Received: 16 February 2022 | Revised: 9 June 2022 | Accepted: 4 July 2022

DOI: 10.1002/pbc.29906

Pediatric Blood & Cancer

GLOBAL ONCOLOGY: RESEARCH ARTICLE

Evidence-based surgical guidelines for treating children with Wilms tumor in low-resource settings

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Abbreviations: GDG, Guideline Development Group; GRADE, grading for recommendations, assessment, development, and evaluation; GSG, Guideline Steering Group; LMIC, low- to middle-income country; WT, Wilms tumor.

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Abstract

Background: Survival of Wilms tumor (WT) is > 90% in high-resource settings but < 30% in low-resource settings. Adapting a standardized surgical approach to WT is challenging in low-resource settings, but a local control strategy is crucial to improving outcomes.

Objective: Provide resource-sensitive recommendations for the surgical management of WT.

Methods: We performed a systematic review of PubMed and EMBASE through July 7, 2020, and used the GRADE approach to assess evidence and recommendations.

Recommendations: Initiation of treatment should be expedited, and surgery should be done in a high-volume setting. Cross-sectional imaging should be done to optimize preoperative planning. For patients with typical clinical features of WT, biopsy should not be done before chemotherapy, and neoadjuvant chemotherapy should precede surgical resection. Also, resection should include a large transperitoneal laparotomy, adequate lymph node sampling, and documentation of staging findings. For WT with tumor thrombus in the inferior vena cava, neoadjuvant chemotherapy should be given before *en bloc* resection of the tumor and thrombus and evaluation for viable tumor thrombus. For those with bilateral WT, neoadjuvant chemotherapy should be given for 6–12 weeks. Neither routine use of complex hilar control techniques during nephron-sparing surgery nor nephron-sparing resection for unilateral WT with a normal contralateral kidney is recommended. When indicated, postoperative radiotherapy should be administered within 14 days of surgery. Post-chemotherapy pulmonary oligometastasis should be resected when feasible, if local protocols allow omission of whole-lung irradiation in patients with nonanaplastic histology stage IV WT with pulmonary metastasis without evidence of extrapulmonary metastasis.

Conclusion: We provide evidence-based recommendations for the surgical management of WT, considering the benefits/risks associated with limited-resource settings.

KEYWORDS
guidelines, nephroblastoma, surgery, Wilms tumor

1 | INTRODUCTION

Wilms tumor (WT), one of the most common solid tumors, is highly curable with affordable interventions.[1] The majority (90%) of patients with WT in high-income countries survive with chemotherapy, adequate surgical local control, and radiation therapy when indicated. However, survival in low-resource settings remains poor (50% to < 30%), reflecting limitations in resources (physical and human) and a lack of process standardization.[2,3] The World Health Organization's Global Initiative for Childhood Cancer targets WT as one of six index cancers included in attempts to reduce disparities in childhood cancer outcomes.[4] Efforts to address resource limitations include workforce training and shared advocacy to establish sustainable resources required for multimodality therapy and family support. Although guidance from high-income countries is available, it may be difficult to implement in low- and middle-income countries (LMICs) due to differences in resources and health systems. For WT, a limited capacity to manage intraoperative bleeding and limited access to diagnostics and radiation therapy are key factors necessitating the adaptation of guidelines to address specific challenges in LMICs. The aim of this work is to provide resource-sensitive recommendations for the surgical management of pediatric WT in limited-resource settings.

2 | METHODS

2.1 | Clinical practice guidelines

The guidelines were developed following the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method

(Supporting Information Table S1).[5] The primary target audience for these guidelines is surgeons providing care to children with WT, particularly in settings with limited resources. The recommendations are also intended to be used by policymakers and senior managers as the basis for developing national and local WT protocols and policies and for supporting staff education and training.

2.2 | Composition of the guideline steering and development groups

A guideline steering group (GSG) was formed, consisting of two methodologists, two clinicians, and a research associate. The guideline development group (GDG) members were identified through St. Jude Global, the International Society of Pediatric Surgical Oncology, and the Global Initiative for Children's Surgery. This group included content experts and a patient advocate and was constructed to maintain geographic and gender representation.

