FROM THE GUEST EDITOR

Bruce Broecker, M.D.

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The management of childhood renal tumors continues to evolve. A panel of experts presented an update on selected areas of this broad topic at the American Academy of Pediatrics in San Francisco in October, 2004. Dr. Mike Ritchey (MR), Professor and Chair of Urology at the University of Texas in Houston presented the current proposals for management of bilateral Wilms’ tumor. Dr. Robert Shamberger (RS), Professor and Chief of Pediatric Surgery at Harvard and Boston Children’s Hospital spoke on the data regarding surgery alone as treatment for the small stage 1 Wilms’ tumor in infants. Both Dr. Ritchey and Dr. Shamberger are uniquely qualified to speak on these topics from their positions as surgical representatives to the renal committee of the Children’s Oncology Group (COG), previously the National Wilms’ Tumor Committee. Dr. Jonathan Ross (JR), Professor and Chief of Pediatric Urology at the Cleveland Clinic, pinch-hitting for Dr. Fernando Ferrer, Chief of Pediatric Urology at the University of Connecticut, presented the current status of management of renal cell carcinoma and Dr. Marty Koyle (MK), Professor and Chief of Pediatric Urology at the University of Colorado and Denver Children’s Hospital, then presented several cases to the panel eliciting discussion about nephroblastomatosis, the incidental renal mass and the “inoperable” Wilms’ tumor. The session was moderated by myself (BB).

FROM THE EDITOR

Anthony A. Caldamone, M.D.

Our current management of Wilms’ tumor continues to evolve at a rapid pace. If one were to have this read monograph 10 years ago, thoughts of disbelief and even negligence might have crossed one’s mind. But here we are continuing to challenge our traditional management protocols in a truly scientific way that could be done only with the organized control trials that we have all come to know through NWTSG, SIOP, and COG. It is a clear testimony to the ultimate in scientific clinical trials and the search for evidence based medicine.

This panel explores the latest evidence in the management of bilateral Wilms’ tumor, the option for no adjuvant therapy following nephrectomy for low risk Wilms’ tumor, and the differentiation of renal cell carcinoma in children compared with adults. I applaud Bruce Broecker and his team of experts for putting together a classic issue on renal tumors in children.
Management of Bilateral Wilms Tumor

Michael Ritchey, MD
University of Texas, Houston

Bilateral Wilms' tumor occurs in five to seven percent of all children with Wilms' tumor. The incidence of metachronous development of Wilms' tumor is approximately one percent, with all other cases presenting with bilateral tumors at presentation. Therapy for patients with bilateral Wilms' tumor is focused on sparing renal parenchyma. Review of National Wilms Tumor Study Group patients has found that 9.1 percent of children with synchronous bilateral tumor developed renal failure (1).

The cause of renal failure in the majority of children with bilateral Wilms' tumor is bilateral nephrectomy for persistent or recurrent tumor of the remaining kidney after initial nephrectomy. Therefore, avoiding total nephrectomy at initial surgery is advisable. There is also concern about the late development of renal failure. In some cases, this occurs at an interval up to 12 years after initial surgery. This may be due to hyperfiltration injury to the remaining nephrons when a minimal amount of renal tissue remains after surgery.

Bishop et al. were the first to advocate preoperative chemotherapy to shrink bilateral Wilms' tumors before surgery (2). They found a comparable survival between patients who underwent nephrectomy at diagnosis and those who had biopsy only. A subsequent report by Blue et al. (3) also recommended a preoperative chemotherapy approach. Although there was no significant difference in survival, they did note that the three-year overall survival for patients with initial biopsy was 57 percent versus 82 percent for those patients undergoing initial resection.

Of note, patients who had all of the tumor removed at one or more operations that had low-stage disease had excellent survival. Extended follow-up of patients with bilateral Wilms' tumor, however, has shown that the overall survival for individuals is only 65 percent. This number is lower than that seen for other patients with unilateral Wilms' tumor and favorable histology (unpublished data). Patients with bilateral tumors can have relapses and death late after initiation of therapy. Only 90 percent of deaths occur within six years from diagnosis (4).

A recent review of NWTS-4 patients has noted several important findings (Ritchey, unpublished data). One is that staging at diagnosis is limited in these patients. Due to the large size of the bilateral tumors, access to the regional lymph nodes is limited at the initial exploration and no patients undergoing biopsy of the tumor alone was identified to have lymph node metastases. Another finding is that there is often a fairly long delay from initiation of therapy to definitive resection. It was also found that the incidence of anaplasia was 10 percent, which is twice that seen for patients with unilateral Wilms' tumor undergoing primary nephrectomy. Recognition of anaplastic tumors is critical, as they are resistant to standard Wilms' tumor chemotherapy and require complete excision for local control. These patients are also treated with a different chemotherapy regimen than that routinely used for other Wilms' tumor patients.

The International Society of Pediatric Oncology (SIOP) has extensive experience with the use of preoperative chemotherapy for management of Wilms' tumor. They routinely use preoperative therapy for patients with both unilateral and bilateral Wilms' tumor. The SIOP group has more recently focused on the response of the tumor to therapy, particularly the pathologic response (5, 6). They have been able to identify patients who have a more favorable outcome based on the response to therapy and are using this to stratify patients for treatment.

