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Multidisciplinary Treatment Strategies for Wilms Tumor: Recent Advances, Technical Innovations and Future Directions

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Significant progress has been made in the management of Wilms tumor (WT) in recent years, mostly as a result of collaborative efforts and the implementation of protocol-driven, multimodal therapy. This article offers a comprehensive overview of current multidisciplinary treatment strategies for WT, whilst also addressing recent technical innovations including nephron-sparing surgery (NSS) and minimally invasive approaches. In addition, surgical concepts for the treatment of metastatic disease, advances in tumor imaging technology and potentially prognostic biomarkers will be discussed. Current evidence suggests that, in experienced hands and selected cases, laparoscopic radical nephrectomy and laparoscopic-assisted partial nephrectomy for WT may offer the same outcome as the traditional open approach. While NSS is the standard procedure for bilateral WT, NSS has evolved as an alternative technique in patients with smaller unilateral WT and in cases with imminent renal failure. Metastatic disease of the lung or liver that is associated with WT is preferably treated with a three-drug chemotherapy and local radiation therapy. However, surgical sampling of lung nodules may be advisable in persistent nodules before whole lung irradiation is commenced. Several tumor markers such as loss of heterozygosity of chromosomes 1p/16q, 11p15 and gain of function at 1q are associated with an increased risk of recurrence or a decreased risk of overall survival in patients with WT. In summary, complete resection with tumor-free margins remains the primary surgical aim in WT, while NSS and minimally invasive approaches are only suitable in a subset of patients with smaller WT and low-risk disease. In the future, advances in tumor imaging technology may assist the surgeon in defining surgical resection margins and additional biomarkers may emerge as targets for development of new diagnostic tests and potential therapies.

Keywords: nephroblastoma, kidney neoplasm, surgical oncology, nephron sparing surgery, minimal invasive surgery, nephrectomy, therapy, biomarkers

INTRODUCTION

Renal solid tumors account for ∼5% of all childhood tumors with 8.3–15.1 cases per one million person-years worldwide (1–3). Over 90% of these renal malignancies are Wilms tumors (WT; syn. nephroblastoma) presenting at a peak incidence of 2–3 years of age (4). The majority of cases are sporadic, whereas 10–15% present in relation to genetic malformation syndromes predisposing to tumor development such as Beckwith-Wiedemann, Denys-Drash or WAGR (i.e., WT, aniridia, genitourinary anomalies and range of intellectual disabilities) (5).

The first successful nephrectomy for a WT in a 2-year-old boy by Thomas Richard Jessop in 1877 (Leeds, England), the first histopathological description of WTs by "Max" Wilms in 1899 (Leipzig, Germany) as well as the introduction of radiation therapy and cytotoxic chemotherapy in the 1950s and 1960s are the foremost origins of what has led to today's treatment standards for WT patients (6–8). Collaborative studies by the National Wilms Tumor Study Group (NWTS)/Renal Tumor Committee of the Children's Oncology Group (COG) in North America and by the International Society of Pediatric Oncology (SIOP) in Europe laid the groundwork for protocol-driven treatment plans. Today, a combination therapy of surgical resection, adjuvant and/or neoadjuvant chemotherapy and in some cases irradiation achieves an overall survival (OS) exceeding 90% for localized WT, 75% for metastasized WT and 50% in the case of WT recurrence (9).

Despite the good outcome for the majority of patients with WT, some remain at risk for poor survival or have a treatment related long-term risk of side effects (10). Risk factors for reduced event-free survival (EFS) and OS are: more than two-third blastemal cells within the tumor after induction chemotherapy (SIOP protocol, 8–9% of patients), anaplastic histology (5–10% of patients), loss of heterozygosity (LOH) at chromosomes 1p/16q (12 and 17% of patients, respectively), (non-resolving) metastasis (12–17% of patients), bilateral WT (5–8% of patients) and recurrent WT (20% of patients) (11–19). These patients need intensive chemotherapy and radiation therapy, thus putting them at risk for treatment related side effects. Overall, 25% of WT patients suffer from subsequent side effects such as renal failure, cardiac toxicity, pulmonary restrictive disease, infertility and secondary malignancies (20, 21).

Recent and ongoing clinical trials drive treatment strategies toward a more and more risk-based and individualized therapy approach. The identification of personal risk factors will eventually confine intensive therapy to smaller subgroups of patients, thus reducing chemotherapy-related and radiation-related side effects for others without reducing survival.

This article provides a comprehensive overview of current multidisciplinary treatment strategies for WT, whilst also addressing recent technical innovations including nephron-sparing surgery (NSS) and minimally invasive approaches. In addition, surgical concepts for the treatment of metastatic disease, advances in tumor imaging technology and potentially prognostic biomarkers will be discussed.

CURRENT DIAGNOSTIC WORK-UP AND STAGING

The incidental palpation of an asymptomatic abdominal mass is the most common presentation of a child with WT. In only 20% of cases, the presentation consists of malaise, pain, fever, gross hematuria or renal hypertension (22, 23). Rarely, an acute abdomen due to tumor rupture is the first presentation of a WT. In other cases, WT is diagnosed by routine ultrasonography in patients with conditions predisposing for WT such as Beckwith-Wiedemann syndrome or in patients in whom metachronous metastasis is suspected.

