Innovations in the management of Wilms' tumor

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Abstract: Advances in the management of Wilms' tumor have been dramatic over the past half century, not in small part due to the institution of multimodal therapy and the formation of collaborative study groups. While different opinions exist in the management of Wilms' tumors depending on where one lives and practices, survival rates have surpassed 90% across the board in Western societies. With more children surviving into adulthood, the concerns about morbidity have reached the forefront and now represent as much a consideration as oncologic outcomes these days. Innovations in treatment are on the horizon in the form of potential tumor markers, molecular biological means of testing for chemotherapeutic responsiveness, and advances in the delivery of chemotherapy for recurrent or recalcitrant tumors. Other technological innovations are being applied to childhood renal tumors, such as minimally invasive and nephron-sparing approaches. Risk stratification also allows for children to forego potentially unnecessary treatments and their associated morbidities. Wilms' tumor stands as a great example of the gains that can be made through protocol-driven therapy with strenuous outcomes analyses. These gains continue to spark interest in minimization of morbidity, while avoiding any compromise in oncologic efficacy. While excitement and innovation are important in the advancement of treatment delivery, we must continue to temper this enthusiasm and carefully evaluate options in order to continue to provide the highest standard of care in the management of this now highly curable disease.

Keywords: innovations, minimally invasive, nephron sparing, Wilms' tumor

History of Wilms' tumor

Wilms' tumor is the most common primary renal malignancy in children. There are a number of syndromes known to confer a predisposition to the development of Wilms' tumor. However, the majority of these tumors arise sporadically in children under 5 years of age [Breslow *et al.* 2006]. Approximately 93% are unilateral [Breslow *et al.* 1988]. The evolution of the diagnosis, treatment and study of Wilms' tumor has been remarkable in the nearly 200 years since it was first described by Thomas F. Rance in 1814. It was finally described as a mixed urogenital tumor by Max Wilms in 1899, carrying his name since. The development of cross-sectional imaging, improvements in multimodal therapy and the development of collaborative study groups have had a tremendous impact on the management and enhanced survival of patients with Wilms' tumor. It has transitioned from being a universally fatal

disease at the turn of the twentieth century, to a survivable disease, to a disease where the long-term morbidity associated with treatment has become the primary investigational focus, as modern day survival rates have surpassed 90%.

Numerous syndromes are associated with a predisposition to the development of Wilms' tumor (Table 1). Rates of Wilms' tumor with any associated abnormality vary from 8% to 17% [Dumoucel *et al.* 2014], whereas rates of Wilms' tumor associated specifically with predisposition syndromes (Beckwith-Wiedemann Syndrome (BWS), Denys-Drash Syndrome (DDS), Fanconi Anemia (FA), WAGR Syndrome) from 3.8% [Ng *et al.* 2007] to 4.7% [Dumoucel *et al.* 2014]. As a result, children with these types of syndromes undergo routine imaging screening (usually ultrasound) in an effort to identify these tumors as early as possible, with the hope of finding smaller tumors at an earlier

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Table 1. Anomalies associated with an increased risk of Wilms' tumor.

	Anomaly
Low	Isolated hemihypertrophy Li-Fraumeni
Moderate	Beckwith-Wiedemann Simpson-Golabi-Behmel
High	Denys-Drash WAGR Perlman Familial Wilms Fanconi anemia

stage that might be more amenable to nephron-sparing surgery after chemotherapy.

The philosophies regarding the therapy of Wilms' tumor have been divided primarily into two distinct camps based on which side of the Atlantic Ocean one lives. Historically, the three primary 'Western' academic bodies have been the National Wilms Tumor Study Group (NWTSG), since replaced by the renal tumor section of the Children's Oncology Group (COG), the Société Internationale d'Oncologie Pédiatrique (SIOP) and the UK Children's Cancer Study Group (UKCCSG). The NWTSG was initiated in 1969 and established clinical trials and protocols to study Wilms' tumor. It merged with several other oncologic groups in 2001 to become the COG. The SIOP also formed in 1969 with the goal of studying all types of pediatric malignancies, including Wilms' tumor. The conclusions of the ensuing studies are summarized in Table 2. The UKCCSG formed in 1977. In 2006 it merged with the UK Childhood Leukaemia Working Party to form the Children's Cancer and Leukaemia Group (CCLG). While these are some of the most widely referenced Wilms study groups, there are numerous other collaborative bodies including: Associazione Italiana Ematologia Oncologia Pediatrica, Gesellschaft für Pädiatrische Onkologie und Hämatologie, Sociedade Brasileira de Oncologia Pediátrica, and Société Française d'Oncologie Pédiatrique. For the purposes of this review, we focus on the three larger collaborative groups.

