

Surgery for wilms' tumor, Does Preoperative Chemotherapy Ease its Surgical Procedure?

Saad D. Farhan* FIBMS, FABHS, FEBU (urology)

Summary:

Background: The optimal timing of surgery for Wilms' tumor has been debated for many years. It appears dubious whether surgical ease or per operative complications consistently improved after preoperative chemotherapy.

Objective: To compare the use of immediate nephrectomy versus delayed nephrectomy or partial nephrectomy following neo adjuvant chemotherapy for treatment of non metastatic Wilms' tumor, in terms of surgical morbidity and per operative complications .

Materials and Methods: This is a cross section study ,the sample collected from January 2009 to November 2012 .Thirty four patients were selected after informed consent . Patients aged between 10 months and 5 years who were newly diagnosed with Wilms' tumors. including (17) patients with unilateral wilms tumors received immediate nephrectomy without preoperative chemotherapy according to the National Wilms' Tumor Study Group protocol (NWTS) and (16) patients with unilateral Wilms' tumors and one patient with bilateral wilms tumor received delayed nephrectomy or partial nephrectomy following preoperative chemotherapy according to the International Society of Pediatric Oncology(SIOP) WILMS TUMOR 2001/ UK Final Version /January 2002 protocol.

Results: there is significant change in the maximal tumor size (more than 50% reduction in the maximal tumor diameter) was observed in 52.9% of patients receiving pre operative chemotherapy. There is reduction in the complication rate in those patient receiving pre operative chemotherapy. These observed specifically for decreasing residual tumor and tumor spillage episodes. Bilateral partial nephrectomy after neo adjuvant chemotherapy was done for one patient (5.6%) with bilateral wilms tumor. We found significant decrease in the complication rate mainly for those patients with high risk score receiving pre operative chemotherapy rather than those with low risk score.

Conclusion: We would favor tumor resection when it is possible as early in therapy as is practical and safe, when there is concern about the safety of primary tumor resection the pre operative chemotherapy can be safely initiated.

Keywords: Wilms' tumor, Surgery for wilms' tumor, pre op chemotherapy for wilms' tumor.

*Fac Med Baghdad
2013; Vol.55, No. 3
Received: April, 2013
Accepted June. 2013*

Introduction:

Wilms' tumor is the most common malignant tumors of the kidney in children. The treatment of Wilms' tumor can be considered as the paradigm for multimodal treatment of malignant solid tumors in childhood. Progress has occurred from the times when this tumor was universally fatal to this era when more than 85% of the patients can be completely cured with localized disease and over 70% for metastatic disease. Major research and randomized controlled trials performed by several co-operative groups have made the future of Wilms' tumor patients very bright. (1).

The two major groups which have tremendous contributions in the management of Wilms' tumor are National Wilms' Tumor Study (NWTS) and the International Society of Pediatric Oncology (SIOP).(2, 3).

With the availability of several protocols in the management of Wilms' tumor, there is dilemma in the minds of the treating oncologists or pediatric Urological onco-surgeons as to whether the child should receive upfront chemotherapy or should be operated upon primarily.

*Dept. of urology, College of medicine, university of Baghdad.

Since 1969, the National Wilms' Tumor Study (NWTS) has provided the cornerstone for the treatment of Wilms' tumor in North America. All of the NWTS treatment regimens for unilateral Wilms' tumors used up-front tumor resection whenever possible. (4).

Across the Atlantic, The International Society of Pediatric Oncology (SIOP) has taken a different approach, using preoperative chemotherapy without biopsy. (5).United Kingdom Children's Cancer Study Group Wilms' tumor trial(UKW3) study trials use pre nephrectomy chemotherapy, but unlike SIOP, they perform biopsy before treatment.(6)(7).

It is necessary for us to understand why do we follow either of the protocols, While deciding which protocol to follow, it is imperative to know the pros and cons of the treatment strategies and also to study the outcome patterns in both the treatment regimes which is what this article highlights. (8).

