International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Comparison of SIOP and NWTSG Protocols in Clinico-Histological Spectrum of Childhood Renal Tumors - A Tertiary Center Experience

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ABSTRACT

International Society of Pediatric Oncology (SIOP) grading of childhood renal tumors receiving preoperative chemotherapy judiciously delineates subclasses and subgroups as per chemotherapy induced changes which guides clinicians for planning further course of management.
A total of 32 cases were enrolled in our study, of which 23 received preoperative / neoadjuvant chemotherapy while 9 underwent upfront nephrectomy. Of 23 neoadjuvant chemotherapy received cases, all were clinico-radiologically suspicious for nephroblastoma; however 4 had different histological diagnosis viz clear cell sarcoma of kidney (CCSK) in 2 and 1 each rhabdoid tumor and neuroblastoma. All 9 cases of upfront nephrectomy were histologically nephroblastoma and managed as per National Wilms Tumor Study Group (NWTSG) protocol. Among rest of the cases treated as per SIOP protocol, significant response of epithelial and stromal elements to chemotherapy as well as reduction in tumor size was noted. However, blastemal predominant and diffuse anaplastic variants as well as other high risk tumors like CCSK, rhabdoid tumor and neuroblastoma had nil or minimal response and had to be considered for further chemotherapy.
To conclude, management of childhood renal tumors especially nephroblastoma by SIOP protocol offers distinct advantage over NWTSG treated cases by efficient reduction in viable tumor load along with demarcation of high risk cases which require further chemotherapy.

Keywords: Nephroblastoma, SIOP, NWTS, Neoadjuvant chemotherapy, Response

INTRODUCTION

Childhood renal tumors comprise 7-8% of all pediatric age tumors. Of these, nephroblastoma or Wilms' tumor is most prevalent [1] (85%) while renal cell carcinoma (3-5%), mesoblastic nephroma (3-4%), clear cell sarcoma of kidney (3%), rhabdoid tumor (2%), and miscellaneous (2%) constitute the rest. [2] International Society of Pediatric Oncology (SIOP) Working Classification of Renal Tumors of Childhood (1994) advocated use of neoadjuvant chemotherapy and accordingly formulated three prognostic groups: low, intermediate and high risk tumors. [3] Later in 2001 some features and guidelines were revised to incorporate results of trials and studies based upon earlier prevalent SIOP protocols. Intermediate risk group now, unlike the previous classification, incorporates varied histological subtypes based upon predominance of residual elements after chemotherapy. However treatment regimes remain same for all subtypes. Reporting histopathologists are expected and encouraged to report in terms of subtypes as per SIOP (2001) protocols and to study their prognostic significance in prospective follow up. [4] Those cases which underwent upfront nephrectomy without any

neoadjuvant chemotherapy remained to be classified as National Wilms Tumor Study Group (NWTSG) protocol. [5]

Patients are treated according to their tumor histology and stage. Low risk tumors with stage I require no postoperative chemotherapy while high risk tumors irrespective of stage require aggressive postoperative approach. Intermediate risk tumors need a methodical management approach in correlation with their stage. For example, presence of chemotherapy induced changes in renal sinus or perinephric fat is not an adverse prognostic factor and does not require further management, however presence of same at resection margins or lymph nodes necessitates postoperative chemotherapy. [6]

This study is undertaken with the aim to analyze the neoadjuvant chemotherapy induced histological changes in childhood renal tumors and to study their prognostic significance.

MATERIALS AND METHODS

A total of 32 cases of childhood renal tumors were enrolled in our study with clinico-radiological suspicion of nephroblastoma. Of these 23 received neoadjuvant chemotherapy for 4 weeks and were histologically evaluated using SIOP protocols, while 9 others underwent upfront nephrectomy. These 9 cases were designated as controls and were histologically evaluated using National Wilms Tumor Study group (NWTSG) staging system.