They have identified a group of patients with low-risk tumors, defined as those that have complete necrosis (less than 1 percent viable tumor), after four weeks of preoperative chemotherapy. These patients have a very low rate of relapse, and in SIOP they do not receive additional chemotherapy after the surgery is done (5). Other tumors classified as low risk are cystically differentiated nephroblastoma and fetal rhabdomyomatous nephroblastoma. The incidence of completely necrotic tumors is 5 percent after the patients receive four weeks of dactinomycin and vincristine. Of note, patients with Stage IV disease who receive these two drugs and anthracycline had a 17 percent rate of complete necrosis. More importantly, the SIOP group has identified high-risk patients. This includes anaplastic tumors that have long been known to be poorly responsive to routine Wilms' chemotherapy regimens (7). SIOP has also identified a group with a poor prognosis that is termed “nephroblastoma blastemal type.” The latter is defined as a tumor that after chemotherapy remains more than one-third viable, but the viable tumor consists of greater than two-thirds blastema. In the SIOP-9 study, patients with these tumors had a 31% relapse rate (6). Therefore, these patients have been selected to receive more intensive chemotherapy in the ongoing SIOP study.

Of particular importance in patients with bilateral Wilms' tumor is that differentiation of the tumor can occur due to chemotherapy. Epithelial and stromal predominant tumors are much more common after therapy. SIOP noted this to occur in 14 percent of patients after preoperative therapy (5). In patients who undergo immediate nephrectomy without preoperative therapy, these patterns are seen in only 1.6 percent of patients. Patients who develop these differentiated tumors are noted to have less reduction in tumor volume with chemotherapy. However, these tumors have an excellent prognosis if completely excised, with low rates of relapse. Of course, these data from SIOP are based on patients who undergo complete nephrectomy for unilateral tumors. If complete excision of such tumors is performed in patients with bilateral Wilms' tumors, one would expect that the same excellent prognosis could be maintained. The other type of tumor histology that is known to have a poor response to chemotherapy is the fetal rhabdomyomatous nephroblastoma (8), which was classified as a low-risk tumor by SIOP.

The response of tumor to the chemotherapy versus its inherent aggressiveness based on its biology has been described by Beckwith (9). If a tumor is very responsive to adjuvant therapy and the tumor has extended outside the boundary of the kidney margin, such as to the lymph nodes or lungs, then the chemotherapy will have an effective kill rate and the overall survival will be good. On the other hand, if the tumor is poorly responsive, such as anaplastic tumor, then extension outside the kidney assumes much greater importance, as a high percentage of patients with these tumors will not be cured by adjuvant therapy.

The Children’s Oncology Group is currently developing a strategy for treatment of patients with bilateral Wilms' tumor. One of the underlying principles of this new protocol is earlier biopsy in tumors that are not responding adequately to the initial chemotherapy regimen. This is
done primarily to identify high-risk patients who need a change in their chemotherapy. It is also important for the identification of differentiated tumors and completely necrotic tumors, as such patients also need earlier surgical management. These tumors are less likely to respond to continued therapy. The SIOP classification of tumors after chemotherapy will be used to direct chemotherapy treatment after definitive therapy is performed. The goal is to continue to improve the overall survival in this group of children and yet maintain a high rate of renal preservation to decrease the late incidence of renal failure.

REFERENCES

Nephrectomy Only for Low Risk Wilms Tumor

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In medical practice, the benefits of a treatment should be weighed against the risks, medical as well as financial and other psychosocial factors. Indwelling central venous catheters commonly used for chemotherapy administration are associated with an increased risk of venous thromboembolic disease (1). Life-threatening hepatic toxicity occurs during the first ten weeks of treatment in approximately 3.5% of patients with nephrectomy only who have favorable histology (FH) Wilms’ tumors that weigh less than 550 grams (11) .

For this reason, on one arm of the NWTS-5 protocol, infants under 2 years of age with small unilateral Wilms’ tumors (stage I) in whom the tumor and kidney weighted less than 550 grams were selected to not receive any postoperative chemotherapy or radiotherapy. The quantitative measure of therapeutic outcome used for the study design was the percentage of patients who were alive and disease-free two years following nephrectomy. Patients who relapsed, or who died of toxicity or other causes without prior relapse, were to be counted as failures. Previous NWTS studies demonstrated that, for FH Wilms’ tumor patients, the two-year relapse-free survival (RFS) percentage was nearly equal to the percentage of children who were long-term relapse-free survivors. Later events included the very occasional appearance of new disease in the contralateral kidney or death from unrelated causes (12,13,14).

Interim analyses were planned after two, three, and four years of patient accrual. If the trial was not stopped early, accrual was planned to continue for five years. The stopping rule was calculated so that, if the true long-term, relapse-free percentage was no better than 90%, the probability of stopping early and/or concluding that “no treatment” (i.e., treatment with nephrectomy only) had failed was 95%. The conservative design was based in part on the assumption that only 50% of the patients with recurrence could be successfully salvaged, as observed in patients who relapsed following initial treatment with combination chemotherapy (15). On the other hand, if the true two-year, relapse-free percentage was 95% or better, the probability of continuing patient accrual and ultimately concluding that “no treatment” had succeeded was 80% (16). In June 1998, the three-year interim analysis showed a two-year event free survival of 86.5%, so the study was closed to further accrual, and children with recent nephrectomy were advised to receive actinomycin D and vincristine chemotherapy per treatment regimen EE4A. The 75 children who were entered into the study have been followed closely since that time.

