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Consensus statement

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Updated favourable-histology Wilms tumour risk stratification: rationale for future Children's Oncology Group clinical trials

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Abstract

Patients with Wilms tumour have benefited from the results of decades of large collaborative clinical trials, leading to improved care. In the National Wilms Tumor Study Group and now Children's Oncology Group (COG) trials, risk stratification evolved and expanded with each generation of studies and, therefore, ensuring that each patient receives the appropriate therapy has become increasingly complex. A new risk stratification system has been developed that forms the basis of the upcoming COG favourable-histology Wilms tumour (FHWT) study. Topics of diagnostic and prognostic uncertainty, such as the findings of tumour pulmonary emboli or extra-abdominal lymphadenopathy at diagnosis, will be integrated into the central review determination of staging of FHWT by committee consensus to facilitate clinical classification for therapeutic studies. Clear documentation of the elements of current risk stratification are of particular importance as refinement of the classification of patients with FHWT continues in an effort to optimize research, personalize treatment and provide an educational resource.

Sections

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Introduction

Great advances have been made in the field of paediatric oncology in the treatment of patients with Wilms tumour through sequential, collaborative group clinical trials conducted by the National Wilms Tumor Study (NWTS) Group (NWTSG), Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (RTSG)[1–3]. Most patients (~94%) with Wilms tumour have favourable-histology Wilms tumour (FHWT)[4], and tremendous progress in its treatment has occurred, with survival now exceeding 90%, despite very few new chemotherapy agents being introduced in the past six decades. Most of this progress is attributable to serial randomized clinical trials, the results of which helped to define optimal treatment of patients with FHWT, and enabled the refinement of risk-stratification.

In NWTSG trials, risk stratification was based on stage, then also histology, and subsequently age and tumour weight were integrated. Tumour molecular analysis[5] and metastatic site response to chemotherapy[6] have now also been incorporated into COG trial risk stratification (Tables 1 and 2). In the completed COG FHWT studies AREN0532 and AREN0533 studies, both intensified and de-intensified treatment strategies were examined, with an overarching goal of maintaining or improving outcomes while decreasing toxic effects for patients with FHWT[7–9]. Novel prognostic features were discovered for subsets of patients enrolled in those studies[10–12], and from ongoing analyses of previous studies[13,14], leading to the need to further refine risk stratification for FHWT.

In this Consensus Statement, we describe the details of the evolution of risk-based treatment of FHWT and outline the rationale for the new risk stratification that will be used in the recently opened COG therapeutic trial for FHWT, AREN2231. We highlight prognostic factors that have previously been studied in prospective clinical trials, and those that have been identified through retrospective analyses of trial data but will be incorporated into risk-adapted treatment for the first time on AREN2231. Additionally, we highlight areas of diagnostic and prognostic uncertainty, albeit rare, which, out of necessity for clinical classification for therapeutic studies, have been integrated into the central review determination of staging of FHWT by expert consensus rather than based on conclusive data. These topics are of particular importance as we aspire to continue to refine patient classification to optimize treatment and research.

Table 1 | First-generation Children's Oncology Group favourable-histology Wilms tumour risk stratification

Stage	Age	Tumour weight	Molecular features	Lung nodule response	EPM	Risk group[a]
I	<2 years	<550 g	Any	NA	NA	Very low risk
I	<2 years	>550 g	Normal	NA	NA	Low risk
I	>2 years	Any	Normal	NA	NA	Low risk
II	Any	Any	Normal	NA	NA	Low risk
I	Any	Any	Combined LOH	NA	NA	Standard risk
II	Any	Any	Combined LOH	NA	NA	Standard risk
III	Any	Any	Normal	NA	NA	Standard risk
IV	Any	Any	Normal	RCR	No	Standard risk
III	Any	Any	Combined LOH	NA	NA	Higher risk
IV	Any	Any	Combined LOH	Any	No	Higher risk
IV	Any	Any	Any	SIR	No	Higher risk
IV	Any	Any	Any	Any	Yes	Higher risk

Combined LOH, LOH of both 1p and 16q; EPM, extrapulmonary metastases; LOH, loss of heterozygosity; NA, not applicable; Normal, absence of combined LOH; RCR, rapid complete response; SIR, slow incomplete response. [a]Risk group assignment does not necessarily indicate the optimal treatment. Treatment changes in AREN0532 or AREN0533 did not improve outcomes for all patients, yet these risk group categories still represent relative differences in outcomes for these groups of patients. Adapted with permission from ref. 16, Wiley.

Methods

This review of risk stratification has been developed by a multidisciplinary group of COG Renal Tumor Committee members, including paediatric oncologists, surgeons, radiologists, pathologists, radiation oncologists, biostatisticians and other investigators. The Renal Tumor Committee has a structured leadership with appointed Chair, Vice Chair and leads for each of the disciplines. Committee members are invited to the committee based on demonstrated interest and expertise in the care and study of children and young adults with renal tumours. Primary authors of this paper were members of the FHWT working group, most of whom are also primary authors of the current COG therapeutic trial AREN2231 (Risk Adapted Therapy for Unilateral FHWT). The FHWT working group was established by Renal Tumor Committee leadership to include current and past committee chairs and vice chairs, current and past study chairs and vice chairs of FHWT tumour trials, as well as relevant committee discipline leads and members. This group has extensive collective experience in the conduct and analysis of clinical trials for FHWT, including designing and implementing the AREN03B2 risk assignment processes and determinations for patients with FHWT over the last 20 years. COG study AREN03B2, the Renal Tumor Classification, Biology and Banking study, opened in 2006 as an overarching study to classify patients with renal tumours through real-time expert panel review and risk stratification, to define eligibility for, and support conduct of, therapeutic trials, and to develop a well-annotated tumour bank to support clinical and translational research into children with renal tumours[1,15].

To develop a new COG study for patients with FHWT, this group revised the risk stratification system that was developed and adopted for the first generation of COG 'AREN' therapeutic studies[16]. Through deliberations in regular videoconferences and teleconferences and at annual, multiple-day, in-person meetings, the study committee designed the revised system based on new data that became available through both prospective and retrospective analyses of patients with FHWT treated or followed from the NWTS-5, AREN03B2, AREN0532, AREN0533 and AREN0534 clinical trials. We reviewed and have included pertinent literature when available, including relevant publications from the NWTSG, COG and SIOP, when applicable. Each potential risk factor was discussed to reach a unanimous agreement amongst the multidisciplinary study committee about which factors should be used for risk stratification in the prospective therapeutic trial under development. In the very rare situation in which definitive data guiding whether to integrate a particular clinical feature into risk stratification was absent, the feature was debated based on available data as well as on real-world stratification challenges faced in AREN03B2 until unanimous expert agreement (or lack of dissent) was reached among the multidisciplinary members of the study committee.

