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Pediatrics

Wilms Tumor in India: A Systematic Review

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Abstract

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Background Cure rates of childhood malignancies are inferior in India compared with upper-middle-income countries. There is paucity of quality data addressing outcome of childhood Wilms tumor (WT) from India. This systematic review was conducted to assess the disease trends, treatment strategies, and outcome indicators in WT across India.

Materials and Methods We conducted a systematic search of MEDLINE, Google Scholar, and SCOPUS database, and additionally screened International Society of Pediatric Oncology conference abstracts. Data concerning WT or nephroblastoma published from India were extracted.

Results A total of 17 studies containing 1,170 patients were included in this review. Ninety-four percent of the studies were published after the year 2010. Advanced stage (III and IV) disease was seen in 46% of included patients. In seven studies, patients underwent a pretreatment biopsy before commencement of therapy. A hybrid approach consisting of "surgery first" in a selected subset and "neo-adjuvant chemotherapy" in all others was the most common treatment strategy adopted in half of the studies. The overall survival ranged between 48 and 89%. Key prognostic factors influencing survival across studies included increased tumor volume, metastatic disease, and unfavorable histology. Nonrelapse mortality (2.7–8.5%) was noted to be high.

Conclusion Substantial proportion of children with WT from India present with advanced stages of the disease. Despite several limitations, the current systematic review showed a modest survival among Indian children with WT. Adopting strategies through collaboration to ensure early access to expert care along with involvement of social support team to improve compliance may further improve survival of WT in India.

Keywords

- Wilms tumor
- India
- survival
- prognostic factors

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Introduction

Wilms tumor (WT) is one of the major success stories in pediatric oncology.[1] Most of the data pertaining to WT has emerged from two major cooperative groups, SIOP (International Society of Pediatric Oncology) and COG (Children's Oncology Group), which have shown improved outcomes over the years with intensive multimodality treatment. The emphasis has been on accurate histological diagnosis and risk stratification, tailored surgical resection, and timely radiotherapy and chemotherapy. While outcomes of localized favorable histology (FH) and that of metastatic WT in developed countries have exceeded 90 and 80%, respectively, the outcomes in lower and middle-income countries (LMICs) and low-income countries (LICs) are relatively inferior.[1–5] Several factors, including poor access to care, delayed diagnosis and referral, treatment abandonment, treatment related mortality, malnutrition, and lack of expertise in local management are considered to be the contributing factors.[4,6–8] The purpose of this systematic review is to provide a succinct overview of the epidemiology, clinical characteristics, treatment strategies, outcomes, and prognostic variables in WT across India, based on published literature.

Materials and Methods

We conducted a systematic search of the MEDLINE, Google Scholar, and SCOPUS database for published studies on WT in India. A literature search was performed using text words "Wilms tumor," "nephroblastoma," and "India." Articles published from time of inception of database till 31/08/2021 were included. In addition, studies published as SIOP conference abstracts from the year 2011 to 2020 were screened for data regarding WT published from India. Studies that were published languages other than English and studies containing less than 10 subjects were excluded. Literature search was as per preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

Study Selection

The review authors independently screened the titles and abstracts yielded by the search against the inclusion and exclusion criteria. Full reports for all titles and abstracts were obtained if they appeared to meet the inclusion criteria and also in case of any uncertainty. Two reviewers independently extracted the data to reduce the bias and errors in data extraction. In case of disagreements, a third reviewer was consulted for a final decision. The data obtained were integrated into evidence tables and were verified by the two reviewers.

Data Items

The information that was extracted from each study included the surname of first author, year of study, age with range, number of patients, sex ratio, symptomatology, diagnostic approach (biopsy, imaging modality), laterality of disease, data regarding biopsy, staging of disease, timing of surgery, chemotherapy backbone, event-free survival, overall survival, and prognostic factors.

