

Wilms Tumor “state-of-the-art” update 2016

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Abstract Despite an impressive increase in survival rate over the last decades, there is still a need to improve the survival of specific subgroups of Wilms tumor (anaplastic, metastatic, bilateral) and to decrease the late effects of treatment in term of renal function and heart toxicity. We aim to explore new areas of improvement, from diagnosis to treatment: in the field of radiology the increased use of MRI and exploration of its diffusion weighted imaging capabilities to predict WT histology at diagnosis and for preoperative assessment; in biology the emergence of new biomarkers that could be integrated into the decision-making process; and surgical techniques with more accurate indication of nephron sparing surgery that is no longer reserved for bilateral WT and the minimally invasive approach. The long-term outcome of patients with WT should thus be a strong indicator of the improvement in adapting and personalizing the treatment to each individual.

Keywords: Wilms tumor, biology, MRI, minimally invasive surgery, bilateral disease, NSS

Introduction on general considerations in Wilms Tumor

Impressive progress has been made for children with Wilms Tumor (WT) with long-term cure rates greater than 85% collectively. A significant amount of this success is due to two multidisciplinary cooperative groups, Société Internationale d'Oncologie Pédiatrique (SIOP) and Children's Oncology Group (COG-formerly the National Wilms Tumor Study Group [NWTSG]).¹ Although there are some philosophical differences in approach, these groups have conducted a series of well-designed clinical and biological studies that have provided a large body of evidence-based knowledge to help establish the optimal treatments for children WT.²⁻⁵ Recent investigations have looked at the impact of centralized surgical, radiological and pathological review; in vivo histological response through MRI research, response-based outcomes, new biomarkers (somatic and genetic predisposition) and impact of nephron sparing surgery (NSS) in selected cases. The goal is to develop a more individual risk-adapted approach that optimizes event free survival (EFS) and minimizes late effects. Despite these advances, challenges remain: a significant number of children with WT (e.g. anaplastic histology or stage IV disease) have unacceptable EFS and/or late effects. The purpose of this state-of-the-art review is to present the current and future status of the biological understanding, diagnosis and treatment of a child with WT.

Presentation Diagnosis and tumor staging: comparative and innovative aspects of diagnosis

Most children with WT present with an asymptomatic palpable mass found by a parent or physician. Up to 20% of children present with hematuria, hypertension, fever and/or flank pain.⁶ Rarely a child can present with an acute abdomen secondary to tumor rupture and uncontrolled bleeding. Health systems and access to health are important aspects of how a disease is diagnosed. An interesting study by Pritchard-Jones et al compared the health system of Germany and the United Kingdom (UK) with respect to the diagnosis of renal tumors in children.⁷ In the UK primary care givers are generalists (“family doctors”) whereas in Germany children have direct access to pediatricians. Pritchard-Jones et al demonstrated that in the UK, children present with a larger size tumor and later stage than those in Germany. There was a 3% difference in EFS/ overall survival (OS). The small sample size and generally effective treatment regimens for children with WT likely played a role but the results are though provoking nevertheless. In Germany, a greater proportion of WT are detected incidentally whereas in the UK, the majority presented with tumour-related symptoms, suggesting that the primary care system for children in the UK may not be ideal for early detection of renal tumors.

Ultrasound (US) with doppler and CT scan or MRI are used to define the origin, extent and metastatic sites for renal masses. For many years chest X-Ray was the imaging study to assess pulmonary metastasis, however this has largely been replaced by CT scan. When CT was first used, it resulted in smaller lung nodules being detected, creating both diagnostic and therapeutic challenges.⁸⁻¹¹ Alternatively it led to realization that not all patients with pulmonary disease required pulmonary radiation. Over the last several years, MRI imaging of the abdomen has increased over CT scan, however CT scan of the chest is still preferred to assess metastatic lung disease.