Table 2 | Evolution of prognostic factors in Wilms tumour studies in the NWTS Group and the COG

Study	Prognostic factors included												Refs.
NWTS-1	Stage	–	–	–	–	–	–	–	–	–	–	–	17,41
NWTS-2	Stage	–	–	–	–	–	–	–	–	–	–	–	18,115
NWTS-3	Stage	Histology	–	–	–	–	–	–	–	–	–	–	19,51
NWTS-4	Stage	Histology	–	–	–	–	–	–	–	–	–	–	20,28, 116
NWTS-5	Stage	Histology	Age	Tumour nephrectomy weight	–	–	–	–	–	–	–	–	5,14,21, 42,65
COG first-generation studies (AREN0321, 0532, 0533, 0534)	Stage	Histology	Age	Tumour nephrectomy weight	LOH of 1p and 16q	Lung metastatic response	Extrapulmonary metastases	Bilateral/ predisposition	Post-chemotherapy histology (bilateral/ predisposed only)	–	–	–	7–9,11, 27,47
COG second-generation studies (AREN2231, to be decided)	Stage	Histology[a]	Age[b]	–	LOH of 1p and/or 16q	Lung metastatic response	Extrapulmonary metastases	Bilateral/ predisposition	Post-chemotherapy histology (all)	LOH 11p15[c]	1q gain	Lymph node involvement	–

COG, Children's Oncology Group; LOH, loss of heterozygosity; NWTS, National Wilms Tumor Study. [a]New histological groups incorporated. [b]Age cut-off changed from 2 to 4 years. [c]Loss of imprinting of 11p15 also prognostic but not incorporated into AREN2231 as current testing technologies are not routinely available and do not return results fast enough to be used in upfront clinical decisions at this time.

Risk stratification

Risk stratification has become increasingly complex since the first NWTSG study, NWTS-1 (Table 2).

Evolution of risk stratification

In NWTS-1 and NWTS-2, patients were only stratified by stage[17,18]. In the subsequent two studies, NWTS-3 and NWTS-4, tumour histology (favourable or unfavourable) was incorporated into stratified treatment[19,20]. Finally, in NWTS-5, two new variables, patient age and tumour nephrectomy weight (TNW), were added to stratification[5,21]. The results of these five NWTSG studies established the clinical and biological features employed for risk stratification in the initial series of COG 'AREN' therapeutic studies[16] (Table 1). These features include stage, histology (including post-chemotherapy histology for patients with bilateral or predisposed Wilms tumour), age, TNW, loss of heterozygosity (LOH) of 1p and 16q, response of pulmonary metastases to chemotherapy and the presence of extrapulmonary metastases. Chemotherapy regimens studied and currently used in risk-adapted, first-line treatment of FHWT include EE-4A, DD-4A, VAD, regimen I and regimen M (Table 3).

Evidence from previously conducted studies has informed the newly developed recommendations regarding the prognostic factors included in risk stratification, including prospectively studied factors, retrospectively studied factors and factors of less certain importance.

Prospectively studied prognostic factors

The prognostic features of stage, histology, age, TNW, LOH of 1p and 16q, response of pulmonary metastases to chemotherapy and the presence of extrapulmonary metastases have all been previously studied in prospective NWTSG or COG therapeutic studies, which has informed their use in the updated model.

Stage. In NWTSG and COG, FHWT is staged using a combination of radiological and surgicopathological staging (Table 4). Cross-sectional imaging of the chest, abdomen and pelvis is required for all patients, to determine the resectability of the tumour and for detection of metastatic and bilateral disease. Local (abdominal) stage is determined using surgicopathological staging from an initial diagnostic procedure. In the first NWTSG studies, patients with metastatic disease clearly had worse outcomes than those with localized disease treated with the same chemotherapy, although the study was not designed to demonstrate this difference[17]. Observations from subsequent studies have enabled narrowing of the outcome gap between patients with stages I and IV disease by use of intensified therapy strategies for increased stages[8,9,11,22–24]. Notably, either chest X-ray or CT scans were accepted for diagnosis of pulmonary metastases in the NWTS studies[22]. Results of the SIOP 2001 study showed that patients with CT-only lung nodules (nodules visible on CT but not visible on chest X-ray) had better outcomes than those with lung nodules visible on chest X-ray and worse outcomes than those with localized disease[25]. In NWTS study results, patients with CT-only lung nodules had improved event-free survival (EFS) when treated with intensified chemotherapy, thereby supporting prognostic value and enhancing risk stratification; therefore, CT scans are now required for staging[22].

Patients with stage V (bilateral) FHWT have historically experienced poor outcomes[26]. In AREN0534, the first prospective study involving these patients, an intensified neoadjuvant chemotherapy regimen was adopted and delayed nephrectomy histology was incorporated to determine the subsequent treatment regimen[27].

Table 3 | Children's Oncology Group chemotherapy regimens

Name	Chemotherapeutic agents	Duration
EE-4A	Vincristine, dactinomycin	19 weeks
DD-4A	Vincristine, dactinomycin, doxorubicin (cumulative doxorubicin, 150 mg/m^2)	25 weeks
VAD[a]	Vincristine, dactinomycin, doxorubicin (35 mg/m^2 per cycle)	6–12 weeks
Regimen I	Vincristine, doxorubicin (cumulative 225 mg/m^2), cyclophosphamide (cumulative 15.4 g/m^2), etoposide (cumulative 2,000 mg/m^2)	25 weeks
Regimen M	Vincristine, dactinomycin, doxorubicin (cumulative 195 mg/m^2), cyclophosphamide (cumulative 8.8 g/m^2), etoposide (cumulative 2,000 mg/m^2)	31 weeks

[a]VAD is a pre-resection regimen used only in patients with bilateral Wilms tumour, Wilms tumour in a solitary kidney or unilateral Wilms tumour in a patient predisposed to the development of bilateral Wilms tumours (such as those with a predisposition syndrome or multicentric Wilms tumour).

Markedly improved outcomes (4-year EFS 84.2%) were achieved using this approach compared with patients treated using NWTSG study approaches (4-year EFS 65%)[27]. Except when explicitly stated, throughout this manuscript the discussion of features incorporated into risk stratification pertain to unilateral FHWT. The influence of features such as LOH of 1p and 16q and lung metastatic response to chemotherapy on bilateral FHWT is currently uncertain but is an area of active investigation.

Subtle changes to staging definitions have occurred over time; therefore, stage shifting needs to be considered. For example, in NWTSG studies, intraoperative local tumour spill that was confined to the flank, which also applied to the rare patients who had a biopsy and then subsequently underwent complete nephrectomy before starting chemotherapy, was not considered an indication for stage III designation[11]. However, in COG studies, any biopsy or local tumour spill was designated as stage III, after recognizing that patients who had local tumour spill but otherwise met stage II criteria experienced an increased risk of local recurrence[28–30] (Table 4). The terms 'spill' and 'rupture' have historically been inconsistently defined and used, and at times conflated in previous studies and analyses; thus, 'spill' will be clearly defined in future COG studies to be an intraoperative event involving tumour capsule disruption at the time of surgery (including biopsy), whereas 'rupture' will be defined as a preoperative event leading to tumour capsule disruption, determined either intraoperatively by the surgeon or identified by a pathologist. Because 'rupture' (regardless of symptoms or imaging findings) is an indication for whole-abdomen irradiation (WAI), this distinction is important for accurate risk stratification and therapy decisions. This distinction will be further emphasized in future COG studies to improve data collection and treatment decisions. Additionally, with widespread availability of CT scans and improved outcomes with detection of CT-only lung nodules, COG requires chest CTs for accurate staging.