Results

Literature Search

A total of 826 studies and 14 SIOP conference abstracts were obtained after the initial search. After removing duplicates and screening the tile and abstract of the publications, full text of 29 studies were selected for eligibility and 25 could be retrieved. From these, 6 studies included less than 10 patients, 2 studies were duplicates, 1 study did not include WT, 2 studies did not have required data, and 1 study included patients outside India. All these 12 studies were subsequently excluded. Of the 14 SIOP abstracts, 10 abstracts were excluded because of less than 10 patients being enrolled ($n = 3$), desired outcomes not being available ($n = 2$), studies being subsequently published ($n = 3$), and study population overlap ($n = 2$). Eventually, 17 studies were included in the systematic review. The PRISMA flowchart is shown in ►Fig. 1.

Quality of Studies

The Newcastle-Ottawa scale adapted for cross-sectional studies was used to assess the quality of included studies (►Supplemental Table S1, available online only).[9] The quality of the study was unsatisfactory in 3 of the 16 studies included in the systematic review.

Characteristics of the Studies

Of the 16 studies, 2 (13%) were prospective, 1 (6%) was ambispective, and 13 (81%) were retrospective. The salient features of the studies are summarized in ►Table 1.

Patient Characteristics

A total of 1,170 patients were included from the 17 studies.[10–26] Data on presenting symptoms was gathered from eight studies,[13,14,16,18,19,22,25,26] among which abdominal lump was the most common. Abdominal pain, hypertension, and hematuria were other symptoms seen in 19 to 39%, 8 to 42%, and 4 to 16%, respectively. Systemic symptoms, namely fever, were noted in 26 to 30% of patients.[14,16,26] Median duration of symptoms prior to presentation at place of care varied between 28 and 35 days.[19,26] Presence of concomitant congenital anomalies/syndromic associations was noted in three studies that was 3.7, 6.6, and 16%, respectively.[13,19,22]

All studies employed ultrasonography (US) or computed tomography (CT) to assess locoregional extent and chest radiograph or CT chest to screen for distant metastases. However, the categorical proportion of patients who underwent either US/CT abdomen/CT chest was available in three studies.[10,16,19] Measurements on tumor volume at baseline were available in two studies, who observed a reduction from mean volume of 523 mL and 481.7 mL to 208 mL, and 109 mL, respectively, following neoadjuvant chemotherapy.[16,17] Data on baseline staging was available in 16 studies