The objective of this study is to compare the use of immediate nephrectomy and delayed nephrectomy following neo adjuvant chemotherapy for the management of wilms' tumor , We investigated volume changes after chemotherapy and

compared all possible variables at a single center using the same surgical team.

Materials and Methods:

This is a cross sectional study was carried out in the Urology department, Surgical specialties hospital, Medical City Complex, Iraq. From January 2009 and November 2012 .Thirty four patients were selected after informed consent.

Patients aged between 10 months and 5 years who were newly diagnosed with wilms tumors. Including (17) patients with unilateral wilms tumors received immediate nephrectomy without preoperative chemotherapy according to the National Wilms' Tumor Study Group protocol (NWST) and (16) patients with unilateral wilms tumors and one patient with bilateral wilms tumor received delayed Surgery following preoperative chemotherapy according to the International Society of Pediatric Oncology (SIOP) WILMS TUMOR 2001/UK Final Version /January 2002 protocol. The recommended chemotherapy to be administrated following the accurate imaging procedure and percutaneous biopsy, the pre operative chemotherapy protocol include 3 chemotherapeutic agents giving along 8 weeks period as shown in (Figure1),(9).

The patient post chemotherapy regimen was evaluated with imaging studies (CT scan and ultrasonography) to detect the change in the maximum tumor diameter was performed at week 9 (Figure 2).

Those patients with previous surgery for wilms' tumor , metastatic tumor or small renal masses less than 4 cm were excluded from this study.

All The operative procedures was done under general anesthesia through the transperitoneal incision by the same surgical team after complete discussion with the parents of the patients about the treatment options ,the Risks and advantages of early surgery and the side effects and the potential benefits of the neo adjuvant treatment .(Figures 3,4).

The pre op patient's performance status was evaluated using Karnofsky performance status score. (10). The Karnofsky scale describes the quality of life that patient possesses and the ability of the patient to carry out activities on a scale of 100percent (No signs of the disease) to 0 percent (dead patient).

The patients in this study classify into two risk score groups: those with high risk score due to presence at least one positive risk factors (advanced stage, unfavorable histology, and large tumor size) and those with low risk score are those with no risk factors .Surgical procedure parameters (Operative Time, per operative complications and hospital stay) were subject to Statistical analysis.

Statistical analyses were done using SPSS version 20 computer software (Statistical Package for Social Sciences). The statistical significance of difference in median of an ordinal scale variable between 2 groups was assessed using the nonparametric Mann-Whitney test. P value less than 0.05 was considered statistically significant. The 95% confidence interval for RR is a statistical procedure to anticipate or predict the expected range of possible values of the calculated sample estimate of any statistic (like RR) in the reference population

with 95% confidence.

RR = incidence of out come among exposed group/ Incidence of out come among Un exposed group

We considered those patients underwent surgery without pre operative chemotherapy as a control group whiles those with pre operative chemotherapy as intervention group.

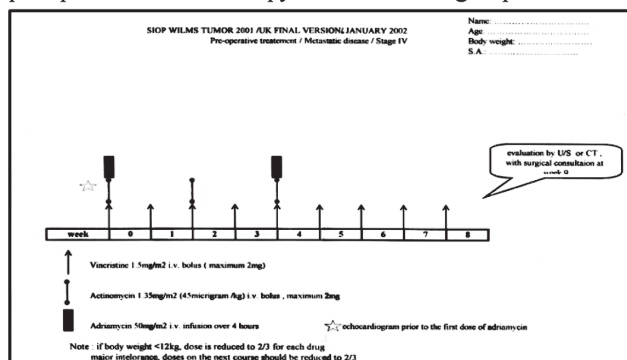


Figure 1: Pre operative Chemotherapy Regimen: International Society of Pediatric Oncology (SIOP) WILMS TUMOR 2001/UK Final Version /January 2002 protocol. (9).