Lymph-node sampling (LNS) is important for accurate staging. The presence of tumour within abdominal lymph nodes confers a local stage III designation and is a predictor of EFS and overall survival (OS)[11,24]. In NWTSG and COG staging, the finding of a non-viable tumour within a lymph node is considered lymph-node involvement. Enlarged abdominal lymph nodes on imaging are well established to be frequently reactive rather than involved with tumour; thus, surgical sampling is required for accurate staging[31]. In a Surveillance, Epidemiology and End Results and Florida Cancer Data System study, survival was observed to be lower for patients who did not undergo LNS than for those who did (5-year OS 87%) versus 1–5 (91%); 6–10 (93%); or >10 (95%) lymph nodes sampled ($P = 0.005$). A survival advantage for patients having 1–5 lymph nodes (hazard ratio (HR) 0.6, $P = 0.016$), 6–10 lymph nodes (HR 0.521, $P = 0.048$), and >10 lymph nodes (HR 0.403, $P = 0.039$) sampled compared with patients with zero lymph nodes examined was shown on multivariate analysis[32]. In NWTS-5, failure to sample lymph nodes was associated with an increased risk of relapse in patients with stages I or II disease, suggesting that some patients had undetected lymph node involvement (that is, really had stage III disease) owing to the absence of LNS[33]. Similarly, in AREN0532, a non-statistically significantly reduced EFS was observed in patients who did not have LNS, with 4-year EFS of 84% among patients with stage III disease without LNS ($n = 148$) versus 89% ($n = 387$, $P = 0.067$) in those with LNS[11]. A combined analysis of AREN03B2 and AREN0532 showed improved outcomes for patients with stage III disease who had LNS (4-year EFS 90.3%) relative to those without LNS (EFS 80.0%, $P = 0.0037$)[34].

A review of the National Cancer Database showed that lymph nodes are not sampled in 10–15% of patients[35], and in AREN03B2, failure to sample lymph nodes was the most common surgical protocol violation[36]. The likelihood of finding a positive lymph node increases with increasing number of lymph nodes sampled[37,38], en bloc sampling increases the number of lymph nodes sampled[39], and sampling between 6 and 10 lymph nodes decreases the false-negative rate to <10%[35]. Formal lymph-node dissection (such as retroperitoneal lymph-node dissection) is not necessary; however LNS is required for accurate staging. In previous NWTSG and COG Wilms tumour studies, patients were staged and enrolled without LNS as if their lymph nodes were negative, meaning that a patient could be assigned stages I or II without examination of an uninvolved lymph node[40]. For future COG unilateral FHWT trials, patients will be ineligible if LNS does not occur. Any patient either ineligible for enrolment (upfront nephrectomy without LNS) or removed (enrolled, delayed nephrectomy without LNS) will receive whatever treatment their treating institution or team recommends. The COG is a research organization and does not provide guidance regarding individual patient management outside the confines of research protocols.

Histology. The presence of anaplasia was first recognized as an adverse prognostic factor owing to the results of NWTS-1 (ref. 41). It was subsequently shown to indicate chemotherapy resistance and tumour aggressiveness[42], and incorporated into risk stratification. Tumours with anaplasia were classified as unfavourable histology in NWTS-3 and subsequent studies[19]. Identification of anaplasia, and its classification as focal or diffuse[43], can be a challenge. Tumour heterogeneity means that anaplasia is often not discovered on biopsy but is identified subsequently, when the entire tumour is removed[42,44], which is one reason among others why the COG advocates for upfront nephrectomy. Additionally, use of central pathology review has identified that many patients with diffuse anaplasia are not recognized as having anaplasia on institutional pathology review[42,45], which highlights the value of pathological expertise in making this diagnosis. This observation is a key factor that prompted the requirement for centralized pathology review for eligibility in COG Wilms tumour trials.

The COG integrates post-chemotherapy histology into risk stratification for patients with bilateral FHWT, treating these patients with neoadjuvant chemotherapy and resection, followed by adjuvant

treatment based on stage and histological classification, which has been adapted from the SIOP classification but is not identical to it[2,46–48]. In the upcoming unilateral FHWT trial, histological types that affect potential de-escalation or escalation of therapy will include upfront epithelial Wilms tumour, and post-chemotherapy completely necrotic or blastemal-predominant Wilms tumour.

Age. In NWTS-1, age <2 years was identified as a favourable prognostic factor in a subset of patients with stage I disease[17], although the results of NWTS-2 suggested that the inferior outcomes observed among patients of increased age were attributable to advanced stage or anaplastic histology[18]. In one United Kingdom Childhood Cancer Study Group (UKCCSG) analysis, increased age was associated with poor survival in those with stage I disease when treated with vincristine only[49], with results of other UK studies showing age >4 years to be an independent risk factor[49,50]. Age has not been shown to be significant in other multivariate analyses[30,51,52]. In SIOP–RTSG studies, age cohorts with cut-off points of 2, 4 or 10 years of age were associated with inferior EFS compared with age 6 months to 2 years in multivariate analyses; however, OS was not significantly different except in patients >4 years[50]. In NWTS-4, age >4 years lost significance as an adverse prognostic factor when adjusted for histology and lymph-node involvement[53]. For patients with stage I FHWT enrolled in AREN03B2, no association with age and EFS was demonstrated[54].

Age has not been used in risk stratification for patients with high-stage FHWT. Some data indicate that substantially older (≥15 years) patients with Wilms tumour ('adult Wilms tumour' or 'adolescent and adult Wilms tumour') have poor outcomes[55,56]; however, the reasons for this observation are unclear. Hypotheses for differential outcomes include possible differences in tumour genetics or treatment tolerance[55,57–59].

Tumour nephrectomy weight. The combination of age <2 years and TNW (the weight of the nephrectomy specimen including tumour and kidney) <550 g was identified as a favourable characteristic of FHWT in the 1970s[60,61]. Increasing intensity of treatment did not improve the outcome of patients with these characteristics; therefore, chemotherapy might not be necessary[61]. An initial study including eight patients with these characteristics treated without chemotherapy resulted in only one recurrence, which occurred as a metachronous tumour in the contralateral kidney in a child with a genitourinary anomaly, raising the possibility of a genetic predisposition (new primary tumour rather than relapse)[62]. Analyses of NWTSG studies suggested that the risks of adjuvant chemotherapy might outweigh the benefits for this subset of patients[63,64], subsequently termed having very-low-risk (VLR) Wilms tumour.

Validation of a very-low-risk subgroup. In NWTS-5 patients with VLR Wilms tumour were hypothesized to maintain excellent outcomes without chemotherapy[21]. Results showed that 5-year EFS was 84% and 5-year OS was 98% among 77 patients with VLR disease treated initially with surgery alone[65]. The study was closed when the EFS fell below 85% meeting prespecified study closure parameters; however, because OS remained high, the strategy of surgery only was further studied in AREN0532, in which 116 patients with VLR disease (requiring real-time central review confirming negative lymph nodes, and lack of a predisposition syndrome or radiological contralateral nephrogenic rests) were enrolled[7]. The results of this study demonstrated excellent results, with 4-year EFS of 89.7% and 4-year OS of 100%[7].

Table 4 | Children's Oncology Group staging of Wilms tumour

Stage	Criteria	Changes from NWTS
I	Tumour is limited to the kidney AND completely resected Renal capsule is intact Tumour is not ruptured or biopsied before removal No involvement of the renal sinus No tumour at or beyond the resection margins All lymph nodes sampled are negative	NA
II	Tumour is completed resected with no tumour at or beyond the resection margins All lymph nodes sampled are negative Tumour extends beyond the kidney with one of the following: Penetration of the renal capsule Extensive invasion of the soft tissue of the renal sinus Blood vessels outside of the renal parenchyma (including the renal sinus) contain tumour cells Vascular extension of the tumour completely removed en bloc with the nephrectomy specimen	NA
III	Residual, non-haematogenous tumour confined to the abdomen, including: Gross residual tumour (for example, any biopsy of a renal tumour or non-renal tumour, incomplete resection) Biopsy performed before tumour removal Microscopic residual tumour (for example, tumour at the surgical resection margin) Lymph nodes in the abdomen or pelvis involved by the tumour Tumour implants on the peritoneal surface Tumour has penetrated through the peritoneal surface Tumour rupture before surgery Intraoperative tumour spillage Tumour removed in more than one piece (including vascular extension removed separately from the nephrectomy specimen)	Addition of upfront biopsy as the sole criterion for stage III; in NWTS, stage II was allowed if patients underwent resection after biopsy and otherwise met the stage II criteria
IV	Haematogenous metastases (for example, lung, liver, bone, brain) Lymph nodes outside the abdomen or pelvis involved by the tumour	NA
V	Tumour involving bilateral kidneys at diagnosis	NA

NA, not applicable; NWTS, National Wilms Tumor Study.