Of the seventy-five children treated with nephrectomy only prior to closure of the protocol eleven patients relapsed or developed metachronous disease in the contralateral kidney 0.3 – 2.3 years after diagnosis (median - 4 months, mean - 0.64 years)(17). The sites of relapse were: lung – 5 (3 bilateral, 2 unilateral) and operative bed – 3. Three patients developed disease in the contralateral kidney. This occurred

**Based on all of these findings, a new protocol for very low risk patients has been proposed. It will be a single armed study in which patients will be entered if they meet very strict criteria.**
1.1 and 1.4 years after nephrectomy in two patients treated with nephrectomy only, and 1.4 years after initiation of treatment with vincristine and actinomycin D in the third patient, following the protocol amendment in June 1998.

Patients who developed metachronous tumors were treated based on the stage of the tumor and not as “relapsed” disease (16), while patients with local recurrence or new metastatic disease were treated with DD4A therapy plus pulmonary and/or abdominal radiotherapy based on the site of relapse. The overall survival of these patients is 94% as of June 2001. The salvage rate in this cohort of patients from NWTS-5 is much higher (94%) than the postulated rate of 50%, a finding that supports a less conservative lower limit for the two-year disease-free survival percentage in future trials. Although the cohort size is limited, due to early closure of the study, these results support the hypothesis that surgery alone may be adequate treatment for this limited group of children. Another study is needed in order to confirm this hypothesis and answer the other questions raised by this treatment approach for patients with very low risk, stage I FH/WT.

This study also provided important information regarding the impact, if any, of chemotherapy on the conversion of nephrogenic rests to Wilms’ tumor. There is little information to suggest whether chemotherapy suppresses the development or progression of a Wilms’ tumor within an existing rest, or contributes to genetic events that promote Wilms’ tumorigenesis. While the percentage of patients who developed metachronal contralateral Wilms’ tumors in the NWTS-5 cohort was too small to adequately analyze statistically, it appeared similar to that reported in previous studies two years after diagnosis in patients of similar ages who received chemotherapy for their initial tumor (18). Additional follow-up is necessary to adequately evaluate this outcome in a larger cohort.

A decision analysis comparing the outcomes of these very low risk children treated with EE4A (NWTSG), vincristine alone (United Kingdom Children’s Cancer Study Group [UKCCSG-privileged communication]) or surgery alone (NWTS-5:arm closed early) demonstrated nearly identical overall survival between the vincristine alone group and the surgery alone group (98.5 vs 98.8%).

Based on all of these findings, a new protocol for very low risk patients has been proposed. It will be a single armed study in which patients will be entered if they meet very strict criteria. The patient must be under two years of age with a stage I favorable histology tumor which is less than 550 grams in specimen weight. There will be mandated central rapid reviews of the case to be completed by 14 days after resection: the pathologist must confirm that the tumor meets the defined criteria, the radiologist must confirm the absence of pulmonary metastases by computed tomography, and by the surgeon to confirm no deviations of therapy (i.e., flank incision, failure to obtain lymph node biopsy, intraoperative tumor biopsy) and adequate surgical staging. Patients with lesions on computed tomography >1 cm in diameter must be proven benign by biopsy before entry onto this protocol. If loss of heterozygosity is demonstrated by the biologic evaluation, the patient will be removed from this protocol and will become eligible for the intermediate risk protocol without penalty to the enrolling institution. This is expected to be an infrequent event: only one of seventy-five patients in the NWTS-5 cohort had loss of heterozygosity.

The goal of this protocol is to reduce the exposure of these low risk children to the potential toxic effects of adjuvant therapy while maintaining an equivalent, maximum rate of cure. The primary end points will be event-free and overall survival. The secondary end point will be the incidence of contralateral metachronous tumors.

After enrollment on the study patients will be closely monitored (clinically and radiographically) for evidence of recurrent or metachronous disease. During the first 2 years after resection, when the risk for recurrence is greatest, children will be examined and have a chest radiograph and abdominal ultrasound every two months and computed tomography every other visit (i.e., every 4 months). After the first two years this follow-up will occur every three months for one year and then every six months for two additional years, until 5 years following resection.

Therapy for children with recurrent disease will be based on their ‘new’ stage and will follow guidelines established for children with newly diagnosed disease in the Children’s Oncology Group Renal Tumor Protocols. Thus, therapy for children with pulmonary, hepatic and/or local recurrence will be as for children presenting initially with stage IV disease (i.e., DD4A) not according to a protocol designed for children whose disease recurred after adjuvant therapy. Children who develop metachronous disease will be treated according to the stage of the tumor on the current bilateral Wilms’ tumor protocol, with an effort to decrease the size of the new tumor by the use of preresection chemotherapy, to maximize the preservation of renal parenchyma and minimize the risks of renal failure.

REFERENCES
Pediatric Renal Cell Carcinoma

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Renal cell carcinoma (RCC) is a rare tumor in children, comprising only 1.8-6.6% of all pediatric renal tumors.\(^{1,17}\) By comparison, RCC is the most common renal tumor in adults and accounts for 3% of all adult malignancies\(^{9,17}\). Identification of the genomic abnormalities associated with adult RCC, such as Von Hippel Lindau (VHL) gene abnormalities, chromosomal trisomy, etc., have profoundly improved our understanding of the pathogenesis of this lesion. The pathogenesis of pediatric renal cell carcinoma has remained an enigma until recent studies have revealed the molecular basis of this tumor.