SIOP protocols and COG protocols differ in the initial treatment approach to the tumors. SIOP protocols prefer initial chemotherapy (with or without a biopsy to determine pathology) followed by surgery and adjuvant therapy with chemotherapy and/or radiation. Staging, risk assessment in most cases is done after the initial surgery. COG protocols prefer an initial nephrectomy followed by adjuvant chemotherapy and/or radiation if required. Final abdominal and disease staging is done after surgery but the factors used for staging classification are different (Table 1). Risk stratification for both protocols also includes different factors and use of biological markers and response. Furthermore although many of the chemotherapy drugs are similar, the timing and dosing of the chemotherapy are different in each protocol and in COG protocols surgery alone can be the only therapy. As expected over the years, these differences in approaches have often resulted in debates about “which is better”, however in reality both philosophical approaches have excellent EFS and OS for the standard risk tumors and more challenges in treating higher risk patients. What is more useful in the authors opinion is to examine how each approach has improved understanding of tumor biology and treatment as well as stimulating research. For example one area of controversy has been the impact of a diagnostic biopsy on the risk of local recurrence and tumor staging. Patients treated on a COG protocol who underwent an open or imaged based renal biopsy because the treating team felt the tumor was unresectable have always been treated as stage III diseases. In addition those patients with a large intra-operative tumor spill were also treated as stage III disease. Alternatively if a patient underwent an intraoperative biopsy and at the same time had a nephrectomy, or during surgery had a small rupture these patients were treated as stage II on COG protocols. A paper by Shamberger et al examined surgical factors that predicted local recurrence from the NWTS-4 study.¹² In a nested case control study, it showed local tumor recurrence was significantly increased if there was a tumor

spill regardless of small or large and if there was an intraoperative biopsy followed by a nephrectomy. Based on these results, the most recent COG studies made all spills (small or large) and any intraoperative biopsy a stage III criterion. This resulted in 11 patients (of approximately 400) being upstaged from II to III.¹³

SIOP studies have also examined the impact of biopsy on local recurrence. SIOP currently does not make all patients stage III when they biopsy their patients. Interestingly, UK patients are all biopsied at diagnosis by percutaneous cutting needle biopsy, preferably with a co-axial technique to obtain multiple cores. In the UKW3 trial running from 1991 to 2001, the two approaches were compared, the SIOP approach being associated with a biopsy at diagnosis (in contrast to the usual practice in Europe). This study showed an association between biopsy and any local relapse following univariate analysis but this lost formal statistical significance once anaplastic histology and increasing tumor size were taken into account. For distant relapse, biopsy was less clearly associated in univariate analysis. Indeed, older age and anaplastic histology were the overriding factors associated with metastatic relapse.¹⁴ As the small number of events limited the multivariate analysis, the study was extended to the whole SIOP 2001 trial and suggested that in SIOP protocols an upfront biopsy does not increase the risk of local relapse.¹⁵ How these results will affect future staging decision in COG studies within the groups' treatment and risk stratification is unclear.

Risk based therapy for renal tumors requires appropriate staging and risk stratification. WT also need both an abdominal stage and a disease stage. This can sometime be challenging for an institution which may only treat one or two cases each year. To help address this issue the COG study ARENO3B2 study (biology and risk classification) provided real time (within 7 days) central review of pathology, radiology and surgery followed by a risk classification for a

therapeutic study.¹⁶ This process showed that up to 20% of patients may have a change in interpretation based on central review as compared to institutional review. To date this has been done with over 6000 patients. SIOP has used central review to improve the quality of staging and histological risk classification by centralized national and international pathology panel review.¹⁷ National review of imaging at diagnosis has been performed in Germany, and more recently in the UK, and is planned as part of the forthcoming SIOP-RTSG “UMBRELLA” study.