Both neoadjuvant chemotherapy received (Group 1) and upfront nephrectomy (Group 2 / control) cases were categorised in to low, intermediate and high risk tumors. Group 1, in addition to group 2 features, incorporated chemotherapy related histopathological findings too. In low risk tumors, group 1 has an additional entity as completely necrotic nephroblastoma too besides mesoblastic nephroma and cystic partially differentiated nephroblastoma as in group 2. In intermediate risk tumors, group 1 has epithelial/ stromal/ mixed/ regressive types of nephroblastoma besides focal anaplastic nephroblastoma as in group 2. In high risk tumors, group 1 has additionally nephroblastoma blastemal type besides diffusely anaplastic nephroblastoma, clear cell sarcoma and rhabdoid tumor of kidney as in group 2. [6]

Staging involved 5 stages for both groups as: I, tumor limited to kidney with no vessel / ureter wall infiltration; II, tumor invades renal capsule / perinephric fat / renal sinus / adjacent organs but is completely resected with clear resection margins; III, Incomplete excision of tumor which extends beyond resection margins / involved abdominal lymph nodes / tumor implants on peritoneal surface/ tumor thrombi at resection margins/ wedge biopsy of tumor prior to surgery or chemotherapy; IV, tumor with hematogenous/ lymph node metastases; V, bilateral renal tumors. [6]

RESULTS

23 cases which received neoadjuvant chemotherapy were classified as per SIOP grading in to low, intermediate and high risk tumors. Low risk group comprised 2 cases, 1 cystic partially differentiated nephroblastoma and 1 completely necrotic nephroblastoma each. Both cases had stage I presentation. Intermediate risk group consisted of 12 cases, 8 of which were mixed nephroblastoma and 2 each regressive and focal anaplastic nephroblastomas. Regressive cases had stage I and focally anaplastic cases had stage II presentation. Among the mixed nephroblastomas 1 case had stage I, 5 cases had stage II and 2 cases had stage III presentation. High risk tumors comprised of 9 cases, of which 4 had histology other than nephroblastoma. In the rest 5, 3 were blastemal component predominant while 2 showed diffuse anaplasia; barring 1 blastemal predominant case with stage II presentation, rest 4 demonstrated stage III. 4 cases with histology other than nephroblastoma were as: 2 clear cell sarcoma (stages III and IV respectively), 1

neuroblastoma (stage II) and 1 rhabdoid tumor (stage IV). (Figure 1)

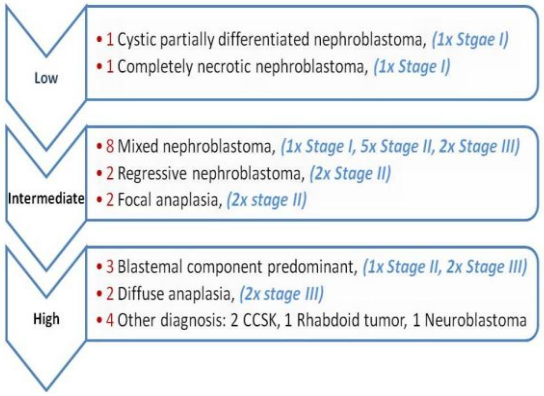

Figure 1: Distribution of cases that followed SIOP protocol

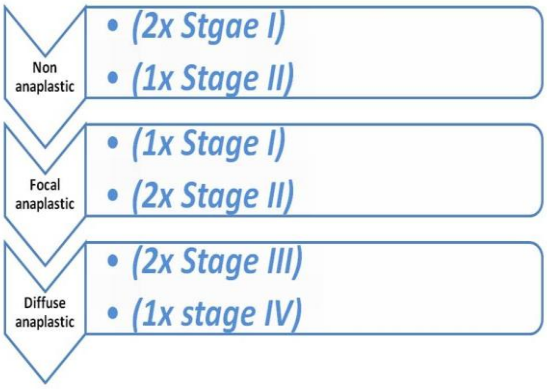

Figure 2: Distribution of cases that followed NWTSG protocol

	Grade wise categorisation of SIOP & NWTS treated cases		
	SIOP	NWTS	
Low grade	2 *1.36* (0.30)	0 *0.64* (0.64)	2
Intermediate grade	12 *12.21* (0.00)	6 *5.79* (0.01)	18
High grade	5 *5.43* (0.03)	3 *2.57* (0.07)	8
	19	9	28

