UPDATE ON WILMS’ TUMOR IN CHILDREN

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ABSTRACT: Although rare, Wilms’ tumor is the most common primary renal malignancy in children and is associated with a number of congenital anomalies and documented syndromes. Appropriate laboratory, radiologic and pathologic investigations are necessary components of the evaluation of children with suspected Wilms’ tumor. This provides accurate diagnosis and subsequent staging; information which is essential to generate a multidisciplinary treatment plan utilizing surgery, chemotherapy and radiotherapy. Patients treated for Wilms’ tumor as children must continue to be monitored for possible long-term sequelae as adults including secondary malignancies as well as treatment-related toxicity.

INTRODUCTION

Wilms’ tumor is the most common primary renal malignancy of childhood and accounts for approximately 6–7% of all pediatric cancers [1]. It represents one of the few malignancies in which, over the past several decades, advances in biomedical technology have led to significant improvements in patient survival. By employing a multidisciplinary approach incorporating surgery, radiotherapy and chemotherapy, the management of Wilms’ tumor represents an ideal model of cancer therapy. However, as these advances have better defined high-risk patients who obviously benefit from intensified treatment regimens, ongoing investigations are attempting to delineate those patients with low-risk disease whom could be spared the possible long-term sequelae of more intensive treatment without compromising cure rates. We present an update on Wilms’ tumor in childhood including its epidemiology, biology, pathology, clinical presentation and diagnosis, as well as the current treatment of all stages of the disease.

Epidemiology

The incidence of Wilms’ tumor ranges from 8-10 cases per million population [2-3]. The median age at presentation is 3.5 years although bilateral disease and those with associated syndromes tend to present at an earlier age. Wilms’ tumor accounts for over 80% of genitourinary malignancies in children less than 15 years of age and 90% of children are diagnosed before age 7.

Frequently, Wilms’ tumor is associated with a number of congenital anomalies or documented syndromes. A number of these syndromes share somatic overgrowth as a key feature and include the Beckwith-Wiedemann syndrome (BWS) and hemihypertrophy. BWS is characterized by excess cellular growth leading to macroGLOSSIA, nephromegaly, hepatomegaly and hemihypertrophy [4]. Overall, the risk of tumor development including Wilms’, adrenal cortical carcinoma and hepatoblastoma is 10-20% in patients with BWS while the risk of Wilms’ tumor alone is estimated to be 4-10% [5]. Nephromegaly appears to be the most significant risk factor for the subsequent development of Wilms’ in patients with BWS [6]. A number of other overgrowth syndromes have also been identified which appear to impart an increased risk of the development of Wilms’ tumor including Soto, Simpson-Golabi-Behmel and Perlman syndromes [7-8].

Other associations include the WAGR and Denys-Drash syndromes. WAGR consists of Wilms’, aniridia, genitourinary anomalies, and mental retardation while the Denys-Drash syndrome is characterized by male pseudohermaphroditism, renal mesangial sclerosis and Wilms’ tumor [9-10]. Currently, it is recommended that children with syndromes known to be associated with an increased risk of Wilms’ tumor undergo semiannual screening abdominal ultrasonography. Finally, approximately 4.5% of patients with Wilms’ tumor also present with other genitourinary abnormalities not otherwise specified by a specific syndrome including hypospadias, cryptorchidism, and renal fusion anomalies including horseshoe kidneys [11].

Biology of Wilms’ Tumor

Wilms’ tumor was one of the original examples of the Knudson two-hit hypothesis of tumorigenesis where two separate genetic alterations are necessary for tumor formation [12]. Initially, susceptible individuals carry a germline mutation either from parental inheritance or from a de novo mutation. Thereafter, only one somatic mutation is necessary to induce malignant change. Alternatively, individuals without an initial germline mutation (sporadic disease) require two relatively rare, separate genetic mutations in the same cell in order for tumorigenesis to occur. The fact that some patients with Wilms’ tumor presented at an earlier age and had asso-
PATHOLOGY OF WILMS’ TUMOR

Most pediatric renal tumors were previously classified as either favorable or unfavorable Wilms’ tumors; however, the National Wilms’ Tumor Study Group (NWTSG), a North American multicenter collaborative research consortium, identified that some tumors initially classified as unfavorable variants were in fact separate malignancies [19]. Subsequent trials from the NWTSG excluded both clear cell sarcoma of the kidney (CCSK) and rhabdoid tumor of the kidney (RTK) from further evaluation. The present NWTSG-5 has separate treatment protocols for both CCSK and RTK (see below).

Grossly, Wilms’ tumor tends to be soft and friable, compresses adjacent normal renal parenchyma, and is usually associated with central hemorrhagic necrosis. Microscopically, it classically contains a triphasic pattern of cell types including blastema, epithelium and stroma (Figure 1). Occasionally, biphasic or even monophasic Wilms’ is identified. Due to its embryonic nature, heterologous tissue is frequently encountered including skeletal muscle, squamous epithelium, cartilage, bone and fat [20].

