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Wilms' tumor in low- and middle-income countries: survey of current practices, challenges, and priorities

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Abstract

Purpose: To identify the current practices and priorities in Wilms' tumor management for surgeons in low- and middle-income countries (LMICs).

Methods: One hundred thirty-seven pediatric surgeons from 44 countries completed surveys on *Wilms' tumor surgical strategy in LMIC*. This survey was distributed through the Global Initiative for Children's Surgery, Pan-African Pediatric Surgical Association, and Latin American Pediatric Surgical Oncology Group.

Results: Ninety-two respondents (67.2%) participated from 19 lower middle-income countries (43.2%). Twenty-one respondents (15.3%) participated from nine lower income countries (20.5%). Nineteen respondents (13.9%) participated from 13 upper middle-income countries (29.5%). Most providers do not obtain biopsy for suspected Wilms' tumor (79%). Delayed resection after preoperative chemotherapy is the preferred approach (70%), which providers chose due to protocol (45%), to decrease tumor rupture (22%), and to decrease complications (8%). The providers' goal was to prevent tumor spillage and upstaging (46%) or to prevent bleeding, complication, or other organ resections (21%). Most surgeons believed that upfront resection increased the risk of tumor spillage (72%).

Conclusion: Providers in LMICs prefer delayed resection after preoperative chemotherapy to reduce the incidence of tumor spillage and upstaging of Wilms' tumor. An evidence-based guideline tailored to the LMIC context can be developed from these findings.

Keywords: Wilms' tumor, Nephroblastoma, Pediatrics, Oncology, Global surgery

Introduction

Cancer is the second leading cause of death globally, with nearly 9 million deaths recorded in 2015 [1]. Approximately 60% of pediatric cancers remain undiagnosed and untreated worldwide, with a greater burden concentrated in south Asia, southeast Asia, and sub-Saharan Africa [2]. Of those diagnosed, 80% of all pediatric

cancer cases occur in low- and middle-income countries (LMICs) [2, 3]. In 2018, the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer, which aims to increase survival of children with cancer around the world to 60% by 2030 [4]. This initiative has targeted Wilms' tumor as one of the six most common and curable cancer types. Wilms' tumor, also known as nephroblastoma, is the most common solid organ malignancy in childhood in LMIC and carries up to 97% survival rate in high-income countries (HICs) [5–7]. Reported survival of Wilms' tumor in LMICs is far less than in HICs, ranging from 11 to 56.5% in Africa [8,

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9]. In fact, Wilms' tumor has both the highest incidence and lowest survival in low-income countries [7, 10]. This survival gap is due to limited access to appropriate health services, delayed presentation, reduced capacity to deliver cancer therapy and supportive care, and high treatment abandonment rates.

Standardizing Wilms' tumor surgical practice is one of the least expensive and highly impactful measures to optimize local control and staging of the disease [11, 12]. This cross-sectional observational study examined the current practices of Wilms' tumor treatment globally, discussed the perceived advantages and disadvantages of each approach, and reviewed the goals and priorities for LMIC providers in caring for children with Wilms' tumor. We hypothesized that the management approach to Wilms' tumor is variable in LMICs; however, identifying common priorities in LMICs may help standardize surgical approach and improve perioperative outcomes.

Methods

The target study population was defined as providers who care for patients with Wilms' tumors in LMICs. This included both pediatric surgical oncologists and medical oncologists. A questionnaire regarding the approach to Wilms' tumor was developed in collaboration with international experts in pediatric surgery from the Global Initiative for Children's Surgery (GICS), a worldwide consortium of providers, institutions, and allies dedicated to improving the delivery of surgical care to every child [13]. This organization currently consists of more than 755 members from across 89 countries. There are 417 members from LMICs (55%) and 344 from HICs (45%). For pilot testing, nine pediatric surgeons with experience in managing Wilms' tumor reviewed the survey for content relevance. The instrument was modified accordingly.

Based on the World Bank list of analytical income classification of economies calculated using the World Bank Atlas method for the current 2021 fiscal year, lower-income countries are defined as those with a Gross National Income (GNI) per capita of less than \$1035, lower middle-income within \$1036 and \$4045, upper middle-income within \$4046 and \$12,535, and high-income countries greater than \$12,536 [14].

To enhance survey participation and completion, the instrument was designed to be web-based and brief with only six questions. Participants were anticipated to complete the survey within 5 min. The survey instrument is shown in Fig. 1.

The survey was administered through a readily accessible online platform, which was circulated through the GICS network as well as directly to the Pan-African Pediatric Surgical Association (PAPSA) and the Latin American Pediatric Surgical Oncology Group (LAPSO).