$\chi^2 = 1.064$, df = 2, $\chi^2/df = 0.53$, $P(\chi^2 > 1.064) = 0.5873$

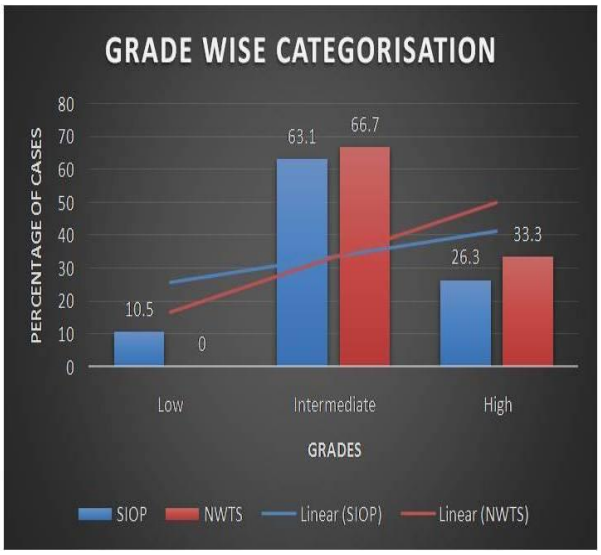

Figure 3: Grade wise comparison of SIOP and NWTSG protocols treated cases

	Stage wise categorisation of SIOP & NWTS treated cases		
	SIOP	NWTS	
Stage I	3 *4.07* (0.28)	3 *1.93* (0.60)	6
Stage II	10 *8.82* (0.16)	3 *4.18* (0.33)	13
Stage III	6 *5.43* (0.06)	2 *2.57* (0.13)	8
Stage IV	0 *0.68* (0.68)	1 *0.32* (1.43)	1
	19	9	28

$\chi^2 = 3.665$, df = 3, $\chi^2/df = 1.22$, $P(\chi^2 > 3.665) = 0.2999$

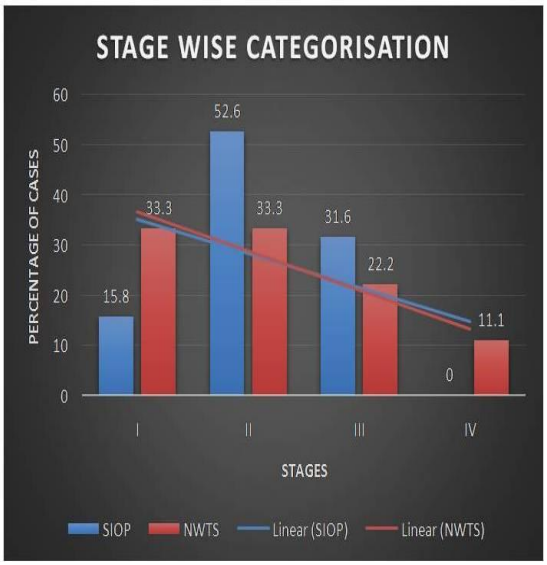

Figure 4: Stage wise comparison SIOP and NWTSG protocols treated cases

Preoperative chemotherapy offered a clear cut advantage in mixed / focally anaplastic nephroblastoma cases by downgrading and downstaging of tumors. Of the 12 cases in intermediate grade tumors, only 2 had maximal stage III presentation. However in high risk tumors, involving blastemal predominant and diffusely anaplastic nephroblastoma cases, only 1 of 5 presented with stage II. Rest others were in stage III. Besides, there was no intraoperative tumor spillage in any of the cases.