The most clinically significant histopathological finding is that of unfavorable histology (defined as enlarged, polyploid nuclei) which, although present in only 10% of tumor specimens, was associated with almost 50% of the deaths in the early NWTSG results [21]. Furthermore, anaplasia is known to confer an increased resistance to chemotherapy and, although rare in the first two years of life, its incidence increases to 13% in older children [22]. Anaplasia has been further characterized as either focal or diffuse and, depending on tumor stage, alters NWTSG-5 present treatment protocols.

For many years the presence of precursor lesions, termed nephrogenic rests have been identified in as many as one-third of kidneys resected for Wilms’ tumor [23]. Nephrogenic rests have been identified in approximately 1% of infant postmortem examinations [24]. These lesions consist of postnatally persistent embryonal cells which may undergo subsequent maturation, sclerosis, and involution or, in a minority, malignant degeneration. The presence of multiple nephrogenic rests is termed nephroblastomatosis and is associated with an increased risk of bilaterality and recurrent disease and requires close radiographic and clinical follow-up [23].

CLINICAL PRESENTATION AND DIAGNOSIS

Wilms’ tumor most commonly presents in childhood as an asymptomatic abdominal mass (Figure 2). Other signs and symptoms include abdominal pain, hematuria and fever. Approximately 25% of patients present with hypertension attributable to elevated plasma renin activity while up to 10% have an identifiable coagulopathy secondary to acquired Von Willebrand’s disease [25]. Intracaval extension of Wilms’ is found in 4-10% and presents with varicocele, peripheral edema, hepatic congestion, ascites or even overt heart failure [26]. Rarely, children can present with an acute abdomen and evidence of hemodynamic compromise secondary to hemorrhage within a Wilms’ tumor or even from intrabdominal rupture.

Following a careful history and physical examination (including a search for stigmata of Wilms’ associated...
syndromes or other anomalies), the initial evaluation of a child with an abdominal mass is a complete abdominal ultrasound. This non-invasive test will determine if the lesion is of renal origin, cystic or solid, and associated with other intra-abdominal lesions such as adenopathy. Other differential diagnoses to consider include hydro-nephrosis, multicycstic dysplastic kidney, polycystic kidney disease, neuroblastoma, and various other visceral lesions such as splenomegaly and gastrointestinal duplication anomalies (Figure 3). Fortunately, the abdominal ultrasound will elucidate the underlying origin for many of these masses and, if the lesion is found to be of renal origin, subsequent investigations are directed toward its diagnosis and staging.

Cross sectional imaging, either CT or MRI, is the next most appropriate radiologic investigation as it not only evaluates the extent of the primary lesion including extrarenal extension, contiguous organ invasion, intracaval invasion, and locoregional metastases, but, with the use of intravenous contrast agents, also determines the presence of a functioning contralateral kidney. Furthermore, CT or MRI can accurately identify bilateral Wilms’ tumor, identified synchronously in 5% of patients, which (as will be described) requires a significantly altered approach to management [27]. Further radiographic staging includes either plain film chest x-rays or, more commonly, chest CT. Other imaging studies are reserved for specific clinical situations including radionuclide bone scan and skeletal survey for all children diagnosed with clear cell sarcoma as well as brain CT or MRI for those with either clear cell sarcoma or rhabdoid tumor as both are associated with intracranial metastases [28-29].

Laboratory investigations for children with suspected Wilms’ tumor include a complete blood count, electrolytes, renal function, liver enzymes, serum calcium and urinalysis. Following the completion of all radiologic and laboratory investigations, usually within 2-3 days, a multidisciplinary team approach including pediatric urology or surgery, hematology/oncology, social work, and nursing is utilized to provide the patient, and their family, the optimal therapeutic regimen.

Staging
The most common staging system used for Wilms’ tumor is from the NWTS and is based on the anatomical extent of disease.

**STAGE I** • Tumor confined to the kidney, without evidence of capsular penetration or positive margins, and completely excised. The renal hilar vessels are not involved and the tumor was not biopsied prior to removal (small fine-needle aspiration biopsies are excluded).

**STAGE II** • Tumor extends beyond the kidney but is completely excised without evidence of margin positivity or nodal involvement. There is evidence of capsular penetration, invasion of renal hilar vessels, and local flank spillage during resection, or previous biopsy of the tumor.
STAGE III • Residual non-hematogenous tumor confined to the abdomen remains following surgery including gross or microscopic resection margins, positive abdominal lymph nodes, peritoneal penetration or tumor implants, transected tumor thrombus, or gross tumor spillage involving peritoneal surfaces.

STAGE IV • Hematogenous metastases or lymph node metastases outside the abdominopelvic region are present (eg. lung, liver, brain, bone).

STAGE V • Bilateral Wilms’ tumors.

Accurate staging allows comparisons between various treatment regimens and enables large scale studies to further improve patient survival. Although presently still investigational, genetic markers are expected to be included in staging and guide therapy in the future. For example, one study demonstrated that LOH on a portion of chromosomes 16q and 1p imparted a poorer 2-year relapse-free and overall survival than those without LOH [30].