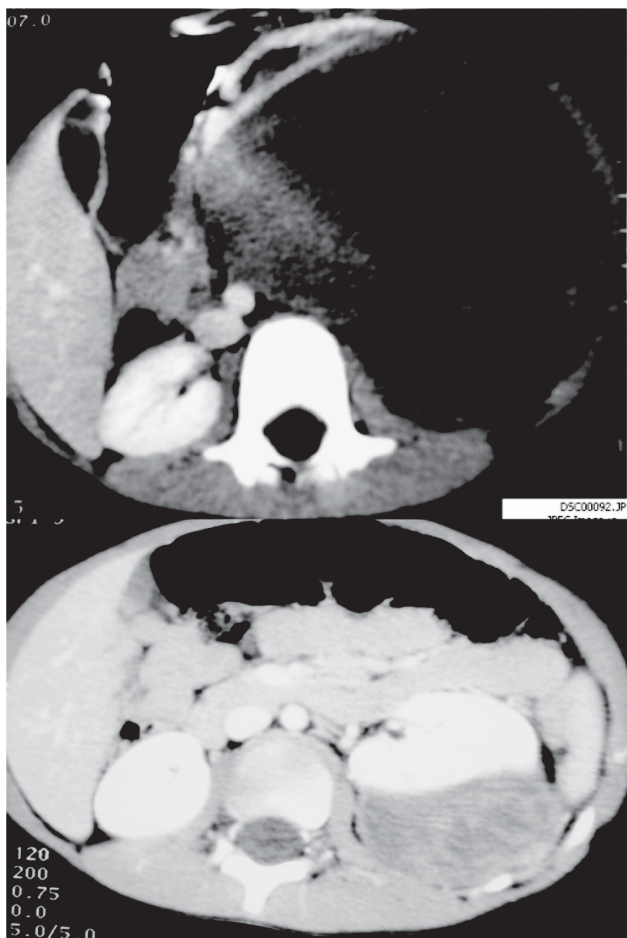


Figure 2: Reduction of the size of wilms' tumor after neo adjuvant chemotherapy



Figure 3: Surgery for Wilms' tumor; Radical nephrectomy.

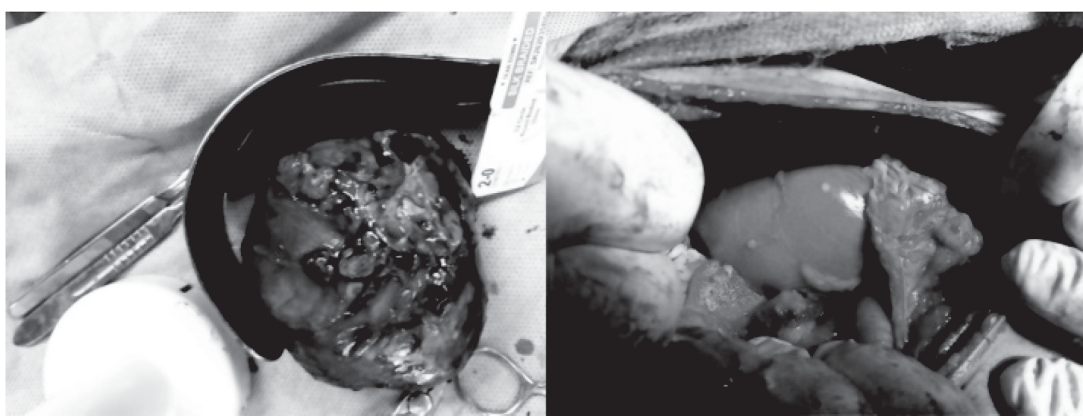


Figure 4: Partial Nephrectomy for wilms' tumor.

Results:

Thirty four patients were selected, Patients aged between 10 months and 5 years who were newly diagnosed with wilms tumors. There were 19 male and 15 female child included in this study. Average patient age, the male to female ratio, the pre operative tumor size and performance status were similar between the two groups (P values = 0.7[NS].0.18 [NS], 0.5[NS] and 0.7[NS]respectively).

