Evidence-Based Surgical Guidelines for Treating Children with Wilms Tumor in Low-Resource Settings

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Abstract

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 out-

comes. 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 non-anaplastic histology stage IV WT with pulmonary metastasis. Conclusion: We provide evidence-based recommendations for the surgical management of WT, considering the benefits/risks associated with limited-resource settings.

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.

METHODS

Clinical practice guidelines

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

Composition of the guideline steering and development groups

A Guideline Steering Group (GSD) 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.

Disclosure and management of potential conflicts of interest

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

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.

Outcomes

The GSD 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.

Summary of the evidence

For questions with available data, evidence profiles were produced denoting the quality 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.

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 quality 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]

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.

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.

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.

Update plan

Guidelines are to be updated every 4 years.

Source of funding

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

RESULTS

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

RECOMMENDATIONS

Preoperative phase

The panel recommends expedited initiation of treatment for the management of WT *(Strong recommendation, Quality of evidence: Very Low).*

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 (Supplemental Table S3) should be avoided. To facilitate 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. Strengthening referral networks and prioritizing chemotherapy and surgery for childhood cancer are essential to facilitate access to timely care.

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

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.[11-15] When scaling-up surgical oncology care (Supplemental 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.[16]

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

Panel deliberation. Cross-sectional imaging provides more in-depth knowledge of tumor anatomy, including focality and extent, which is important for preoperative surgical planning.[17-22] 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.

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

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.[23-27] When CT is not available, chest x-ray may guide therapy without compromising overall survival.

The panel recommends against biopsy for patients with typical clinical features of WT. *(Strong recommendation, Quality of evidence: Very Low)*

Panel deliberation. Children who present with typical clinical features of WT (Supplemental 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 complications. Open biopsy can upstage WT, thereby compromising local control.[28,29]

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

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 (Supplemental Table S3). In these scenarios, pre-therapy biopsy is indicated.[30] 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.

Operative phase

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

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.[31-33]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 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.[34,35]

The panel suggests adequate trans-peritoneal laparotomy incision for resection of WT. *(Weak recommendation; Quality of evidence: Very Low; Table 4)*

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.[36-39]

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

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 (Supplemental Table S3).[28,40-45]

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; Quality of evidence: Very Low)*

Panel deliberation. Determining lymph node involvement by histology is feasible both before and after

neoadjuvant chemotherapy.[46] 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.[28,40-45] At the time of sampling, five to seven lymph nodes should be obtained to reduce the risk of a false-negative finding.[41,44]

The panel recommends neoadjuvant chemotherapy for the management of WT with inferior vena cava thrombus extension. *(Strong recommendation; Quality of evidence: Very Low; Table 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.[19,47-50]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.

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

Panel deliberation. Up to two thirds of tumor thrombi include viable tumor cells.[51,52] Viable tumor thrombus in the context of incomplete macroscopic resection increases the risk of WT relapse and death.[51,52] 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.

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

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.[51,52] 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.[53]

The panel recommends neoadjuvant chemotherapy for 6 to 12 weeks for patients with bilateral WT requiring nephron-sparing resection.*(Strong recommendation; Quality of evidence: Very Low)*

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.[54] 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.

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 resection. *(Weak recommendation; Quality of evidence: Very Low)*

Panel deliberation. Large series have demonstrated that nephron-sparing surgery can be successfully completed using intermittent manual compression.[55,56] However, selected patients may require more complex hilar control maneuvers. Surgeons should avoid prolonged ischemia (more than 20 min)[57,58] of the residual renal tissue, as it is associated with adverse outcome of renal function.

The panel suggests intraoperative histologic confirmation of uncertain margins in patients with WT requiring nephron-sparing resection.*(Weak recommendation; Quality of evidence: Very Low)*

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.

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

Panel deliberation. Nephron-sparing surgery for unilateral WT may be associated with increased risk of tumor spillage and is not the standard of care.[59-63] 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.

Postoperative phase

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

Panel deliberation. Postoperatively, patients who need radiation therapy, especially those with high-risk WT, should be referred to a radiation oncologist within 1 week of surgery to receive abdominal radiation within 14 days. A radiation oncologist should be part of the multi-disciplinary 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 non-metastatic patients is associated with suboptimal local control.[64-66] In contrast, for patients with metastatic disease, radiation of the abdominal primary within 14 days post nephrectomy is of no clear significance. 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.

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; Quality of evidence: Very Low)*

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 non-anaplastic histology 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 surgically cleared nodules.[60-62,67,68] Resection of residual nodules may be helpful when institutional protocols/guidelines allow the omission of whole-lung radiotherapy in patients with non-anaplastic histology and no viable tumor in respected lesions.

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. 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. Establishing a multidisciplinary team discussion or tumor boards is a cornerstone of building capacity for pediatric oncology care. 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 quality. 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. 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.

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