The spread of MRI as the best imaging for diagnosis and follow-up has pushed its use as a very useful research tool in accurately predicting WT histology with the development of diffusion-weighted images (DWI). DWI is a MR technique that provides information on the biophysical properties of tissues such as cell density, microstructure and microcirculation .¹⁸ By tracking the microscopic rate of water diffusion within tissues, it defines an apparent diffusion coefficient (ADC) that showed inverse correlation with tumor cellularity.¹⁹ Very recently, it has been shown that high-risk blastemal-type WT had a lower ADC value compared with intermediate-risk stromal, regressive and mixed-type WT and that no significant difference in ADC exists between blastemal-type and intermediate-risk epithelial-type WT .²⁰ The predominant viable tissue subpopulation in every stromal-type WT underwent a positive shift in the mean ADC value after chemotherapy [Hales 2015].²⁰ Such evaluation in the pre-operative chemotherapy phase may be of value in planning the timing of nephron-sparing surgery, especially in bilateral tumours.

Approaches to surgical treatment in unilateral Wilms tumor, including metastatic disease

What are the goals of the surgery and how it impacts further therapy?

The goals of surgery are to perform a safe operation, remove the kidney without intraoperative spill, sample lymph nodes, and document all findings, such as preoperative or intraoperative tumor rupture, extension into other structures and the presence of peritoneal metastasis. *Failure to sample lymph nodes is the most common mistake made by surgeons and without it, the child cannot be properly staged.* Some children have very favorable tumors and may not need chemotherapy or radiation therapy to achieve a cure, BUT the lymph node status must be known. Preoperative rupture and peritoneal metastasis mandate whole abdomen radiation and increased chemotherapy. Intraoperative spill from the tumor, ureter or vascular system mandates flank radiation and increased chemotherapy. Failure to give radiation/chemotherapy in these situations increases the risk of relapse. Obtaining central venous access where appropriate with a tunnel catheter or port should also be done at the same time if possible. A discussion with your anesthesia team about post-operative pain management should also occur prior to surgery.

Standard technique

Surgery is usually performed through a transperitoneal transverse approach, allowing a complete exposure of the abdomen. The essential difference between COG and SIOP approach is the time for surgery, upfront for COG and after first line chemotherapy for SIOP. The standard procedure is a total nephro-ureterectomy with lymph nodes (LN) sampling. Although it has been proven that the absence of LN sampling is a risk factor for recurrence ¹², there are no formal recommendations for the number to sample. In a recent retrospective study from COG, a minimum of seven LN sampled increased the chances of detecting a metastasis but after controlling for tumor histology and stage, the number of LNs sampled did not predict EFS

variations .²¹ In SIOP 93-01 study, change in tumor volume under preoperative chemotherapy was not a predictor for LN status at surgery, although larger initial volume was associated with a higher risk of LN invasion .²²

The major risk of surgery is the rupture of the tumor with intraoperative spill into the abdomen. This risk has been assessed at 9.7% for 1131 patients enrolled in AREN03B2 whereas in SIOP studies, it has been estimated between 2.8 and 6% .^{23,24} The difference is likely explained by tumor shrinkage and less vascularity following chemotherapy that renders the tumor firmer to handle. Not all SIOP tumors are biopsied prior to initiating chemotherapy. Misdiagnosis rates as high as 8% and use of inappropriate treatment in 5.2% have been reported although this has dropped to below 1% recently ^{17,25,26]}

Vascular extension

WT extension may occur through the renal vein into the inferior vena cava and up to the atrium. In large published series, caval extension was reported between 2% and 5% and atrial extension in 0.2% to 1.2% .^{27,28} Intraoperative management of a tumor thrombus requires proximal and distal vascular control. In case of renal vein thrombus, the thrombus should be gently milked out although extensive thrombus may be best managed with a venotomy to facilitate thrombus mobilization .²⁹ Sometimes, the thrombus adheres to the intimal layer of the vein, leading to a piecemeal removal that will be responsible for upstaging the tumor and increasing the burden of treatment with possible risks on long-term morbidity . The most important is to manage these patients with a multidisciplinary team, including particularly cardiac surgeons to perform cardiopulmonary bypass if the thrombus is up to the atrium .³⁰