2.3 | Disclosure and management of potential conflicts of interest

All members of the GSG and GDG provided conflict-of-interest disclosures prior to the voting process.

2.4 | Clinical questions

The key questions addressed were formulated based on the assembled list of priority topics, questions, and critical outcomes from the scoping exercise identified by the GSG and GDG.

2.5 | Outcomes

The GSG and GDG discussed and identified important outcomes for patients undergoing treatment for WT. The following outcomes were considered during the development of the recommendations: overall survival, mortality, tumor spillage, local recurrence, bleeding, complications, intensity of therapy, and wrong therapy.

2.6 | Summary of the evidence

For questions with available data, evidence profiles were produced denoting the certainty of evidence and summary of findings for each outcome. The GDG members were invited to review and comment on all evidence prior to the panel's meeting.

2.7 | Review of the evidence

Selection criteria for each question were determined a priori. Only comparative studies (systematic reviews, randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies) were considered for inclusion. If randomized data were available, data from nonrandomized studies were excluded. Electronic and manual searches were conducted for each question. We searched PubMed and EMBASE through July 7, 2020. Additionally, we manually reviewed the reference lists of all relevant systematic reviews and included studies to find additional eligible studies. The titles and abstracts of all identified references were reviewed by a clinician and a methodologist from the GSG. Studies identified for full-text review were then reviewed by all members of the GSG, and any reasons for exclusion were noted.

Data from included studies were extracted by two members of the GSG. The certainty of evidence from each included study was assessed using the appropriate risk-of-bias tool for each study design. The Cochrane RCT tool was used for randomized controlled trials.[6] The Newcastle-Ottawa tool was used for cohort and case-control studies.[7] QUADAS was used for diagnostic accuracy studies.[8] Data on outcomes from similar studies were pooled when appropriate by using the random-effects model. All analyses were performed using RevMan,[9] and all information was summarized as evidence profile tables.[10]

2.8 | Development of recommendations

All training, deliberations, and voting were conducted virtually. Prior to the panel's discussion, the GSG members presented the background and evidence profile for each key question. The GDG members discussed the benefits and disadvantages for patients, patients' preferences, clinical impact, and the feasibility of each proposed intervention.

2.9 | Grading recommendations

All questions were converted into recommendations prior to anonymous voting. Panelists initially voted for or against each recommendation, followed by a vote on the strength of the recommendation (strong or weak). A simple majority of > 50% was considered in favor or against a recommendation. In the case of a tie, the text of the recommendation was modified to achieve a majority vote for or against the recommendation.

2.10 | External review

The recommendations were peer-reviewed by an external review group, which provided overall feedback on the manuscript but did not change the voting outcomes.

2.11 | Update plan

Guidelines are to be updated every 4 years.

2.12 | Source of funding

This guideline development effort was supported by funds from the American Lebanese Syrian Associated Charities (ALSAC).

TABLE 1 Comparisons of high-volume versus low-volume settings for the treatment of patients with Wilms tumor

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with low-volume center[b]	Risk difference with high-volume center[c]
Overall survival	3848 (3 observational studies)	⨁◯◯◯ VERY LOW [d]	**HR 0.91** (0.72 to 1.14)	80 per 1000	**7 fewer per 1000** (22 fewer to 11 more)
Lymph node sampling	3058 (2 observational studies)	⨁◯◯◯ VERY LOW [d,e]	**RR 0.66** (0.40 to 1.10)	197 per 1000	**67 fewer per 1000** (118 fewer to 20 more)
Tumor spillage	791 (1 observational study)	⨁◯◯◯ VERY LOW [d]	**RR 0.24** (0.12 to 0.49)	126 per 1000	**96 fewer per 1000** (111 fewer to 64 fewer)
Recurrence: Data reported per surgery	757 (1 observational study)	⨁◯◯◯ VERY LOW [d]	**RR 0.70** (0.28 to 1.79)	31 per 1000	**9 fewer per 1000** (22 fewer to 25 more)
Recurrence: Data reported per patient	147 (1 observational study)	⨁◯◯◯ VERY LOW [d]	**RR 0.70** (0.36 to 1.36)	308 per 1000	**92 fewer per 1000** (197 fewer to 111 more)
Radiation therapy	790 (1 observational study)	⨁◯◯◯ VERY LOW [d]	**RR 0.83** (0.69 to 1.00)	395 per 1000	**67 fewer per 1000** (122 fewer to 0 fewer)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI: confidence interval; HR: hazard ratio; RR: risk ratio.

