

Pediatric Urologic Oncology

a report by

Hsi-Yang Wu, MD and **Fernando A Ferrer, MD**

Director, Pediatric Urology Research, Children's Hospital of Pittsburgh, and Director, Pediatric Urology, Connecticut Children's Medical Center

Introduction

Wilms' tumor, neuroblastoma, rhabdomyosarcoma (RMS), and testis tumors are treated by pediatric urologists and pediatric surgeons in conjunction with trials sponsored by the Children's Oncology Group (COG) of the National Cancer Institute. COG has assumed responsibility for trials formerly run by the National Wilms' Tumor Study (NWTs) group and Intergroup Rhabdomyosarcoma Study (IRS) group. The multimodal approach of combining surgery, radiotherapy, and chemotherapy has resulted in significant improvements in survival while reducing treatment-related morbidity. The next generation of studies is being designed using risk stratification systems based on clinical and molecular criteria. As more children survive treatment, long-term concerns including secondary malignancy, bone deformity, and genitourinary dysfunction are being addressed by the COG.

Wilms' Tumor

Wilms' tumor is the most common pediatric urologic tumor – 75% of patients present between one and five years of age, with an equal incidence between boys and girls. Patients present with an abdominal mass, which rarely crosses the midline. Contrast computed tomography (CT) of the chest, abdomen, and pelvis is obtained to evaluate both the mass and possible metastatic disease. Surgical exploration is performed through a subcostal transverse incision. Classically, the recommendation has been that in cases of unilateral disease, the contralateral kidney must be explored due to 7% of patients having false-negative pre-operative studies.¹ This recommendation may be changing because it appears that patients with missed small contralateral lesions did well with post-operative chemotherapy.² In cases of bilateral disease, an open biopsy of the tumor is performed, chemotherapy is given, and delayed bilateral nephron-sparing surgery is performed. The next generation of studies may use upfront chemotherapy for bilateral tumors without biopsy, as recommended by the International Society of Pediatric Oncologists (SIOP). The patient's prognosis is dependent on the tumor histology and

stage. Chemotherapy with dactinomycin and vincristine results in a 90% overall cure rate for low-stage tumors. For favorable histology tumors, stage I–II (completely resected) have a 92% to 97% survival, stage III (lymph node positive or intraoperative spill) 84%, and stage IV (distant lymph nodes or lung involvement) 83%. Radiotherapy and doxorubicin are added for stage III disease and metastatic sites (stage IV).³ Long-term survival for children with bilateral disease (stage V) is 70%.⁴

The NWTs approach in the US is different from the SIOP approach. The NWTs asks for open biopsy and, if possible, resection before chemotherapy. This avoids giving chemotherapy for a non-Wilms' tumor, but at the expense of a higher rate of intraoperative spill, and more children receiving radiotherapy for stage III tumors. The SIOP approach of pre-operative chemotherapy allows for safer surgery, but gives more chemotherapy. One key problem with the SIOP approach is the possibility of down-staging tumors, and undertreating patients. The tradeoff is that patients with stage II tumors receive doxorubicin on SIOP protocols, but not on NWTs protocols. Overall survival is essentially the same between the latest NWTs and SIOP protocols, so the argument over which approach is better for a given child depends on the skill of the physicians treating the child.⁵ In NWTs V, selected good risk patients (stage I disease, less than two years of age, tumor <550g) were managed without chemotherapy, but it became apparent due to a high number of relapses, that all patients with Wilms' tumor require chemotherapy.⁶ This point will likely be revisited in upcoming studies, as many of these children were rescued by chemotherapy. Other aspects of NWTs V included investigation of chromosome 16q and 1p loss of heterozygosity as markers of poor prognosis. Also, new chemotherapeutic regimens for rhabdoid tumor (carboplatin, etoposide, and cyclophosphamide) as well as diffuse anaplasia and clear cell sarcoma (etoposide and cyclophosphamide) were studied.

