

## Etiopathological and management profile of Wilms tumour – A single centre experience

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**Abstract:** Wilms tumour is the most common renal tumor of childhood that typically affects children under the age of 6 years. It is the subject of intense academic interest due to its occurrence in paediatric age group with significant mortality which has been significantly reduced with relapse free survival rates due to collaborative protocols like SIOP (international society of paediatric oncology) and COG (children's oncology group). The study aimed to assess the various prognostic factors that determine the outcome of Wilms tumour, to analyze the prognostic value of histopathology and tumour staging in Wilms tumour and to identify the causes for early mortality. It is a retrospective and cross sectional study done in the Department of Paediatric surgery, Coimbatore Medical College, Coimbatore from December 2008 to December 2017. Hospital charts and surgical notes were reviewed and the results of 25 children with Wilms tumour were analyzed. Stage I tumours had 100% survival rate. The mortality rate was higher in Stage III and Stage IV tumours (more than 75%). The unfavorable histology group had 80% mortality rate. Higher mortality rate was observed in less than 24 months age group. Resectability of the tumour at the time of initial diagnosis has significant prognostic value. Tumour spillage and lymph nodal involvement are associated with early mortality and recurrent tumour.

**Keywords:** Wilms tumour, tumour grade, unfavourable histology

Date of Submission: 12-10-2018

Date of acceptance: 27-10-2018

### I. Introduction

Wilms tumour (WT) is the most common renal tumor of childhood typically affects children under the age of 6 years. The overall annual incidence of Wilms' tumor is approximately 7.6 cases per million children under 15 years of age. Wilms' tumor accounts for 6–7% of all childhood cancers. It is the subject of intense academic interest due to its occurrence in paediatric age group with significant mortality.

This has been significantly reduced with relapse free survival rates due to ongoing scientific research and various cooperative protocols like National Wilms Tumor Study Group (NWTSG), Society for International Paediatric oncology group (SIOP), United Kingdom Children Cancer Study Group (UKCCSG).

New treatment protocols with addition of chemotherapy and radiotherapy have contributed in improving the survival especially in the low risk Wilms tumour.

Unfortunately patients with unfavourable histology, lung and liver metastasis, major tumour spillage and bilateral tumours have worst outcome.

The present study is to analyse the various prognostic factors that determines the outcome of Wilms tumour and to analyze the prognostic significance of tumour staging and histopathology in Wilms tumour patients treated at our hospital.

### II. Materials And Methods

#### Study design:

It is retrospective and cross sectional study evaluating the various prognostic factors that determines the outcome of Wilms tumour in our hospital.

#### Study Period:

December 2008 to December 2017

#### Study Centre:

Department of Paediatric surgery, Department of Pathology, Coimbatore Medical College, Coimbatore.

#### Inclusion Criteria:

- All patients with Wilms tumour admitted between December 2008 to December 2017 were included in this study.

- Age group – 0 to 12 Years.

Exclusion Criteria:

- Two cases of Wilms tumour who expired before starting the treatment were excluded from this study.

All the patients with renal mass admitted in our department were evaluated thoroughly by clinical examination and the following investigations.

**Laboratory Studies**

- Complete blood count
- Basic metabolic panel, including serum calcium levels
- Coagulation abnormalities (acquired von Willebrand disease has 8% coincident in Wilms tumor)
- Liver function tests
- Renal function tests
- Urinalysis and urine culture

**Imaging Studies**

- **Ultrasonography**
  - Initial diagnosis of a renal or abdominal mass, possible renal vein or inferior vena cava (IVC) thrombus (Doppler flow study may be helpful in the setting of vascular invasion.)
  - Information regarding liver and other kidney
- **CT scanning of the chest and abdomen**
  - Differential diagnosis of a kidney tumor versus adrenal tumor (neuroblastoma)
  - Liver metastases
  - Status of opposite kidney
  - Lymph node assessment
  - Status of chest with respect to metastases
- **Chest radiography** - As a baseline for pulmonary metastases
- **Magnetic resonance imaging**
  - Typically, these tumors appear inhomogeneous on gadolinium-enhanced MRI, while the nephrogenic rests (which sometimes are precursors of Wilms tumor [WT]) appear as homogeneous masses.
  - MRI is also useful for magnetic resonance venography to aid in the diagnosis of thrombus of the renal vein of the IVC.
  - MRI scanning of the head is recommended in patients with suspected rhabdoid and clear cell carcinoma of the kidney.

All following datas relating to the patients and the biological characteristics of the tumour were obtained from case records. These information were recorded on a separate proforma that was designed specifically for this study.