[a]An RR or HR of < 1 favors the intervention group and an HR or RR of > 1 favors the comparison group. An HR or RR of 1 indicates no difference between the intervention and the comparison groups. 95% CI not including 1 in the HR or RR indicates a statistically significant difference in favor of intervention if the 95% CI is < 1 and in favor of comparison in case of > 1.

[b]Represents the risk in the comparison group.

[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.

[d]High risk for representativeness of exposed and unexposed cohorts.

[e]High level of heterogeneity between studies (I^2 value > 60%).

3 | RESULTS

The priority questions guiding the evidence review and synthesis for these guidelines are listed in Supporting Information Table S2. The glossary of terms and phrases and their meanings for this guideline are summarized in Supporting Information Table S3.

4 | RECOMMENDATIONS

4.1 | Preoperative phase

1. The panel recommends expedited initiation of treatment for the management of WT *(Strong recommendation; Certainty of evidence: Very low)*.

4.1.1 | Panel deliberation

WT is a rapidly growing malignancy with a doubling time of less than 2 weeks. Therefore, any delay in diagnosis or initiation of therapy (Supporting Information Table S3) should be avoided.[11] To facilitate the early identification of patients with WT, community awareness should be raised regarding the signs and symptoms of WT, favorable outcomes with timely treatment, and the urgency to seek health care.[12] Strengthening referral networks and prioritizing chemotherapy and surgery for childhood cancer are essential to facilitate access to timely care.[11]

2. The panel suggests surgery at a high-volume setting for patients with WT undergoing resection. *(Weak recommendation; Certainty of evidence: Very low; Table 1)*.

TABLE 2 Chest CT compared with chest X-ray for staging of patients with Wilms tumor

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence(GRADE)	Relative effect(95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with chest X-ray[b]	Risk difference with chest CT[c]
Event-free survival	375 (3 observational studies)	⨁◯◯◯ VERY LOW [d]	**HR 0.46** (0.24 to 0.89)	306 per 1000	**151 fewer per 1000** (222 fewer to 28 fewer)
Overall survival	375 (3 observational studies)	⨁⨁◯◯ LOW	**HR 0.95** (0.54 to 1.67)	135 per 1000	**6 fewer per 1000** (60 fewer to 80 more)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

Abbreviations: CI: confidence interval; HR: hazard ratio.

[a]An HR of < 1 favors the intervention group and an HR of > 1 favors the comparison group. An HR of 1 indicates no difference between the intervention and the comparison groups. 95% CI not including 1 in the HR indicates a statistically significant difference in favor of intervention if the 95% CI is < 1 and in favor of comparison in case of > 1.

[b]Represents the risk in the comparison group.

[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.

[d]Moderate inconsistency ($I^2 = 52\%$).

4.1.2 | Panel deliberation

Cancer units may have the capacity to offer common diagnostic and treatment services; however, pediatric oncologic surgery requires multidisciplinary capacity available at national cancer referral centers.[13–17] When scaling up surgical oncology care (Supporting Information Table S2), it is fundamental to balance the competing priorities of quality and access. National cancer centers should be accessible and well connected with a network of primary health and cancer units to deliver affordable, equitable, and high-quality care. The cost-effectiveness of treating cancer in centers with higher capabilities was shown in the third edition of Disease Control Priorities.[18]

3. The panel recommends abdominal and pelvic cross-sectional imaging for preoperative planning in patients with suspected WT *(Strong recommendation; Certainty of evidence: Very low)*.

4.1.3 | Panel deliberation

Cross-sectional imaging provides more in-depth knowledge of tumor anatomy, including focality and extent, which is important for preoperative surgical planning.[19–24] Surgeons should develop skills to adequately interpret cross-sectional imaging delineating tumor extent and laterality for surgical planning. Although there is a paucity of evidence to compare outcomes of ultrasound-guided management versus cross-sectional imaging–guided management, the latter approach provides more comprehensive images of the tumor and its critical anatomy for the operating surgeon. When cross-sectional imaging is not readily available, abdominal ultrasound imaging may be used to guide therapy and provide valuable details about tumor origin, extent, and laterality.