TREATMENT

Following appropriate laboratory and radiographic staging investigations, complete surgical resection remains the standard initial therapy in North America. NWTSG-5 recommends a transperitoneal approach in order to adequately stage the locoregional extent of disease, including inspection of the contralateral kidney to exclude bilaterality prior to nephrectomy [31]. Suspicious lymph nodes are sampled, however, formal lymph node dissection is neither recommended nor beneficial. Care must be taken to avoid tumor spillage as this results in upstaging (from stage II to III), and necessitate postoperative radiotherapy. Tumors deemed unresectable at the time of initial exploration are biopsied and the patient is treated with appropriate chemotherapy; surgical resection is then undertaken following downsizing of the mass. Other NWTSG-5 indications for preoperative chemotherapy include vascular invasion and bilaterality.

Controversy remains regarding partial nephrectomy for primary lesions and is not presently recommended in the routine treatment of unilateral Wilms’ tumor. Long-term follow-up has demonstrated that the majority of patients do not progress to end stage renal disease [32]. Furthermore, at the time of initial presentation, only a small number of patients could be considered for partial nephrectomy due to the large size and central location of most Wilms’ tumors [33]. Nephron-sparing surgery is reserved for those patients with solitary kidneys, intrinsic renal disease or those with, or at risk for, bilateral disease.

Adjuvant chemotherapy ± radiotherapy is then undertaken depending on tumor stage and histology. Treatment regimens presently recommended by NWTSG-5 are outlined in table I. One of the primary goals of NWTSG-5 is to reduce treatment for those patients with favorable histology without compromising cure rates while continuing to maximize therapy for those with high-risk disease.

An alternative treatment approach, employed by the Société internationale d’oncologie pédiatrique (SIOP) involves preoperative chemotherapy followed by surgical resection and histopathological confirmation. Patients undergo initial staging investigations and subsequently embark on a course of chemotherapy without histological diagnosis. Thereafter, repeat imaging is performed, and surgery planned accordingly. Proponents state that this approach facilitates subsequent surgery and may allow partial nephrectomy to be performed [34]. Furthermore it reduces the risk of tumor rupture and evaluates tumor responsiveness to chemotherapy which allows early modifications to postoperative chemotherapy in those who do not respond to neoadjuvant therapy [35]. However, the approach advocated by the SIOP must be weighed against the risks of chemotherapy without tissue diagnosis as chemotherapy is initiated without pathological confirmation of disease.

Bilateral Wilms’ Tumor

As previously mentioned, the presence of bilateral disease mandates a significantly altered treatment regimen. Fortunately, the resolution of modern CT or MRI allows the preoperative identification of bilaterality in

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Histology</th>
<th>Radiotherapy</th>
<th>Chemotherapy regimen</th>
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<td>18</td>
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<td>RTK</td>
<td>Yes</td>
<td>RTK*</td>
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</table>

EE4A : vincristine + pulse-intensive dactinomycin
1 : vincristine, doxorubicin, cyclophosphamide, & etoposide
CCSK : clear cell sarcoma of the kidney
DD4A : vincristine + pulse-intensive dactinomycin & doxorubicin
RTK : rhabdoid tumor of the kidney
RTK* : carboplatin, etoposide, & cyclophosphamide
the vast majority of cases [36]. A nephron-sparing approach is initially undertaken and both kidneys undergo either incisional or needle biopsy only. However, complete resection is appropriate only if an entire lesion can be excised without significant compromise to the remaining normal renal parenchyma. Following 6-8 weeks of chemotherapy, the patient is reassessed and complete resection is then undertaken if deemed technically feasible. This second-look procedure is then followed by adjuvant chemotherapy and, if necessary, radiotherapy.

**Long-term Effects of Treatment**

Patients treated for Wilms’ tumor as children must continue to be monitored for possible long-term sequelae as adults. Musculoskeletal abnormalities (such as scoliosis), hypogonadism and ovarian failure have all been described following abdominal radiation [37-38]. Cardiotoxicity secondary to doxorubicin therapy may result in congestive heart failure in as many as 4% of patients and secondary malignancies have been documented in 1% of long-term Wilms’ tumor survivors. Lifelong follow-up of these patients is essential in order to identify and treat these potential complications [39-40].

**CONCLUSION**

Wilms’ tumor is the most common primary renal malignancy in childhood. Fortunately, with a multidisciplinary approach to its management as well as ongoing genetic and molecular advances, over 85% of children with Wilms’ tumor can be expected to be long-term survivors. As large scale cooperative studies mature (such as NWTSG-5), further refinements in treatment will undoubtedly limit adjuvant therapy, and consequently treatment related morbidity, in those considered low risk, while still maximizing therapy, and cure rates, in those with high-risk disease.

**REFERENCES**

26. Ritchey ML, Kelalis PP, Breslow N et al. Intracaval and atrial involvement with nephroblastoma : review of Na-