handling the tumor is stressed to avoid capsular rupture [32]. Radiation, when indicated, is delivered to the renal fossa, with total abdominal radiation limited to cases with diffuse tumor spillage or peritoneal implants. Chemotherapy is begun in the immediate postoperative period and consists of actinomycin D and vincristine. Evaluation of the benefit of adding adriamycin and/or cyclophosphamide in more advanced stages is ongoing [15].

The principles and regimens set forth in the NWTS protocols are generally applicable to the adult and adolescent patient. There is limited evidence that actinomycin D may not be as effective in adults as it is in children, but most authors nonetheless recommend its use [46]. The rarity of the disease in this age group makes a comparative analysis between adults and children difficult, and specific recommendations regarding the treatment of adults have been developed via extrapolation from data on pediatric patients.

Principles for the management of bilateral Wilms' tumor have undergone significant evolution, but no universally accepted scheme exists yet. Strict adherence to the algorithms for unilateral disease would jeopardize renal function on the basis of both extensive surgical excision and the possibility of radiation-induced nephritis. In earlier years, the major controversies centered on the choice of immediate resection with or without perioperative radiation versus the exclusive use of radiation therapy [5]. The results of early surgical intervention followed by aggressive adjuvant therapy in unilateral disease has prompted most centers to adopt a plan of early exploration in bilateral disease.

Most current approaches involve an attempt at total gross tumor excision in one, two, or three stages followed at each stage by chemotherapy and radiation when indicated. When surgically feasible, this will result in total nephrectomy with contralateral heminephrectomy or bilateral heminephrectomy. This approach is possible in only about 50% of cases because of massive or multifocal involvement of both kidneys. In these cases, regimes of chemotherapy and radiation are used along with liberal surgical re-exploration to control the remaining tumor.

Bilateral nephrectomy and allotransplantation for Wilms' tumor was first reported in 1968 and has since been advocated by a number of groups as an acceptable choice of therapy [17–19, 39]. One review showed significantly lower survival in transplanted patients (29% vs 67%), with most of the excess mortality secondary to septic complications [19]. Delaying transplantation beyond 1 year following the initial treatment significantly reduced the incidence of such complications. Another study noted a higher recurrence rate in patients treated with transplantation within 1 year following bilateral nephrectomy and recommended a 1–2-year delay in transplantation if feasible [39]. Newer immunosuppressive therapy may significantly affect these results.

In general, treatment of bilateral Wilms' tu-

mor must be highly individualized and, based on recent reviews, may be summarized as follows [6, 18, 47]: in all cases of Wilms' tumor, both kidneys should be thoroughly palpated or inspected. Originally, surgical attitudes favored gross total removal of tumor by nephrectomy, nephrectomy plus contralateral partial nephrectomy, or bilateral partial nephrectomy while sparing enough tissue (15%–35%) [41] to ensure adequate renal function. More recent publications [26] suggest that a more conservative surgical approach may be appropriate, stressing biopsy at initial exploration with subsequent second- and third-look operations and preservation of at least 60% of renal tissue. The use of chemotherapy and radiation depends upon the stage of the more involved side as dictated by the NWTS protocols. Radiation doses must be adjusted to limit exposure of any remaining renal tissue to 1500 rads. If gross total removal is impossible, chemotherapy and radiation should begin immediately and a second-look procedure should be performed, generally following 3 months of treatment. This may be variable and depends upon the patient's response as judged by noninvasive evaluation. Bilateral nephrectomy and subsequent transplantation should be reserved for patients with otherwise unresectable tumor who do not respond well to the other treatment regimens.

Prognosis

Early in this century, survival for all cases of Wilms' tumor was less than 10% [31]. During the first half of the century, overall survival improved to 40%–50%; however, cures remained uncommon in adults or patients with bilateral disease [15, 25, 42, 43]. With combined multimodal therapy, which has become standard since the 1960's, 2-year survival has increased to 95% in stage I patients [16, 38]. Survival rates in adults have been estimated to be 44% at 18 months [27]; however, lack of standardization of therapy and delay in diagnosis have undoubtedly influenced these results unfavorably. Many authors feel that the same results seen in children are attainable in adults with early diagnosis and aggressive management [1, 15]. In patients with bilateral disease, improvement in survival has been noted to parallel the overall improvement in Wilms' tumor treatment from 13.8% reported in the early 1970's [20] to 67%–87% in more recent reviews [6, 19, 23, 24]. Some controversy still exists as to whether synchronous and metachronous cases of bilateral Wilms' tumor represent two separate entities with

different prognostic implications. One report has shown reduced survival in patients with metachronous presentations [34] while another shows no difference other than that seen in similarly staged synchronous bilateral or unilateral cases [11].

In conclusion, the coincidence of these two unusual presentations (bilaterality in an adolescent) for Wilms' tumor is extremely rare. We have been able to identify four cases in the world literature, with no cures reported [4, 28, 30, 44]. In at least two of these four previously reported cases, diagnosis was made at postmortem examination. Details were insufficient to reveal how the diagnosis was made in the other two patients; similar difficulties are encountered in reviewing staging and therapeutic planning in these patients.

Bilateral Wilms' tumor in older patients is extremely rare, and successful treatment hinges on early diagnosis. Rational approaches for the management of bilateral disease continue to evolve; however, the lack of standardized substaging in this group will continue to preclude a meaningful comparison of the various treatment regimens.

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