Abdominal ultrasonography is the first diagnostic choice to confirm a renal mass. To differentiate a WT from other renal masses (e.g., kidney malformations) or masses in close proximity to the kidney (e.g., neuroblastoma), abdominal MRI- and CT-scans are the current standards of imaging. Urine analysis for catecholamines and metaiodobenzylguanidine scintigraphy can also help to discriminate neuroblastoma from WT. Further work-up includes laboratory tests screening for tumor-associated anemia and thrombocytopenia, kidney malfunction, altered liver enzymes in case of liver metastasis and disrupted coagulation such as WT-acquired von Willebrand disease.

In the NWTS-4, patients with a diagnostic biopsy had a higher risk for local recurrence leading to an upgrading of a stage I and II tumor to a stage III tumor in later protocols (24). An upstaging is not recommended in the SIOP protocol, as studies have not confirmed local recurrence (except in case of open tumor biopsy) (25). In general, biopsies should only be considered when a tumor different to WT is suspected. This is usually the case when renal tumors present at an age older than 6 years, the mass is completely extra renal or imaging shows distinct calcifications suggesting a histology other than WT (26).

MRI, CT and ultrasound scans contribute to pretreatment staging. The contralateral kidney should be screened for synchronous bilateral disease. Aortocaval and hilar lymph nodes, lung and liver need to be screened for metastasis. CT scans (with or without contrast) have replaced plain X-ray images of the chest to detect lung metastasis (27–30). Contrast MRI (or CT) and ultrasound examinations will need to assess extension of the tumor into the renal vein and vena cava. Echocardiography is warranted to assess heart function and the venous extension of a tumor thrombus into the atrium (31–33).

Current staging systems of WT are based on imaging and surgical findings such as local tumor stage (e.g., complete vs. incomplete resection, perioperative tumor rupture or lymph node metastasis), bilateral disease and hematogenous metastasis to the lung and liver (rarely bone, brain or other sites) (**Table 1**). The histopathology of the resected tumor defines the prognostic risk group. The NWTS/COG classifies tumors in favorable and unfavorable, whereas SIOP differentiates low-, intermediate- and high-risk tumor histopathology according to the predominant cell components within the tumor (30, 34, 35) (**Table 2**).

In recent years, central review panels assist in staging, radiology interpretation, surgical decision-making and histology examinations of patients with WT [established by

TABLE 1 | Current staging systems of WT according to NWTS/COG and SIOP (post-surgery).

Stage		NWTS/COG staging	SIOP staging
I	Complete resection with negative margins	Primary tumor within renal capsule, no capsule involvement No extension to renal sinus	Tumor is confined to the kidney, no penetration of the renal capsule No tumor infiltration of the vessels at the renal sinus, the renal pelvis and the ureter
II	Complete resection with negative margins	Primary tumor penetrating renal capsule but not Gerota's fascia Lymphatic and venous involvement at renal sinus Tumor extension into renal vein/vena cava	Viable tumor is present within – soft tissue of renal sinus – the wall of renal pelvis or ureter Viable tumor is present but completely resected within – perirenal fat – blood vessels/lymphatic vessels at the renal sinus – adjacent organs (except adrenal gland) – vena cava
III	Incomplete resection, residual tumor	Macroscopic or microscopic residual disease – Preoperative biopsy of the tumor (including open and percutaneous biopsy) – Tumor rupture pre- or intraoperatively, removal of tumor tissue in fragments – Positive retroperitoneal/abdominal lymph node(s) – Peritoneal involvement – Positive resection margins at ureter, renal vein, main tumor	Viable tumor – at the resection margin – at the site of tumor rupture Viable or non-viable tumor – in abdominal lymph nodes – thrombus at the resection margin of ureter, renal vein, vena cava – implants within the abdominal cavity – penetrating through the peritoneal surface Venous tumor thrombus resected piecemeal Open tumor biopsy prior to chemotherapy
IV	Metastatic disease	Hematogenous metastasis (e.g., lung, liver, bone or brain)	Hematogenous metastasis (e.g., lung, liver, brain or bone) Lymphatic metastasis beyond abdominal and retroperitoneal lymph nodes
V	Bilateral disease	Bilateral synchronous disease (+ stage should be evaluated for each side separately)	Bilateral synchronous disease (+ stage should be evaluated for each side separately)

TABLE 2 | Prognostic risk groups for WT according NWTS/COG and SIOP relating to the histopathology of embryonal renal tumors in childhood.

NWTS/COG		SIOP	
Prognostic risk group	**Histology (pre-chemotherapy)**	**Prognostic risk group**	**Histology (post-chemotherapy)**
Mesoblastic histology	Mesoblastic nephroma*	Low-risk	Mesoblastic nephroma* Cystic partially differentiated nephroblastoma* Completely necrotic WT after neoadjuvant chemotherapy
Favorable histology	WT with – epithelial – stromal – blastemal – or mixed (triphasic) cell components	Intermediate- risk	WT with – epithelial – stromal – or mixed cell components Regressive histology features Focal anaplasia
Unfavorable histology	WT with focal and diffuse anaplasia	High-risk	WT with – blastemal cells – diffuse anaplasia Renal rhabdoid tumor* Renal clear cell sarcoma* Renal cell carcinoma*

**Non-Wilms tumors.*

the NWTS/COG (i.e., AREN03B2 umbrella study) as well as by the SIOP-Renal Tumor Study Group (RTSG) (i.e., UMBRELLA SIOP-RTSG 2016; https://fnkc.ru/docs/SIOP-RTSG2016.pdf)] (30, 34, 36). It has been shown that the COG central review adjusted the initial risk stratification in ∼20% of cases (23). Centralized review and assistance by WT study groups may eventually lead to more concise outcome data. To integrate and combine the complex sets of medical data, e-health tools have been developed such as "p-medicine" utilized by the UMBRELLA SIOP-RTSG protocol.