Long-term complications are most easily assessed in patients with bilateral Wilms' tumor. Maintaining renal function in the face of surgery, chemotherapy,



Hsi-Yang Wu, MD



Fernando A Ferrer, MD

Hsi-Yang Wu, MD, is Director of Pediatric Urology Research at the Children's Hospital of Pittsburgh and Assistant Professor of Urology at the University of Pittsburgh. His clinical interests include pediatric urologic oncology, cryptorchidism, and voiding dysfunction. His NIH-supported lab studies neural and smooth muscle maturation in pediatric bladder function, with an aim to develop new treatments for pediatric urinary incontinence.

Fernando A Ferrer, MD, is Director of Pediatric Urology at Connecticut Children's Medical Center and Assistant Professor of Surgery (Urology), Pediatrics, and Oncology at the University of Connecticut. His clinical interests include pediatric urologic oncology and major reconstructive surgery for urinary continence. He serves on the Children's Oncology Group (COG) committees that study Wilms' tumor (Renal Tumor Committee) and late complications (Late Effects Committee), and is involved in developing new protocols for tumor treatment.

and radiation is the primary reason why nephron-sparing surgery is performed. In NWTs 2–4, 35% of patients who underwent renal-sparing surgery and radiation for bilateral Wilms' tumor developed an elevation in blood urea nitrogen (BUN) >25 or creatinine >1.5 at a median follow-up of 27 months.⁷ At 15 years post-treatment for bilateral Wilms', the incidence of ESRD approaches 15%.⁶ The use of nephron-sparing surgery in cases of unilateral disease has been studied in Europe in patients who had received pre-operative chemotherapy. Outcomes for favorable histology patients were equivalent to those undergoing total nephrectomy.⁸ The use of nephron-sparing surgery must balance the very low risk of end-stage renal disease from a total nephrectomy (0.25%) with the risk of local recurrence.⁹

Future studies for Wilms' tumor will likely focus on understanding the molecular biologic characteristics of the tumors. The association of p53 abnormalities with anaplasia, integrase interactor-1 (INI1) abnormalities in rhabdoid tumors, and chromosomal translocation in children with renal cell carcinoma are examples.^{10–12} From a therapeutic perspective, the use of new chemotherapeutic agents, such as topoisomerase inhibitors (irinotecan),¹³ and changes in protocol such as omitting biopsy before treatment in bilateral tumors and revisiting omitting chemotherapy in select cases can be expected.

Neuroblastoma

Neuroblastoma is the most common malignancy of infancy, with 50% of patients presenting before age two and 75% of patients presenting before age four. It affects boys and girls equally and is responsible for 15% of all childhood cancer deaths. While some subsets of patients have enjoyed improved survival, outcomes of those with high-risk tumors have only improved modestly. Both CT and magnetic resonance imaging (MRI) are useful in evaluation of the primary lesion and metastases. Current COG protocols stratify tumors into low-, intermediate-, and high-risk groups based on International Neuroblastoma Staging System (INSS) stage, patient age, Shimada evaluation of histopathology, DNA index, and MYCN amplification. MYCN amplification has proven to be an important prognostic marker, and a recently completed COG trial will assess its impact among patients with low risk disease.¹⁴ Low-stage (stage 1 – localized, stage 2 – local lymph node involvement, not crossing the midline) neuroblastoma responds to surgery with an 80% survival rate, and chemotherapy is not necessary.¹⁵ Unfortunately, high-stage neuroblastoma (stage 3 – bilateral lymph nodes, stage 4 – distant metastases) responds poorly to standard chemotherapy, with a 10% to 40% survival. Most patients with stage IV-S disease (stage I or II with skin, liver, bone marrow

metastases) can expect spontaneous regression, with a five-year 92% survival rate. For high-stage neuroblastoma, high-dose chemotherapy (cyclophosphamide, ifosfamide, cis-platinum, carboplatinum, and doxorubicin) followed by autologous bone marrow transplant is used, but there is a significant mortality (5% to 10%) and relapse rate (60% at four years).¹⁶ New approaches are currently being evaluated by COG, including observation for select perinatally diagnosed tumors, monoclonal antibodies directed to tumor-associated antigens, such as disialoganglioside GD2, and new chemotherapy agents, such as topotecan and irinotecan. Other experimental approaches, including the use of differentiating agents such as retinoids, antisense oligonucleotides, and immunotherapy, are being investigated.¹⁷