Loss of heterozygosity of 1p and 16q. Analysis of NWTS-3 and NWTS-4 studies showed that LOH of 1p or 16q, present in 12% and 17% of patients with FHWT, respectively, was associated with reduced relapse-free survival and OS[66]. In NWTS-5, the hypothesis that LOH at these loci was associated with a poor prognosis was prospectively tested[5]. Risk of relapse and death was increased with either, and the worst outcomes occurred in patients with combined LOH of both 1p and 16q (henceforth referred to as 'combined LOH')[5]. In AREN0532 and AREN0533, intensified therapy for patients with combined LOH was prospectively studied, improving survival to a 4-year EFS of 87.3% for stages I or II

(versus 68.8% in NWTS-5, $P = 0.042$), and 90.2% for stages III or IV (versus 61.3% in NWTS-5, $P = 0.001$)[9].

Lung metastatic response to chemotherapy. In NWTSG studies, all patients with pulmonary metastases identified on chest X-ray were treated with whole-lung irradiation (WLI), whereas radiotherapy for CT-only lung metastases was left to the discretion of the treating institution[22]. Differential outcomes for patients with complete versus incomplete response of lung nodules to an initial 6 weeks of chemotherapy were first identified in SIOP studies[67]. In AREN0533, de-intensification of therapy (continued DD-4A with omission of WLI) for patients with lung-only metastases with rapid complete response (RCR) of pulmonary nodules to two cycles of chemotherapy, and intensification (regimen M with WLI) for those whose pulmonary disease had a slow incomplete response (SIR) after two cycles, were prospectively studied. Patients with RCR had a 4-year EFS of 79.5% (versus an expected 85% based on NWTS-5) and an OS of 96%; and those with SIR had an EFS of 90% (versus an expected 75%) and OS of 96%[8]. 1q status had a substantial effect on the EFS of patients with RCR, but not those with SIR.

Extrapulmonary metastases. Most patients with stage IV FHWT present with pulmonary metastases alone, but others present with extrapulmonary metastases with or without lung involvement, with liver being the most common extrapulmonary metastatic site[68]. In NWTS-4 and NWTS-5, there was no significant difference in EFS or OS between patients with stage IV FHWT with liver (with or without lung metastases) ($n = 96$) and those with stage IV FHWT with lung-only metastases ($n = 513$)[68]. In AREN0533, patients with extrapulmonary metastases were assigned to chemotherapy with regimen M, intensified from DD-4A received in NWTS-5. In a COG analysis in which patients with extrapulmonary metastases from NWTS-5, AREN0533 and AREN03B2 were pooled, outcomes were inferior for patients with extrapulmonary metastases (observed 4-year EFS of 77.3%)[69], compared with those with lung-only stage IV (EFS 85.4%) treated using the AREN0533 treatment strategy[8]. No statistical differences in EFS or OS were found between patients with extrapulmonary metastases treated in AREN0533 compared with those in NWTS-5, but the small cohort sizes, heterogeneous patient characteristics and metastatic sites, flawed data collection, and lack of consistent local control management confounded assessment of the role of regimen M; thus, the optimal chemotherapy for patients with extrapulmonary metastases remains uncertain[69]. The role and quality of evidence supporting local treatments of sites of extrapulmonary metastases vary by metastatic site. Radiotherapy is recommended for nearly all metastatic sites, but the role of surgery for extrapulmonary metastases is not certain, and has not been strictly prescribed or reported in past studies.

Apart from metastatic sites of the liver, brain and bones, the specifics of what defines extrapulmonary metastasis have not been clearly established. For the purposes of AREN03B2 and AREN0533, certain findings (such as pulmonary tumour emboli, malignant pleural effusions and extra-abdominal lymph nodes (cervical and intrathoracic or mediastinal)), when identified at institutional review, were consistently designated as extrapulmonary metastases, a decision made by consensus opinion of the central reviewers, and not based on data. Notably, peritoneal implants or pelvic tumours identified at diagnosis, presumed to be a result of local 'drop mets' from tumour rupture rather than haematogenous spread, are not considered sites of extrapulmonary metastases.

Retrospectively studied prognostic factors

Some prognostic features of FHWT have been identified retrospectively, and have yet to be prospectively studied or integrated into risk stratification. These include epithelial histology; 1q gain; LOH 11p15; combination of LN involvement with isolated LOH of 1p or 16q; and post-chemotherapy blastemal-predominant histology in the COG treatment context.

Features relevant to very-low-risk disease. Features relevant to VLR disease include molecular characteristics, epithelial histology and TNW.

Molecular features of VLR disease can be used to predict risk of relapse. The results of AREN0532 validated findings from NWTS-5 that LOH of 11p15 is associated with relapse in patients with VLR Wilms tumour treated without chemotherapy[5,7]. LOH of 11p15 was present in 37% of patients with VLR Wilms tumour (40 of 108), with 20% (8 of 40) experiencing disease relapse, accounting for 67% of all VLR relapses (8 of 12)[7]. Loss of imprinting of 11p15 was present in 7.4% (8 of 108 patients), and was also associated with relapse in 25% (2 of 8 patients). Combined LOH of 1p and 16q was rare in patients with VLR (3 of 108); 33% (1 of 3 patients) relapsed, but small numbers preclude statistical conclusions from being drawn[7]. Last, 1q gain, a poor prognostic factor in stage I (non-VLR) disease in NWTS-5 (ref. 53) and in higher stage disease[14], was found in 5.5% (6 of 108) of patients with VLR. Of these 6 patients, 1 experienced relapse, but small numbers limit conclusions about its prognostic influence in patients with VLR disease[7].

Regarding epithelial histology, Wilms tumours are designated as 'predominant' for a particular histopathological component (epithelial, blastemal or stromal) if that component comprises >66% of the tumour histology[45]. The importance of post-chemotherapy Wilms tumour histological classification is well-described by SIOP[46] and increasingly in the COG context, but the importance of pre-chemotherapy histology is less clear. To evaluate the hypothesis that epithelial-predominant Wilms tumours might not require adjuvant chemotherapy[70], patients with stage I epithelial-predominant Wilms tumour in AREN03B2 ($n = 177$) were analysed. The results revealed a 4-year EFS of 96.2% and OS of 100%[71]. Overall, 117 patients received regimen EE-4A (4-year EFS of 96.1%), and 57 had nephrectomy only (4-year EFS of 98.2%); $P = 0.549$ (ref. 71). Low-risk epithelial Wilms tumour has been associated with *TRIM28* loss-of-function mutations[72], further supporting the view that epithelial Wilms tumour is a distinct and favourable FHWT subtype, which can also be distinguished from metanephric tumours that harbour BRAF V600E mutation[73–75].