Metastatic extension

Metastatic extension is most often to the lungs or the liver and complete metastatic remission may be achieved with chemotherapy alone. These patients have the better outcome. There are few data on the role of complete surgical excision of persistent but responding metastases, though this is usual practice in some centers. There are more convincing data on the benefit of radiotherapy in slowly responding lung metastases. The major challenge is defining clinically significant lung metastases at initial presentation owing to the increased quality of CT scan that finds pulmonary nodules never seen before on X-ray. The impact of these "CT-only" nodules is still to be determined although a recent COG analysis found that patients with CT-only lung lesions may have improved EFS but not OS from the addition of doxorubicin but do not appear to benefit from pulmonary radiation.³¹ In SIOP 2001 study, EFS and OS were inferior for patients with "CT-only" nodules compared to those without any doubtful nodules at diagnosis but the outcome was not significantly better in those treated with 3-drug chemotherapy.¹⁰ However, both EFS/OS of the "CT-only" group were intermediate between those with localized disease and normal chest CT scan and those with metastatic disease visible on CXR. In the recent COG trial (ARENO533) one aim was to withhold pulmonary radiation for those patients who had complete resolution of pulmonary disease after 6 weeks of DD4A. 119/302 patients (39%) responded. Twenty four patients recurred within 2 years with 22 in the lung, one just in the abdomen and one had a second malignancy. Thus 95/119 avoided pulmonary radiation. There were also some patients who had stable disease or had only 1 or 2 remaining lesions. It is possible that some of these patients had benign lesions, necrotic WT, or well-differentiated WT that may not require radiotherapy and could be cleared by thoracoscopy with small lesions

sometimes requiring image-guided localization. Future research is needed to investigate this possibility.

Nephron sparing surgery in unilateral WT

Partial nephrectomy is well established for bilateral WT but an area of controversy for unilateral WT. The goal of preserving renal function is laudable but has to be balanced with the exceedingly low rate of long-term renal dysfunction after total nephrectomy³²⁻³⁴ and the equivocal high-rate of stage III patients due to positive margins.^{35,36} Another consideration is that the main causes of renal failure in children with WT are disease progression and exposure to abdominal radiation. Only 3 to 9 % of non-syndromic patients treated according to SIOP and COG seem to fulfill NSS criteria.^{36,37} New guidelines from the next SIOP protocol have defined strict indications of NSS for unilateral WT: unifocal tumor restricted to one pole of the kidney with an estimated volume of less than 300 ml at diagnosis, no preoperative rupture, no venous or local extension and enough remnant healthy kidney tissue to avoid hyperfiltration.³⁸

Place of laparoscopy

The decision to use minimally invasive surgery (MIS) for WT should be made after weighing risks and benefits. From an early experience of 24 WT resected by transperitoneal laparoscopy within SIOP 2001, the authors concluded at the feasibility of the procedure, though challenging and requiring huge expertise by operating surgeons.³⁹ Recognized indications for MIS in WT were small tumors not crossing the midline, i.e. the lateral edge of the vertebra at the time of

surgery being a certain limit, that have no venous extension, no adhesions to adjacent organs or preoperative rupture or spillage. MIS was not performed for tumors diameter bigger than 8 cm but size in itself was not considered as an absolute contra indication .⁴⁰ These criteria are similar to those for NSS but NSS overcomes MIS and should be performed each time it is feasible. As for open approach, lymph nodes should be taken away safely and properly

Horseshoe kidney

The incidence of horseshoe kidney in WT patients approximates 0.5% [Neville 2002]. The main problem is the recognition at diagnosis of the presence of horseshoe kidney on imaging to fully assess the precise anatomy of both tumor and kidney for the most accurate surgical planning. Horseshoe kidney is not a contra indication to upfront surgery but may exhibit higher surgical complications rate with injuries to the collecting system .⁴¹

Surgical Complications

Intestinal obstruction is the most frequent complication (5.1%), followed by extensive hemorrhage (1.9%), wound infection (1.9%), and vascular injury (1.5%). Factors associated with an increased risk of complications include intravascular tumor extension nephrectomy performed through a flank or paramedian incision tumor diameter of 15 cm or larger.