9 cases which underwent upfront nephrectomy were categorised as per NWTSG protocol in to non-anaplastic, focally anaplastic, and diffusely anaplastic nephroblastoma, 3 cases each. Among non-anaplastic cases, 2 had stage I while 1 had stage II presentation. Among focally anaplastic cases, 1 had stage I while 2 had stage II presentation. 2 of the diffusely anaplastic cases presented with stage III, while 1 had stage IV which underwent intraoperative spillage. (Figure 2)

Respective grade wise comparison of SIOP and NWTSG treated cases yielded an increasing propensity of NWTSG ones towards higher grades. (Figure 3). However similar stage wise comparison depicted almost a matching trend for both the protocols data wise despite the fact that none of the SIOP treated cases ended up in stage IV. (Figure 4)

Cases that received neoadjuvant chemotherapy had a statistically significant reduction in tumor size (p value < 0.001, confidence interval 1.248-1.983). Average tumor sizes before and after chemotherapy were 11.65 cms and 10.03 cms respectively. Decision of complete nephrectomy in two of the cases was modified to renal sparing surgery in form of partial nephrectomy due to marked reduction in post neoadjuvant chemotherapy tumor size. (Figure 5)

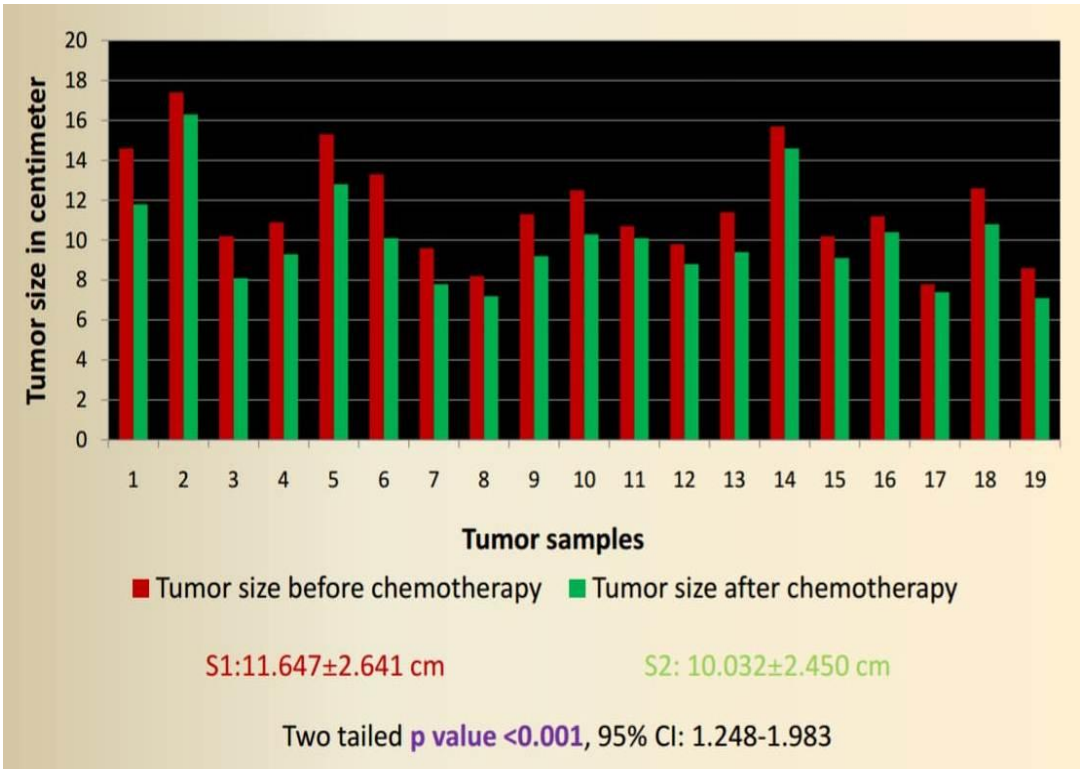

Figure 5: Effect on tumor size in cases following SIOP protocol

Regarding incidence of tumor spillage in SIOP protocol treated cases; no incidence was reported even in the higher stages. However 2 of the 3 NWTSG protocol treated cases in stages III/IV showed incidence of tumor spillage / peritoneal implants / distant spread