Tumour weight was not prognostic in multivariate analysis of patients with stage I disease treated with vincristine monotherapy in a UKCCSG study[49], despite previous results suggesting that it might be[60,61,76]. Analysis of 658 patients with stage I FHWT enrolled in AREN03B2 demonstrated that TNW had no significant association with EFS[54]. As TNW does not influence risk stratification for any other FHWT subgroups, whether TNW is a prognostic factor when other variables (for example, tumour biology) are considered is now uncertain.

1q gain. Retrospective analysis of data from NWTS-5 showed that 1q gain was associated with increased stage, present in 20%, 26%, 32% and 44% of stages I, II, III and IV, respectively, and had an adverse effect on survival (8-year EFS 77% versus 90%, $P < 0.001$) that was observed across stages[14]. This analysis showed that 1q gain and combined LOH are not independent events, and that in patients with 1q gain, combined LOH no longer influenced outcomes (however, it remains prognostic in

the absence of 1q gain). The influence of 1q gain on survival is greatest among patients with stage IV disease (EFS 64% versus 91% and OS 74% versus 92%; all patients treated with DD-4A)[14]. Similar prevalence and differences in outcome by 1q gain status have been observed in SIOP studies[77,78].

1q status was not prospectively incorporated into AREN0533, but retrospective examination of its influence in the stage IV lung-only group revealed that among patients with RCR (who received DD-4A without WLI), those with 1q gain had strikingly lower 4-year EFS than those without 1q gain (EFS 57% versus 86%, $P = 0.0013$)[8]. Patients in the SIR group (who received regimen M and WLI) with 1q gain had statistically similar outcomes to those without 1q gain (4-year EFS of 86% versus 92% ($P = 0.15$), and OS 93% versus 96% ($P = 0.45$))[8], suggesting that the intensified regimen overcame the adverse prognostic importance of 1q gain in this subgroup.

Combination of lymph node involvement with isolated loss of heterozygosity. Data from AREN0532 demonstrated that patients with stage III disease with abdominal lymph nodes positive for tumour and with LOH of 1p or 16q (henceforth referred to as 'isolated LOH') had reduced EFS of 74% (OS 92%), whereas those with negative lymph nodes and without LOH had outstanding outcomes (EFS 97% and OS 99%)[11]. A subsequent analysis, in which data from similarly treated patients from AREN03B2 and AREN0532 were combined, supported the observation that patients with positive lymph nodes and isolated LOH have significantly worse 4-year EFS (77% versus 91%) than those with stage III disease with negative lymph nodes or no LOH (HR 3.01, $P = 0.0004$)[34]. These results reinforced the importance of LNS for prognostication and risk stratification.

Post-chemotherapy histology. A minority of patients (~20%) in the COG setting undergo upfront tumour biopsy and delayed nephrectomy after neoadjuvant chemotherapy[11], owing to surgical contraindications to upfront nephrectomy. The influence of post-chemotherapy histology (classified using a system analogous to the one developed by SIOP[2,11,46,48]) was examined in AREN0532 for such patients with stage III disease resulting from initial diagnostic biopsy to confirm FHWT[11]. Low-risk histology was defined as completely necrotic, high-risk histology as blastemal-predominant histology and intermediate-risk histology encompassing all other non-anaplastic histologies. Outcomes varied by histology, with particularly poor outcomes among patients with high-risk histology (7 patients, 4-year EFS 28.6%) and favourable outcomes among those with low-risk (7 patients, EFS 100%) or intermediate-risk (63 patients, EFS 90.5%) histologies[11].

Another retrospective study of data from patients with overall stage III or IV disease enrolled in AREN0532, AREN0533 or AREN03B2-only who underwent delayed nephrectomy supported the notion that patients with post-chemotherapy blastemal-predominant histology have the worst outcomes compared with other histologies, and patients with low-risk histology have the best outcomes[12].

Peritoneal and pelvic metastases. Peritoneal and pelvic metastases are rare but should be looked for and noted by the surgeon at the time of the diagnostic procedure, as they confer a stage III designation and are an indication for WAI. Increased intra-abdominal recurrences occurred in NWTS-2 when radiotherapy fields were 'too small' (that is, flank radiotherapy when WAI was indicated)[79]. A review of patients with abdominal stage III disease enrolled in NWTS-4 and NWTS-5 showed that 57 of 1,584 (3.5%) had peritoneal metastases. The use of WAI for the majority (82%) of patients with peritoneal metastases in NWTS-4 and NWTS-5, along with resection and DD-4A chemotherapy resulted in EFS and OS that were similar to those with abdominal stage III disease without peritoneal metastases[28].

Features of less certain importance

In staging Wilms tumour, several findings, such as tumour pulmonary emboli, pleural effusions, malignant ascites and enlarged extra-abdominal lymph nodes, with uncertain prognostic importance, are occasionally encountered, and their inclusion in staging decisions has been made for patients enrolled in AREN03B2 to facilitate cohesive clinical classification for therapeutic studies. For these situations, staging decisions were made by expert consensus among the multidisciplinary AREN03B2 study committee and central review expert panel in the absence of definitive published data (Table 5). Because these decisions determined disease stage, in some scenarios, they would have affected assigned treatments, including chemotherapy regimen and/or receipt of radiotherapy[69].

Pleural effusions. In one single-centre study including 233 patients with Wilms tumour, pleural effusions were identified in 4.3% of patients, all occurring on the side of the primary kidney tumour. Only 2 of the 10 patients underwent thoracentesis (both were negative for tumour cells), and all 10 survived with stage-based treatment that was not adjusted for the effusion[80]. In a larger, multicentre study including 1,259 patients with Wilms tumour, 7.5% presented with a pleural effusion at diagnosis[81]. Overall, 14 of 94 underwent thoracentesis; 3 of these had malignant cells identified using cytology, all of whom had concomitant pulmonary metastatic disease[81]. Thoracentesis might help from a therapeutic perspective, but the diagnostic and prognostic implications are uncertain based on the existing literature. Nonetheless, current consensus is that pleural fluid with histologically identified malignant cells is considered a site of extrapulmonary metastasis and an indication for radiotherapy to the involved lungs and pleura.

Tumour pulmonary emboli. Tumour pulmonary emboli can be identified using diagnostic chest CT, particularly when performed with contrast medium. Because they are, by definition, haematogenous tumour spread, they have been, and will continue to be, considered extrapulmonary metastases and therefore an indication for radiotherapy[69]. The optimal radiotherapy field, either WLI or involved lungs, remains uncertain as it has not been specified or studied in previous FHWT trials.

Extra-abdominal lymph nodes. Lymph nodes outside the abdominal cavity (such as mediastinal, supraclavicular or cervical) that are pathologically confirmed to be Wilms tumour are considered to be extrapulmonary metastases; however, extra-abdominal lymph nodes are an uncommon site of Wilms tumour spread at initial presentation[69] and not always pathologically examined. Furthermore, enlarged abdominal lymph nodes on imaging are frequently reactive rather than tumour metastases[31]. Thus, the prognostic and staging importance of enlarged extra-abdominal lymph nodes on cross-sectional imaging without pathological confirmation of Wilms tumour is uncertain, and providers must make a staging determination based on the clinical context of the patient.