- Age
- Gender
- Histopathology – Favourable and unfavourable
- Tumour spillage
- Microscopic involvement of surgical margins
- Abdominal lymph node involvement
- Tumour thrombus involving the Inferior Vena Cava

Staging was assessed according to the system used by the recent NWTSG protocol.

**III. Results**

Hospital charts and surgical notes were reviewed and the results of 25 children with Wilms tumour were analyzed.

**Table no 1 : Shows gender distribution**

	Number	Percentage	Death	Percentage
<b>Male</b>	12	48%	5	41%
<b>Female</b>	13	52%	5	38%

**Table no 2 : Shows age group distribution**

	Number	Percentage	Death	Percentage
<b>0-23 Months</b>	5	20%	3	60%
<b>24-47Months</b>	12	48%	4	33%
<b>&gt;48 Months</b>	8	32%	3	37%

**Table no 3 :** Shows tumour staging distribution

	Number	Percentage	Death	Percentage
Stage I	6	24%	-	0%
Stage II	5	20%	1	20%
Stage III	8	32%	5	62%
Stage IV	4	16%	3	75%
Stage V	2	8%	1	50%

**Table no 4 :** Shows distribution of histopathological features

	Number	Percentage	Death	Percentage
Favourable	17	62%	3	17%
Unfavourable	8	32%	7	87%

**Table no 5 :** Shows lymph nodal involvement

	Number	Percentage	Death	Percentage
Not Found	9	36%	-	0%
Node Negative	4	16%	1	25%
Node Positive	12	48%	8	68%

**Table no 6 :** Shows Resectability of the tumour at the time of initial diagnosis.

	Number	Percentage	Death	Percentage
Yes	20	80%	6	30%
No	5	20%	4	80%

**Table no 7 :** Shows Tumour Spillage

	Number	Percentage	Death	Percentage
Yes	7	28%	5	71%
No	18	72%	5	27%

#### IV. Discussion

Wilms' tumor normally develops in otherwise healthy children; however, 10% of cases occur in individuals with recognizable phenotypic syndromes - either overgrowth or non-overgrowth(1). The commonest syndromes associated with WT are WAGR syndrome, Beckwith-Widemann syndrome and Denys-Drash syndrome.

Several epidemiological studies have investigated parental, occupational, environmental and lifestyle characteristics as well as birth weight of the child as potential risk factors for Wilms' tumor, but findings to date have been inconsistent and have not been consistently replicated in multiple, high-quality studies in different populations(2,3). Future epidemiologic studies may benefit from more detailed exposure assessment, validated by environmental and biologic measurements.

Wilms' tumor is predominantly a sporadic disease. Genetic predisposition, however, has been demonstrated in a few patients. Substantial bodies of genetic and molecular studies have contributed important insights into understanding the pathogenesis of WT with several genes being implicated in its etiopathogenesis(4,5).

There are no specific clinical features of WT. Most commonly patients present with a palpable abdominal mass accidentally noted by the parents or in the course of a routine clinical examination. However, about one-third of patients present with abdominal pain, anorexia, vomiting, malaise or a combination of these symptoms. Gross or microscopic hematuria is found in 30% of patients.

#### IMAGING

Although most patients undergo Ultrasonography (US) as the initial imaging study, the conventional imaging modality for WT has been a computed tomography (CT) scan. It ascertains features of the renal mass, the extent, status and function of the contralateral kidney and intravascular extension of tumor. Real-time ultrasonography can identify the patency and presence of tumor thrombus in the renal vein and the inferior vena cava.

The value of MRI in this disorder is yet to be established, however, a recent study indicated contrast-enhanced CT and T1-W MR images to be of similar potential and superior to US in the diagnosis of nephroblastomatosis and due to the significant radiation dose of serial CT, MR imaging should be the method of choice wherever it is available(6).

The role of CT scan in the evaluation and subsequent management of pulmonary lesion found only on chest CT scan is controversial and its prognostic importance is equivocal(7,8). A recent review from National Wilms' Tumor Study (NWTs) 5 of children who had CT-only lung disease demonstrated an inferior outcome

for patients treated with vincristine and dactinomycin (two-drug therapy) only, with or without pulmonary radiation therapy (RT), compared with those who received doxorubicin (DOX) in addition to vincristine and dactinomycin (three-drug therapy)(9).

In addition, there appeared to be no beneficial effect from lung irradiation on the outcome of CT-only patients when chemotherapy was considered. Another study demonstrated CT-only lesions are not invariably tumor, demonstrating the need for histopathological confirmation(10).