Survey responses were collected through the online platform SurveyMonkey (SVMK Inc., San Mateo, CA, USA). Respondents' identity could not be determined through any of the questionnaires' items. Only fully responded surveys were included in the analysis. Demographic data were summarized with descriptive statistics. Frequencies and percentages are reported for categorical data. Association of variables analyses were determined unfeasible given the information retrieved. The study was approved by the GICS Steering Committee.

Results

There were 137 respondents representing pediatric general surgeons from 44 countries (Fig. 2). Most participants were from lower middle-income countries, with 92 respondents (67.2%) representing 19 lower middle-income countries (43.2%). Second, there were 21 participants (15.3%) representing nine lower income countries (20.5%). Third were 19 respondents (13.9%) representing 13 upper middle-income countries (29.5%). Finally, five participants (3.6%) were from three high-income countries (6.8%).

The average time spent to complete the survey was 2 min and 39 s. Most providers did not routinely obtain biopsy for suspected Wilms' tumor (79%). Delayed resection after preoperative chemotherapy was the preferred approach in LMICs (70%). There were many reasons for this approach, predominantly to follow specific protocol (45%), to decrease tumor rupture (22%), and to decrease other organ resection or other complication (8%). Respondents felt that the most important goal for timing of resection was to prevent tumor spillage and upstaging (46%) or to prevent bleeding, complication or other organ resections (21%). Most providers also agreed that upfront resection increased the risk of tumor spillage or complication in the LMIC setting (72%). Responses were summarized in Table 1.

Discussion

This study aimed to assess current Wilms' tumor management practices in LMICs from a large sample of providers globally through the GICS network, PAPSA, and LAPSO. Results revealed that providers avoided initial biopsy and preferred delayed resection after preoperative chemotherapy due to concern for tumor spillage and upstaging the tumor. The potential clinical advantages and disadvantages of the three clinical approaches derived from this survey were detailed below and summarized in Table 2.

In 2013, the International Society of Pediatric Oncology, also known as the Société Internationale D'Oncologie Pédiatrique (SIOP), section on Paediatric Oncology in Developing Countries (PODC) released a recommended

Wilms tumor surgical strategy in LMIC

1. Do you obtain biopsy routinely first for image suspected Wilms tumor?

- Yes
- No

2. What is your approach to Wilms tumor?

- Upfront resection
- Delayed resection after preoperative chemotherapy

3. Why you adopted this approach?

- To decrease tumor rupture
- To decrease other organ resection or complications
- Because of delayed access to surgery
- Because of delayed access to chemotherapy
- To decrease intensity of therapy required
- To follow specific protocol
- To follow oncologist or surgeon preference
- To decrease treatment abandonment

4. Select the MOST important goal in LMIC setting that timing (upfront vs. after chemotherapy) of resection may affect?

- Prevent tumor spillage and upstaging
- Prevent bleeding, complication, and other organ resection
- Prevent wrong chemotherapy or overtreatment of patients with favorable biology
- Prevent delayed initiation of therapy
- Ensure accurate staging of lymph nodes