OVERVIEW OF CURRENT MULTIDISCIPLINARY TREATMENT STRATEGIES

The two most commonly applied treatment regimens for WT derive from the NWTS/COG and SIOP. Current treatment protocols of both groups are based on the concept of risk-adapted therapy including surgery, chemotherapy and irradiation. Throughout the multiple WT studies, patients have been identified as requiring either intensified or reduced therapy according to their individual risk factors. The NWTS/COG-based protocols have followed the concept of upfront tumor resection to plan therapy according to biological information and local stage of the tumor. In contrast, the SIOP protocol includes upfront chemotherapy before surgical resection to shrink and downstage the tumor, thus increasing the chance for complete resection and minimizing the operative risk of a tumor rupture. However, in case of a kidney tumor in a child under 6 months of age, the SIOP protocol recommends upfront tumor resection, as most kidney tumors in this age group either need no further therapy (e.g., congenital mesoblastic nephroma) or need intensified chemotherapy at the outset (e.g., malignant rhabdoid tumors) (30). Local stage and tumor biology findings are used for a risk-modified treatment. Despite these strategic treatment differences between the NWTS/COG and SIOP approach, patient outcome is nearly identical.

Metastatic Disease

About 10–12% of patients with WT present with metastasis. Lymph node, lung and liver are the most prominent metastatic sites. In recent studies, particular attention has been given to the treatment of lung metastasis in WT. Standard treatment for lung metastasis has consisted of escalated systemic therapy and whole lung radiation therapy (WLRT) regardless of lung nodule response. In the NWTS/COG AREN0533 study, patients with complete response in chest CT scans after 6 weeks of DD-4A did not receive further WLRT. However, patients with incomplete response and those with LOH at chromosomes 1p/16q received additional intensified therapy with four cycles of systemic cyclophosphamide and etoposide and WLRT according to the NWTS/COG protocol (**Box 1**). Both groups, complete and incomplete responders, had significantly improved 4-year EFS and OS estimates (85.4 and 95.6%, respectively) compared to the previous NWTS-5 (72.5 and 84.0%, respectively) (27). Similar results have been stated by SIOP (17) (**Box 2**). In uncertain lung lesions on chest CT or in so-called "slow incomplete responders" assessed by chest CT imaging, some studies encourage to biopsy (at least two) such lesions to certify metastasis before WLRT is applied (37).

Aspects of Surgical Intervention

Complete resection with tumor-free margins remains the primary surgical aim for cure of WT. Generally, the NWTS/COG protocol schedules surgical resection initially after diagnosis before any further treatment. Neoadjuvant chemotherapy is only given to NWTS/COG protocol-treated patients in cases, in which the tumor has ruptured preoperatively, the tumor is deemed to be irresectable (e.g., large tumors with intraoperative risk for rupture, extensive organ invasion with the risk for organ removal and venous tumor extension beyond the hepatic veins) or the patient is at risk for anesthesia-related complications due to cardiocirculatory compromise by a high tumor burden or extensive venous thrombosis. In contrast, SIOP protocol-treated patients are typically operated after four cycles of neoadjuvant chemotherapy.

General Surgical Principles

In unilateral WT, complete tumor nephroureterectomy through a transabdominal approach is the standard of surgical care for NWTS/COG- and SIOP-treated patients. The ureter should be resected along the tumor kidney and divided as close as possible to the bladder as the tumor may extend along the ureter. For local staging, hiliar and (inter-)aortocaval lymph node sampling as well as peritoneal exploration is required. Lymph node sampling should be performed even in cases of negative nodal preoperative imaging. An insufficient nodal dissection may lead to under-staging and under-treatment in cases positive lymph nodes remain undetected (24, 38). The impact of an undefined lymph node status in patients with WT has been reviewed by many studies. For instance, NWTS-4 and NWTS-5 both demonstrated an increased likelihood of finding a positive lymph node when more than seven lymph nodes were sampled (39). OS has also been shown to improve significantly with the number of resected lymph nodes (i.e., 5-year OS of 87% with no lymph nodes sampled to 95% with more than 10 lymph nodes sampled) (40). In the current treatment protocols, dissection of at least seven lymph nodes is therefore recommended (30, 34).

The general nature of WT growth is expansion (i.e., pushing organs away). In rare cases, adherence or invasion to adjacent organs such as liver, diaphragm, adrenal gland or bowel is seen. **Table 3** summarizes general surgical principles in (unilateral) WT.

Special (surgical) considerations have to be respected in case of large tumors, ruptured tumors, intravascular tumor extension, bilateral tumors, tumors in syndromic patients and tumors in a horseshoe kidney.

Large Tumors and Tumor Rupture

Preoperative tumor rupture or intraoperative tumor spill is of particular concern in WT as it creates a risk for local recurrence (24, 47). Spontaneous or traumatic tumor rupture is detected on preoperative imaging at a rate ranging between 3 and 23% (24, 48, 49). Intraoperatively, tumors larger than 12 cm in diameter are noted to be at risk for rupture (50). Patients treated according to the NWTS/COG protocol (i.e., no preoperative chemotherapy) have a risk of intraoperative tumor spillage of up to 10% (38, 50). An intraoperative spillage rate of 12% has been reported by SIOP in patients who had not received preoperative chemotherapy treatment (51). However, among SIOP-treated patients with neoadjuvant chemotherapy, the risk for intraoperative tumor spillage had decreased to around

BOX 1 | Basic treatment principles of WT as per NWTS/COG (covering most clinical situations).