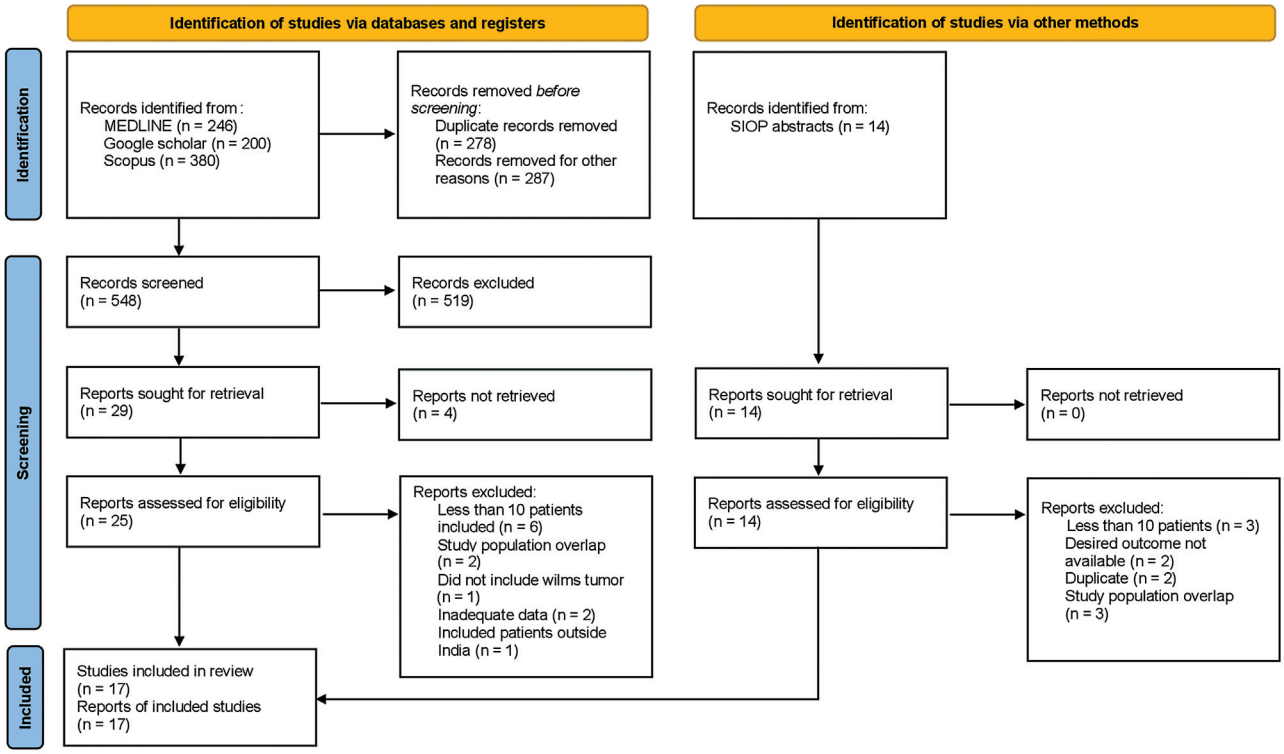

Fig. 1 Flow diagram of the systematic review according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

of which 1 study each included only metastatic patients and bilateral tumors (Stage V).[12,20] Of the remaining 14 studies, the proportion of patients with stage III and IV disease ranged between 9–55% and 6-30%, respectively. Overall, the mean incidence of advance stage disease, i.e. stage III and IV combined, was 45% (95%CI: 37–54%). Mean incidence of bilateral WT was 5.8% (95%CI: 4–7.6%).

Information on histological subtypes was available in 13 studies. The pathological subclassification and usage of terminologies were noted to be congruent with the treatment backbone (SIOP vs. NWTS) in eight (62%) of these studies.[10,16,20–24,26] Overall, high risk/anaplasia/unfavorable histology was reported to be 14% (95%CI: 8-20%) from these studies.

Treatment Strategy

Patients in seven studies had pretreatment histological confirmation prior to initiation of therapy by way of fine-needle aspiration (FNA)[12,24] or biopsy.[10,11,14,16,21,26] Data on treatment modality was available from 13 studies and differed across centers. Preoperative chemotherapy and upfront surgery were the standard practice in three (23%) and two (15%) studies, respectively, while remaining seven (54%) studies used a hybrid approach utilizing the benefits of both the approaches: "surgery first" in a selected subset and "neo-adjuvant chemotherapy" in others. One study employed the former strategy for a period of 8 years and switched to the latter after 2008 until present.[15]

Among the studies where information on chemotherapy was available ($n = 15$), International Society of Pediatric Oncology (SIOP)-based protocol was used in four (27%) studies, National Wilms Tumor Study Group/Children's Oncology Group (NWTSG/COG)-based in five (33%) studies, UK WT3 regimen in one (6%) study, and institutional-based protocol in three (20%) studies. Two (13%) studies used different protocols at different time points.[13,14]

Outcome

Nonrelapse mortality attributable to toxic deaths was 2.7 to 8.5%.[10,12,16,17,19] Surgical complications were reported in six studies[15,16,18–20,24] and varied between 11 and 29% of which postoperative ileus and sepsis were most common. Kajal et al noted a high incidence of intestinal perforation (13%), while Verma and Kumar attributed 50% of toxic deaths to postoperative complications.[18,19] Jain et al noted a higher incidence of intraoperative tumor spillage, mortality, and tumor recurrence among patients who underwent upfront surgery.[15] Survival estimates for the individual studies are summaries in ►Table 1. Regional nodal disease, increased tumor volume, metastatic disease, and unfavorable histology were noted to be adversely influencing survival, in the above studies.