5. Do you think that upfront resection may increase risk of tumor spillage or complications in LMIC setting?

- Yes
- No

6. Your hospital name and country?

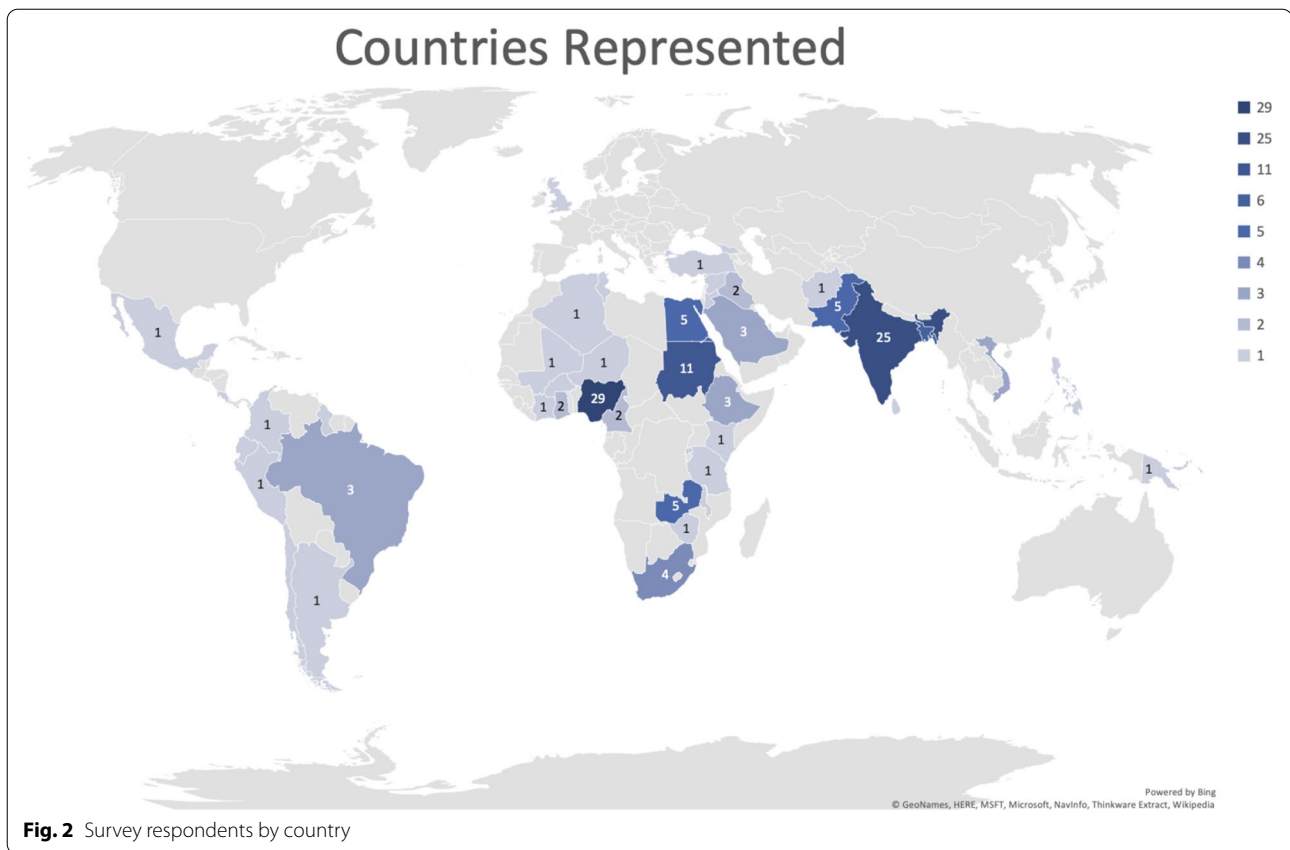
Hospital

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Powered by
SurveyMonkey

Fig. 1 Online survey instrument



protocol that utilized preoperative chemotherapy [5]. In contrast, the National Wilms' Tumour Study (NWTs) protocol (which was developed in the USA and merged in 2011 with the Children's Oncology Group or COG), favored immediate surgery. Post-resection therapy was decided based on pathological staging and tumor biology in both protocols. Since the percentage of cases in which biopsy changed management was lower than the incidence of procedural complications, neither protocol required pre-treatment biopsy, except in selected patients including those who had atypical clinical and imaging presentation for Wilms' tumor [15].

Review of data from the USA and Canada demonstrated rates of intraoperative tumor spill for Wilms' tumor in approximately 10% of cases of upfront resection, with right-sided and larger tumors associated with higher risk of spillage [16]. In the UKW3 trial, delayed resection was associated with fewer complications, most significantly reflected by the difference in tumor rupture (14.6 vs 0%) [17]. The improved overall survival was similarly reflected in a 25-year retrospective review at Tygerberg hospital in Cape Town, South Africa, which reported improved survival with delayed resection versus upfront resection (stage 1 and 2 survival 91% vs 76%; stage 3 and 4 survival 82 vs 43%) [18].

Preoperative chemotherapy has been demonstrated to be feasible with manageable toxicity, despite levels of malnutrition and other comorbidities in LMIC patients [19–23].

In a study comparing SIOp-93-01 and NWTs-5, the incidence of intraoperative tumor rupture was significantly higher in upfront resection (2.2% SIOp vs. 15.3% NWTs, $p < 0.001$) [24]. Also, resection of other organs was significantly different between the SIOp group and the NWTs group (6.9% SIOp vs. 15% NWTs, $p < 0.001$). Delayed surgery significantly improved stage distribution compared to immediate nephrectomy, resulting in 20% fewer children receiving radiotherapy or doxorubicin [25]. In many LMIC settings, radiotherapy was not available and toxic death was high; lowering the stage allowed for less intense postoperative chemotherapy without radiotherapy.