Stage I (patients <2 years of age): Tumors with favorable histology and tumor kidney weight <550 g: RN without further treatment
Stage I and II: Tumors with favorable histology: RN + adjuvant chemotherapy with regimen EE-4A for 18 weeks; tumors with favorable histology and LOH 1p/16q: RN + adjuvant chemotherapy with regimen DD-4A for 24 weeks
Stage III: Tumors with favorable histology: RN + adjuvant chemotherapy with regimen DD-4A for 24 weeks + flank RT; tumors with favorable histology and LOH 1p/16q: RN + adjuvant chemotherapy with regimen M for 31 weeks + pulmonary RT
Stage IV: Tumors with favorable histology and isolated lung metastasis: RN + adjuvant chemotherapy with regimen DD-4A for 24 weeks + whole-lung RT; tumors with favorable histology and LOH 1p/16q: RN + adjuvant chemotherapy with regimen M for 31 weeks + pulmonary RT
Stage V: Neoadjuvant chemotherapy with DD-4A for 6–12 weeks, partial nephrectomy, adjuvant chemotherapy depends on path

LOH, loss of heterozygosity; RN, radical nephrectomy; RT, radiation therapy; regimen EE-4A (vincristine, dactinomycin for 18 weeks); regimen DD-4A (vincristine, dactinomycin, doxorubicin for 24 weeks), regimen M (vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide).

BOX 2 | Basic treatment principles of WT as per SIOP (covering most clinical situations).

Stage I–III: Neoadjuvant chemotherapy (except patients <6 months of age: RN) with AV for 4 weeks followed by RN, adjuvant therapy is determined by local stage and histology:

- **Stage I:** No further treatment to patients with RN and low-risk histology, all other patients receive chemotherapy with either AV for 4 weeks (intermediate-risk tumors, TV <500 ml) or AVD for 27 weeks (high-risk tumors, TV >500 ml)
- **Stage II:** Chemotherapy with AV for 27 weeks (low- and intermediate-risk tumors, TV <500 ml) or with HR-1 for 34 weeks (high-risk tumors, TV >500 ml) + flank RT for high-risk tumors
- **Stage III:** Chemotherapy with AV for 27 weeks (low- and intermediate-risk tumors, TV <500 ml) + flank RT for intermediate-risk tumors or with HR-1 for 34 weeks + flank RT (high-risk tumors, TV >500 ml)

Stage IV: Neoadjuvant chemotherapy with AVD for 6 weeks, re-imaging of metastatic lesions before RN, continuation adjuvant therapy depending on remission of metastasis:

- Complete remission of metastasis: AVD for 27 weeks
- Incomplete response of metastasis: HR-1 for 34 weeks + RT of metastatic organ, surgical resection of metastatic lesions can be attempted when feasible without risk of organ morbidity
- High-risk histology of the primary tumor: HR-1 for 34 weeks + RT of metastatic organ

Stage V: Neoadjuvant chemotherapy with AV for 4–6 weeks (12 weeks maximum) followed by surgery with the aim of nephron-sparing surgery, adjuvant chemotherapy according to the histopathological subtype + abdominal/flank RT in appropriate cases.

AV, (actinomycin D, vincristine); AVD, (actinomycin D, vincristine, doxorubicin); HR-1, (etoposide, carboplatin, cyclophosphamide, doxorubicin); low-risk, (i.e., complete necrosis); intermediate-risk, (i.e., blastemal tumor components); high-risk, (i.e., predominant blastemal, anaplastic components); RN, radical nephrectomy; RT, radiotherapy; TV, tumor volume after neoadjuvant therapy.

3%. This is advocated as one of the major surgical advantages of the SIOP approach (51, 52). Once rupture of the tumor capsule is evident (pre- or intraoperatively), NWTS/COG stage I-II tumors are upgraded to stage III tumors. Upon preoperative surgical assessment, the NWTS/COG protocol provides the option for neoadjuvant chemotherapy when preoperative tumor rupture is evident, tumor spill is likely at surgery or the tumor deems unresectable without significant morbidity due to its size (24). The UMBRELLA SIOP-RTSG 2016 protocol also adjusts treatment to stage III when viable tumor cells are detected microscopically at the area of rupture (34). In addition to the upstaging of the tumor with intensified chemotherapy, whole abdominal irradiation for diffuse tumor spillage or an irradiation boost to the flank is applied in most cases (30, 53).

Intravascular Extension

In 4–10% of patients with WT, the tumor extends into the renal vein or inferior vena cava, whereas an extension into the right atrium or ventricle occurs in around 1–3% of cases (43, 54–57). A complete picture of a possible intravascular extension is essential for planning anesthesia and surgery. For example, an extensive tumor thrombus to the cardiac atrium may lead to cardiac deprivation and the need for cardiopulmonary bypass surgery for its resection (31, 56, 58). As the venous tumor extension is not always seen on preoperative imaging, intraoperative exploration by manual palpation and/or ultrasonography of the renal vein is mandatory. In general, excision of a tumor thrombus needs to be achieved in continuity, as dissection will upstage the tumor to stage III. The NWTS/COG protocol therefore recommends neoadjuvant treatment when intravascular tumor extends up to or above the hepatic veins (43, 59). It has been demonstrated that in 45–87% of patients with a tumor thrombus in their inferior vena cava, preoperative chemotherapy led to a size reduction improving surgical conditions (43, 60, 61). However, cardiac tumor extensions are often less responsive to neoadjuvant therapy, but in cases of good responds, cardiopulmonary bypass surgery can be avoided (43, 56).