RMS

RMS is the most common soft tissue sarcoma, of which 20% involve the bladder, prostate, or paratesticular area. RMS has two peaks, ages two to four and ages 15 to 19. Similar to Wilms' and neuroblastoma, a risk-based stratification system is used. Tumors of the paratesticular area are by definition favorable risk, whereas bladder and prostate primaries are intermediate risk. Paratesticular primaries usually present as a painless scrotal mass. Bladder and prostate tumors may present with difficulty urinating or gross hematuria. Ultrasound is usually performed first, followed by CT or MRI scan of the chest, abdomen, and pelvis to determine the extent of the disease. Bone scan and bone marrow biopsy are also necessary. Positron emission tomography (PET) scan can also be used to detect metastases.¹⁸ The IRS IV have shown that initial biopsy, followed by chemotherapy, can successfully preserve pelvic organs while maintaining a high survival rate. Patient survival was 86% in IRS IV, which used vincristine, dactinomycin, cyclophosphamide (VAC) chemotherapy. Exenterative procedures are currently reserved for tumors unresponsive to chemotherapy. In IRS IV, VAC was shown to be as effective as two other three-drug regimens (VIE/VAE – ifosfamide, etoposide).¹⁹ Because cyclophosphamide is cheaper and has lower toxicity, VAC is the current standard chemotherapy. IRS-V was designed to evaluate new agents such as topotecan for advanced disease while attempting to decrease cyclophosphamide and radiotherapy dosing for low-risk patients.²⁰

Bladder and prostate primaries are initially diagnosed by endoscopic, open, or transrectal biopsy after CT reveals the mass in the affected organ. IRS III included intensified chemotherapy (dactinomycin, VP-16) and six weeks of radiotherapy increasing the functional bladder salvage rate from 25% to 60%.²¹ In IRS IV, half of patients were managed with biopsy, 37% had partial cystectomy,

and 13% had prostatectomy.²¹ Renal function as assessed by serum BUN and creatinine was normal in 95%.²² 'Normal' bladder function was maintained in only 40% of the entire group of patients.²³ A more objective evaluation of the success of functional bladder salvage using urodynamic studies will hopefully be included in future RMS studies undertaken by the COG.²⁴

Paratesticular tumors may mimic testicular tumors, so serum beta human chorionic gonadotrophin (β HCG) and alpha-fetoprotein (AFP) are obtained preoperatively. The tumor is resected by inguinal orchiectomy, and post-operatively a CT scan of the chest, abdomen, and pelvis is obtained. Depending on age and stage, retroperitoneal lymph node dissection (RPLND) may be recommended. In IRS III, all patients underwent RPLND, which was not recommended if the CT scan was negative in IRS IV. This led to a significant understaging of disease, and some patients with radiologically normal retroperitoneums did not receive chemotherapy, leading to a decrease in failure-free survival. Of those patients who required retreatment, 30% had negative CT scans and were over 10 years of age.²⁵ For IRS V, patients under the age of 10 with negative CTs and patients over the age of 10 with negative RPLNDs receive vincristine, dactinomycin (VA) chemotherapy. Patients under the age of 10 with positive CTs and all patients over the age of 10 undergo RPLND. Those with negative retroperitoneal lymph nodes undergo VA chemotherapy, whereas those with positive lymph nodes have VAC (vincristine, dactinomycin, cyclophosphamide) and radiotherapy.²⁵

Other complications of therapy included sex hormone replacement being required in 29% of patients, and 11% were shorter than expected.²² Radiotherapy increases the risk of a secondary neoplasm, often another sarcoma. Complications specific to surgical treatment from 1972–1984 include intestinal obstruction, anejaculation, and lower extremity edema after RPLND.²⁶ However, with newer surgical techniques designed to preserve ejaculation, better outcomes are expected.