For those patients receiving pre op chemotherapy the mean pre chemotherapy maximum tumor diameter was 9.3 cm (range between 4.5 – 13.6cm) and post chemotherapy mean maximum tumor diameter was 5.3cm (2.7cm - 8.6cm) and there is significant change in the maximum tumor size (more than 50% reduction in the maximum tumor diameter)was observed in 52.9 % of patients(table 1).

Table 1: Frequency distribution of intervention group by observed change in tumor size after chemotherapy.

Change in size of tumor		
No observable change	2	11.7
< 25%	3	17.6
25-49%	3	17.6
50%+	9	52.9
Total	17	100.0

We taste the effect of neo adjuvant chemotherapy on the reduction of specific complications that reported to complicate this type of surgery (3). And we found that there is reduction in the complication rate in those patients receiving pre op chemotherapy. These observed specifically for decreasing residual tumor and tumor spillage episodes. (Table 2).

Table 2: The difference between intervention and control groups in the incidence rate of selected complications.

Complications of surgical procedure	Study group				P
	Control group (Without pretreatment)		Intervention group (Pretreated with chemotherapy)		
	N	%	N	%	
None	9	52.9	13	76.4	
Significant bleeding requiring blood transfusion	3	17.6	2	11.7	1[NS]
Tumor spillage	2	11.8	0	0.0	0.2[NS]
Residual tumor	3	17.6	2	11.7	0.61[NS]
Total	17	100.0	17	100.0	

Bilateral partial nephrectomy was feasible after neo adjuvant chemotherapy for one patient (5.6%) with bilateral wilms tumor.

For better evaluation of the effect of pre op chemotherapy on the surgical per operative morbidity for patients with wilms tumor, the patients classify into two risk scores groups (low and high) due to presence of one of the following risk factors: advanced stage, unfavorable histology, and large tumor size; And we tested the effect of the prep chemotherapy on the surgical out come after adjusting for risk scores. We found significant decrease in the complication rate mainly for those patients with high risk score receiving preop chemotherapy rather than those with low risk score. (Table 3).

Table 3: The difference between intervention and control groups in the incidence rate of significant complications stratified by risk score (having at least one positive risk factors for unfavorable outcome) categories.

	Total		Significant complications		95% confidence interval RR	P
	N	N	%	RR		
None of the following factors) (advanced stage, unfavorable, large size)						
Study group						0.47[NS]
Control group (Without pretreatment)	9	2	22.2	Reference		
Intervention (Pretreated with chemotherapy)	8	1	20.0	0		
Efficacy of intervention = 100%						
At least one positive risk factors (advanced stage, unfavorable, large size)						
Study group						0.005 [S]
Control group (Without pretreatment)	8	6	75.0	Reference		
Intervention (Pretreated with chemotherapy)	9	1	11.3	0.67	(0.27 to 1.63)	
Efficacy of intervention = 33.3%						

There is no statically significant in the duration of the surgical procedure (range between 80min- 160 min.) although short duration of surgery(less than 90 minutes) was observed in 3 cases (16.8%) of wilms' tumors receiving neoadjuvant chemotherapy. Also there is no statistically significance in the duration of hospitalization (range from 1-3 days) between two groups.

The most important adverse effect of the pre-op chemotherapy is the effect on the performance status; we use the Karnofsky performance status score(10)to compare the pre op. performance status for both groups. And although the performance status of the intervention group was less than those with control group but it is statistically was not significant. (Table 4).

Table 4: The difference between intervention and control groups in the pre op performance status using Karnofsky performance status score.(10).