The development of effective systemic chemotherapy in the 1960s rapidly changed the outcome and approach to treatment of Wilms' tumor. Randomized clinical trials have been conducted by NWTSG, SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG) to determine the appropriate role for each of the therapeutic modalities available. Patients are stratified into different treatment groups based on extent of disease and histopathologic features. The goals of these trials are to allow a reduction in the intensity of therapy for most patients, while maintaining overall survival, and to decrease potential late sequelae.

After instituting the various recent modalities of treatment in Wilms tumour, the overall survival rate significantly increased from 20% in 1920 to 90 % in 2000 as per recent NWTSG reports.

Due to the different treatment schedules adopted by the two large cooperative study groups, two major staging systems are currently used. A forthright, surgery-based system developed by the NWTSG and a delayed surgery-based system developed by SIOP. Although a direct comparison is not practical due to the difference in surgical timing, both staging systems are valuable in predicting outcomes.

## **PATHOLOGY**

A classic WT is triphasic, with variable proportions of blastemal, stromal and epithelial components. Some WT are monophasic and have a highly aggressive biological behavior. Histological features in the nephrectomy specimen provide important prognostic information for planning treatment. Presence of nuclear atypia, focal/diffuse anaplasia and sarcomatous elements indicate an unfavorable histology, seen in about 5% of all WT(11). These account for nearly half of all deaths from this disease. Anaplasia is a marker of resistance to chemotherapy but whether it actually signifies aggressiveness is unknown.

## **Prognostic Factors**

The tumor stage at diagnosis, histological features (favorable vs. unfavorable, presence of diffuse anaplasia) and patient age are the most important prognostic determinants which impact on treatment selection and oncological outcome(12). The LOH at chromosome 1p and 16q was prospectively analyzed by NWTSG-5(13). Tumor-specific LOH for both chromosomes was found in approximately 5% of patients with FH WT and was associated with increased risk of relapse and death.

Wilms' tumor can be considered a model for successful multidisciplinary management of cancer, with improvement in survival from a mere 30% in the 1930s to more than 85% at present. It is also an ideal example wherein the treatment protocols have been devised and modified repeatedly depending on evidence emerging from randomized trials conducted by several cooperative groups and individual institutions. In our study the overall survival rate is 60% (15 out of 25 children).

In another report from our country (Bhagawat et al.)<sup>43</sup> shows 83% overall survival rate in a large cohort of patients. Marilia Fornaciari et al. from Brazil report 84.6% overall survival rate in 132 patients.

Most of our cases present late and majority of the cases were in advanced stages (14 of 25 were stage 3 and stage 4), which may be the possible cause for lower survival rates.

Another possible explanation is – loss of Heterozygosity(LOH) i.e., chromosomal loss in 1p and 16q may be the cause for poor prognostic outcome.

Five children with stage I tumour and three children with stage II tumours have survived more than 5 years. This is comparable with recent NWTSG and SIOP trials.

Out of the 25 children 13 were female and 12 were male. Male female ratio is almost equal and the mortality rate is also comparable with both groups(41% Males and 38% Females). So gender has no prognostic significance in our study.

More number of deaths(60%) have occurred in less than 23 months age group(3 out of 5 cases), but in the Brazilian study and recent NWTSG reports prognosis is good in this age group(10% mortality in Brazilian Study(14). Again advanced stages and unfavourable histology in 2 children maybe the possible explanation for higher mortality.

Mortality in later age group 24 to 47 months and more than 48 months is 33% and 37% respectively. This is comparable with Brazilian study.

Tumour staging is one of the main prognostic indicator that determines the outcome of treatment and survival in Wilms tumour. The survival rate based on staging is comparable to other studies except in Stage III tumours.

Even though it is difficult to explain, the higher mortality rate in our group compared to NWTs results, irregular follow-up for the treatment, and toxicity to chemotherapy may be possible explanations for this. So early cases in Stage I and Stage II tumours response well to treatment and prognosis good.

Children with favourable histology (Triphasic pattern and no anaplasia) has good prognostic outcome. Only 3 deaths occurred out of 17 cases in our group as comparable to higher mortality rate (87%) in unfavourable histology group. (Focal or diffuse anaplasia).

This observation with comparable with Brazilian study. But NWTs reports the mortality rate in unfavourable histology group is 40%.

In our series, 5 patients had received pre-operative chemotherapy. Of this 5 cases, only 1 patient had remnant of blastimal elements in final pathology report. That patient expired.

In 2002, SIOP trials noted that certain histology features that remain after pre-operative chemotherapy, such as blastema or prognostic significance whereas others not.

Therefore in the further SIOP trials, a revised classification of renal tumours to be followed for the treatment purposes.

- