ORIGINAL ARTICLE

UPFRONT NEPHRECTOMY VERSUS PREOPERATIVE CHEMOTHERAPY IN WILM'S TUMOUR

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Background: Wilms tumour is the most common renal tumour in paediatric age group. This study was done to compare the two approaches used for treatment, namely upfront nephrectomy versus pre-operative chemotherapy. **Methods;** A descriptive cross-sectional study was done enrolling all the patients of Wilms tumour reporting to Oncology unit Children's Hospital during the study period. A total of 80 patients were divided into 2 groups. One group (n=40) had upfront surgery while the other (n=40) received pre-op chemotherapy before surgery. Both groups were compared for outcomes including whether treatment completed and declared cured, lost during treatment against medical advice, or died during treatment. **Results;** It was found that stage 2 patients were more likely to get upfront surgery done while stage 3, 4 and 5 were likely to get pre-operative chemotherapy before nephrectomy. Also, favourable histology was associated with better outcome overall outcome.

Keywords: Wilms tumour; Nephrectomy; Chemotherapy; Preoperative Chemotherapy

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INTRODUCTION

Wilm's tumour is the commonest renal tumour in children.[1,2] It is basically a pre-schooler malignancy with a median age of 3.5 years at presentation. It generally has a good outcome even in advanced stages thanks to the development of multidisciplinary approach and the progress in management modalities over the past few decades.

Most of the studies for the better management of Wilm's tumour patients have been done by two cooperative groups namely the International Society of Paediatric Oncology (SIOP) and the National Wilm's tumour Study Group (NWTSG) which became Children's Oncology Group (COG) after merging with certain other research bodies in 2001.[2] The recommendations by both these groups are the basis of the treatment protocols used today in different countries. The main difference in both regimens is that SIOP recommends 4 to six weeks of pre-operative chemotherapy followed by surgery while NWTSG recommends upfront surgery followed by chemotherapy.

In addition to this, both groups have done remarkable work to reduce the treatment related toxicities, improve general wellbeing of patients receiving chemotherapy and minimize the short and long term side effects while not losing the efficacy of therapy.

In Pakistan there is no National tumour Registry so we don't actually know the frequency, treatment methods and outcomes of Wilm's tumour at National level as well as the overall outcome. The aim of this study is to compare the outcomes of patients receiving pre-operative chemotherapy to those undergoing upfront surgery.

Similar studies have previously been performed in Egypt and India but there is a paucity of Data from Pakistan so we decided to compare our experience with other countries.

MATERIAL AND METHODS

A descriptive study was conducted on the patients registered at the Paediatric Oncology Department Children's Hospital at the Pakistan Institute of Medical Sciences Islamabad from 1st January 2009 to 31st December 2015. All patients below 12 years of age who presented to Oncology unit Children's Hospital PIMS with Wilms tumour were included in the study.

All the 80 patients underwent history taking, thorough clinical examination and relevant laboratory and radiological investigations.

The chemotherapy protocol used was the SIOP 2001 high risk protocol. The pre-operative chemotherapy given included vincristine, actinomycin D and Doxorubicin given for 6 weeks.

After completion of 6 weeks of pre-op chemotherapy, a CT scan of Abdomen was repeated and patient referred for surgery. Post-surgery a dose of Vincristine was given on day 5 to all patients who were operated at our centre or who presented to us immediately after being operated elsewhere.

For those patients who already presented post operatively to us or for whom the surgeon decided to do upfront nephrectomy (n=40), the post op chemo regimen recommended by SIOP for High risk patients was used. This regimen included carboplatin, etoposide, cyclophophamide and doxorubicin. These drugs were

given in pairs alternating in 3 weekly cycles for a total of 12 cycles over 34 weeks. Tumour bed Radiation therapy was used for stage 3 tumours having Unfavourable Histology or those having gross residual disease after surgery. The dose of radiotherapy was 16Gy.

The outcome of all the patients was recorded as whether completed treatment and were declared cured, left before or during definitive treatment and reason for abandoning treatment, and death during treatment and cause of death.