Score %	Description	Control Group (%)	Intervention Group (%)	P Value
100	The Patient show No complaints or signs of disease	3 (17.6%)	1 (5.8%)	
90	Exhibits minor signs and symptoms	5 (31.5%)	5 (31.5%)	
80	Shows some signs and symptoms of the disease.	6 (35.5%)	6 (35.5%)	0.7[NS]
70	Can care for him but is unable to work and be active.	3 (17.6%)	4 (23.4%)	
60	Requires occasional assistance	0	1 (5.8%)	

Discussion:

Great strides have been made in the treatment of Wilms' tumor although high-grade Wilms' tumor still needs further studies and improvement in outcomes. Perhaps the most fundamental question in the management of a suspected malignant renal tumor in a child is the timing of surgery. With upfront nephrectomy (11), A trans-abdominal, trans-peritoneal incision is recommended to permit removal of the tumor mass , inspection of sites of involvement and to facilitate the biopsy of suspicious sites .But this approach is not always possible especially for large size tumor and there is higher risk of Tumor spillage intra-operatively, which increases the

risk of local abdominal relapse and subsequent poor outcome. (11,12).

This study show increased complication rate for patients underwent immediate nephrectomy especially for those patients with high risk score. In some situations, preoperative chemotherapy is routinely recommended, including children with bilateral Wilms' tumors, tumors inoperable at surgical exploration and tumor extension into inferior vena cava above the hepatic veins. The latter two conditions are associated with an increased risk for surgical complications if primary nephrectomy is undertaken, The rationale for preoperative chemotherapy in bilateral disease is to decrease the high rate of renal failure noted in these children.(13, 14). Whereas the benefit of Pre op chemotherapy approaches (neo adjuvant chemotherapy)lies in reduction of tumor volume and downstaging the tumor and thus reducing the chances of intra-operative tumor spillage. Repeat imaging is performed after 9 weeks of chemotherapy. Experience in SIOP has shown that the majority of the reduction in tumor volume occurs in the first 4 weeks. And possible role of renal sparing surgery in the affected kidney could be evaluated with the tumor size reduced pre-operatively.(15,16). Other advantage of preoperative chemotherapy is that response to treatment may provide a valuable prognostic indicator. After adequate shrinkage of the tumor has occurred, definitive resection can be completed. A clinically good response (by imaging) is usually associated with a pathologically good response in terms of regressive histological changes. (17). In this study we are routinely perform pre op true cut biopsy before giving pre op chemotherapy. This will provide us with a solid histo pathological based for giving pre op. chemotherapy and eliminate the possibility to give the neo adjuvant treatment for other non wilms' tumors, A further concern, that of seeding of the needle tract during biopsy, did not seem to be of significant consequence on the basis of the Different studies as well as this study that shows no evidence of tumor occurrence in the needle tract.(7).

The disadvantage of this approach is the effect of pre op chemotherapy on the performance status. This study shows although the performance status of the patients receiving neo adjuvant chemotherapy is lower than those of the control group but still the difference is statically nonsignificant and this will not affect the timing of subsequent surgery.

The major positive impact of neo adjuvant chemotherapy noticed in this study Is the decrease of the tumor size and intra operative tumor spillage this findings correlate with the UKW3 study which demonstrated no tumor spillage in the delayed surgery group, compared with 15% in the immediate nephrectomy group. (18, 19).

Finally it is becoming increasingly clear that there is more than one 'best' way to care for a child with Wilms' tumors, thereby giving the clinician validated options. Bias will continue to have a role in clinical decision making. Simply put, neither of the giants is likely to yield, but parents and clinicians alike can be assured that in skilled hands, both approaches work equally well. (12).

Our parting opinion, however, is that patients with cancer

are, in general, better off with their tumors in the pathology lab rather than in the abdomen. Therefore, we would favor resection when it is possible as early in therapy as is practical and safe, when there is concern about the safety of primary tumor resection the pre operative chemotherapy can be safely initiated.