As a result of the prevalent delayed presentation, the incidence of stage 1 Wilms' tumor in LMICs was almost unheard of. In LMICs, tumors were typically large in size and in advanced stages at presentation [19, 26, 27]. Thus, the percentage of patients who were eligible for upfront resection or surgical treatment alone was low. In the case of locally advanced disease, preoperative chemotherapy aided in tumor down-staging, simplified resection, and

Table 1 Current approach to Wilms' tumor management in LMICs

	n (%)
Initial biopsy	
<i>Do you obtain biopsy routinely first for imaging suspected Wilms' tumor?</i>	
Yes	29 (21.2%)
No	108 (78.8%)
Approach	
<i>What is your approach to Wilms' tumor?</i>	
Upfront resection	42 (30.7%)
Delayed resection (after preoperative chemotherapy)	94 (68.6%)
Omitted	1 (0.7%)
Reason for approach	
<i>Why have you adopted this approach?</i>	
To follow specific protocol	60 (43.8%)
To decrease tumor rupture	30 (21.9%)
To decrease other organ resection or complications	11 (8.0%)
To follow oncologist or surgeon preference	9 (6.6%)
To decrease intensity of therapy required	8 (5.8%)
Because of delayed access to surgery	7 (5.1%)
To decrease treatment abandonment	6 (4.4%)
Because of delayed access to chemotherapy	4 (2.9%)
Omitted	2 (1.5%)
Goal for timing of resection	
<i>Select the most important goal of therapy that timing of resection may affect.</i>	
Prevent tumor spillage and upstaging	63 (46.0%)
Prevent bleeding, complication, or other organ resections	28 (20.4%)
Prevent wrong chemotherapy or overtreatment in favorable biology	18 (13.1%)
Prevent delayed initiation of therapy	18 (13.1%)
Ensure accurate staging of lymph nodes	10 (7.3%)
Tumor spillage	
<i>Do you think that upfront resection may increase risk of tumor spillage or complications in LMIC setting?</i>	
Yes	97 (70.8%)
No	40 (29.2%)

Table 2 Potential clinical advantages and disadvantages of Wilms' tumor resection strategies

	Advantages	Disadvantage
Upfront resection	Avoid misdiagnosis Avoid chemotherapy in Stage 1	Tumor rupture Complications
Delayed resection	Low risk of tumor rupture Nephron sparing resection MIS	Chemotherapy may not be indicated, or wrong chemotherapy may be given Under staging Dependent on availability of chemotherapy Tumor biology may be less chemosensitive in some populations
Customized approach	Avoid misdiagnosis Avoid overtreatment Decrease incidence of rupture and complications	Criteria to stratify (clarity, implementation, and validation) Small tumors are also at risk of rupture Requires imaging diagnostic capacity

decreased risk of tumor rupture, bleeding, organ resection, and other complications.

This approach facilitated preoperative identification of patients who may be treated with surgery alone or decreased intensity chemotherapy, therefore decreasing treatment related morbidity and mortality. In a prospective study at a tertiary referral center in India, a customized approach led to high overall survival rate of 88% [28]. During a 6-year period, Qureshi and colleagues treated 64 patients (77%) with preoperative chemotherapy and only 19 patients (23%) with upfront resection. This may reflect that preoperative chemotherapy was more appropriate in LMICs. Furthermore, preoperative image identification of surgical risk factors was not validated in Wilms' tumor and reliability of image based customized approach may still be questionable especially in the context of limited diagnostic capacity.

A multidisciplinary approach to the development of surgical capacity is key. Over the past two decades in Tanzania, this approach has been exemplified through a partnership between the Kilimanjaro Christian Medical Centre, Tumaini University Makumira, and University of Oxford to promote workforce education and training and increase surgical capacity in collaboration with the nonprofit organization Kids Operating Room (KidsOR) [29]. To date, KidsOR has established 29 operating rooms across 14 countries to enable more than 31,369 operations in Africa and Latin America [30].

The way forward: priority areas for Wilms' tumor

Timing of tumor resection was not a significant determinant of outcome in HICs. HIC settings often have the capacity to perform therapy intensification to salvage upstaged patients and maintain excellent overall survival. This may also be true in middle-income countries with good access to health care, adequate infrastructure, specialized workforce, and low treatment-related mortality and abandonment rates. For example, patients with Wilms' tumor from 1979 to 2003 at Red Cross Children's Hospital in South Africa reported approximately 80% 5-year overall survival [31].

Recent studies demonstrated that multicenter collaborations in treatment of Wilms' tumor in sub-Saharan Africa were feasible and improve outcomes. The French African Pediatric Oncology Group Study (Groupe Franco-Africain d'Oncologie Pédiatrique or GFAOP) utilized SIOP 2001 protocol with 72% overall survival for patients from 2005 to 2011. From 2014 to 2017, the Collaborative Wilms' Tumour Africa Project, including six centers in Malawi, Cameroon, and Ghana, followed the SIOP PODC protocol with improvement in overall survival (68.5% from 52%) and treatment abandonment (12% from 23%) [32]. Of note, not all participating

centers completed this study. For example, an institution in Uganda reported higher than expected early recurrence rates on adjuvant therapy where chemotherapy was minimized, and thus opted out of the study.