NWTSG/COG and SIOP stand apart with regard to the criteria for the various diagnostic stages and resultant treatment protocols. Broadly speaking, the NWTSG/COG advocates a surgery followed by chemotherapy protocol, whereas SIOP advocates a neoadjuvant chemotherapy followed by a surgical strategy. While the staging is generally the same between the groups, there are

several key differentiating criteria for stages II and III (Table 3). These differences relate to the degree of local disease spread, and were established as a result of the approaches taken by some of the early pioneers in Wilms' tumor surgery. In the USA, Gross, of Boston Children's Hospital, demonstrated mortality rates of less than 1% with a surgical approach to disease management. This early experience, as well as an initially poor experience with radiation therapy, defined the subsequent practices of the NWTSG/COG group favoring primary surgery. This approach favors accurate initial staging by the submission of lymph nodes with the kidney specimen, and of course allows unaltered histopathological examination of the specimen. In contrast, Bamberger and Schweisguth of France encountered a Wilms' tumor population primarily from North Africa. The delayed presentation of these tumors led to a disease state that was considered inoperable due to advanced disease and large size, and thus they advocated for preoperative radiation followed by nephrectomy. The UKCCSG/CCLG initially recommended an approach similar to NWTSG/COG with surgery as the first therapeutic intervention. Subsequent changes in their protocol, as a result of the UKW3 randomized trial, led to a hybrid of the NWTSG/COG and SIOP approaches by adding pretreatment biopsy to assess the pathology of the tumor, followed by chemotherapy and ultimately delayed surgery [Mitchell *et al.* 2006]. Whereas the SIOP approach is associated with a misdiagnosis (and hence inappropriate treatment) of up to 5%, and of course the inability to assess histopathology (favorable *versus* anaplastic), the UK approach adds these factors by this initial biopsy. While the tumor stage was shown to be downstaged using this approach, the overall survival was equal between the groups [Mitchell *et al.* 2006]. The downside is the risk of tumor tract seeding and spillage, leading to upstaging. In North America, any biopsy leads to tumor upstaging to a stage III, which requires more comprehensive therapy per NWTSG protocol. In addition, risk stratification is slightly different between groups, summarized in Table 4.

Current management

Advantages of different protocols

SIOP advantages

- (1) Preoperative shrinkage (Figure 1) and downstaging of the tumor, leading to easier resection, less risk of tumor rupture/

Table 2. Conclusions of NWTSG and SIOP studies.

	NWTSG/COG
NWTSG-1	Stage I disease does not require postoperative radiation Vincristine and dactinomycin are more effective in combination than individually
NWTSG-2	Vincristine/dactinomycin comparably effective when given for 6 <i>versus</i> 15 months in stage I tumors Doxorubicin improves 2-year relapse-free survival in advanced disease
NWTSG-3	11 weeks of vincristine/dactinomycin effective for stage I disease Doxorubicin unnecessary for stage II disease 10 Gy of radiation sufficient for stage III disease Cyclophosphamide of no benefit in stage IV favorable histology disease
NWTSG-4	Pulse delivery of dactinomycin and doxorubicin improves hematologic toxicity 6 months of chemo sufficient for stages II–IV disease Tumor spillage increases risk of local recurrence
NWTSG-5	Loss of heterozygosity at chromosomes 1p and 16q predicts recurrence of favorable histology tumors 100% survival at 2 years for children <2 years old with <550 g, stage I, favorable histology tumors treated with nephrectomy
SIOP	
SIOP-1	Survival equal for preoperative radiation <i>versus</i> immediate surgery Preoperative radiation reduced tumor rupture Relapse-free survival lower in patients following intraoperative rupture
SIOP-2	Tumor rupture reduced when pretreated with radiation and dactinomycin <i>versus</i> immediate surgery
SIOP-5	Preoperative vincristine/dactinomycin equivalent to radiation with dactinomycin for preventing tumor rupture
SIOP-6	Vincristine/dactinomycin comparably effective when given for 17 <i>versus</i> 38 weeks in stage I tumors Recurrence higher in stage II tumors with negative lymph nodes if radiotherapy not received
SIOP-9	Vincristine/dactinomycin comparably effective when given for 4 <i>versus</i> 8 weeks with regard to stage distribution and tumor shrinkage
SIOP-93-01	Stage I, intermediate risk, anaplastic tumors have equal 2-year event-free survival with 4 weeks <i>versus</i> 18 weeks of adjuvant chemotherapy
COG, Children's Oncology Group; NWTSG, National Wilms Tumor Study; SIOP, Société Internationale d'Oncologie Pédiatrique.	