4. The panel suggests chest computerized tomography (CT)-guided staging for the management of WT. *(Weak recommendation; Certainty of evidence: Very low; Table 2)*

4.1.4 | Panel deliberation

Chest CT is significantly more sensitive than chest X-ray; management guided by chest CT is associated with improved event-free survival but not overall survival.[25–29] Salvage of recurrent WT in LMICs is low, and chest CT in this setting may be more important to avoid relapse. When CT is not available, chest X-ray may guide therapy; however, event-free survival is lower when using this strategy.

5. The panel recommends against biopsy for patients with typical clinical features of WT. *(Strong recommendation; Certainty of evidence: Very low)*

4.1.5 | Panel deliberation

Children who present with typical clinical features of WT (Supporting Information Table S3), including age (> 6 months and < 7 years), symptoms, laboratory test results, and imaging features, should receive neoadjuvant chemotherapy without tissue diagnosis. In the context of limited diagnostic capacity, routinely performing biopsies in patients with typical WT presentation may delay therapy and increase com-

TABLE 3 Neoadjuvant therapy compared with upfront surgical resection for patients with typical clinical features of Wilms tumor

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with Upfront resection[b]	Risk difference with neoadjuvant care[c]
Tumor spillage	342 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	**RR 0.11** (0.04 to 0.31)	210 per 1000	**187 fewer per 1000** (201 fewer to 145 fewer)
Non-Wilms tumor incidence	368 (3 RCTs)	⨁◯◯◯ VERY LOW [d,e,f]	**RR 0.25** (0.00 to 14.74)	111 per 1000	**83 fewer per 1000** (111 fewer to 1527 more)
Overall survival	368 (3 RCTs)	⨁◯◯◯ VERY LOW [d,e,f]	**HR 1.78** (0.46 to 6.86)	172 per 1000	**113 more per 1000** (89 fewer to 554 more)
Recurrence-free survival	239 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	**HR 0.95** (0.62 to 1.47)	563 per 1000	**18 fewer per 1000** (161 fewer to 141 more)
Stage shifting (stage III)	342 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	**OR 0.30** (0.16 to 0.54)	269 per 1000	**170 fewer per 1000** (214 fewer to 103 fewer)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.
Abbreviations: CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: risk ratio.
[a]An RR or HR or OR of < 1 favors the intervention group and an HR or RR or OR of > 1 favors the comparison group. An HR or RR or OR of 1 indicates no difference between the intervention and the comparison groups. 95% CI not including 1 in the HR or RR or OR indicates a statistically significant difference in favor of intervention if the 95% CI is < 1 and in favor of comparison in case of > 1.
[b]Represents the risk in the comparison group.
[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.
[d]Method of randomization and allocation concealment not specified. Also, all trials were open label.
[e]High level of heterogeneity ($I^2 = 87\%$).
[f]Very wide confidence interval for the pooled effect.

plications. Open biopsy can upstage WT, thereby compromising local control.[30,31]

6. The panel recommends biopsy (or upfront surgical resection when safe) for patients with renal tumor with an atypical clinical feature. *(Strong recommendation; Certainty of evidence: Very low)*

4.1.6 | Panel deliberation

Other tumors that are not of renal origin, such as neuroblastoma and Burkitt lymphoma, should be excluded by clinical examination, laboratory investigations, and imaging. Patients who present with primary renal tumors but with clinical features that are atypical of WT should have tissue confirmation to plan therapy appropriately. Atypical presentations of WT include age older than 7 years or younger than 6 months, absence of imaging features that are typical of WT, infants with pulmonary metastases, extrapulmonary/hepatic metastases, lactate dehydrogenase levels more than four times the normal limits, and hypercalcemia (Supporting Information Table S3). In these scenarios, pretherapy biopsy is indicated.[32] Image-guided core needle biopsy, if available, is the approach of choice; open biopsy is associated with the risk of tumor spillage and should be avoided. Alternatively, if the tumor is deemed resectable, then upfront resection may be considered to provide tissue diagnosis and plan appropriate further treatment.