RESULTS

A total of 80 children suffering from Wilm's tumour were enrolled in the study. The patients were divided into those who received pre-operative chemotherapy (n=40) and those getting only post-surgery chemotherapy (n=40). Overall the mean age of patients was 3.6 years with male preponderance (68.8%). The side of tumour was right kidney in 41 (51.2%) cases and left kidney in 30 (37.5%) whereas 9 (11.0%) cases had bilateral involvement. Out of total 80 cases, 22 (27.5%) had stage II of disease, 40 (50.0%) patients had stage III of disease. Similarly, 16 (20.0%) patients had stage IV of disease and 9 (11.0%) patients were found to have stage V disease. The histopathology investigation was performed in total 66 cases, 45 (68.0%) had favourable findings whereas 21 (32.0%) patients had unfavourable result. (Figure-1). Fourteen (17.5%) patients did not get operated due to inoperable tumours and also didn't have a pre-chemotherapy biopsy done.

Further analysis was done according to pre and post-surgery chemotherapy categories. The outcome of patients was analysed between pre and post-surgery chemotherapy groups. It was noted that of the 40 pre-operative patients, 20 (50.0%) completed treatment, 18 (45.0%) were LAMA whereas 2 (5.0%) patients died. In the post-operative group, out of the total 40 patients, 11 (27.5%) had completed treatment whereas 29 (72.5%) were LAMA cases. It was noted that pre-operative patients were more likely to complete therapy (*p*-value, 0.02). (Table-1)

Similarly, the findings of histopathology and stage of disease were analysed between pre and post-operative categories. Favourable findings were more prevalent in post op chemotherapy group whereas unfavourable findings were found more prevalent in pre-op chemotherapy patients (*p*-value, 0.02). The patients having stage II disease were more prevalent in post-operative group whereas patients in stage III, IV and stage V were more prevalent in pre-operative group (*p*-value, 0.007). (Table-2)

The histology findings and stage of disease were also analysed according to the outcome of patients. It was noted that majority of cases with favourable histopathology findings 34/55 (72.3%) completed their treatment. Moreover, unfavourable histopathology findings were equally distributed between LAMA and complete treatment. The stage of disease was found equally distributed between LAMA, complete treatment and death outcomes. Moreover the 2 patients who died were in stage III and stage IV of disease. (Table-3)

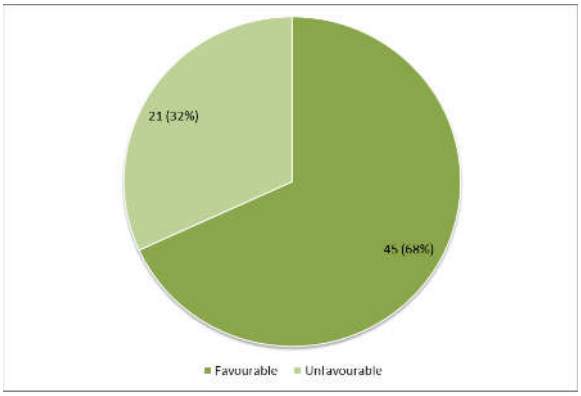

Figure-1: Findings on histopathology (n=66)

Table-1: Outcome of patients between pre and post-surgery chemotherapy

	Pre-surgery chemotherapy (n=40)	Post-surgery chemotherapy (n=40)	Total (n=80)	*p*-value
LAMA	18 (45.0%)	29 (72.5%)	47 (58.8%)	0.02
Mortality	2 (5.0%)	0 (0.0%)	2 (2.5%)	

Table-2: Stage of disease and histopathology findings according to pre and post surgery chemotherapy

	Pre-surgery chemotherapy (n=40)	Post-surgery chemotherapy (n=40)	Total (n=80)	*p*-value
Histopathology findings				
Favourable	12 (30.0%)	33 (82.5%)	45 (56.3%)	0.02
Unfavourable	17 (42.5%)	4 (10.0%)	21 (26.3%)	
Not done	11 (27.5%)	3 (7.5%)	14 (17.5%)	
Stage of disease				
II	5 (12.5%)	17 (42.5%)	22 (22.5%)	0.007
III	22 (55.0%)	18 (45.0%)	40 (50.0%)	
IV	11 (27.5%)	5 (12.5%)	16 (20.0%)	
V	2 (5.0%)	0 (0.0%)	2 (2.5%)	

Table-3: Stage of disease and histopathology findings according to outcome of patients

	LAMA (n=31)	Completed treatment (n=47)	Death (n=2)	*p*-value
Histopathology findings				
Favourable	11 (36.6%)	34 (72.3%)	0 (0.0%)	0.001
Unfavourable	9 (26.8%)	12 (25.5%)	0 (0.0%)	
Not done	11 (36.6%)	1 (2.1%)	2 (100.0%)	
Stage of disease				
II	5 (16.1%)	15 (31.9%)	0 (0.0%)	0.70
III	17 (54.8%)	21 (44.6%)	1 (50.0%)	
IV	6 (19.3%)	9 (19.1%)	1 (50.0%)	
V	1 (3.2%)	1 (2.1%)	0 (0.0%)	

DISCUSSION

Wilm's tumour is the commonest primary renal tumour in paediatric population[1] and accounts for approximately 6% of all paediatric malignancies[2]. These tumours are mostly of embryonic origin, grow rapidly and show a good response to therapy.[1] Like many other childhood malignancies, the role of genetics cannot be overlooked in development and outcome of Wilm's tumour. Loss of heterozygosity at 16q and 1p loci is shown to be associated with poorer prognosis.[3] The p53 tumour suppressor gene has been associated with most cases of anaplastic histology.[4] Reduced expressions of WT1 is associated with stromal predominant type of Wilm's tumour[4] and its deletion is seen in WAGR and Denys-Drash syndromes.[5]

Wilms tumour is one of the few malignancies which have a better overall survival despite being diagnosed at advanced stages. Worldwide two types of approaches are taken by the treating physicians/surgeons. One is to do an upfront surgical excision along with lymph node sampling to have a comprehensive staging of disease before embarking on any chemotherapy or radiotherapy. This approach is favoured by the NWTS group and is mostly used all over North America and in many other countries as well.[6] The other common approach is to do a core biopsy followed by neoadjuvant chemotherapy to downstage the disease before surgery, and then to continue with post-surgery chemotherapy with or without tumour-bed radiation. This is the preferred way according to SIOP guidelines.[7] In previous studies, about 12% of renal tumours which were radiologically consistent with Wilms tumour were found to have other diagnosis on biopsy.[8]

In developing countries due to lack of central tumour registry and unavailability of standard local guidelines, either SIOP or NWTS guidelines are followed. We, at our centre tend to follow both approaches depending upon case to case variations and preferences of surgeons or oncologist. As we usually get advanced stage disease with large inoperable tumours unlike in Europe or US, we decided to analyse and publish our experience using both approaches according to our local circumstances. There are few studies from India[6] and Egypt[2] comparing both protocols which state that no major difference in outcome was noted. We also found that there was no significant difference in both groups (*p*-value= 0.02).

Our study found out that around 50% of patients had right sided tumour while 11% had bilateral tumours. Other studies found bilateral tumours in 5% of patients[7] and 10% of these patients showed diffuse anaplasia on histology[7]. About 32% patients in this study had unfavourable histology including anaplasia; rhabdoid differentiation etc, while 17.5% had no biopsy done and were found to be inoperable after pre-operative chemotherapy. To overcome this issue, it is advisable to perform a guided biopsy in all cases of renal tumour in whom preoperative chemotherapy is planned. This is also the latest SIOP recommendation now.

There was a high rate of treatment abandonment in our study 45%. Multiple factors are involved including low educational and socioeconomic levels among the population, coming from far flung areas and unavailability of a place to stay, advanced disease which is inoperable and not amenable to treatment. This highlights the need for multi-disciplinary tumour boards to discuss each problematic case and devise an effective treatment strategy for individual cases as well as standard guidelines to be followed at local centres. There is also need for effective communication with the family so that they understand the nature and stage of disease and treatment plans.

A biopsy must be obtained in all cases of renal tumours prior to pre-operative chemotherapy to confirm histological diagnosis and plan treatment accordingly. More emphasis should be put on effective communication with attendants before deciding the treatment plan and the family

of patient should be kept in the loop at all stages of therapy.

CONCLUSION

As per our results, there is no significant difference in outcome of patients having upfront nephrectomy versus those having pre-operative chemotherapy followed by nephrectomy.

Favourable histology is the most important prognostic factor for the outcome of Wilms tumour.

AUTHORS' CONTRIBUTION

RM: Conceived the idea, planned the study and wrote the manuscript. NY: Helped in the write-up of the study and critically reviewed the manuscript. Both the authors intellectually contributed significantly to the completion of the study.

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