spillage and becoming more amenable to nephron-sparing approaches.

- (2) Obtain information about the tumor's *in vivo* response to chemotherapy.

NWTSG advantages

- (1) Definite diagnosis of Wilms' tumor with appropriate treatment for non-Wilms' diagnoses (Table 5).
- (2) Provision of accurate surgical and pathologic staging.
- (3) Avoid treatment with ineffective chemotherapy if different histological malignancy is present.
- (4) No modification of tumor histology from chemotherapeutic pretreatment.
- (5) Possible avoidance of chemotherapy in very low risk group.

Despite a significant and fundamental difference in the approach to these tumors, the NWTSG/COG and SIOP outcomes have been remarkably similar with overall survival over 90% (Table 6). Much of the overall success is due to the advances made in the delivery of chemotherapeutic agents, as most of these tumors are highly chemo- and radiosensitive.

Single agent dactinomycin was used by Farber and colleagues in 1956 [Wright, 1988] and was associated with a significant cure rate, as well as an improvement in 2-year disease-free survival from 11% to 62%. Single agent vincristine was also used in the 1960s and the two were used in combination as the first randomized trial of the NWTSG, and continue to be the treatment used in earlier stage tumors. Doxorubicin was later found to have efficacy in Wilms' tumor, as were cyclophosphamide, etoposide and carboplatin, which are now a

Table 3. Staging of Wilms' tumor, NWTSG and SIOP.

	NWTSG/COG	SIOP
Stage I	Tumor confined to kidney – complete resection Intact renal capsule No extension to renal sinus No residual tumor	Tumor confined to kidney – complete resection Tumor encroaching, but not invading, pelvic system No extension to renal sinus vessels
Stage II	Tumor extension beyond capsule – complete resection Extension to renal sinus Tumor present in extrarenal vessels	Tumor extension beyond capsule – complete resection Extension to renal sinus Infiltration of adjacent organs or vena cava
Stage III	Incomplete tumor resection Lymph node involvement Positive surgical margin Tumor spillage Peritoneal implantation Nonhematogenous tumor within abdomen	Incomplete tumor resection Lymph node involvement Positive surgical margin Tumor spillage Peritoneal penetration/implantation Tumor thrombi at margins of vessels or ureter Surgical biopsy prior to chemotherapy or surgery
Stage IV	Metastatic (hematogenous) spread to lung, liver, brain, or bone	Metastatic (hematogenous) spread to lung, liver, brain, or bone Lymph node metastasis outside of the abdomen/pelvis
Stage V	Bilateral tumors	Bilateral tumors
COG, Children's Oncology Group; NWTSG, National Wilms Tumor Study; SIOP, Société Internationale d'Oncologie Pédiatrique.		

Table 4. Classification and risk stratification of Wilms' tumors.

	NWTSG/COG	SIOP
Low risk	Mesoblastic	Mesoblastic nephroma Cystic partially differentiated
Intermediate risk	Favorable histology	Nonanaplastic Focal anaplasia
High risk	Anaplastic Clear cell sarcoma Rhabdoid	Diffuse anaplasia Clear cell sarcoma Rhabdoid
COG, Children's Oncology Group; NWTSG, National Wilms Tumor Study; SIOP, Société Internationale d'Oncologie Pédiatrique.		

standard part of the treatment protocols for more advanced and recalcitrant cases.

Current NWTSG/COG protocol calls for a small subset of patients with very low risk disease to forgo any adjuvant chemotherapy following nephrectomy [Shamberger *et al.* 2010]. The stage I, favorable histology tumors weighing less than 550 g and found in children under 24 months of

age can be managed with surgery only [Green *et al.* 2001]. Although the 2-year disease-free survival was only 86.5%, all patients were alive at the end of the study, having been salvaged with adjuvant therapies, thus avoiding chemotherapy in a particular group of patients without compromising oncologic outcomes.