Historically, RCC in children was assumed to be similar to that occurring in adults. More recently, clinicians suspected that pediatric RCC differs from that of its adult counterpart based on observed clinical and pathologic differences. A summary of these differences follows: adult RCC is a relatively common malignancy accounting for approximately 3% (31,900 new cases) of all adult cancers in 2003\(^{23}\). By comparison, pediatric RCC is rare, accounting for <0.1% of cancers in children. Adult RCC has a peak occurrence in the fifth and sixth decades of life and has been noted to exhibit a male preponderance of 2:1\(^{5}\). In children, the average age at presentation is 8-11\(^{1,4,5,7,8,12}\), and unlike adult RCC, no clear male preponderance has been demonstrated in children with RCC\(^{(1,3,5)}\). Like adults, children may present with gross hematuria, abdominal/flank pain, or an abdominal mass, but this classic triad has been documented in at most 6-8% of children\(^{(1,4,5,12-14)}\). Hematuria is less common in children than in adults, while a palpable mass is thought to be more common\(^{(1)}\). Approximately 30% of adult patients with RCC present with metastatic disease\(^{25}\). In studies involving more than ten patients, anywhere from 13-38% of children with RCC presented with metastatic disease\(^{(1,4,5,14,24,26)}\). While the available data is not definitive, it has led some to conclude that fewer pediatric patients present with metastatic disease.

Another point of comparison is the incidence of paraneoplastic syndromes. Adult RCC has been referred to as the “Internist’s Tumor,” because of its multiple presenting signs and symptoms\(^{(25)}\). Of adult patients with RCC, 20-40% may present with paraneoplastic manifestations, including weight loss, malaise, hypertension, anemia, fever, hypercalcemia, and hepatic dysfunction\(^{(27,28)}\). Paraneoplastic findings are not as well documented in children with RCC, and have been suggested to occur less frequently\(^{(4,26,13,12,14)}\). As in adults, there have been documented cases of pediatric RCC associated with genetic syndromes, including tuberous sclerosis or VHL, however, they are much less frequently associated with pediatric tumors\(^{(4,21)}\). Adult RCC has been associated with multiple environmental factors such as cigarette smoking, analgesic abuse, dialysis, and obesity. Few environmental risk factors are associated with pediatric cancer in general, and none have been identified for pediatric RCC\(^{(21,5,22)}\).

Adult RCC is classified as conventional (clear cell), papillary, chromophobe, and collecting-duct. Conventional tumors in adults account for approximately 75% of tumors while papillary lesions represent only 10-15%\(^{(9)}\). In contrast, available literature suggests that the most common histology of RCC in children is papillary or tubulopapillary, comprising 30-50% of pediatric RCC\(^{(4,6)}\). Conventional, or non-papillary, tumors seen in children include clear cell, granular, chromophobe, sarcomatoid, and collecting-duct types\(^{(9)}\). It is the belief of the authors that the reporting of histopathology of pediatric RCC is greatly confused by the lack of standardized classification system. While some authors report individual cell types and aggregate cell patterns, not all studies report cell patterns. This observation notwithstanding it appears that the histopathology in children differs from that of adults. These and other differences have prompted clinicians to believe that pediatric RCC is a different entity than its adult counterpart.

Molecular Comparison and Advances

Recent discoveries regarding the molecular biologic features of pediatric RCC support the conclusion that adult and pediatric tumors are distinct entities. It has been shown that papillary tumors in children lack the characteristic complete chromosomal gains seen in adult papillary RCC, i.e., tetrasomy 7, trisomy 10, 12, 16, 17, and 20. Additionally (VHL) gene abnormalities, which result from genetic loss on chromosome 3p are well documented in adults RCCs, are uncommon in children\(^{(29)}\).

As early as 1986, a translocation between chromosomes X and 1 was demonstrated in pediatric papillary RCC\(^{(29)}\). A translocation involves the aberrant movement and fusion of regions of DNA\(^{(30)}\). A whole chromosome or portion of a chromosome becomes attached to or interchanged with another whole chromosome or portion during translocation. In 1996, Sidhar et al. made the seminal observation that pediatric papillary RCC’s are associated with the translocation\(^{(t(X;1)p(11.2;q21.2)}, which results in the novel gene PRCC (Papillary Renal Cell Carcinoma) on chromosome 1 fusing with the TFE3 (Transcription Factor E3) gene on the X chromosome. This chimeric PRCC-TFE3 gene appeared to accompany the loss of all normal TFE3 transcripts. Such disruption of transcriptional control is well-documented in the etiology of pediatric sarcomas and leukemias, and Sidhar, et al documented its importance in the development of papillary renal carcinoma\(^{(34)}\).

The TFE3 gene encodes a member of the basic helix-loop-helix (BHLH) family of transcription factors\(^{(34)}\). Helix-loop-helix (HLH) transcription factors mediate selective pairing among members of an important transcription factor family involved in cell fate determination\(^{(35)}\). TFE3 translocations also have been associated with other chromosomal sites resulting in different fusion proteins. Examples of these include the PSF (splicing factor) gene, ASPL (alveolar soft part sarcoma locus) gene, and CLTC (clathrin heavy-chain) gene\(^{(31-33)}\). The translocations that have been associated with pediatric tumors are summarized in Table 1 (see next page.)