Bilateral WT

About 6–7% of patients develop synchronous and <1% metachronous bilateral WT (15, 62). The prevalence is higher

TABLE 3 | General surgical principles in unilateral WT to achieve local control.

Organ/Structure	Surgical measure	Comment	References
Tumor kidney	Radical resection, avoid tumor spillage	Tumor spillage will lead to stage upgrading and more intensive therapy, tumor rupture is associated with relapse	(24, 41)
Ureter	Division at the most distal level (closest to the bladder)	To achieve negative margins in case of tumor involvement of the ureter	(42)
Renal vein, inferior vena cava	Palpation and/or intraoperative ultrasonography to rule out tumor extension, en-bloc excision of a venous tumor thrombus	Complete tumor removal, en-bloc resection of the tumor thrombus together with the primary kidney tumor to avoid tumor tissue dissection and upstaging of the tumor	(43)
Lymph node	Sampling of hiliar, paracaval and paraaortic lymph nodes (and suspicious mesentery lymph nodes)	Local staging, sampling of more than seven lymph nodes	(34, 41)
Ipsilateral adrenal gland	Can be left *in situ* when easily separated from the tumor kidney and when without signs of tumor involvement	Incidence of tumor invasion into the gland in <5% of cases	(44)
Diaphragm	En-bloc resection in case of adherent tumor	To avoid spillage dissecting the tumor off the diaphragm	(30)
Liver	Extensive en-bloc resection or partial hepatectomy is not recommended in case of direct spread	Minimize secondary liver complications, no benefit shown for survival in case of extensive hepatic resection	(24, 45)
Bowel	Partial resection of intestine/colon	In case of tumor infiltration	
Peritoneum	Peritoneal exploration	Local staging, sign of tumor extension	
Contralateral kidney	Exploration	Only in case of a suggested contralateral kidney lesion or enlarged contralateral lymph nodes in pre-operative imaging, exploration should be done prior to tumor nephrectomy of the primarily involved kidney to adapt the surgical approach intraoperatively	(24, 38, 46)

in patients with genetic predisposition syndromes carrying WT1 gene mutations and loss of imprinting (LOI) at 11p15 (15). As these genetic alterations are driving factors for early-disrupted embryologic differentiation of the kidney tissue, (multifocal) nephrogenic rests or nephroblastomatosis lesions are often seen in bilateral WT (63, 64). Conditions predisposing to metachronous bilateral WT are Denys-Drash syndrome, WAGR syndrome, Beckwith-Wiedemann syndrome, Fanconi anemia and familial WT. In these patients, up to 90% of WTs occur within the first 7 years of life necessitating close routine screening programs (15, 64).

Data from early studies revealed that patients with bilateral WT have a higher risk to suffer from end-stage renal disease (ESRD) within 20 years after treatment (cumulative incidence of 12% in bilateral WT vs. <1% in unilateral WT) (65). In patients with predisposing conditions, renal insufficiency rates are even higher (e.g., 83% in Denys-Drash syndrome and 43% in WAGR syndrome) (66, 67). In cases of synchronous or potentially metachronous bilateral WT, renal tissue can be preserved by NSS. Best conditions for successful NSS are low volume tumors in the kidney's periphery (67, 68). Neoadjuvant chemotherapy to confine the tumor enabling surgical resectability is therefore part of all treatment protocols. In a selected group of patients with bilateral WT, bilateral nephrectomy and kidney transplantation may be considered as a treatment option to eliminate the risk of initial or metachronous WT development (68, 69). This subgroup includes patients with Denys-Drash syndrome in whom prophylactic or secondary bilateral nephrectomy (in case of ESRD) is an acceptable procedure (64, 70, 71). In these patients, kidney transplantation is usually performed after 1–2 years of disease-free survival (64, 67).

Horseshoe and Solitary Kidneys

Wilms tumor in a horseshoe kidney is an exceptionally unique situation. There is a historic collection of 41 patients reported from the NWTS/COG (72). Surgical aims are the same as for unilateral WT with complete tumor nephroureteroectomy and lymph node sampling. However, some surgeons advocate NSS (73). The treatment of WT in solitary kidneys is guided by the same principles as for bilateral WT (30).

RECENT TECHNICAL INNOVATIONS

Nephron-Sparing Surgery

Performance of NSS is a necessity in children presenting with bilateral WT (74). In unilateral WT, NSS must be considered in syndromic patients with an increased risk of metachronous development of (contralateral) WT, in patients with a solitary kidney or an afunctional contralateral kidney as well as in patients who are at risk of kidney failure (46). In non-syndromic unilateral WT, NSS is not a standard procedure (75). Potential benefits are prevention of functional renal impairment and ESRD, whereas some long-term follow-up data suggest good renal function even after unilateral radical nephrectomy (RN) for WT (65, 76–79). However, higher rates of postoperative stage III WTs due to positive resection margins have been reported (75). This required conversion to RN and/or additional radiation therapy. Still, EFS and OS were comparable to patients with RN (75, 80). If NSS is considered in unilateral WT, careful patient selection should be performed preoperatively (80). Davidoff et al. (81) prospectively analyzed patients on NSS feasibility according to radiological imaging and concluded that 8% of patients could be treated with NSS. The SIOP-RTSG surgical panel formulated

a list of preconditions under which NSS for unilateral WT may be performed (i.e., tumor restricted to one pole, tumor volume <300 ml, no tumor rupture, no tumor in renal pelvis, no continuous organ invasion, no venous tumor thrombus, functioning kidney remnant after NSS) (30, 82).