Peritoneal fluid. The presence and characteristics of peritoneal fluid should be noted at the time of surgical resection as it can suggest preoperative tumour rupture[82]. Peritoneal fluid is sometimes sampled

Table 5 | Levels of evidence for favourable-histology Wilms tumour risk-stratification features

Level of evidence[117]	Feature	Part of updated COG risk stratification?
I	Stage	Yes
	Histology	Yes
	LOH of 1p and 16q	Yes
	Lung metastatic response to chemotherapy	Yes
II	Lymph node sampling	Yes
	Age	Yes
	Tumour nephrectomy weight	No
	Extra pulmonary metastasis[a]	Yes
	11p15 status in patients with very-low-risk disease	Yes
	Epithelial-predominant histology	Yes
	1q gain	Yes
	Lymph node involvement with isolated LOH 1p/16q	Yes
	Post-chemotherapy blastemal-predominant histology	Yes
	Peritoneal metastases	Yes[b]
	Partial nephrectomy for unilateral Wilms tumour	No
	Unilateral multifocal tumours	No
III	Tumour involving adrenal gland	No[b]
	Inferior vena cava thrombus	No[b]
IV	Extrarenal Wilms tumour	No
V	Malignant pleural effusions	Yes[b]
	Tumour pulmonary emboli	Yes[b]
	Extra-abdominal lymph nodes not pathologically sampled	No[b]
	Malignant ascites (peritoneal fluid)	No
	Contralateral nephrogenic rests	No
	Tumour in renal collecting system	No[b]
	Genetic predisposition to Wilms tumour	Yes[c]

Data collated from refs. 5,7–9,11,12,14,17,22–24,27,28,34,41,53,54,60,61,66,67,69,71,79–81,83–86,88,100–102,105,106,108,109. Level I is a high-quality prospective cohort study with adequate power or a systematic review of these studies. Level II is a reduced-quality prospective cohort study, retrospective cohort study, untreated healthy participants from a randomized control trial or a systematic review of these studies. Level III is a case–control study or a systematic review of these studies. Level IV is case series. Level V is an expert opinion, a case report or clinical example, or evidence based on physiology, bench research or 'first principles'. LOH, loss of heterozygosity. [a]Some features considered extrapulmonary metastasis have reduced-quality evidence. [b]Feature is incorporated into stage, but not independently factored into risk stratification. [c]Patients with genetic predisposition to Wilms tumour are excluded from treatment with nephrectomy only.

for cytology in patients with Wilms tumour[83], although it occurs at the discretion of the surgeon and data surrounding this practice are limited. The finding of malignant cells in peritoneal fluid cytology can be a false positive (mononuclear and mesothelial cells can be difficult to distinguish)[84], and even when truly positive, it is of uncertain importance[83]. Caution should be taken before deciding to alter therapy based on cytological evaluation (such as upstaging and/or consideration of WAI), because of poor evidence of the need or benefit of therapy intensification. Thus, in the upcoming COG unilateral FHWT trial, peritoneal fluid cytology will not be evaluated, nor will disease be upstaged or treatment altered based on the presence of malignant ascites.

Partial nephrectomy for unilateral Wilms tumour. In COG protocols, partial nephrectomy for unilateral Wilms tumours is only recommended for patients with Wilms tumour-predisposing conditions or a single functioning kidney in the setting of a nephron-sparing treatment approach, and should occur following neoadjuvant chemotherapy to maximize preservation of kidney parenchyma. In a study including 60 patients who did not have a condition predisposing them to Wilms tumour and had small tumours that were stage I after complete nephrectomy, just 5 (8%) were amenable to an upfront partial nephrectomy[85], indicating that this approach should only rarely be considered. Performance of an upfront partial nephrectomy does not automatically yield a stage or risk adjustment, but positive margins are frequently found, which requires a designation of local stage III. In a study including 39 patients not predisposed to Wilms tumour in AREN03B2 who underwent an upfront partial nephrectomy, 9 (of the 11 with stage III disease) were upstaged for intraoperative tumour spill and/or microscopic residual tumour that probably would have been avoided with complete nephrectomy, exposing them to avoidable treatment intensification[86]. In the SIOP renal tumour protocols, partial nephrectomy for unilateral Wilms tumour is allowed; however, <3% of patients are deemed eligible by pre-defined criteria[87].

The small tumours that might be amenable to upfront partial nephrectomy could also meet criteria for VLR Wilms tumour and be treated with nephrectomy only with excellent survival, and long-term kidney failure rates <1%[7,65,88]. Evidence suggests that in addition to loss of nephrons, reasons for eventual kidney failure include exposure to radiotherapy or anthracyclines[89,90], so preventing treatment intensification for avoidable positive margins will also aid in the preservation of kidney function. Thus, partial nephrectomy for non-predisposed unilateral Wilms tumour is generally discouraged, but can be considered provided that the risks (including being ineligible for treatment with nephrectomy only in a study) and benefits are carefully considered and discussed with the family.

Unilateral multifocal tumours. Patients with unilateral multifocal Wilms tumour, defined as more than one discrete tumour in a single kidney[91], were eligible for the nephron-sparing treatment approach in AREN0534 owing to the concern that they could be at an increased risk of developing of bilateral disease[47]. Treatment in COG unilateral protocols was also permitted for patients who underwent an upfront complete nephrectomy[92,93]. In AREN0534, patients treated with a nephron-sparing approach received preoperative EE-4A chemotherapy[47]; however, among the 10 enrolled patients only 4 underwent partial nephrectomy (6 underwent complete nephrectomy), with one experiencing relapse in the abdomen associated with a positive partial nephrectomy margin[47]. Examination of patients enrolled in AREN03B2 with unilateral multifocal Wilms tumour who underwent an upfront complete nephrectomy has not occurred. Defining who may benefit from a nephron-sparing surgical approach and who may be more optimally be managed with an upfront complete nephrectomy remains an area of active investigation. When upfront nephrectomy reveals multifocal tumours that are all FHWT, some clinicians perform molecular testing on more than one tumour[94]. The prognostic

implication of disparate molecular findings is currently uncertain, so this practice is not considered standard. When performed, the highest risk biological feature should be incorporated into risk stratification.

Staging of multifocal tumours of different histologies. Pathological examination of multifocal tumours within a single kidney sometimes enables identification of different histologies (anaplastic versus FHWT) and stages for discrete tumours[95]. The overall stage and histology for each kidney is designated as the highest stage and 'worst' histology found, such that a kidney with a stage II tumour with diffuse anaplasia and a stage III tumour with FHWT would be classified as a stage III diffuse anaplastic Wilms tumour[27,96].

Contralateral nephrogenic rests. Some patients with a large unilateral renal tumour are found to have a small lesion in the contralateral kidney on imaging[97–99]. Small lesions examined pathologically are often nephrogenic rests; however, the accuracy of imaging in the diagnosis of nephrogenic rests remains poor[100]. Some data indicate an optimal size cut-off of 1.75 cm to distinguish a nephrogenic rest from a Wilms tumour[100]. In AREN03B2, lesions ≥1 cm were centrally defined as 'tumour'; however, final determination was performed by the sites for the purposes of treatment protocol risk assignments[27]. In AREN0534, the management of contralateral lesions depended on the number of lesions, their size, and the age of the patient[27]. Given the subjective nature of these criteria, until future data emerge, decisions concerning how to manage a patient with contralateral nephrogenic rests must be individualized.

Venous extension: inferior vena cava thrombus and renal vein margin. Tumour invasion of the renal vein, inferior vena cava (IVC) and atrium creates special treatment challenges. Renal vein tumour thrombi have been noted in 11% of patients with Wilms tumour, and caval and atrial involvement in 5% and 1% of patients with Wilms tumour, respectively[101,102]. Preoperative ultrasonography and CT will usually help to identify intravascular tumour extension; however, the renal vein and IVC should still be carefully palpated intraoperatively before ligation to rule out tumour extension[82]. Tumour extension into the renal vein and proximal IVC can in most cases be removed en bloc with the kidney[33,103,104], affording the chance to be stage II when a negative margin is achieved. However, primary resection of tumours that extend up the IVC to the retro-hepatic IVC and particularly to the atrium is associated with increased operative morbidity[102]. In these circumstances, preoperative chemotherapy is the recommended approach (after biopsy of the primary tumour) to decrease the size and extent of the tumour thrombus and facilitate safer excision[102].