4.2 | Operative phase

1. The panel suggests neoadjuvant chemotherapy for the treatment of patients with the typical clinical features of WT. *(Weak recommendation; Certainty of evidence: Moderate; Table 3)*

4.2.1 | Panel deliberation

Neoadjuvant chemotherapy goals are to decrease tumor size, prevent tumor spillage, and risk-stratify postoperative treatment based on tumor response. Neoadjuvant chemotherapy is also associated with lowering the incidence of tumor spillage and decreasing the stage of the disease.[33–35] This may be particularly relevant in limited-resource settings, where tumor stage at diagnosis is mostly advanced, and therapy intensification is challenging because of barriers to accessing radiation therapy and supportive care. In some settings, upfront surgical resection is considered a measure to adapt to issues related

TABLE 4 Open surgery compared with laparoscopic surgery for Wilms tumor

Outcomes	No. of participants (studies)Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with laparoscopic surgery[b]	Risk difference with open surgery[c]
Tumor rupture	94 (2 observational studies)	⨁◯◯◯ VERY LOW [d,e]	**OR 0.32** (0.01 to 8.23)	21 per 1000	**14 fewer per 1000** (21 fewer to 130 more)
Recurrence	94 (2 observational studies)	⨁◯◯◯ VERY LOW [d,e]	**OR 3.21** (0.60 to 17.20)	43 per 1000	**82 more per 1000** (17 fewer to 391 more)
Survival rate	77 (2 observational studies)	⨁◯◯◯ VERY LOW [d,e]	**OR 0.35** (0.01 to 9.38)	967 per 1000	**56 fewer per 1000** (742 fewer to 30 more)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

Abbreviations: CI: confidence interval; OR: odds ratio.

[a]An OR of < 1 favors the intervention group and an OR of > 1 favors the comparison group. An OR of 1 indicates no difference between the intervention and the comparison groups. 95% CI not including 1 in the OR indicates a statistically significant difference in favor of intervention if the 95% CI is < 1 and in favor of comparison in case of > 1.

[b]Represents the risk in the comparison group.

[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.

[d]Average volume of tumors in the two groups was significantly different thus the groups were not comparable.

[e]Very wide confidence interval.

to chemotherapy supply chain and accessibility. In these cases, surgical resection is performed at the time of diagnosis at the reference center, followed by chemotherapy close to the patient's residence. Upfront resection may prevent the administration of inappropriate therapy in a small percentage of patients and may help select patients with very low–risk WT who can be treated with surgery alone. However, a surgery-only approach is more appropriate in the context of advanced diagnostic capacity supporting molecular and genomic tumor analysis.[36,37]

8. The panel suggests adequate transperitoneal laparotomy incision for resection of WT. *(Weak recommendation; Certainty of evidence: Very low; Table 4)*

4.2.2 | Panel deliberation

WT surgical oncology principles include optimal visualization of vital anatomical structures to avoid injury, minimal tumor handling to prevent tumor spillage, and adequate surgical staging, particularly with lymph node sampling. Minimally invasive surgery is an attractive approach for treating small tumors; however, it should not compromise staging, lymph node sampling, or prevention of tumor capsule injury.[38–41]

9. The panel recommends adequate and documented surgical staging for the management of WT. *(Strong recommendation; Certainty of evidence: Very low)*

4.2.3 | Panel deliberation

Postsurgical therapy relies on pathologic staging and surgical staging. In some scenarios, especially in the context of limited diagnostic capacity, documented surgical findings may be the only indicator of tumor spillage. Failure to perform lymph node sampling results in suboptimal tumor staging. This may lead to inadequate therapy or, conversely, to overtreatment with associated potential toxicities. Adequately documented surgical staging should include lymph node sampling and documentation of local invasion, seeding or tumor spillage, and vascular extension (Supporting Information Table S3).[30,42–47]

10. The panel recommends sampling of lymph nodes at the time of resection of WT; pathologic assessment of lymph node histology before and after chemotherapy is feasible and of value in staging. *(Strong recommendation; Certainty of evidence: Very low)*