Abdominal external beam radiotherapy was first administered at Boston Children's Hospital in 1935 for patients with Wilms' tumor and was subsequently advocated for all patients due to an improvement in survival [Green, 2013]. However, with improvements in chemotherapeutic regimens, the need for radiation therapy began to be questioned and studied further, and the long-term effects of radiation to children have become more apparent. A study of the Surveillance, Epidemiology and End Results database between 1976 and 2008 showed the proportion of patients with Wilms' tumors receiving radiation therapy decreased from 73% in 1976 to 53% in 2008 [Jairam *et al.* 2013], and radiotherapy is generally decreasing among many other pediatric malignancies as well.

Surgical resection of a Wilms' tumor, either up front or after neoadjuvant chemotherapy, has

Figure 1. Effect of neoadjuvant chemotherapy on a large tumor in a child with Beckwith-Wiedemann syndrome, intraoperative and postoperative images.

Table 5. Alternative diagnoses potentially missed by Société Internationale d'Oncologie Pédiatrique protocols and pretreatment with chemotherapy.

Angiomyolipoma	Renal cell carcinoma
Mesonephric nephroma	Rhabdoid tumor
Metanephric adenoma	Clear cell carcinoma
Multilocular cystic renal tumor	Ossifying renal tumor of infancy
Nephroblastomatosis	Lymphoma

traditionally been via a radical nephrectomy (including adrenalectomy) through a generous transverse abdominal incision. Coupled with regional lymph node sampling, this has allowed for adequate surgical and pathologic staging, and

is the current standard of care. The mortality rate is extremely low, and tumor spillage or other complications are uncommon.

The UKCCSG/CCLG has advocated percutaneous biopsy of any renal mass prior to initiation of chemotherapy. This approach is supported by their 2003 study, which revealed a 12% rate of renal tumors that, while clinically and radiologically consistent with Wilms' tumor, proved to be tumors other than Wilms [Vujančić *et al.* 2003].

Late effects/morbidities

The late and long-term effects of treatment in children with Wilms' tumors are not insignificant,

Table 6. Modern survival rates in Wilms' tumor, NWTSG and SIOP.

	Stage	Relapse/event-free survival (%)	Overall survival (%)
NWTSG-4	I	94.9 (2 years)	98.7 (2 years)
	II	83.6 (8 years)	93.8 (8 years)
	III	88.9 (8 years)	93 (8 years)
	IV	80.6 (2 years)	89.5 (2 years)
NWTSG-5	I (age < 2 years, tumor < 550 g)	86.5 (2 years)	100 (2 years)
SIOP-9	I	88 (2 years)	93 (2 years)
	II, N0	85 (2 years)	88 (2 years)
	II, N1 and 3	71 (2 years)	85 (2 years)
SIOP-93-01	I	88.3 (5 years)	97 (5 years)

NWTSG, National Wilms Tumor Study; SIOP, Société Internationale d'Oncologie Pédiatrique.

and are becoming more apparent as the survival rate of this disease continues to improve. Congestive heart failure (CHF), second malignant neoplasms and end-stage renal disease (ESRD) are the commonest issues these patients face the further away from treatment they get.

Sadak and colleagues reported the results of two large studies and showed a 24-fold increased risk of CHF in children with Wilms' tumors compared with healthy siblings [Sadak *et al.* 2013]. However, doxorubicin (known to have cardiotoxic effects) alone did not explain the increased risk and was not statistically significant. The highest risk was seen in patients who were exposed to both doxorubicin and external beam radiation, but radiation alone was associated with a sevenfold increased risk.

Second malignancies are also increased in this population. Results of NWTSG studies show an increased risk of death due to second malignancies even 20 years after treatment [Cotton *et al.* 2009] and second malignancies were seen in 3% of survivors with 25-year follow up [Termuhlen *et al.* 2011]. Breslow and colleagues analyzed an international cohort of 13,351 subjects with Wilms' tumor diagnosed between 1960 and 2004. They showed a 6.7% risk of development of a solid tumor malignancy by the age of 40 and leukemia being mostly seen within 5 years of diagnosis of Wilms' tumor [Breslow *et al.* 2010]. Interestingly, they inferred some differences between NWTSG/COG and SIOP protocols. They found that significantly more North American patients are exposed to radiation, while Europeans are more likely to be exposed to anthracycline chemotherapy. Although not statistically evident in

the current study, theoretically the NWTSG/COG-treated patients are at greater risk of radiation-related second malignancies and SIOP-treated patients are more at risk of leukemias associated with topoisomerase II inhibitors.