Nephron-sparing surgery can be carried out by partial nephrectomy (i.e., tumor resection with a rim of normal renal tissue) or enucleation of the tumor (i.e., tumor resection without a rim of normal renal tissue) (30). At present, there are no available data comparing both methods. Method selection is highly dependent on tumor localization, size and the presence of multifocal lesions.

The main aim of NSS is to preserve as much healthy kidney tissue as possible. Preoperative chemotherapy may contribute to the preservation of renal tissue. The COG-AREN0534 reviewed 34 patients with predisposing conditions to bilateral WT presenting with unilateral tumors. This study showed that partial nephrectomy was feasible in 65% of patients after neoadjuvant chemotherapy, avoiding tumor nephrectomy and sparing renal tissue without compromising EFS and OS (46).

To assure a bloodless dissection and good visibility when dissecting through the kidney's parenchyma, intermittent clamping of the renal vasculature may be helpful. Some surgeons have advocated adopting operative techniques from adult kidney cancer surgery such as inducing renal hypothermia (e.g., application of ice water into the kidney bed) in the attempt to maximize the preservation of kidney tissue (62, 83, 84). As this is not yet a standard approach, future studies will need to address possible outcome benefits of this technique.

Another surgical adjunct is the use of intraoperative ultrasound in NSS. For example, ultrasound-guided mapping of the tumor nodules can aid to optimize surgical dissection lines, thus preserving healthy kidney tissue. Still, its use has to be critically reviewed as it does not guarantee tumor-free resection margins (83).

Minimally Invasive Approaches

Laparoscopic RN and laparoscopic-assisted partial nephrectomy is becoming more common for the treatment of WT as comparable outcomes have been reported. Nevertheless, the outcome analysis may be biased by the fact that laparoscopically resected tumors have lower stages of disease (75, 85–90). Additionally, robotic-assisted laparoscopy (RAL) is a developing field in pediatric surgical oncology (91–94). However, the experience of RAL in WT surgery is yet limited and its indications need to be carefully discussed in tumor and surgical reference boards (82, 94). In general, minimally invasive tumor resection is limited to tumors confined to the kidney with good exposure of the hilar vessels (85, 95). Large tumors may not leave enough operating space for laparoscopy. Therefore, patient selection is of the utmost importance (95, 96). In the UMBRELLA SIOP-RTSG 2016 protocol, the following prerequisites for laparoscopic RN including RAL have been proposed: small, central tumors with a rim of non-malignant renal tissue, extraction of the specimen in a bag without morcellation, no venous tumor thrombus, no continuous organ infiltration, no extension of the tumor beyond the ipsilateral boarder of the spine, no imminent tumor rupture (i.e., in case of no response to chemotherapy) and feasibility of lymph node sampling as well as the operating surgeon is expected to be experienced in minimally invasive nephrectomy (30, 82). In all instances, performance of minimally invasive surgery must adhere to the same general surgical principles of WT treatment such as complete lymph node sampling and thoroughness of resection (30).

ADVANCES IN TUMOR IMAGING TECHNOLOGY

Diffusion-weighted imaging (DWI) MRI technique has added a new quality to the available imaging modalities for WT. By defining the whole-tumor apparent diffusion coefficient, it provides information on the "cell density" of a tumor lesion, assisting the radiologist in defining necrotic from viable lesions after chemotherapy and small lesions in nephroblastomatosis (97–99). Imaging research studies aim at defining histological subtypes of WTs by DWI for radiologic assistance in risk stratification (100–102).

Detecting hiliar and retroperitoneal metastatic lymph node disease is critically important in WT (103, 104). Lymph node metastasis can be occult and may not necessarily be apparent by lymph node enlargement during the operation. To improve lymph node sampling in WT, first feasibility studies have been conducted to establish the concept of intraoperative sentinel lymph node detection. Two techniques have been described in the attempt to delineate the lymphatic drainage of the involved kidney: injection of a radioactive tracer (e.g., technetium-99 m phytate detected with an intraoperative gamma probe) or a fluorescence dye (e.g., indocyanine green visible under near-infra red laparoscopy) (103, 104). In this recently published study, including unilateral WTs with indication for tumor nephrectomy, sentinel lymph nodes were most frequently detected in the aorto-caval space after injection of a radioactive tracer into the normal kidney tissue adjacent to the WT (104). Further systematic studies will be needed to standardize and verify the advantages of this technique.

Surgical research on fluorescence-guided kidney surgery has also evolved. Surgical procedures delineating perfusion of the kidney including separation of the upper and lower pole, visualizing renal masses (cysts) or mapping lymphatic drainage (e.g., in lymphatic sparing varicocelectomy) have been successfully executed (105, 106). These new surgical imaging techniques may eventually have the potential to transform the surgical approach in WT treatment.

PROGNOSTIC BIOMARKERS

The number of newly identified biomarkers in WT is growing constantly. To date, more than 30 (epi-)genetic and protein biomarkers have been suggested (107). Most of these biomarkers are closely linked to tumorigenesis and predisposition of WT. Some may eventually play a role in targeted therapy. One such candidate is an antagonist of the Wnt/beta-catenin pathway, tegavivint (BC2059), which is currently under investigation by

the COG for its antitumor activity in recurrent and refractory pediatric solid tumors including WT. Currently, patients with WT-associated CTNNB1 oncogene mutations leading to Wnt/beta-catenin pathway activation can be included in this study (https://clinicaltrials.gov/ct2/show/NCT04851119) (108).