4.2.4 | Panel deliberation

Determining lymph node involvement by histology is feasible both before and after neoadjuvant chemotherapy.[48] Lymph node sampling is an integral part of staging and should be completed at the time of tumor resection, regardless of whether neoadjuvant chemotherapy was given.[30,42–47] At the time of sampling, five to seven lymph nodes should be obtained to reduce the risk of a false-negative finding.[43,46]

TABLE 5 Neoadjuvant chemotherapy compared with upfront surgical resection for patients with Wilms tumor and inferior vena cava thrombus extension

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with upfront resection[b]	Risk difference with neoadjuvant chemotherapy[c]
Need for cardiovascular bypass	312 (5 observational studies)	⨁◯◯◯ VERY LOW[d,e,f]	**OR 0.46** (0.19 to 1.11)	213 per 1000	**102 fewer per 1000** (164 fewer to 18 more)
Complications	282 (4 observational studies)	⨁◯◯◯ VERY LOW [d]	**OR 0.37** (0.18 to 0.78)	257 per 1000	**143 fewer per 1000** (198 fewer to 44 fewer)
Survival	75 (2 observational studies)	⨁◯◯◯ VERY LOW [d,f]	**OR 1.84** (0.29 to 11.80)	909 per 1000	**39 more per 1000** (166 fewer to 83 more)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

Abbreviations: CI: confidence interval; OR: odds ratio.

[a]An OR of < 1 favors the intervention group and an OR of > 1 favors the comparison group. An OR of 1 indicates no difference between the intervention and the comparison group. 95% CI not including 1 in the OR indicates a statistically significant difference in favor of intervention if the 95% confidence intervals is < 1 and in favor of comparison in case of > 1.

[b]Represents the risk in the comparison group.

[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.

[d]Significant differences between groups in confounding variables.

[e]High level of heterogeneity between groups ($I^2 = 80\%$).

[f]Very wide confidence interval for the pooled effect.

11. The panel recommends neoadjuvant chemotherapy for the management of WT with inferior vena cava thrombus extension. *(Strong recommendation; Certainty of evidence: Very low; Table 5)*

4.2.5 | Panel deliberation

Neoadjuvant chemotherapy is associated with the mitigation of complications during the surgical resection of WT with tumor thrombus in the inferior vena cava. Also, the need for cardiopulmonary bypass may be reduced in patients with pretreated supra-diaphragmatic vena cava thrombus.[21,49–52] Neoadjuvant chemotherapy should be used in all patients with WT and tumor thrombus in the inferior vena cava; this is particularly relevant in limited-resource settings.

12. The panel recommends evaluating the presence of viable tumor cells within the thrombus for patients with WT and inferior vena cava extension. *(Strong recommendation; Certainty of evidence: Very low)*

4.2.6 | Panel deliberation

Up to two thirds of tumor thrombi include viable tumor cells.[53,54] Viable tumor thrombus in the context of incomplete macroscopic resection increases the risk of WT relapse and death.[53,54] When complete gross resection of the tumor thrombus is achieved, the viability of the thrombus may be considered in determining the need for radiation therapy.

13. The panel recommends neoadjuvant chemotherapy followed by *en bloc* surgical resection of WT with the inferior vena cava thrombus extension. *(Strong recommendation; Certainty of evidence: Very low)*

4.2.7 | Panel deliberation

Intravascular tumor extension increases the complexity of surgical resection and is associated with an increased risk of bleeding and other complications; however, resection is an integral part of the local control strategy of tumor thrombus. Complete resection of the tumor thrombus should be the goal of surgery whenever possible.[53,54] WT with inferior vena cava extension should be managed in a referral center. Extending neoadjuvant therapy beyond 6 weeks is not associated with improved surgical resection, further thrombus regression, or survival advantage.[55]

14. The panel recommends neoadjuvant chemotherapy for 6 to 12 weeks for patients with bilateral WT requiring nephron-

sparing surgery. *(Strong recommendation; Certainty of evidence: Very low)*

4.2.8 | Panel deliberation

Tumor response to chemotherapy should be assessed at 6 weeks and 12 weeks; maximal tumor shrinkage occurs within the first 12 weeks of neoadjuvant chemotherapy.[56] Tumors that show no response to chemotherapy after 6 weeks should be resected to prevent the side effects of protracted chemotherapy. Protracted chemotherapy may subject patients with stromal-type tumor to unnecessary toxicities or delay appropriate therapy for patients with anaplasia.