After division of the renal vein, the vein border can retract[103]. In the setting of renal vein tumour thrombus extending towards the IVC, vein retraction can make the determination of margin status difficult. Direct communication between the surgeon and pathologist is crucial to determine the extent of invasion of the vein wall and tumour thrombus margin status for correct disease staging.

Tumours in the renal collecting system. Wilms tumours can extend into the renal pelvis and down the ureter[105]. During resection, the ureter should be palpated before its division to prevent transection of the tumour and upstaging of the tumour to stage III[82,105]. Gross haematuria might be a sign of tumour extension into the collecting system and warrants consideration of intraoperative, pre-nephrectomy cystoscopy with retrograde pyelogram, which could delineate the presence and extent of invasion[105]. Cystoscopic tumour biopsy results in a stage III designation.

Adrenal gland. Adrenal involvement is not an independent factor for poor prognosis[106], and is designated stage II if resected en bloc with the tumour with a negative margin[107]. The adrenal gland can be left in situ at the time of nephrectomy; however, if it is abutting the tumour it should be removed en bloc with the tumour to avoid a positive margin[106].

Extrarenal Wilms tumour. Wilm tumour sometimes originates outside of the kidney, most commonly in the retroperitoneum, but also in the pelvis and paraspinal or inguinal regions, among others[108,109]. Evidence suggests an association between extrarenal Wilms tumour and horseshoe kidneys, with coexistence of the two seen in almost 13% of reported instances in one series[108]. Most have favourable histology[108], and patient outcomes are similar to those with intrarenal Wilms tumour[109]. Staging of extrarenal Wilms tumour has not always been defined in previous clinical trials, but for COG Wilms tumour studies, extrarenal Wilms tumour cannot be stage I as they are outside the renal parenchyma, and are stage II if resected with a negative margin, or stage III if biopsied or resected with a positive margin[107]. Given their rarity, no standardized treatment exists, although most seem to be managed similarly to intrarenal Wilms tumour[108,109]. Despite the limited data, extrarenal Wilms tumours are eligible for the upcoming FHWT clinical trial and will undergo the same risk stratification as intrarenal tumours, including the requirement for at least one lymph node to be sampled and pathologically confirmed on central review.

Genetic predisposition to Wilms tumour. Many children with Wilms tumour have syndromes that predispose to the development of Wilms tumour[110], including Beckwith–Wiedemann syndrome/spectrum; idiopathic hemihypertrophy/isolated lateralized overgrowth; Denys–Drash syndrome; WAGR (Wilms tumour, aniridia, genitourinary anomalies, range of developmental delays) syndrome; trisomy 18; Simpson–Golabi–Behmel syndrome; and Bohring–Opitz syndrome[111], with novel genes and syndromes emerging[112]. The presence of a predisposition syndrome has not been used in risk stratification per se; however, predisposed patients have been ineligible for the nephrectomy-only treatment strategy for VLR Wilms tumour, with the premise that nephron-sparing surgery should be prioritized in the management of patients who have a predisposition syndrome owing to their risk of chronic kidney disease[88], and the belief that chemotherapy might prevent new tumour development[113]. Additionally, in AREN0534, for patients who underwent biopsy of a bilateral Wilms tumour (many of whom had a genetic predisposition), the biopsy was not (by itself) an indication for radiotherapy, whereas radiotherapy is indicated for all others who undergo biopsy[27]. This approach was based on the added risk of chronic kidney disease from radiotherapy to the preserved kidney.

Levels of evidence for factors that influence FHWT staging and treatment differ, but for the purposes of therapeutic clinical trial development in which similar patients must be assigned the same treatments, standardized and precisely defined staging is needed. The staging definitions used for the study and recommended surgical approaches to diagnostic nephrectomy are outlined in the protocol to help clinicians treating these patients.

Risk stratification recommendations

An updated FHWT risk stratification built on all the available data was needed to justify and support prospective clinical trials, and to

Table 6 | Children's Oncology Group 2024 favourable-histology Wilms tumour treatment stratification

Stage	Age	Molecular Features	Lymph-node positive	Lung-nodule response	Extrapulmonary metastases	Post-chemotherapy histology	Other	AREN2231 final stratum assignment	Relapse risk
I	Any	Normal	NA	NA	NA	NA	Epithelial histology AND no Wilms tumour-predisposing condition[a]	Nephrectomy only	Lowest
I	<4 years	Normal	NA	NA	NA	NA	No Wilms tumour-predisposing condition[a]	Nephrectomy only	
I	Any	Combined LOH, 1q gain OR 11p15 LOH	NA	NA	NA	NA	NA	EE-4A	
I	>4	Any	NA	NA	NA	NA	NA	EE-4A	
II	Any	Normal	NA	NA	NA	NA	NA	EE-4A	
II	Any	Isolated LOH	NA	NA	NA	NA	NA	EE-4A	
III	Any	Normal	Any	NA	NA	NA or low risk or intermediate risk	NA	EE-4A ± radiotherapy[b,c]	
III	Any	Isolated LOH	No	NA	NA	NA or low risk or intermediate risk	NA	EE-4A ± radiotherapy[b,c]	
II	Any	Combined LOH or 1q gain	NA	NA	NA	NA	NA	DD-4A vs VIVA	
IV	Any	Normal	Any	RCR	No	NA or low risk or intermediate risk	NA	DD-4A ± radiotherapy[b]	
IV	Any	Isolated LOH	No	RCR	No	NA or low risk or intermediate risk	NA	DD-4A ± radiotherapy[b]	
III	Any	Combined LOH or 1q gain	Any	NA	NA	NA or low risk or intermediate risk	NA	Regimen M vs MVI+RT	
III	Any	Isolated LOH	Yes	NA	NA	NA or low risk or intermediate risk	NA	Regimen M vs MVI[d]+ radiotherapy	
IV	Any	Combined LOH or 1q gain	Any	Any	No	NA or low risk or intermediate risk	NA	Regimen M vs MVI+ radiotherapy	
IV	Any	Isolated LOH	Yes	Any	No	NA or low risk or intermediate risk	NA	Regimen M vs MVI[d]+ radiotherapy	
IV	Any	Any	Any	SIR	No	NA or low risk or intermediate risk	NA	Regimen M vs MVI+ radiotherapy	Highest
IV	Any	Any	Any	Any	Yes	NA or low risk or intermediate risk	NA	Regimen M vs MVI+ radiotherapy	
III	Any	Any	Any	NA	NA	High risk	NA	Regimen UH-3+ radiotherapy	
IV	Any	Any	Any	Any	Any	High risk	NA	Regimen UH-3+ radiotherapy	