So far, only one genetic biomarker, i.e., LOH at chromosomes 1p/16q, has been integrated as a decision-making factor into the current COG treatment protocol. In the presence of LOH at chromosomes 1p/16q, patients with stage I and II favorable WT histology will be upstaged from low to standard risk receiving regimen DD-4A (i.e., vincristine, dactinomycin and doxorubicine for 24 weeks) instead of regimen EE-4A (i.e., vincristine and actinomycin D for 16 weeks) after nephrectomy. The previous NWTS-5 showed a significantly improved EFS and OS in patients with intensified therapy (27). Intensified chemotherapy is also given to patients with LOH at chromosomes 1p/16q and lung metastasis in the NWTS/COG protocol. Although it serves as a sensitive marker for risk stratification, LOH at chromosomes 1p/16q is only applicable in a small subset of patients and presently it does not offer possible treatment targets.

With 30% of favorable histology WT cases, one of the most prevalent outcome predictors is gain of function (GOF) at chromosome 1q. It is associated with significantly poorer EFS and OS, as reported by the NWTS/COG and SIOP study groups, and is currently under reinvestigation in the UMBRELLA SIOP-RTSG protocol for its prognostic value (30, 109, 110).

In general, WT is considered an embryonal tumor consisting of primordial renal cells disrupted to mature into differentiated kidney tissue. Variable proportions of blastemal (i.e., renal stem cells), epithelial and stromal cells have great influence on tumor behavior and outcome. During kidney development, organogenesis passes the stage of nephrogenic differentiation. This stage of development can persist as intra- or perilobar nephrogenic rests throughout the first few years of life and is a very likely origin for WT tumorigenesis. One important factor in driving embryonal renal differentiation is the transcription factor WT1 on chromosome 11p13. Its mutation is linked to the development of WT. WT1 mutations are reported in 10–20% of sporadic WT cases (111). Together with mutations in the CTNNB1 and AMER1 (WTX) tumor suppressor genes, it unfolds its tumorigenic role by upregulation of the Wnt/beta-catenin pathway (112). As germline alterations, WT1 mutations are common in syndromic predisposition syndromes (e.g., Denys-Drash syndrome and WAGR syndrome), bilateral WT and WT with synchronous nephrogenic rests (5, 113, 114). Another transcription factor that plays a role in bilateral as well as in predisposing syndromes is WT2 on chromosome 11p15. Mutations in this gene are much more abundant (i.e., 70% of cases) with 40% in sporadic cases and 30% in Beckwith-Wiedemann syndrome (115).

In recent research, mutations have been identified in microRNA (miRNA) processing genes in about 20% of patients with WT (116, 117). These alterations in miRNA processing are thought to conserve the embryonal stage of kidney development (116, 118). However, data concerning their influence of clinical behavior in WT have not yet been specifically reported.

When analyzing molecular markers in tumor tissues, it is important to consider that tumors consist of miscellaneous tissue parts containing different levels of marker expression. This has been shown for GOF at chromosome 1q, leaving a general uncertainty in biopsies (109, 119).

In the majority of cases, biomarkers identify WTs with treatment resistance and poor prognosis. **Table 4** provides an overview of transcription factors, oncogenes and tumor suppressor genes directing at multiple different pathways potentially involved in tumorigenesis of WT.

FUTURE DIRECTIONS

The concept of "personalized medicine" has already improved the treatment of children with WT. The future trend will increasingly be driven by two principles: (1) de-escalation of therapy with the aim to define the appropriate level of treatment to achieve the best outcome while minimizing secondary side effects, and (2) identifying tumor-related and personal risk factors justifying escalation of therapy. To address these principles, the two large WT consortia of the COG and SIOP have designed new prospective studies (i.e., AREN03B2 umbrella study within the COG registry "*Project: Every Child*" and UMBRELLA SIOP-RTSG protocol, respectively) to collect and overlay clinical and biological data on a profound scale. Within these registries, both groups have established systematic biospecimen banks with tumor and blood samples available for prospective and retrospective analysis. Due to the fact that many prognostic (bio-)markers, such as blastemal histology or LOH at chromosomes 1p/16q, are only identified in a small subset of patients, treatment centers worldwide are encouraged to enroll patients (30).

Molecular research has identified a multitude of genetic and protein biomarkers for WT that may eventually assign patients into more specific risk groups. Among the most prevalent and promising prognostic markers for adverse outcome is GOF at chromosome 1q, which is currently under investigation as part of the UMBRELLA SIOP-RTSG protocol. Other markers may potentially serve as therapeutic targets. Patients with recurrent or refractory WT and alteration of the Wnt/beta-catenin pathway can be included in a therapeutic phase I/II application study of tegavivint (BC2059). The study is open for a number of different pediatric solid tumors with refractory treatment response and mutational activation of the Wnt/beta-catenin pathway.

Genomic sequencing programs such as TARGET (Therapeutically Applicable Research to Generate Effective Treatments) in the United States and FACT (Factors Associated with Childhood Tumors) in the United Kingdom have accelerated the discovery of inherited and acquired factors possibly responsible for the development of WT (128–130). The growing knowledge on tumor biology and genetics will increasingly influence the decision-making process, and contribute to the general understanding of tumorigenesis of WT.

Another important field of research with respect to WT biomarkers is the identification of tumor DNA in blood or urine samples. In patients enrolled in SIOP and UKCCSG/CCLG

TABLE 4 | List of selected biomarkers with potential relevance for WT prognosis and/or tumorigenesis.