The various TFE3 fusion carcinomas appear to have unique histopathologic features that allow their differentiation. The general histopathologic appearance of TFE3 renal cell tumors is that of papillary carcinoma comprised of clear cells. This may explain the previously mentioned confusion in pathologic classification of these tumors. The tumors underexpress several epithelial markers, eg, cytokeratin, epithelial membrane antigen, and vimentin. S-100 protein, desmin, and HMB45

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Table 1—TFE3 Translocations Associated with Pediatric Carcinoma

<table>
<thead>
<tr>
<th>CHROMOSOMES</th>
<th>GENES</th>
<th>RESULT</th>
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<tbody>
<tr>
<td>t(X;1)(p11.2;q21.2)*</td>
<td>PRCC-TFE3</td>
<td>fusion proteins in PRCC, aberrant transcription factor, alters the activity of normal TFE3 proteins</td>
</tr>
<tr>
<td>der(17)t(X;17)(p11.2;q25)</td>
<td>ASPS-TFE3</td>
<td>RNA transcripts in ASPS</td>
</tr>
<tr>
<td>t(X;17)(p11.2;q25)*</td>
<td>ASPL-TFE3, TFE3-ASPL</td>
<td>fusion proteins in PRCC, aberrant transcription factor</td>
</tr>
<tr>
<td>t(X;1)(p11.2;q34)*</td>
<td>P5F-TFE3</td>
<td>fusion protein in PRCC, interference with normal splicing</td>
</tr>
<tr>
<td>inv(X)(p11.2;q12)*</td>
<td>NonO-TFE3</td>
<td>fusion protein in PRCC, interference with normal splicing</td>
</tr>
<tr>
<td>t(2;17)(p23;q23)</td>
<td>CLTC-ALK</td>
<td>fusion proteins in ALCL and IMT</td>
</tr>
<tr>
<td>t(X;17)(p11.2;q23)*</td>
<td>CLTC-TFE3</td>
<td>fusion protein in PRCC</td>
</tr>
<tr>
<td>t(6;11)(p21.1;q13)</td>
<td>Alpha-TFEB</td>
<td>Upregulation of TFEB mRNA in pediatric RCC</td>
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(Pr RCC, Papillary Renal Cell Carcinoma. ASPS, Alveolar Soft Part Sarcoma. ALCL, Anaplastic Large Cell Lymphoma. IMT, Inflammatory Myofibroblastic Tumor.)

*Associated with Pediatric Renal Cell Carcinoma.

are consistently negative. All of these tumors test positive the TFE3 protein. This nuclear labeling is also found in ASPS tumors but has not been identified in other adult renal cell carcinomas (2). They also test positive for the renal cell carcinoma marker and CD10 (37). ASPL-TFE3 carcinomas are composed of cells with voluminous, clear to eosiinophilic cytoplasm, discrete cell borders, vesicular nuclear chromatin, and prominent nucleoli. Psammoma bodies are found throughout, often within hyaline nodules. Most of these tumors demonstrate membrane-bound cytoplasmic granules. PRCC-TFE3 cancers have abundant cytoplasm—but less than ASPL-TFE3 tumors—demarcated by sharp cell borders, fewer psammoma bodies, fewer hyaline nodules, and a more nested, compact architecture (2). They have a fibrous pseudocapsule, typically calcified (37). Some PRCC-TFE3 tumors reveal distinct intracisternal microtubules. These tubules have also been seen in malignant melanoma and extraskeletal myxoid chondrosarcoma (2). CLTC-TFE3 tumors demonstrate features of ASPL and PRCC-TFE3 tumors. Like the ASPL-TFE3 tumors, they have polygonal cells with clear, voluminous cytoplasm. Hyaline nodules and calcifications, specifically psammoma bodies, are seen frequently. Like PRCC-TFE3 tumors, the CLTC-TFE3 tumors have a calcified fibrous pseudocapsule harboring a compact nested pattern with fibrovascular septae separating islands of tumor cells (42). Alpha-TFEB tumors do not label for epithelial markers cytokeratin or EMA, but do label for melanocytic markers HMB45 and Melana-A. They produce abundant basement membrane material, similar to that of epithelioid angiomylolipoma (2). These tumors also have polygonal cells arranged in nests separated by capillary-sized vessels (38). Accurate pathologic classification of specific TFE3 related tumors may have prognostic value.

**Treatment and Outcomes**

The limited number of cases, variation in staging systems as well as adjuvant therapy used in retrospective reports, coupled with the lack of prospective studies have conspired to make treatment recommendations unclear for children with RCC (1). Three central questions that remain unanswered are: 1) What should adjuvant therapy be for patients with advanced disease; 2) Is their any therapeutic or prognostic benefit to lymphadenectomy at the time of nephrectomy; and 3) Should patients with nodal disease receive additional treatment? In 1986, Booth's compilation of 11 of his own 14 cases and 89 well-documented pediatric cases in the literature demonstrated that primary adjunctive therapy may be of value in cases of extrarenal extension, but not low-stage disease (26). Further studies have demonstrated that chemotherapy has minimal or no efficacy, and children with low-stage disease appear to do well without adjuvant treatment (10, 11, 13, 14). Radiation has been proposed for the control of local disease, but its effectiveness has not been proven in controlled studies (14). More recently Freedman, Manion, and Indolfi et al. have reported that radiotherapy does not provide a survival benefit (1, 7, 14). Thus at this time standard chemotherapy and radiotherapy appear to be of little benefit to these patients.