The role of VEGF and other pro-angiogenic molecules, such as basic fibroblast growth factor and interleukin (IL)-8, are currently being explored. Anti-VEGF antibodies have a dramatic effect on RMS growth in animal models.^{27,28} COG is currently studying the use of anti-sense therapy directed at the proto-oncogene B-cell (BCL)-2, in conjunction with chemotherapy for children with relapsed solid tumors.

Prepubertal Testis Tumor

These tumors peak in the two- to four-year-old range and are much more benign than adult testis tumors. They present as a painless mass, although a history of trauma is often volunteered by the patient. Similar to paratesticular RMS, a serum β HCG and AFP are obtained pre-operatively. A scrotal ultrasound is obtained pre-operatively, the tumor is resected by inguinal orchiectomy, and post-operatively a CT scan of the chest, abdomen, and pelvis is obtained. Yolk sac and teratoma are the most common pathologies reported.

Stage I yolk sac tumors (negative CT scan with appropriate drop in AFP) do not require chemotherapy. However, patients are required to maintain a vigorous program of surveillance with AFPs, chest X-rays, and CTs for two years. Patients with stage II disease receive cis-platinum, etoposide, bleomycin (PEB), no radiotherapy, and can expect a 99% survival. Patients with stage II disease with persistent mass or persistent elevated AFP after chemotherapy should have RPLND. Those in stage III (retroperitoneal lymph nodes) and stage IV (distant metastases) undergo chemotherapy and RPLND. Overall survival for all stages approaches 100%.²⁹ Teratomas can be managed with testis-sparing surgery in the prepubertal patient, because they do not show metastatic behavior as they do in adults. The scrotal ultrasound will show a relatively heterogeneous mass compared with yolk sac tumor, and the AFP should be normal. If the patient is entering puberty, then a radical orchiectomy should be performed.²⁹ ■

References

1. Ritchey M L, Green D M, Breslow N B, et al., "Accuracy of current imaging modalities in the diagnosis of synchronous bilateral Wilms' tumor", *Cancer* (1995), 75 pp. 600–604.
2. Ritchey M L, Shamberger R C, Hamilton T, et al., "Fate of bilateral lesions missed on preoperative imaging: A report from the National Wilms' Tumor Study Group", Presented at American Academy of Pediatrics, Section on Urology meeting, Oct. 9, 2004, San Francisco, CA.
3. D'Angio, G J, Breslow, N, Beckwith, J B, et al., "Treatment of Wilms' tumor: results of the third National Wilms' Tumor Study", *Cancer* (1989), 64 pp. 349–360.
4. Montgomery B T, Kelalis P P, Blute M L, et al., "Extended follow-up of bilateral Wilms' tumor: Results of the National Wilms' Tumor Study", *J. Urol.* (1991), 146 pp. 514–518.
5. D'Angio, G J, "Pre- or post-operative treatment for Wilms' Tumor? Who, what, when, where, how, why – and which", *Med.*