15. The panel suggests not to routinely use complex hilar techniques, including continuous vascular clamping and bench surgery, for bleeding control in patients with bilateral WT requiring nephron-sparing surgery. *(Weak recommendation; Certainty of evidence: Very low)*

4.2.9 | Panel deliberation

Large series have demonstrated that nephron-sparing surgery can be successfully completed using intermittent manual compression.[57,58] However, selected patients may require more complex hilar control maneuvers. Surgeons should avoid prolonged ischemia (more than 20 min)[59,60] of the residual renal tissue, as it is associated with adverse outcomes of renal function.

16. The panel suggests intraoperative histologic confirmation of uncertain margins in patients with WT requiring nephron-sparing surgery. *(Weak recommendation; Certainty of evidence: Very low)*

4.2.10 | Panel deliberation

Intraoperative margin biopsy should be considered for areas of uncertain margins and potential residual disease. Frozen sections, however, are not needed routinely, especially when the tumor was resected with either a margin of normal renal parenchyma or an intact capsule.

17. The panel suggests that nephron-sparing surgery not be performed in patients with unilateral WT. *(Weak recommendation; Certainty of evidence: Very low; Table 6)*

4.2.11 | Panel deliberation

Nephron-sparing surgery for unilateral WT may be associated with an increased risk of tumor spillage and is not the standard of care.[61–65] Nephron-sparing surgery may be feasible, especially in small polar tumors; however, the primary priority is to achieve complete tumor resection with negative margins. Nephrectomy for unilateral WT is associated with high overall survival and high recurrence-free survival, with an extremely low incidence of renal failure in patients who do not have cancer-predisposition syndrome. Nephron-sparing surgery is indicated primarily for patients with unilateral WT in the context of cancer-predisposition syndrome or for those who have only one kidney.

4.3 | Postoperative phase

18. The panel suggests postoperative abdominal radiation therapy within 14 days of surgery for patients with WT who require adjuvant radiation therapy. *(Weak recommendation; Certainty of evidence: Very low)*

4.3.1 | Panel deliberation

Postoperatively, patients who need radiation therapy, especially those with high-risk WT, should be referred to a radiation oncologist within one week of surgery to receive abdominal radiation within 14 days. A radiation oncologist should be part of the multidisciplinary team discussion of all patients at diagnosis, so referral and need for radiation therapy can be anticipated. Delayed radiation therapy of the abdominal primary tumor in nonmetastatic patients is associated with suboptimal local control.[66–68] In contrast, for patients with metastatic disease, radiation of the abdominal primary within 14 days post nephrectomy is of no clear significance. As these patients will be treated with 6 weeks of chemotherapy upfront, they will likely undergo surgical resection after neoadjuvant chemotherapy. Therefore, in these patients, abdominal irradiation can be performed at the same time as lung irradiation (when indicated). Suboptimal nutritional status of patients should be considered when combining whole-lung radiation therapy with flank versus whole-abdomen radiation therapy.

19. The panel suggests that resection of residual pulmonary oligometastasis after completion of chemotherapy (when feasible) be considered in a setting of local protocols that allow the omission of whole-lung irradiation in patients with favorable histology, stage IV WT with pulmonary metastasis. *(Weak recommendation; Certainty of evidence: Very low)*

4.3.2 | Panel deliberation

The decision to omit whole-lung irradiation is based on tumor biology, histological risk group of the abdominal primary, and chemosensitivity and can be applied in the context of local treatment protocols. Lung irradiation can be avoided for patients with nonanaplastic histology without evidence of extrapulmonary metastasis who are complete responders (i.e., those who have no residual pulmonary metastases on a chest CT after chemotherapy). In patients with residual post-chemotherapy oligometastasis that are amenable to resection, radiation therapy can be omitted if there was no residual viable tumor in the

TABLE 6 Nephron-sparing surgical resection compared with radical nephrectomy for patients with unilateral Wilms tumor