As a direct result of the adult experience, immunotherapy with IL-2 and/or Interferon have been proposed as adjuvant therapy for pediatric RCC. Unfortunately, controlled studies have not been possible and the literature only provides anecdotal evidence of benefit. In 1994, MacArthur et al. reported that recombinant Interlekin-2 provided a pediatric patient with stage IV disease complete resolution (10). Similar results for one patient were reported by Bauer et al in 1995 (39). In 1999, Asanuma et al reported that three of four pediatric RCC patients who received interferon postoperatively were alive and disease free at 30-86 months of follow-up (13). Uchiyama et al. reported on two pediatric patients with advanced disease treated with interferon that experienced long term survival (13). Given the lack of evidence of benefit from standard chemotherapy or radiotherapy it appears that children with disseminated disease are candidates for immunotherapy.

With regards to regional lymphatic involvement, Freedman et al reviewed their experience with 3 patients with positive regional nodes. 2 of these three have had long term disease free survival after removal of the primary tumor and regional lymphadenectomy. The 3rd patient received adjuvant therapy in addition to lymphadenectomy. These outcomes prompted the authors to suggest that regional lymphadenectomy may provide a survival advantage (1). The literature review by Ebert et al. in 2003 concluded lymph node dissection does have a positive effect on survival (41).

The proposed survival benefit of lymphadenectomy in children with RCC is in part based on the assumption that survival for these patients should be similar to that of adults with regional adenopathy. Lymph
node-positive disease is a known indicator of poor prognosis in adults, with 5 and 10 year survival rates ranging from 5-30% and 0-5% respectively (40). However, a recent report by Geller et al. has called into question the validity of this assumption. In their meta-analysis of children with lymph node positive disease, but no known metastases, 72.4% (42/58) were disease free at last follow-up. Of this subset of 58 patients, 94% (15/16) of children who received no additional treatment after surgery were alive and well, while 70% (22/31) of those who received adjuvant therapy were alive and well at follow-up. The authors concluded that lymph node involvement is not a predictor of poor outcome in pediatric RCC. It is difficult to extrapolate the efficiency of lymph node dissection from this report because the patients included in this review revealed varying degrees of lymph node dissection. However, it seems prudent to consider regional lymph node dissection for patients with clinically suspicious nodes that are proven positive on frozen section.

Conclusions

New molecular information suggests that pediatric RCC is a fundamentally different lesion than adult RCC. Although rare, in the second decade of life its incidence is equal to that of Wilms’ (11, 19). Inclusion of this tumor in upcoming Children’s Oncology Group renal tumor protocols will allow for standardization of therapy, evaluation of results, evaluation of the frequency of TFE3 abnormalities and correlation of outcome with specific TFE3 translocations. Current evidence suggests that nephrectomy and regional lymph-node dissection may be adequate therapy for stage I-III tumors, while patients with metastatic disease should be considered for immunotherapy.

Bibliography

18. Gellers extensive review of 243 patients with RCC determined stage-specific survival rates to be 92.5%, 84.6%, 72.7%, and 12.7% for stage I-IV respectively.”
CASE PRESENTATIONS

Three cases were presented for discussion by a panel consisting of Dr. Martin A. Koyle, Denver Children’s Hospital, Drs. Mike Ritchey (MR), Robert Shamberger (RS), Jonathan Ross (JR) and Bruce Broecker (BB).

Case #1: A now 13 year-old female with Beckwith-Wiedemann Syndrome. A screening renal ultrasound has been done every four months since birth. At 21 months of age a renal ultrasound is normal but an MRI demonstrates several non-enhancing lesions in the right kidney (Figure 1A and 1B).

MK: Should anything be done about this MRI finding?
MR: It is known that children with Beckwith-Wiedemann Syndrome have an increased risk of developing Wilms’ tumor. The risk is approximately 7%. They also have an increased incidence of nephrogenic rests. These lesions shown here have the appearance of perilobar rests. I think that if you follow this patient these lesion are very likely to progress.
RS: I would agree with Mike Ritchey that these lesions have the appearance of perilobar nephrogenic rests. The Renal Committee of the Children’s Oncology Group (COG) has debated what to do with these lesions. In the surgery only study for small Wilms’ tumors in infants in NWTS-5, there was a suggestion that fewer contralateral tumors developed when patients with nephrogenic rests were treated with chemotherapy. Bruce Beckwith, the former NWTS pathologist, felt that all patients with diffuse nephroblastomatosis should be treated with chemotherapy. In this particular patient where the volume of the nephrogenic rest appears small, it would make sense to observe the child.
JR: I recently had a similar patient but with more extensive nephroblastomatosis and one lesion a little more suspicious for Wilms’ tumor. We treated with chemotherapy and it all resolved except for the one suspicious lesion. That was removed surgically and proved to be a small Wilms’ tumor. I have been impressed that the MRI is more sensitive at picking up these lesions than ultrasonography.