The main drivers of poor outcomes in setting with limited resources include access to quality cancer care and treatment-related mortality and abandonment. Indeed, a recent study of patients with common, curable cancers in Malawi revealed that 42% of children either abandoned treatment or died during treatment [33]. In a systematic review of the last two decades, Ekenze and colleagues reported 57.7% of patients in Africa presented with advanced disease (stages III or IV) and only 57.3% completed treatment [8].

Treatment abandonment in LMIC was due to poor access to care, suboptimal communication regarding treatment plan and expectations, and financial barriers. Financial barriers can be addressed by covering treatment expenses and covering transportation and other out-of-pocket expenses. As exemplified by many international NGOs, parents may also be supported through provision of accommodation and sustenance throughout their child's treatment. To improve parents' understanding and commitment to treatment plan, measures need to be implemented to educate both parents and care providers, standardize cancer care and ensure high quality communication. Regrettably, many families believed that their child was cured with removal of the tumor, despite the need for chemotherapy and postoperative care.

Intraoperative tumor rupture for patients who had upfront resection in HIC is approximately 10 to 15% [16, 34]. In LMIC health systems with suboptimal medical records, the true rate of intraoperative tumor rupture may have been higher than reported. The importance of preventing intraoperative tumor rupture and upstaging cannot be overemphasized, especially in settings of limited resources and high treatment related mortality. Achievement of this high surgical priority can be facilitated by delayed resection after chemotherapy-induced tumor shrinkage. Suboptimal surgical and histological records may also dampen retroperitoneal lymph node status and thus, postoperative staging and risk-adapted adjuvant therapy. Of note, the most common departure from surgical protocol in HICs is the lack of lymphadenectomy, which leads to understaging and impacts survival [35].

Despite both SIOP and NWTS recommendations, 21% of survey respondents reported performing routine biopsy. Current evidence supports initial biopsy only for atypical age or atypical imaging findings [15]. While most participants (70%) opted for preoperative chemotherapy akin to SIOP, only 60 surgeons (44%) reported that timing of resection followed a specific protocol. This is

further complicated by the inconsistency of approaches within a country. In fact, this internal variability amongst providers was demonstrated within institutions. None of the 12 hospitals with multiple respondents demonstrated concordant rationale for the timing of resection.

Study limitations

While these survey results provide insight into the perspectives of LMIC providers caring for patients with Wilms' tumors, some study limitations are acknowledged. First, our results may be limited in generalizability due to non-response. Regionally, the survey was not strongly representative, as there were very few to no respondents from West, Central, East, and Southeast Asia. Secondly, the respondents were exclusively surgeons. Future studies may investigate additional disciplines, including medical oncology, radiology, and pathology. Next, the aim to create LMIC-context specific guidelines will serve as a recommendation rather than a mandate. While these guidelines may not be universally followed, they may help serve as benchmarks for quality improvement studies in the future. Additionally, this study did not investigate on the availability and timeliness of ultrasound-guided core biopsy, pathology review, or chemotherapy, which may also play a role into decision-making in LMICs. Finally, these results are exclusively based on provider perceptions. A large-scale prospective trial across multiple LMICs regionally and internationally would further facilitate the understanding of the ideal approach to Wilms' tumor in the LMIC setting.

Conclusion

In conclusion, most providers in LMICs prefer preoperative chemotherapy prior to resection. Despite the predominant treatment paradigms of SIOP and NWTs groups, many surgeons in LMICs do not follow a specific protocol in treating Wilms' tumor. Furthermore, surgeons from within the same country and even the same institution demonstrated variability in their rationale for the timing of resection. With collaborative efforts between governments, academic institutions, nonprofits, local hospitals, and community leaders, there is the will to build the necessary infrastructure to support essential and oncologic surgery, including Wilms tumor resection. Future research to create an evidence-based guideline tailored to the LMIC setting can be developed from the priority areas identified in this study.

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Authors' contributions

All authors took part in writing the manuscript, reviewing it, and revising its intellectual and technical content. All authors also assume responsibility

and accountability for the results. The author(s) read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by GICS and PAPSA, and ethics approval and consent are waived.

Consent for publication

Not applicable, there are no individual details, images, or videos included.

Competing interests

The authors declare that they have no competing interests.

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