Surgery only for patients with WT

A review of NWTS1-4 found that the use of adjuvant therapy did not enhance the already excellent outcomes of children age 2 or younger with stage 1 favorable histology WT with

tumors less than 550 grams.⁴² For NWTS-5, if a child met these criteria, a surgery only arm was offered.⁴³ The 8-year EFS for surgery-only was 84%; for the patients receiving EE-4A chemotherapy, it was 97% (P=0.002). One death was observed in each group. The estimated 5-year OS was 98% and 99% respectively (P = 0.70). Thus, 85% of the infants avoided any chemotherapy, while those who did receive it for relapse, were treated with three agents, vincristine, actinomycin D and doxorubicin (DD-4A), resulting in an OS equivalent to the group who received chemotherapy. The most recent COG study ARENO532 confirmed this observation with 116 patients treated without chemotherapy, with a 4-year EFS and OS of 89.7% (84-95%) and 100% respectively.⁴⁴

Risk stratification and overall oncological therapy – who gets what chemotherapy and the indications for radiotherapy (545 words)

Risk stratification is a key factor to determine the most appropriate treatment for patients with WT for both COG and SIOP. The difference lies in that COG protocols include age at diagnosis, tumor weight and loss of heterozygosity (LOH) of 1p and 16q in favorable histology (FH) patients in their decision-making process at diagnosis. The most recent series of unilateral WT studies have just been completed and the 4 year EFS and OS outcomes are shown in Table 2. SIOP protocol uses stage and histological risk group assigned by assessment of the tumour's response to neoadjuvant chemotherapy to stratify patients but the recent emergence of 1q gain as a new biomarker of recurrence risk is likely to change the future consideration of biomarkers in the determination of subsequent therapeutic regimens.^{45,46} Before considering 1q gain for clinical use, the heterogeneity of its expression within the tumor needs to be fully assessed and

its prognostic significance needs to be validated in an independent sample set.⁴⁷ Recently, several new Wilms tumour genes have been discovered . This has opened up the possibility of further biomarkers for risk stratification with implications for genetic predisposition to WT and consequences for long term renal function.⁴⁸

Despite these findings, challenges to better treat WT with non-FH, stage IV and V WT and relieve the burden of chemotherapy and radiotherapy in more favorable groups remain. The results of the international, multicenter, open-label, non-inferiority, phase 3, randomized SIOP WT 2001 trial, comparing children with stage II-III intermediate-risk WT assessed after delayed nephrectomy showed that doxorubicin does not need to be included in treatment of stage II-III intermediate risk WT when the histological response to preoperative chemotherapy is incorporated into the risk stratification, thus limiting late cardio toxicity.⁴⁹

However, the combination of unique biological identifiers that would explain the relapse of stage II patients who do not have known elevated risk of recurrence at diagnosis is pending. The current COG trial AREN0532 protocol is examining the impact of intensifying therapy and adding doxorubicin for stage II FH WT with combined LOH 1p and 16q alone.

Diffuse anaplasia has been the first identified risk factor for recurrence and several National WT Studies (NWTS) have proved the efficacy of cyclophosphamide and etoposide in addition to a 3-drug regimen associated vincristine, dactinomycin and doxorubicin. In NWTS-5, 4-year relapse-free survival for patients with stages II-IV diffuse anaplastic WT (DAWT) treated with vincristine, doxorubicin, cyclophosphamide, and etoposide, plus radiotherapy (Regimen I) was 55%. AREN0321 showed that Regimen UH-1, a more intensive regimen containing carboplatin in addition to agents used in Regimen I, and Regimen UH-2 (UH-1 plus Vincristine, Irinotecan)

for patients with stage II-IV DAWT improved EFS (69%, 95%CI 56-80%) albeit with considerable increased cardiac, lung and hepatic toxicity.⁵⁰ This high toxicity leads to look for novel therapeutic approaches, with a more favorable therapeutic benefit ratio, such as integration of biologic therapies, rather than via chemotherapeutic intensification, particularly for patients with advanced-stage disease and perhaps with biologically defined subsets, potentially those with p53 mutation or loss.^{51,52}