Discussion

WT is the most common childhood renal tumor. While the prevalence of unilateral WT is reported to be marginally higher in girls in Western literature,[27] the present review shows a higher male prevalence reflecting the existing gender bias in health-seeking behavior.[28] Though most of the studies did not

Table 1 Characteristics of 17 studies included in the systematic review

Study	Type of publication	Study period	*n*	Mean age (mo)	M:F	Type of study	Baseline biopsy or FNAC	Stage (I/II/III/IV/V)					Timing of surgery	Histological classification	Chemotherapy backbone	Toxic deaths/ NRM	EFS	OS	Poor prognostic factors and other comments
								I	II	III	IV	V							
Qureshi et al 2020[10]	Research article	2015–19	113	42.5	1.6:1	Prospective	Biopsy	16%	18%	24%	35%		Hybrid	LR: 4% IR: 78% HR: 18%	SIOP	5.3%	3-year EFS: 79.6 (95% CI: 71.9–87.2)%	3-year OS: 81.8 (74.1–85.6)%	Lymph node positivity, stage of disease
Jeevarathi and Vadivelu 2020[11]	Research article	2008–11	156	NA	1.7:1	Retrospective + prospective	Biopsy	19%	39%	29%	6%	6%	NA	FH: 98.7% UH: 1.3%	NA	NA	Stage I & II DFS: 97% Stage III DFS: 70%	NA	LOH 1p, LOH 16q
Jain et al 2020[12]	Research article	2000–12	36	56.2	1.8:1	Retrospective	FNAC	–	–	–	100%	–	Hybrid	NA	AIIMS-WT-99	<2.7%	4-year EFS: 42.4% (33.4–67.6)	4-year OS: 48% (41.3–75.9)	Liver metastases, poor response to chemotherapy
Sachdeva et al 2019[13]	Conference paper	2005–18	71	30	NA	Retrospective	NA	20%	20%	43%	10%	8%	Hybrid	FH: 82.9% UH: 13.1%	Before 2013: UKCCSG From 2014: SIOP/ COG	NA	5-year EFS: 79.4%	5-year OS: 87.4%	Upfront chemotherapy, UFH, Stage III/IV
Wani et al 2019[14]	Research article	2010–15	23	48	1:1	Retrospective	Biopsy (in 48% patients)	22%	4%	44%	22%	4%	Hybrid	NA	SIOP and COG	NA	NA	NA	NA
Jain et al 2019[15]	Conference paper	1998–2018	40	36	2.3:1	Retrospective	No	27%	32%	35%	20%	5%	(see note)[a]	NA	NA	NA	4-year EFS Stage I:67–83% II: 42–71% III: 29–42%	NA	Upfront surgery associated with spillage, mortality and tumor recurrence Abandonment rates: 11–31%.
John et al 2018[16]	Research article	2004–14	59	58	1.4:1	Retrospective	Biopsy	38%	16%	9%	30%	10%	Upfront chemotherapy	LR: 7%; IR: 86% HR: 7%	SIOP	8.5%	3-year EFS: 73%	3-year OS: 80%	Stage III and IV
Rahiman et al 2018[17]	Conference paper	2005–16	200	33.5	NA	Retrospective	NA	30%	36%	14%	17%	3%	NA	NA	SIOP	7.2%	3-year EFS: 78.5%	3-year OS: 78.5%	Large tumor volume, Stage IV/V disease Undernutrition Abandonment rates: 20%
Kajal et al 2017[18]	Research paper	2008–12	31	40	0.8:1	Retrospective	NA	36%		55%	9%	4.5%	Hybrid	Anaplasia: 3.2%	NWTS	NA	5-year EFS: 87.3%	NA	NA
Verma and Kumar 2016[19]	Research paper	2005–14	108	33	4:1	Retrospective	No	21%	30%	35%	10%	4%	Hybrid	Anaplasia: 11%	NWTS	5.5%	5-year EFS: 73%	5-year OS:74%	Stage III and IV
Agarwala et al 2014[20]	Research paper	1999–2000	11	Range: 6–30	2.7:1	Prospective	No	–	–	–	–	100%	Upfront chemotherapy	FH: 100%	AIIMS-WT-99	NA	5-year EFS: 31%	8 of 11 alive at follow-up	NA
Rastogi et al 2014[21]	Conference paper	1990–2006	147	40	1.4:1	Retrospective	NA	NA	NA	NA	NA	NA	Hybrid	FH: 98.6%	NWTS	NA	10-year RFS: 84.7%	10-year OS: 89%	NA
Guruprasad et al 2013[22]	Research paper	2003–10	61	40	0.9:1	Retrospective	No	28%	16%	38%	15%	3%	Upfront surgery	FH: 72% Anaplasia: 16.4%	NWTS	NA	5-year EFS: 83.3%	5-year OS: 85.2%	UFH
Yadav et al 2013[23]	Letter to the editor	2005–10	22	34	0.8:1	Retrospective	NA	7%	33%	44%	4%	11%	NA	FH: 74% UFH: 26%	UK WT3	NA	5-year EFS: 82% (FH) 50% (UFH)	5-year EFS/OS: 73%/77%	UFH
Trehan et al 2012[24]	Research paper	1999–2003	20	20	2.3:1	Retrospective	FNAC	20%	65%	15%	–	–	Upfront chemotherapy	FH: 100%	SIOP 6 protocol	NA	NA	75%	NA
Chander et al 2011[25]	Conference paper	2006–09	52	51	2.2:1	Retrospective	NA	78%			22%	NA	NA	FH: 77% UFH: 23%	3 drug regimen (VAC regimen)	NA	DFS: 37.8 mo	NA	NA
Qureshi et al 2007[26]	Research article	1997–2000	20	Range: 9–144	0.8:1	Retrospective	Biopsy (selective)	50%	20%	20%	5%	5%	Upfront surgery	FH: 90% UFH: 20%	NWTS	NA	30% recurrence	NA	NA