DISCUSSION

The importance of accurate histological diagnosis and staging of Wilms' tumor and its impact on the short and long-term outcomes is well-known. The data has emerged from large international multi-centric collaborative trials which include the National Wilms' Tumor Staging Group (NWTSG, now part of the Children's Oncology Group) and the International Society of Pediatric Oncology (SIOP). Both the NWTSG and the SIOP recommendations are aimed at stratification of patients into low and high risk groups and to select the high-risk patients for more intense chemotherapy while minimizing treatment and morbidity for low-risk patients. However, there is a philosophical difference between the two staging groups. The NWTSG recommends upfront nephroureterectomy for all cases of Wilms' tumor unless the tumor is unresectable or bilateral or extending into the inferior vena-cava above the level of hepatic veins or affecting the solitary kidney. Contrarily, neo-adjuvant chemotherapy is an integral part of the SIOP treatment strategy. [7]

In our study, a total of 9 cases underwent upfront nephrectomy and were histologically classified as per NWTSG protocols. Of these, one third cases showed diffuse anaplasia with unfavourable histology along with advanced stages III / IV. These cases should have ideally received neoadjuvant chemotherapy prior to resection.

Of 23 cases which received neoadjuvant chemotherapy prior to nephrectomy, 9 cases were placed in high risk groups, 4 of them being non nephroblastoma cases. Among remaining 5 nephroblastoma cases, 2 showed diffuse anaplasia while 3 were blastemal predominant. Blastemal predominance usually accounts for chemotherapy resistance. Thus only one eighth, namely diffuse anaplastic cases, of the potentially chemotherapy responsive nephroblastomas showed high risk histomorphology.

Reduction in tumor size of nephroblastomas following neoadjuvant chemotherapy was statistically significant and even proved beneficial in two of the cases where renal sparing surgery was performed as against earlier decision of complete nephrectomy. As per study by Provenzi VO et al [8] tumor size after chemotherapy alone is a significant predictor to be considered as prognostic factor in SIOP protocol treated cases.

Both SIOP and NWTSG protocols have their own merits and pitfalls. As per NWTSG investigators, SIOP protocol renders to unnecessary chemotherapy in benign / low grade tumors / cases with diagnosis other than Wilms tumor; modifications in tumor histology; and loss of exact staging information. SIOP investigators clarify that as anaplasia is unresponsive to chemotherapy, risk stratification remains the same. Moreover postoperative doses of chemotherapy and radiotherapy can be suitably tailored depending upon remnant tumor. SIOP investigators further claim that neoadjuvant chemotherapy offers the advantage of reduction in tumor size as well as less tumor spillage thereby enabling simple minimal invasive surgery with better outcomes and even possibility of renal sparing surgery in selected cases depending upon post chemotherapy reduction in tumor size. Renal sparing surgery is especially beneficial in cases of bilateral Wilms' tumor, an advantage which is not possible on NWTSG protocol. In children with Wilms' tumor and aged less than 6 months, NWTSG protocol offers no treatment strategy whereas SIOP advocates less aggressive chemotherapy regimens. NWTSG merits over SIOP in the aspect that it preserves molecular biology of the untreated tumor and thereby of more research benefit. The other advantage of NWTSG protocol as per its investigators is that it prevents unnecessary chemotherapy in low grade cases as well as in cases with histological diagnosis other than Wilms' tumor. SIOP investigators refute this claim

by the standpoint that it worsens prognosis of high grade cases, which have a proportionally significant number, for need of neoadjuvant chemotherapy. [9]

Merits of SIOP as compared to its risks are definitely more and are worthy in consideration with scenario in Indian subcontinent where a significant proportion of patients turn up in advanced grades and/or stages.

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How to cite this article: Singhai A, Kureel M, Babu S et.al. Comparison of SIOP and NWTSG protocols in clinico-histological spectrum of childhood renal tumors - a tertiary center experience. Int J Health Sci Res. 2018; 8(11):69-74.

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