Stage IV WT means spread of the disease beyond the kidney, most often to the lungs. Treatment goals are to control the local/regional extension of the disease and the management of metastases with both chemotherapy and radiotherapy. Concerns about the treatment toxicity and findings of SIOP suggest that radiotherapy omission in rapid early responders might be feasible. The current COG study for stage IV WT (AREN0533) tested dose intensification for patients with slow incomplete response when CT lung metastases were assessed at week 6 and subsequently treated with regimen M (vincristine, dactinomycin, doxorubicin and cyclophosphamide/etoposide) and showed an estimated 3-year EFS and OS of 88% (95%CI: 81-93%) and 92% (95%CI: 86-96%) respectively, that favorably compared with historical controls.⁵³

Surgery for Bilateral Wilms Tumor and Unilateral High Risk Patients

Children with BWT or a predisposition to bilateral tumors are a group with poor EFS (<70%) and a higher rate of renal failure (14% compared to <1% for unilateral patients). Although clinical trials have been performed in children with unilateral WT, it was not until 2009 that the first formal BWT study was started. The Children's Oncology Group Study AREN0534 is the first multicenter, prospective, protocol-driven study of children with BWT, recommending

immediate use of 3 drug (VA + doxorubicin) to test if this would maximize the likelihood for NSS. The SIOP 2001 trial also included a recommended treatment protocol for bilateral WT with 2 drug preoperative chemotherapy. Neither study has yet reported. Both groups recommend an attempt at NSS after 2-4 cycles. More than 4 cycles is not associated with an improved outcome and may increase the risk of anaplasia. Biopsy is not necessary in most cases before initiation of chemotherapy, but is strongly recommended in cases where there are unusual features (e.g. over the age of 8 years, atypical intra-abdominal findings on imaging). In 20 % of BWT cases, the pathology is not the same bilaterally; therefore it is important to sample both kidneys. After two cycles of chemotherapy the tumors should be re imaged to assess response if there is poor (<50%) response, bilateral biopsies should be performed to determine whether there is anaplastic or rhabdomyomatous changes, though it should be noted that needle biopsy often fails to detect diffuse anaplasia in unilateral cases.⁵⁴

MRI and 3D imaging is very important in assessing response to chemotherapy and resectability. It is important to note that the tumor compresses normal renal parenchyma and that radiographic tumor characteristics may underestimate the proportion of BWT that are amenable to NSS.⁵⁵ MRI has become more widely used in cases of BWT especially in those with predisposition syndromes such as WAGR/BWS. The children with inherently abnormal kidney architecture are predisposed to nephrogenic rests and thus WT. Due to the sensitivity of MRI the abnormal kidney architecture can appear as “lesions” which can be confusing. These lesions are usually less than a cm and will not change on repeat MRI. These lesions are particularly relevant when deciding whether to start therapy. Intraoperative US at the time of surgery can help differentiate tumor from just abnormal glomeruli.

There are a variety of techniques in the literature to help with operative resection. In many cases simple manual compression is adequate.⁵⁶⁻⁵⁸ Other adjuncts include vessel clamping, hypothermia, perfusion solution (not widely used and in small children may promote vascular thrombosis), and in rare cases ex vivo resection and autotransplantation. The kidney and tumor should be completely exposed to identify and isolate mesenteric and renal vessels. Tension on the vessels is associated with venous thrombosis. The tumor is excised by scoring the renal surface and carefully separating the tumor and a surrounding rim of normal parenchyma from the adjacent tissue. Intraoperative ultrasound can be used to delineate the tumor in situ to help define resection margins both before and after the tumor has been removed. Enucleation is okay with favorable histology but the kidney will need to be irradiated to prevent recurrence. If the child has anaplastic histology, the margins need to be negative. For intracalyceal tumors, ureteroscopy is helpful to ensure that all involved urothelial tissue has been resected. Collecting system entry is managed with antegrade placement of a ureteral stent, closure of the collecting system with absorbable suture, and placement of external drains. If possible, the kidney is folded together over thrombin-soaked gel foam, and approximated with interrupted horizontal mattress sutures.