ESRD is not common in patients with unilateral tumors without an underlying predisposition syndrome, estimated at under 1%. Most of the patients going on to develop ESRD have WT1 mutations [Lange *et al.* 2011]. A total of 83% of patients with Denys-Drash, 43% with WAGR and 9% with other genitourinary anomalies in addition to Wilms' tumors developed ESRD at 20 years of follow up, well above the overall estimate. Nonetheless, the associated risk underscores the need to consider nephron-sparing approaches, especially in syndromic and bilateral cases.

Controversies

Classically, a radical nephrectomy for Wilms' tumor has been done via a transverse/chevron abdominal incision. While providing excellent surgical exposure, this incision leaves a highly conspicuous scar. Whereas the flank approach has not been favored, new protocols accept this approach as an option. Historically, the adrenal gland has been removed as part of the radical nephrectomy. Moore and colleagues reviewed their experience with 95 radical nephrectomies over an 18 year span. Of these, only one specimen demonstrated tumor in the adrenal gland. Three of the specimens, however, noted tumor within the peri-adrenal fat. As a result, they have advocated for removal of the peri-adrenal fat but sparing of the adrenal gland [Moore *et al.* 2010]. Kieran and colleagues reviewed the NWTSG-4 and

Figure 2. The utility of intraoperative ultrasonography during nephron-sparing surgical approaches.

-5 databases to look at the impact of adrenalectomy on clinical outcome. They noted adrenal involvement in 4.4% of the nearly 4000 patients but found no significant difference in the 5-year event-free survival between patients who underwent adrenalectomy *versus* those who did not. Tumor spillage rates were higher in the adrenalectomy group, which may be due to more advanced tumors or the risks associated with a more radical surgical resection [Kieran *et al.* 2013]. Overall, both studies advocate for adrenal sparing unless there is a high degree of suspicion for adrenal involvement.

More recently, literature has emerged that advocates consideration of a laparoscopic approach to surgical removal of kidneys with Wilms' tumors. While often discussed in patients who have previously undergone chemotherapy with ultimate downsizing of the kidney [Duarte *et al.* 2009], it has also been reported as possible prior to chemotherapy [Barber *et al.* 2009]. In addition, it is reasonable to assume that there will be an emerging role for a robotic-assisted laparoscopic approach for these tumors and its use has already been reported for a Wilms' tumor variant [Piotrowski *et al.* 2010].

Partial nephrectomy has long been recognized as a preferred treatment option when dealing with bilateral Wilms' tumors and those with solitary kidney or renal function impairment. This approach has also been supported by SIOP as a

treatment option for small tumors of low or intermediate histologic risk following a good response to chemotherapy, where negative surgical margins can be assured [Haecker *et al.* 2003]. Patients with predisposition syndromes, due to their increased risk of relapse, may also benefit from partial nephrectomy, even in unilateral cases [Romão *et al.* 2012]. More recently, however, the application of partial nephrectomy for unilateral tumors, without neoadjuvant chemotherapy, has been expanding and coming under increased scientific scrutiny with studies demonstrating no difference in oncologic outcomes compared with radical nephrectomy [Ferrer *et al.* 2013; Cost *et al.* 2012]. In adult renal surgery, open radical nephrectomy dominated the landscape of procedures done for renal tumors until the early part of this century. It is remarkable that for renal cell carcinomas (RCCs) in adults [Novick *et al.* 1989], when no adjuvant therapy is available, nephron-sparing surgery has continued to gain momentum as a primary option, with no untoward effect on long-term survival. Additionally, the number of cases being approached laparoscopically, including laparoscopic partial nephrectomies, are becoming more the standard of care [Smaldone *et al.* 2012]. To that end, laparoscopic/robotic radical and partial nephrectomies are undoubtedly a part of the future in therapy for Wilms' tumors, especially due to the existence of effective adjuvant therapies. Recent advances in the availability of intraoperative ultrasonography (Figure 2) and newer hemostatic and thrombotic agents