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)[a]	Anticipated absolute effects associated with undesirable outcome	
				Risk with radical nephrectomy[b]	Risk difference with nephron-sparing resection[c]
Tumor capsule rupture	2905 (4 observational studies)	⨁◯◯◯ VERY LOW [d]	**OR 3.27** (1.64 to 6.52)	30 per 1000	**62 more per 1000** (18 more to 137 more)
Local recurrence	3712 (5 observational studies)	⨁◯◯◯ VERY LOW [d]	**OR 1.74** (0.67 to 4.57)	21 per 1000	**15 more per 1000** (7 fewer to 68 more)
5-year survival	3678 (4 observational studies)	⨁◯◯◯ VERY LOW[d,e,f]	**OR 0.67** (0.09 to 4.79)	945 per 1000	**25 fewer per 1000** (337 fewer to 43 more)

Note: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

Abbreviations: CI: confidence interval; OR: odds ratio.

[a]An OR of < 1 favors the intervention group and an OR of > 1 favors the comparison group. An OR of 1 indicates no difference between the intervention and the comparison groups. 95% CI not including 1 in the OR indicates a statistically significant difference in favor of intervention if the 95% CI is < 1 and in favor of comparison in case of > 1.

[b]Represents the risk in the comparison group.

[c]Represents the absolute effect for binary outcomes as the number of fewer or more events in the treated/exposed group as compared with the comparison group.

[d]Significant differences between groups on confounding variables.

[e]Moderate level of heterogeneity between studies ($I^2 = 50\%$).

[f]Very wide confidence interval for the pooled effect.

surgically cleared nodules.[60–62,69,70] Resection of residual nodules may be helpful when institutional protocols/guidelines allow the omission of whole-lung radiotherapy in patients with nonanaplastic histology and no viable tumor in respected pulmonary lesions.

5 | DISCUSSION

A clinician panel used the GRADE approach to produce evidence-based recommendations for the surgical management of pediatric WT. Nineteen recommendations were formulated to address preoperative, operative, and postoperative concerns identified by surgeons practicing in limited-resource settings. The guidelines address key questions prioritized by the panel in the three phases of patient care. The panel included multidisciplinary WT experts and maintained geographic and gender balance. It produced recommendations based on the available evidence and the identified priority outcomes and goals relevant in limited-resource settings.

A few themes were identified throughout panel deliberations. In a limited-resource setting, childhood tumor treatment is often effective only if the patient presents early; therefore, access to timely therapy is of paramount importance.[11,71] In addition, a multidisciplinary childhood cancer team incorporating radiologists, pathologists, oncologists, radiation oncologists, and surgical specialists who discuss the case prior to any surgical intervention is essential to ensure high quality of care.[72–75] Establishing a multidisciplinary team discussion or tumor board is a cornerstone of building capacity for pediatric oncology care.[72–75] One of the key limitations identified by the panel was a paucity of evidence to address the selected questions. When evidence exists, it is frequently of low certainty. Well-designed, randomized controlled trials and cost-effectiveness analyses are needed to examine the impact of the included preoperative, operative, and postoperative interventions on the outcome of WT.

Diagnostic capacity is limited in LMICs, and this continues to pose a significant challenge to improving the outcomes of children with WT. When there is no access to cross-sectional images, ultrasound and X-ray images may guide therapy. Thorough disease assessment and planning improve the quality of care and outcome[19–29]; therefore, access to cross-sectional images in centers providing multidisciplinary pediatric cancer care should be prioritized. The availability of pathologic analyses of frozen sections may also be limited in LMICs. However, there is no evidence to support the utility or cost-effectiveness of frozen sections in WT surgery. The therapeutic interventions recommended by the panel are affordable; most are considered standard of care across settings with various resources and are not associated with increased risk to patients. These recommendations are, therefore, practical and can serve as a reference for practice standardization that may improve the surgical outcomes of WT globally.

ACKNOWLEDGMENT

The authors thank Angela McArthur for editing the manuscript and Kathy Pritchard-Jones for providing helpful comments.

6CONFLICT OF INTEREST

There is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Abdelhafeez AH, Reljic T, Kumar A, et al. Evidence-based surgical guidelines for treating children with Wilms tumor in low-resource settings. *Pediatr Blood Cancer*. 2022;e29906. https://doi.org/10.1002/pbc.29906