Long term outcomes, what influences them and how can surgery play a role as part of first line therapy in mitigating the use of therapies that carry these risks

The long-term outcome of patients with WT is underscored by the burden of treatment received. Overall outcome over the different study groups are excellent but some specific subgroups of patients need to be more closely investigated and collaborative studies will be of major benefit owing to the small number of patients to include in each (anaplastic WT, BWT, and metastatic

WT). The role for a surgeon is to perform a complete operation. Failure to sample lymph nodes is the most common mistake by surgeons. In addition avoiding an intraoperative spill is critical as this can influence treatment and subsequent long term effects.⁵⁹

Long-term renal function is of major concern, not only for BWT but also for unilateral WT. Among 9,237 patients enrolled by North American institutions on 1 of 5 NWTS protocol studies between 1969 and 2002, the cumulative incidence of end stage renal disease (ESRD) due to chronic renal failure 20 years after WT diagnosis for either type in non-syndromic patients was 1.7%.⁶⁰ For patients with non-syndromic unilateral FH histology WT, it was 0.6%. For ESRD due to progressive BWT, the incidence was 4.0% at 3 years after diagnosis in patients with synchronous BWT and 19.3% in those with metachronous BWT. The risk factors associated with ESRD due to chronic renal failure were stromal predominant histology (HR 6.4, 95% CI 3.4, 11.9; $p < 0.001$), intralobar NR (HR 5.9, 95% CI 2.0, 17.3; $p = 0.001$), and diagnosis at less than 24 or 48 months (HR 1.7 and 2.8 respectively, $p = 0.003$)⁶¹ For *WT1* syndromic patients, 20-year ESRD cumulative incidence was 82.7% for Denys-Drash, 43.3% for WAGR and 9.4% in patients with genito-urinary anomalies.⁶¹ In addition, the wider availability and accuracy of genomic technologies may identify more WT genes and molecular fingerprints with unknown implications for renal function into adulthood.

Conclusion Despite the good overall survival outcomes of most patients with WT, greater efforts are still needed to decrease the late effects of surgery combined with more accurate risk-stratified use of chemotherapy and radiotherapy. The emerging very long-term follow-up data, particularly in the light of newly discovered genetics, will increase our knowledge of WT treatment burden

and predisposing factors for renal function and toxicity. More accurate radiological assessment in the preoperative phase with the development of DWI-MRI allowing a better surgical planning of the resection (total nephrectomy versus NSS) and also determining the best timing for surgery in both unilateral and BWT should add great value in adapting and personalizing treatment modalities for each patient. This could be ultimately achieved through international collaboration and increased centralized data collection. In this setting, surgeons must be more aware and cognizant of preoperative and postoperative treatment possibilities to achieve the most optimal results for the treatment of patients with WT.

Future studies may examine:

1. The biological basis of 1-q gain and its role as an adverse prognostic biomarker to stratify patients
2. Can the surgery only approach be expanded to a wider group of patients based on recent biological insights?
3. What is the role of molecularly targeted agents in the treatment of very high risk and relapsed WT patients ?
4. Specific surgical questions may include
 - a. What are the minimum number of lymph nodes need to properly asses the risk of disease
 - b. Is there a role for thorascopic surgery to avoid pulmonary radiation in children with stage IV WT who partially respond to three drug chemotherapy
 - c. The long term outcomes and impact on renal function of partial nephrectomy in unilateral WT needs further study, and in relation to the underlying genetics

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Figure and Table Legends

Table 1- Staging systems for SIOP and COG

Table 2 -4 year event free and overall survival of COG studies ARENO 532, 533 and 321.