MK: Should we be screening these patients with MRI rather than renal ultrasound?
BB: The radiologist at our institution very clearly feel that a post-gadolinium MRI is a more sensitive and accurate way of picking up these lesions. It is a more expensive and more invasive test and it is unclear whether all screening should be done with MRI or whether they should be used more selectively, perhaps alternating with renal ultrasound, or some other selective basis. It does seem clear however that the MRI is more sensitive than ultrasound at detecting these lesions.
MR: I think these patients should be screened with ultrasound. MRI is more invasive and requires anesthesia or sedation in these infants. There has been no study of screening at-risk children, such as those with Beckwith–Wiedemann Syndrome, for Wilms’ tumor that has shown a survival advantage. And screening in those studies has been done almost exclusively with RUS. The Renal Committee of COG is planning a prospective imaging study of these patients in its next study if it gets funded by the National Cancer Institute (NCI). Everyone on the committee feels that MRI is a superior imaging study not only in diagnosing these lesions but, perhaps more importantly, in following response while on chemotherapy.

MK: With the lesion seen on the MRI should this patient be treated with chemotherapy?
MR: That’s a tough question. There is no good data to define what volume of nephrogenic rest requires treatment. We don’t know the natural history of lesions that are this size in this setting. My inclination would be to treat the patient, but I would also have no problem with waiting and repeating the renal ultrasound or MRI in three to four months.

MK: Should the patient have a biopsy of the lesion?
MR: No. A small needle biopsy is not going to help distinguish Wilms’ tumor from a nephrogenic rest. You would need to remove the entire lesion and adjacent border of renal parenchyma to make that distinction.
Case #1: The patient was observed for several months and had a follow up MRI which demonstrated growth of the lesion (Figure 1C).

MK: What should be done now?
JR: I would treat with two-drug chemotherapy (dactinomycin and vincristine)
BB: The significant feature on this MRI is that it has not only grown in size but it has become spherical rather than lenticular in shape. That is an indication that it has become a tumor rather than just a nephrogenic rest. I agree that treatment should be started now. We would also use two-agent chemotherapy with dactinomycin and vincristine.

Case #1: The patient was treated with dactinomycin and vincristine for 16 weeks. The lesion disappeared. She is ten years post-treatment and there has been no evidence of recurrent disease.

MK: A final question on this subject. What about the patient with diffuse nephroblastomatosis?
RS: There are very few of these patients so data guiding decisions is scarce. What is being recommended in the next COG study is that these patients with diffuse perilobar nephroblastomatosis receive two-agent chemotherapy. Biopsy of lesions that are diagnostic on imaging would not require biopsy for the very reasons Bruce Broecker mentioned: the needle biopsy will not differentiate between Wilms’ tumor and nephroblastomatosis. Following chemotherapy the patient should have sequential follow up with ultrasound and if there is any question of growth or change in a localized area an MRI scan may better define the lesion. Lesions that appear to be evolving to Wilms’ tumor – growing in size or changing in shape - during therapy should be removed by tumorectomy.

Case #2: A five-year-old female who initially presented with dysfunctional voiding and recurrent lower urinary tract infection. An ultrasound demonstrated a small peripheral renal mass (Figure 2A). The patient did not return for eight months at which time the renal ultrasound appeared unchanged, but a CT scan demonstrated a non-enhancing mass (Figure 2B).

MK: What should be done at this point?
BB: The lack of change in 8 months might make you think of benign lesions but its appearance is troubling and I think either percutaneous biopsy or open exploration and biopsy are warranted.
JR: I agree that it’s worrisome. If you continue following this patient the radiation from repetitive CT scans is not insignificant. Unless there was clinical evidence of infection I would also feel that exploration and biopsy would be appropriate.
Case #2: The patient was explored and frozen-section biopsies were read by the pathologist as Wilms’ tumor.

MK: What do we do now - partial or complete nephrectomy?
What about the lymph node? Should the peritoneum be opened and the nodes sampled?

JR: I would remove the whole kidney and open the peritoneum and sample hilar and peri-aortic lymph nodes.

MR: The problem with this lesion is that even though it is small it is very close to the hilum. It is fine to consider a partial nephrectomy for unilateral tumors but the caveat is that you want to completely remove the tumor intact with a margin of normal tissue.

BB: An MRI with coronal and sagittal images can be very helpful if you’re considering partial nephrectomy.

RS: I want to follow up on Mike Ritchey’s comment. If a child has a partial nephrectomy and the margins are positive it is an incomplete resection. That child will then be treated with abdominal radiotherapy and three agent chemotherapy, including adriamycin. There is considerably more morbidity to this regimen than the regimen for completely resected, stage 1 or 2 disease. I emphatically agree with Jonathan Ross about the need to sample lymph nodes to properly stage the patient. There is a significant difference in treatment and outcome depending on the status of the lymph nodes. Failure to sample lymph nodes can result in understaging of the patient and subsequent undertreatment. This has been clearly shown to increase the frequency of local relapse.

MK: Last question: Should the contralateral kidney be explored?
The patient is in the flank position and it will be difficult.

MR: I am going to go on record now as stating that if you have adequate imaging with a good CT scan or MRI that you can comfortably exclude lesions in the other kidney that would alter therapy and/or outcome.

Case #2: The patient had a partial nephrectomy. The pathology specimen demonstrated a rim of normal tissue and the bed of the resection was negative for tumor. Lymph nodes were sampled and were negative, but the contralateral kidney was not explored. The tumor was considered stage I. Chemotherapy with dactinomycin and vincristine was given for 16 weeks and there has been no evidence of recurrence 12 months following completion of her chemotherapy.