Biomarkers, Gene	Incidence	Relevant findings	Reference
CTNNB1	15%	– Stromal predominant histology – Upregulation of the Wnt/beta-catenin pathway – Patients with CTNNB1 mutations leading to upregulation of the Wnt/beta-catenin pathway are currently included in phase II trials as a possible treatment target for tegavivint (BC2059)	(10, 108, 111)
LOH 1p/16q	5.0% in WT with favorable histology and 9.4% in relapsed WT	– NWTS-5: LOH 1p/16q predicted inferior 4-year EFS and OS in stage III and IV tumors	(11, 107)
LOH 1p	12%	– NWTS-5: Significantly increased rate of relapse and decreased OS independent of tumor stage and histology – Predicting WT relapse (RR 2.93)	(11, 107)
LOH 16q	17%	– NWTS-5: Significantly increased rate of relapse and decreased OS independent of tumor stage and histology – Predicting WT relapse (RR 1.95)	(11, 107)
GOF 1q	30.0% overall and 18.3% in stage IV WT	– No histologic pre-dominance – NWTS-5: Inferior 4-year EFS and OS in stage I, III and IV tumors – Predicting relapse (RR 2.86) unrelated to tumor stage	(107, 109, 110)
WT1 (chr. 11p13)	10–20%	– Predominant stromal histology – Simultaneous presence of intralobar nephrogenic rests – WT1 mutations and LOH 11p15 associated with relapse – Germline mutations in Denys-Drash syndrome and WAGR syndrome – 90% of patients with Denys-Drash syndrome and 50% with WAGR syndrome develop WT	(5, 111, 112, 114, 120)
WT2 (chr. 11p15)	70%	– Germline mutation in Beckwith-Wiedemann syndrome – 4–5% of patients with Beckwith-Wiedemann syndrome develop WT – IGF2 upregulation	(115)
LOH 11p15		– IGF2 upregulation – Increased risk of recurrence – Described in anaplastic WT, relapse, and fatal cases	(107)
LOI 11p15	30–50%	– Leading to H19 and IGF2 activation and unrestrained cell growth – Predicting relapse in low-risk WT treated with surgery alone	(120, 121)
WTX (AMER1)	15–20%	– Upregulation of the Wnt/beta-catenin pathway – Combined with epigenetic 11p15 alterations	(111, 122)
miRNA processing genes	20%	– Mutations in miRNA processing genes including DROSHA (80% of miRNA mutations in WT), DGCR8 and DIS3L2 (Perlman syndrome)	(116–118)
MLLT1	4%	– High prevalence of intralobar nephrogenic rests	(123)
MYCN	<10%	– Described in treatment resistance, relapse, and fatal cases – Detected at higher proportion of pre-treated anaplastic WT (>30%), potential marker for treatment resistance	(124)
LOH 11q		– Higher detection in mixed and diffuse anaplastic WT – Associated with recurrence and fatal cases	(124)
SIX1 and SIX2	5–10%	– Blastemal predominant histology	
TRIM28	5%	– Mature epithelial histology predominant – Excellent prognosis – Frequent in bilateral and familial cases	(107, 125, 126)
TP53 (chr. 17p13)	5%	– 75% in diffuse anaplastic tumors – Found primarily in advanced tumor stages – Significantly poorer outcome in stage III and IV anaplastic tumors – Linked to increased recurrence	(105, 106)
CTR9	Described in four families and sporadic cases	– Non-syndromic WT predisposition	(127)

GOF, gain of function; LOH, loss of heterozygosity; LOI, loss of imprinting; WT, Wilms tumor.

(United Kingdom Children's Cancer Study Group/Children's Cancer and Leukemia Group), a 5–12% rate of misdiagnosis has been reported in patients without biopsy or primary surgery (131). In the near future, so-called "liquid biopsies" may aid in establishing WT diagnosis and screening patients in follow-up programs for recurrent WT (131–133).

Recent studies have focused on the global epidemiology of WT, offering a broad picture of who is at risk for the development of WT not only by world region, ethnic background, gender and age, but also by socioeconomic status and health care accessibility (1, 3, 134). The highest WT incidence rates have been reported in North America in children of African-American

descent, whereas the lowest was seen in children in East Asia (2). Differences in genetics have also been reported by ethnicity and world region. For instance, the genetic alteration of the IGF-2 gene locus playing the driving role in overgrowth syndromes and WT was less frequently seen in children with WT from Japan in comparison to Caucasian children (2, 135, 136). Future research will need to overlay epidemiology with genetic data in larger patient cohorts to identify populations at risk for WT development, treatment resistance or worse outcome.

Centralized review of WT imaging and pathology as well as treatment guidance has more and more been integrated in current treatment protocols. In previous studies, discrepancies in institutional and central histopathology interpretation have been reported in 20–50% of cases (9, 35). Ultimately, centralized data review may lead to more coherent data sets.

Despite significant progress in molecular biology, research defining biomarkers and identification of new treatment targets for WT, technical advances in imaging, surgery and radiation therapy will evenly be important. In the future, artificial intelligence algorithms of tumor imaging and 3-D reconstructions of WT may assist the surgeon in defining surgical resection lines, thus improving surgical outcome particularly in cases of NSS (106, 137). In addition, advances in the application of radiotherapy such as intensity-modulated radiation therapy sparing non-tumorous tissue and limiting radiation-associated toxicity will be beneficial for the WT patients (138, 139).

AUTHOR CONTRIBUTIONS

T-MT, YB, KB, UR, HF, and FF performed the literature search for the work. T-MT and YB outlined and wrote the initial manuscript draft. KB, UR, HF, and FF critically revised the initial manuscript draft for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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