- Pediatr. Oncol. (2003), 41 pp. 545–549.
6. Neville H L, Ritchey M L, “Wilms’ tumor: Overview of National Wilms’ Tumor Study group results”, Urol. Clin. North Am. (2000), 27 pp. 435–442.
 7. Smith G R, Thomas P R, Ritchey M, Norkool P, “Long-term renal function in irradiated bilateral Wilms’ tumor”, Am. J. Clin. Oncol. (1998), 21 pp. 58–63.
 8. Haecker F M, von Schweinitz D, Harms D et al., “Partial nephrectomy for unilateral Wilms’ tumor”, J. Urol. (2003), 170 pp. 939–944.
 9. Ritchey M L, “Editorial comment to Partial nephrectomy for unilateral Wilms’ tumor”, J. Urol. (2003), 170 p. 943.
 10. Bardeesy N, Falkoff D, Petruzzi M J, et al., “Anaplastic Wilms’ tumour, a subtype displaying poor prognosis, harbours p53 gene mutations”, Nat. Genet. (1994), 7 pp. 91–97.
 11. Savla J, Chen T T, Schmieder N R, et al., “Mutations of the hSNF5/INI1 gene in renal rhabdoid tumors with second primary brain tumors”, J. Nat. Cancer Inst. (2000), 92 pp. 648–650.
 12. Argani P, Antonescu C R, Illei P B, et al., “Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents”, Am. J. Pathol. (2001), 159 pp. 179–192.
 13. Slatter J G, Schaaf L J, Sams J P, et al., “Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. infusion of [(14)C]CPT-11 in cancer patients”, Drug Metab. Dispos. (2000), 28 pp. 423–433.
 14. Brodeur G M, Seeger R C, Schwab M, et al., “Amplification of N-myc in untreated human neuroblastoma correlates with advanced disease stage”, Science (1984), 224 pp. 1,121–1,124.
 15. Evans A E, Silber J H, Shpitsky A, et al., “Successful management of low-stage neuroblastoma without adjuvant therapies: A comparison of two decades, 1972 through 1981 and 1982 through 1992, in a single institution”, J. Clin. Oncol. (1996), 14 pp. 2,504–2,510.
 16. Alexander F, “Neuroblastoma”, Urologic Clinics of North America (2000), 27 pp. 383–392.
 17. Henry M C, Tashjian D B, Breuer C K, “Neuroblastoma update”, Curr. Op. Oncol. (2005), 17 pp. 19–23.
 18. Raney R B Jr, Téffi M, Ragab A H, et al., “Disease patterns and survival rate in children with metastatic soft-tissue sarcoma. A report from the Intergroup Rhabdomyosarcoma Study (IRS)-I”, Cancer (1988), 62 pp. 1,257–1,266.
 19. Crist W M, Anderson J R, Meza J L, et al., “Intergroup Rhabdomyosarcoma Study-IV: Results for patients with nonmetastatic disease”, J. Clin. Oncol. (2001), 19 pp. 3,091–3,102.
 20. Raney R B, Anderson J R, Barr F G, et al., “Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of Intergroup Rhabdomyosarcoma”, Study Group experience and rationale for Intergroup Rhabdomyosarcoma Study V, J. Ped. Hematol. Oncol. (2001), 23 pp. 215–220.
 21. Paidas C N, “Results of rhabdomyosarcoma of the bladder and prostate: Is bladder preservation successful?”, Section on Surgery, 2000 American Academy of Pediatrics meeting, Chicago, IL.
 22. Raney B, Heyn R, Hays D M, et al., “Sequelae of treatment in 109 patients followed 5 to 15 years after diagnosis of sarcoma of the bladder and prostate”, Cancer (1993), 71 pp. 2,387–2,394.
 23. Arndt C, Rodeberg D, Breitfeld P P, et al., “Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma?”, Results from Intergroup Rhabdomyosarcoma Study IV, J. Urol. (2004), 171 pp. 2,396–2,403.
 24. Ferrer F, “Re: Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma?”, Results from Intergroup Rhabdomyosarcoma Study IV, J. Urol. (2004), 172 p. 2,084.
 25. Weiner E S, “Evolution in management of paratesticular rhabdomyosarcoma”, Section on Surgery, 2000 American Academy of Pediatrics meeting, Chicago, IL.
 26. Heyn R, Raney B, Hays D, et al., “Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee”, J. Clin. Oncol. (1992), 10 pp. 614–623.
 27. Ferrara N, “VEGF and the quest for tumour angiogenesis factors”, Nat. Rev. Cancer, (2002), 2 pp. 795–803.
 28. Pavlakovic H, Havers W, Schweigerer L, “Multiple angiogenesis stimulators in a single malignancy: Implications for anti-angiogenic tumour therapy”, Angiogenesis (2001), 4 pp. 259–262.
 29. Ross J H, Rybicki L, Kay R, “Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: A summary of the prepubertal testis tumor registry”, J. Urol. (2002), 168 pp. 1,675–1,679.