Case #3: A five-year-old female presents with abdominal pain and an abdominal mass. The CT scan demonstrates a very large renal mass (Figure 3A). The chest CT is normal and there is no evidence of intraabdominal metastatic disease or vena caval thrombus.

MK: Is there a role for pre-operative chemotherapy of this tumor based on its radiographic appearance?
BB: It is difficult to assess operability on CT images alone, but you certainly want to carefully evaluate the interface with the liver and other surrounding organs to try and predict direct invasion as well as carefully evaluating the inferior vena cava and right atrium. Evidence of thrombus above the diaphragm is an indication for pre-treatment based on radiographic appearance alone. I would explore this patient, but with a definite feeling that it very well may be better to biopsy and pre-treat this tumor.

MR: In National Wilms’ Tumor Study (NWTS) and Children’s Oncology Group (COG) studies, the determination of inoperability has to be made surgically. When you elect to pre-treat, it becomes de facto a stage 3 tumor and will receive abdominal radiotherapy and doxorubicin. Large size alone does not equal inoperability.

Case #3: The patient was explored through a transverse upper abdominal incision. Bloody peritoneal fluid and a massive left renal tumor was found. The tumor was growing through the mesentery of the colon. The liver, IVC and lymph nodes appeared normal.

MK: Should you do a biopsy or resect the tumor with the contiguous segment of descending colon?
RS: With diffuse peritoneal spread you have at least a stage 3 tumor and it will require abdominal radiation and three agent chemotherapy regardless of whether you biopsy or completely remove the tumor. I do not think you want to remove contiguous organs if that can be avoided. Mike Ritchey has reported previously that resection of adjacent organs increases the frequency of complications.

MK: As moderator I have the last word. The tumor and part of the descending colon were removed en bloc. The lymph nodes were negative. She recovered quickly, was treated with three-agent chemotherapy and radiotherapy. She is alive and well six years later without evidence of recurrence.

Figure 3A - CT scan at presentation
The Society for Pediatric Urology
54TH Annual Meeting
Saturday, May 21, 2005 - San Antonio, Texas
Salons D, E and F
Marriott Riverwalk Hotel

6:30 AM Registration Opens
7:00 AM BREAKFAST SYMPOSIUM:
Examining Vesicoureteral Reflux in the Pediatric Population:
A Look at Treatment Patterns & Outcomes
(Sponsored by QMed)
8:15 AM INTRODUCTION AND WELCOME
David B. Joseph, M.D.
President, The Society for Pediatric Urology
8:20 AM Complex Hypospadias Reoperation: Options When the Urethral Plate Cannot Be Used
Moderator: Rafael Gosalbez, M.D., Miami, Florida
Skin Flaps: Douglas A. Canning, M.D., Philadelphia, Pennsylvania
Buccal Onlays and Tubes: John M. Park, M.D., Ann Arbor, Michigan
Buccal Inlays and Staged Repairs: Aivar Bracka, M.D. Birmingham, England
9:30 AM State of the Art Lecture - Alternative Views On Hypospadias Surgery
Aivar Bracka, M.D., Birmingham, England
10:00 AM Presentation Of Current Pediatric Urology Fellows
10:15 AM Coffee Break
10:45 AM Urodynamics In Infants With Myelomeningocele: What Should Be the Academic Standard?
Moderator: Antoine E. Khoury, M.D., Toronto, Canada
Discussants: Stuart B. Bauer, M.D., Boston, Massachusetts - John Brock, M.D., Nashville, Tennessee
11:45 AM Presentation of SPU Research Grant Recipients
11:55 AM Annual Member Business Meeting
12:30 PM LUNCHEON AND DISCUSSION:
Pediatric Urology Fellowship Training: How Many Sites, How Many Years?
Moderator: Douglas Husmann, M.D., Rochester, Minnesota
1:45 PM Point-Counterpoint: Surgical Management Of Upper Tract Stones In Prepubertal Children
Moderator: John Pope, M.D., Nashville, Tennessee
PLC/Reimplant: Eugene Minevich, M.D., Cincinnati, Ohio
ESWL: Henri B. Lottman, M.D., Paris, France
2:45 PM SPU Hinman Research Award Presentation
3:00 PM Meredith Campbell Lecture - The Courage To Succeed
Jackie N. Pflug, Eden Prairie, Minnesota
4:00 PM Video Forum On Advanced Injection Techniques
Moderator: Anthony A. Caldamone, M.D., Providence, Rhode Island
Intraluminal Ureteral Injection: Andrew J. Kirsch, M.D., Atlanta, Georgia
Injection Of Duplicated Ureters: Mark A. Barazza, M.D., Jackson, Mississippi
Injection For High-Grade Reflux: Lars J. Clausen, M.D., PhD, Houston, Texas
Redo Injection: Martin A. Koyle, M.D., Denver, Colorado
Stoma Injections: Bradley Kropp, M.D., Oklahoma City, Oklahoma
Bladder neck Injection: Gregory E. Dean, M.D., Philadelphia, Pennsylvania
5:15 PM Adjourn

Schedule subject to change
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MANAGEMENT OF CHILDHOOD RENAL TUMORS

Guest Editor: Bruce Broecker, M.D.