References:

- 1-Green DM; *The treatment of Wilms' tumor: results of the National Wilms' Tumor Studies HematolOncol Clin North Am*9: 1267–1274, 1995.
- 2-Van den Heuvel-Eibrink MM, Grundy P, Graf N, et al: *Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: A collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UHCCSG Wilms' tumor study groups. Pediatric Blood Cancer* 50:1130-1134, 2008. (VL).
- 3-Green DM; *Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. J ClinOncol*16: 3744–3751, 1998.
- 4-Green DM, Breslow NE, Beckwith JB, et al: *Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: A report from the National Wilms' Tumor Study Group. J Clinical Oncol* 19:3719-3724, 2000.
- 5-Bergeron C, Graf N, Van Tinteren H. *Results of SIOP-Nephroblastoma-93-01 Study to SIOP Nephroblastoma 2001 Study. Med PediatricOncol.*41:2899-2905:2003.
- 6-Mitchell C, Jones PM, Kelsey A, et al. *The treatment of Wilms' tumor: Results of the United Kingdom Children's Cancer Study Group (UKCCSG) second Wilms' tumor study. Br J Cancer.*83:602–8; 2010(VL).
- 7-Vujanic MM, Kelsey A, Mitchell C, et al: *The role of biopsy in the diagnosis of renal tumors of childhood: Results of the UKCCSG Wilms' Tumor Study 3. Med Pediatric Oncol* 40:18-22, 2003
- 8-D'Angio G. *Pre- or post-operative treatment for Wilms' Tumor? Who, what, when, where, how, why and which. Med PediatrOncol*41: 545–549, 2003.
- 9-Lemerle J, Voûte PA, Tournade MF, et al: *Effectiveness of pre-operative chemotherapy in Wilms' tumor: Results of an International Society of Pediatric Oncology (SIOP) clinical trial. J ClinOncol* 1:604-609, 1983.
- 10-Karnofsky performance status score: *Oxford Textbook of Palliative Medicine, Oxford University Press.*109; 1993.
- 11-Mitchell C, Pritchard-Jones K, Shannon R, et al. *Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomized trial (UKW3) by the UK Children's Cancer Study Group. Eur J Cancer;* 42:2554–62.2006:(VL).
- 12-Ehrlich PF, Ritchey ML, Hamilton TE, et al. *Quality assessment for Wilms tumor: a report from the National Wilms Tumor Study Group- 5. J Pediatric Surgery;* 40:208–13: 2005.
- 13-Reinhard H; *Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral non-*

metastatic Wilms' tumor. *KlinPadiatr*216:132–140, 2004.

14-Tournade MF, Com-Nougue C, de Kraker J, et al: Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: Results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *J ClinOncol* 19:488-500, 2008. (VL).

15-Boccon-Gibod I, Rey A, Sandstedt B, et al: Complete necrosis induced by preoperative chemotherapy in Wilms' tumor as an indicator of low risk: Report of the International Society of Pediatric Oncology (SIOP) Nephroblastoma Trial and Study 9. *Med Pediatric Oncol* 34:183-190, 2008.

16-Tournade MF, Com-Nougue C, Voûte PA, et al: Results of the Sixth International Society of Pediatric Oncology Wilms' Tumor Trial and Study: A risk adapted therapeutic approach in Wilms' tumor. *J ClinOncol* 11:1012-1023, 1993.

17-Weirich A, Leuschner I, Harms D, et al. Clinical impact of histological subtypes in localized non-anaplastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. *Ann Oncol*; 12:311–19:2001.

18- De Kraker J, Graf N, van Tinteren H, et al: Reduction of postoperative chemotherapy in children with stage I intermediate-risk and an plastic Wilms' tumor UK3 and SIOP 93-01 trial: A randomized controlled trial. *Lancet* 364:1229-1235, 2004.

19-Weirich A, Leuschner I, Harms D, et al. Clinical impact of histological subtypes in localized non-a plastic nephroblastoma treated according to the trial and study SIOP-9/GPOH. *Ann Oncology*.12:311–19:2001.