have made partial nephrectomy a viable option for adult renal tumor surgery, including during laparoscopic and robotic approaches, and can potentially be applied to children with Wilms' tumors. Caution must be used when deciding who would be appropriate for each approach, as complications of peritoneal metastases after laparoscopic nephron-sparing surgery have been reported [Chui and Lee 2011]. This is likely to become an increasingly pertinent discussion as these children live longer and become adults in a world where the rates of chronic kidney disease from numerous etiologies is on the rise [Coresh *et al.* 2007]. Second malignant neoplasms are a concern in patients treated for Wilms' tumor. However, recent reports of RCC as the secondary malignancy have further illustrated the need to strongly consider nephron-sparing approaches whenever feasible, as the future treatment of RCC will inevitably be associated with a decrease in renal function [Rich *et al.* 2010; Lazarus and Moolman, 2009; Kraushaar and Wiebe, 2005]. However, as with any technically challenging operation, only those comfortable and experienced with nephron-sparing approaches (open, laparoscopic or robotic) should attempt these newer means of treating this population to assure that safe and oncologically appropriate treatment is delivered. Also, the multicentric nature of Wilms' tumors must be taken into consideration in unilateral cases being considered for partial nephrectomy and further research into long-term oncologic efficacy is needed to determine if this is a safe option moving forward, knowing that recurrence portends a more dismal prognosis.

The treatment of anaplastic tumors, especially when found in bilateral disease, is also a matter of recent discussion. Bilateral tumors are seen in 5% of patients at presentation and diffuse anaplasia is seen in approximately 10% of patients with stage V disease. Recent subset analysis of this population suggests that partial nephrectomy should be avoided in cases of documented anaplasia, as effective therapy has yet to be identified and thus residual disease must be avoided [Hamilton *et al.* 2006]. Although not yet determined, this would suggest that completion nephrectomy should be undertaken if a partial nephrectomy specimen reveals diffuse anaplasia.

The benefits and risks of screening protocols are also a consideration in those with predisposing conditions. Screened patients with predisposing conditions seem to benefit from an earlier stage at

presentation, having more stage I tumors diagnosed compared with those not screened [Green *et al.* 1993]. However, other studies have shown no observable improvement in stage at presentation or outcomes [Craft *et al.* 1995]. As 90% of all Wilms' tumors are diagnosed by the age of 7 years, a screening protocol of abdominal ultrasonography every 3–4 months in this patient population has been generally accepted. In addition, the cost must always be considered in any screening protocol and it has been estimated that the cost per life-year saved in patients with Beckwith–Wiedemann syndrome undergoing triannual screening with ultrasound was USD\$14,740 [McNeil *et al.* 2001]. In addition to cost, the possibility of false-positive findings exists and leads to increased anxiety and expense, in addition to overtreatment for benign disease.

Recent advances and looking to the future

There are currently no serum tumor markers readily available to assess for micro-metastatic disease, treatment efficacy or recurrences in the management of Wilms' tumor. The increased use of tumor markers in other urologic malignancies (testicular, etc) has been helpful in these respects and has allowed for a less invasive means of post-treatment surveillance [Milose *et al.* 2011]. Although biochemical markers carry limitations with respect to sensitivity and specificity, they have become a standard part of practice for those managing patients with other solid organ tumors associated with reliable markers. Wang and colleagues recently used proteomic technologies to perform protein profiling of the serum of patients with Wilms' tumors and healthy controls. They described two serum proteins as possible candidates for a plausible serum marker in Wilms' tumor. Serum amyloid A and apolipoprotein C-III were found to be highly sensitive and specific in differentiating pre- and postsurgical sera, as well as serum from healthy controls [Wang *et al.* 2012]. Increasing the sensitivity of potential markers so as to be able to detect recurrences earlier could significantly impact the surveillance protocols for these patients. While exciting, the entire body of literature showing promising serum markers is scarce. Continued research in the arena of tumor markers for Wilms' tumor could significantly advance the treatment and specifically the post-treatment management of these patients.