Abbreviations: DFS, disease-free survival; EFS, event-free survival; FH, favorable histology; FNAC, fine-needle aspiration cytology; IR, intermediate risk; HR, high risk; LOH, loss of heterozygosity; LR, low risk; M: F, male: female; NA, not available; NRM, nonrelapse mortality; NWTS, —; OS, overall survival; SIOP, International Society of Pediatric Oncology; UFH, unfavorable histology; VAC, Vincristine, doxorubicin, cyclophosphamide.

[a]Upfront surgery was performed between 1999 and 2007 and Upfront chemotherapy was given between 2008 and 2018.

report on the duration of symptoms, with the available literature from two studies, patients seem to be symptomatic for a prolonged duration (>4 weeks) at the time of presentation. Obtaining a specimen for histology prior to commencing treatment was practiced in 64% of the included studies. Data from the UK-W3 trial and SIOP WT 2001 trial have shown needle biopsy to be safe and not associated with increased local relapse.[29,30] Similar observations have been made on two Indian studies that noted no association between increased tumor rupture, needle tract seeding, or tendency to relapse with a baseline biopsy.[31,32] Two centers have employed FNA cytology[12,24] instead of biopsy for establishing diagnosis, which has a comparable sensitivity and specificity.[33]

The preferred practice in approximately half of the included studies combined the treatment philosophies of both NWTSG/COG and SIOP. The UK-W3 trial evaluated the role of preoperative chemotherapy in achieving a favorable stage distribution and noted that approximately 20% fewer children received doxorubicin or radiation (because of downstaging by neo-adjuvant chemotherapy).[30] Of note, none of the 102 patients who received preoperative chemotherapy had a tumor rupture.[30] In this review, the proportion of patients operated upfront varied between 45 and 68%. While the precise reason for selecting certain patients for upfront surgery and deferring surgery in others is unclear from these studies, one study looked at leveraging the benefits of both these approaches in a prospective manner in pediatric renal tumors.[32] Based on the presence of image-defined risk factors, the study attempted at objectively classifying tumors at high-risk of tumor rupture and slotting them for delayed resection after neoadjuvant chemotherapy. With this approach the authors had noticed a postoperative complication rate comparable to SIOP and COG reports[32] with an excellent survival in the immediate surgery group and a comparable survival in the delayed surgery group. Another factor influencing surgical decision is the baseline tumor size. Several Indian studies have noted the median baseline volume at presentation to be ranging between 480 and 520 mL and the presurgery volume (post neoadjuvant chemotherapy) to be ranging between 200 and 300 mL.[16,17,32] Strikingly, patients treated on SIOP 2001 also had a similar median baseline tumor volume of 570 mL but showed an impressive decline to 180 mL presurgery.[34] However, the proportion of patients presenting in advances stages was higher when compared with that in the SIOP-2001 trial.