Combined LOH, LOH of both 1p and 16q; Isolated LOH, LOH of either 1p or 16q; LOH, loss of heterozygosity; NA, not applicable; Normal, absence of isolated LOH, combined LOH or 1q gain — LOH of other loci only relevant if specified; RCR, rapid complete response; SIR, slow incomplete response. [a]Wilms tumour-predisposing conditions include (but are not limited to) genetic syndromes such as idiopathic hemihypertrophy or isolated lateralized overgrowth, Beckwith–Wiedemann syndrome, Denys–Drash syndrome, WAGR (Wilms tumour, aniridia, genitourinary anomalies, range of developmental delays) syndrome, trisomy 18, Simpson–Golabi–Behmel syndrome, Bohring–Opitz syndrome and unilateral Wilms tumour with multifocal tumours or contralateral nephrogenic rests. [b]Abdominal radiotherapy (flank or whole abdominal irradiation) for all patients with local stage III disease except those with nonmalignant biology and low-risk post-chemotherapy histology. [c]A subset of patients who undergo delayed nephrectomy after 3–4 cycles of DD-4A will not be eligible for de-escalation to EE-4A or omission of radiotherapy, and will receive DD-4A with abdominal (flank or whole abdominal irradiation) radiotherapy. [d]A subset of patients with positive lymph nodes not discovered until nephrectomy after 3–4 cycles of chemotherapy will not be eligible for regimen M versus MVI randomization and will be directly assigned to regimen M.

inform accurate prognostication in routine clinical care. To develop the recently opened COG FHWT study AREN2231 the study committee reviewed outcomes from the first generation of COG AREN'0' clinical trials, including detailed analyses of patients who were similarly treated and followed only on the AREN03B2 study. The results of these analyses have resulted in an enhanced and expanded risk stratification schema (Table 6) that will be implemented and studied.

The updated risk stratification model

Analyses of features and outcomes of patients enrolled in the 'AREN0' studies have resulted in an enhanced and expanded risk stratification schema (Table 6) that will be implemented and studied in AREN2231. This new model incorporates biological and clinical features not included in the first-generation risk stratification, and modifies or omits some features previously used (Table 2). The COG 2024 FHWT

risk stratification schema (Table 6) incorporates stage, histology, age, LOH of 1p and 16q, response of pulmonary metastases to chemotherapy, presence of extrapulmonary metastases, post-chemotherapy histology, LOH of 11p15, gain of 1q and lymph-node involvement. It eliminates TNW and includes modifications to how histology and age are used to stratify some patients.

The updated risk stratification model is primarily based on current established data; however, some aspects of risk stratification have been implemented without data-driven explorations (Table 5), owing to a compelling need for a consistent clinical staging classification to facilitate therapeutic study enrolment. For these clinical features, such as the presence of pleural effusions, malignant ascites, or tumour pulmonary emboli, the committee considered how staging has been assigned in previous studies, and in the absence of clinical data indicating a change to prior practices was indicated, chose to maintain consistency with prior staging decisions. This choice was unanimous, and motivated by the fact that some of the planned statistical analyses in AREN2231 will be compared with outcomes derived from the historical control cohort. We hope that by documenting these decisions and standardizing the staging definitions for these elements, we can generate needed data to consider future changes to the risk classification and treatment of additional FHWT subgroups. At a minimum, the transparency about how these decisions have been made for these small groups of patients will help to inform the care of patients with FHWT.

Recommendations to enable risk stratification

Accurate patient-specific information is required to ensure that each patient receives appropriate clinical care or clinical trial stratum assignment. To support AREN2231 and the clinical care of patients with FHWT, the study committee developed unanimous recommendations for the surgical management of Wilms tumour, collection of necessary tumour molecular biomarkers, and expert review of all clinical information that goes into risk stratification (Box 1).

First, all patients with a new unilateral renal tumour that could be Wilms tumour should have histological confirmation of the diagnosis, unless the patient has a known or suspected condition that predisposes to Wilms tumour. This recommendation is a longstanding in NWTSG and COG, and is not new to this study or risk stratification system. Second, the recommended upfront diagnostic procedure is a nephrectomy with LNS unless a contraindication to doing so exists. When upfront nephrectomy is not felt to be safe or feasible, tumour biopsy should be performed for histological confirmation, and should not be performed by fine-needle aspiration. These recommendations regarding diagnostic procedures are also consistent with NWTSG and COG practices and recommendations over recent decades.

Owing to the risk of missing anaplasia[42,45], and for potential clinical trial eligibility, central review of histology by an expert renal tumour pathologist is recommended, which can occur through the COG APEC14B1 Project: EveryChild study for eligible patients. Once FHWT is diagnosed, diagnostic tumour tissue should be sent for molecular testing, which can detect prognostic abnormalities that are relevant for risk stratification, including LOH of 1p, 16q and 11p15, and gain of 1q. LOH of 1p and 16q have been previously studied in a prospective trial[9], but the retrospective data on LOH of 11p15 (ref. 7) and gain of 1q (refs. 8,14) support changing clinical management for some patients with FHWT based on the results. Routine performance of this molecular testing has been recommended by the National Comprehensive Cancer Network clinical practice guideline for Wilms tumour[114].

For patients with lung metastases at diagnosis, based on high-quality evidence from AREN0533 (ref. 8), a CT scan should be done after two cycles (6 weeks) of DD-4A chemotherapy to evaluate the response of these nodules, to determine the appropriate chemotherapy, radiation and surgical plans. Finally, because of the multidisciplinary nature of the management of FHWT and the way in which sometimes subjective decisions (for example, about which nodules count as metastases, or whether there was pre-operative tumour rupture) can influence staging and treatment, all patients' tumour pathology, surgical findings, biology and imaging should be reviewed among all care providers, ideally in the context of a multidisciplinary tumour board.

Together these recommendations can ensure that each patient receives the most evidence-based and individualized care.

Conclusions

The overarching goal of clinical investigations into FHWT is to improve care by increasing survival for the patients who fare less well with current therapy than other patients with Wilms tumour, and minimizing potential toxic effects and late effects with reduction of therapy for subgroups who do very well with current therapy while preserving good clinical outcomes.

Updated risk stratification algorithms can help to ensure that patients receive accurate diagnostic, staging and biological assessments, leading to optimal treatment. The new risk stratification outlined in this Consensus Statement will enable enhanced personalized medicine. Findings from the COG study AREN2231 will probably lead to further refinement of this risk stratification in the future.

Box 1 | Children's Oncology Group Renal Tumor Committee recommendations for risk stratification of favourable-histology Wilms tumour

- Histological confirmation of a Wilms tumour is recommended for all patients with a new unilateral renal tumour that could be a Wilms tumour, except for those with known Wilms tumour predisposition
- Upfront nephrectomy with lymph-node sampling is the recommended diagnostic procedure, unless it is not safe or feasible to do so
- Patients who cannot undergo upfront nephrectomy should have a tumour biopsy for histological confirmation. Fine-needle aspiration is discouraged as it does not reliably yield adequate tumour material for necessary molecular studies
- Once favourable-histology Wilms tumour is confirmed, diagnostic tissue should be sent for molecular testing that can detect loss of heterozygosity at 1p, 11p15 and 16q, and gain of 1q
- Central review of histology by an expert renal tumour pathologist is recommended to occur through the Children's Oncology Group central review process for eligible patients
- Re-evaluation of lung nodules seen at diagnosis should occur following completion of two cycles (6 weeks) of DD-4A chemotherapy
- Tumour pathology, surgical findings, biology and imaging should be reviewed among all care providers, ideally in the context of a multidisciplinary tumour board

Last, the importance of risk stratification to improve care strongly underscores the crucial need for a multidisciplinary team approach to the care of patients with FHWT. Each subspecialty has a key and specific role in the risk stratification process. For optimal care, tumour pathology, surgical findings, biology and imaging should be reviewed among all care providers, ideally in the context of a multidisciplinary tumour board. This multidisciplinary article helps to facilitate the accurate determination of stage and risk stratification and ensures optimization of personalized treatment plans.

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