MicroRNAs are a class of noncoding RNAs which play an important role in regulating the

expression of target gene transcription. They have been implicated in many processes, including human cancer progression and development [Griffiths-Jones *et al.* 2007]. A recently published study from Europe has suggested that pretreatment biopsy specimens could be analyzed at the molecular level to accurately predict a subset of patients who would be resistant to standard chemotherapeutic modalities, offering a more customized treatment approach [Watson *et al.* 2013]. This new field of study offers a promising advance in the management of patients with Wilms' tumors, but obviously carries the prerequisite of biopsying the tumor, which is not standard in North America.

Despite the lack of good serum markers, advances in genetic and molecular testing have allowed for improved prognostication in Wilms' tumor. Genetic syndromes leading to a predisposition to development of Wilms' tumors, while accounting for 10–15% of cases, are another area of advancement in understanding. Children with these syndromes are at risk for early and multifocal (both synchronous and metachronous) tumors. The commonest syndromes (Beckwith–Wiedemann, Denys–Drash and WAGR) are all associated with mutations on the short arm of chromosome 11 [Davidoff, 2012], and have led to an increased understanding of the genetic causes of this disease. This has helped focus genomic research in isolation of specific gene loci associated with Wilms' tumors, both in syndromic and sporadic cases. For example, the presence of a mutation in the WT1 gene on chromosome 11p13 and loss of heterozygosity (LOH) of chromosome 11p15 have recently been found to be predictive of relapse in patients at very low risk who did not receive adjuvant chemotherapy [Perlman *et al.* 2011]. Of perhaps larger impact, the NWTSG-5 study demonstrated that a LOH for genes on chromosomes 1p or 16q was associated with a worse prognosis in favorable histology Wilms' tumors and was an independent risk factor for relapse and death [Grundy *et al.* 2005]. A relative risk of recurrence of 1.56 and 1.49 respectively and a relative risk of death of 1.84 and 1.44 respectively was found, leading to changes in the NWTSG/COG protocol for adjuvant therapy, intensifying the chemotherapeutic regimen to help reduce these risks. Continued advances in the understanding of the molecular makeup of these tumors will be important moving forward to help direct therapy, intensifying in the higher risk and minimizing in the lower risk groups.

Advances in chemotherapy seem to be on the horizon as well, as refractory and recurrent Wilms' tumors continue to be a main cause of mortality and are admittedly difficult to treat. The Children's Oncology Group has reported success in clinical trials with treatment of recurrent solid malignancies in children with topotecan, with and without combination therapy with cyclophosphamide [Santana *et al.* 2003], and studies suggest treatment with vascular endothelial growth factor inhibitors may begin to play a role in the management of this disease [Rowe *et al.* 1999]. Most reports suggest an overall survival after a recurrence of only 25%. With advances in salvage therapies, the group from St Jude's reported a 5-year overall survival of over 60% in those treated after 1984 [Dome *et al.* 2002], attributed mostly to the treatment with a combination of oxazaphosphorines, platinum drugs and etoposide, as well as a large proportion of them receiving radiation therapy at the time of recurrence. Additionally, an early phase trial of combination therapy with irinotecan, vincristine, bevacizumab and temozolomide has shown promising results in Wilms' and other relapsed solid tumors in children [Venkatramani *et al.* 2013].

Final thoughts

Wilms' tumor stands as a prime example of the gains that can be achieved through protocol-driven treatment plans and careful outcomes analyses. This success, in no small part, has helped fuel a desire to continue to decrease the morbidity that results from the standard management. Principles that apply to the management of adult renal malignancies are increasingly being explored for their role in pediatric renal oncology. It is reasonable to speculate that robotic surgery and focal ablative therapies, which have become common treatment modalities for adult renal malignancies, will be increasingly investigated as options for the management of Wilms' tumor.

It remains important to recognize that these surgical advances need to be carefully evaluated for their suitability to pediatric patients. Minimally invasive surgical techniques carry the potential to increase the risk of tumor spillage, which increases tumor stage and lowers survival. The balancing of surgical progress, targeted radio- and chemotherapeutic modalities and preservation of outcomes will be among the main challenges for groups like NWTSG/COG and SIOP in the years to come.

Key points

- (1) Significant advances have been made in the management of Wilms' tumors, mostly as a result of collaborative efforts and a multidisciplinary approach to research and treatment protocols.
- (2) The survival of this disease has become so good that morbidity and long-term effects are considered as much as oncologic control in this day and age.
- (3) Many advances continue to take place and the future of the management of Wilms' tumor continues to get brighter.

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Conflict of interest statement

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