SIOP and COG Staging Systems

SIOP Staging

| Stage | Criteria |
|-------|--|
| I | The tumor is limited to the kidney or surrounded with a fibrous pseudocapsule if outside the normal contours of the kidney and is completely resected. The tumor may be protruding (bulging) into the pelvic system and dipping into the ureter, but it is not infiltrating their walls. The vessels of the renal sinus are not involved. Intrarenal vessels may be involved. Presence of necrotic tumor in the renal sinus or peri-renal fat does not upstage to stage II. Percutaneous cutting needle biopsy is allowed. |
| II | The tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat, but is completely resected. The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma, but it is completely resected <i>en bloc</i> . The tumor infiltrates adjacent organs or vena cava, but is completely resected. Percutaneous cutting needle biopsy is allowed. |
| III | Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopic tumor remains postoperatively). Any abdominal lymph nodes are involved. Tumor rupture before or during surgery (irrespective of other criteria for staging). The tumor has penetrated the peritoneal surface. Tumor implants are found on the peritoneal surface. The tumor thrombi present at resection, margins of vessels or ureter transected or removed piecemeal by surgeon. The tumor has been surgically biopsied (wedge or open biopsy) prior to preoperative chemotherapy or surgery. |
| IV | Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region. |
| V | Bilateral renal tumors at diagnosis. Each side has to be substaged according to the above classifications. |

COG Staging

| Stage | Criteria |
|-------|---|
| I | The tumor is limited to the kidney and has been completely resected The tumor was not ruptured or biopsied prior to removal. No penetration of the renal capsule or involvement of renal sinus vessels. |
| II | The tumor extends beyond the capsule of the kidney but was completely resected with no evidence of tumor at or beyond the margins of resection. There is penetration of the renal capsule OR There is invasion of the renal sinus vessels |
| III | Gross or microscopic residual tumor remains postoperatively including: inoperable tumor, positive surgical margins, tumor spillage surfaces, regional lymph-node metastases, positive peritoneal cytology or transected tumor thrombus The tumor was ruptured or biopsied prior to removal. |
| IV | Haematogenous metastases or lymph-node metastases outside the abdomen (eg, lung, liver, bone, brain). |
| V | Bilateral renal involvement is present at diagnosis and each side may be considered to have a stage. |

Table 2 Outcomes of COG studies 532, 533 and 321

| Study | # Patients | Chemotherapy Regimen | 4 year EFS/OS |
|--|-------------------|-----------------------------|---------------------------------|
| Very Low Risk Surgery Only FH (Study ARENO532) | 116 | none | EFS 89.7 OS 100% |
| Stage I and II Combined 1p and 16 q LOH positive FH (Study ARENO533) | 35 | DD4A | EFS 83.9% OS 100% |
| Stage III Combined 1p and 16 LOH positive (Study ARENO533) | 52 | M plus XRT | EFS 91.5% OS 97.8% |
| Stage IV lung nodules incomplete responders (Study ARENO533) | 183 | M plus XRT | EFS 88% OS 92% |
| Stage IV lung nodules complete responders at 6 weeks (Study ARENO533) | 119 | DD4A | EFS 80% OS 98.3% |
| High Risk Wilms Tumor AH Stage II Stage III Stage IV (Study ARENO321) | 23 24 46 | Revised UH-1 +/- XRT | . OS 85% OS 74% OS 46% |

Legend

FH= Favourable Histology Wilms Tumor

AH= Anaplastic Histology Wilms tumor

DD-4A = Vincristine, dactinomycin doxorubicin

Regimen M= Vincristine, dactinomycin doxorubicin cyclophosphamide and etoposide .

Revised UH-1= Vincristine, dactinomycin doxorubicin cyclophosphamide carboplatin,etoposide and radiation

XRT= radiation