In addition to stage, histological features also drive the treatment strategy in WT. Hence, precise classification is crucial in differentiating WT from non-Wilms pathologies and identifying high-risk versus low-risk features in a WT. Studies have shown that blastemal predominant WT to be misclassified into a lower risk group in approximately 15% of cases.[35] Histologic terminologies differ between the two treatment philosophies, that is, low-risk/intermediate risk/high risk is used in the context of SIOP/RTSG-guided treatment, whereas NWTS/COG-guided approach uses the definitions as favorable and unfavorable histology. In 58% of the studies, where definitions were noted to be congruent, the incidence of high risk/unfavorable WT was found to be similar to larger studies.[34,35]

Timely radiation therapy forms an important component of adjuvant therapy in at least a third of the patients with WT. A surgery to radiotherapy interval of less than or equal to 14 days correlates with an improved survival.[36] While few of the studies provide the proportion of patients needing adjuvant therapy, details about timing and doses have not been specified. Current systematic review also highlighted a high incidence (3–9%) of toxic deaths in a disease that is treated majorly with less than or equal to 3 chemotherapy drugs on an outpatient basis. Malnutrition, sepsis with multi-drug resistant organisms, inadequate supportive care, and excess postoperative complications are probable incriminating factors. There were difficulties in assessing the outcomes in this review mostly due to inconsistencies with definition of survival and data regarding lost to follow-up or treatment abandonment being not available from most of the studies. Despite these setbacks, the current review showed an acceptable survival of 74 to 87% among Indian patients.

According to World Health Organization, the estimated incidence of WT among children between 0 and 14 years in India is 4.4 age-standardized rates per million.[4] Children of 0 to 14 years constitute 26% of the total 1.38 crore population of India.[37] As of date, the expected incidence of WT in India is 1,600 cases per year. Though the incidence of renal tumors is not associated with economic status, mortality is relatively higher in LICs and LMICs. Several barriers exist in childhood cancer treatment and these extend to WT as well. Inappropriate use of chest radiographs instead of CT scans for screening metastases, inaccurate histopathological risk stratification, lack of adherence to nodal sampling alongside nephrectomy, and inability to deliver timely radiation are some barriers specific to WT. In addition, delayed presentation, delayed diagnosis, sociocultural factors such as illiteracy, gender bias, and poor access to care further hamper survival.[6,38,39] Employing national guidelines to tailor therapy and conducting collaborative trials would improve treatment delivery and build expert clinical capacity.[40] While the developed countries continue to improve upon the benchmark of overall survival of 90%, with insights into tumor biology and molecular classification being the next step, our immediate steps must be directed at surmounting the aforementioned challenges.

Limitations of the Study

This study was limited by predominance of retrospective and poorly designed studies. There were difficulties in assessing the outcomes mostly due to inconsistencies with definition of survival and data regarding lost to follow-up or treatment abandonment being not available from most of the studies.

Conclusion

The current systematic review highlights the disease trends and treatment strategies of WT in India. Substantial proportion of patients present with advance stages of the disease and survival seems to be inferior in comparison to developed countries. There is a need to assess for prognostic factors in

Indian patients that will guide in intensifying therapy in selective patients. In addition, long-term follow-up with assessment of quality of life is necessary to establish overall success of therapy. Population-based registries are required to estimate disease burden that would help in health planning and allocation of resources.

Authors' Contributions

Shyam Srinivasan contributed to conceptualization, methodology, formal analysis, writing—original draft. Subramaniam Ramanathan was involved in formal analysis, data curation, and writing—original draft. Maya Prasad contributed to supervision, writing—review and editing, and project administration.

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Conflict of Interest

None declared.

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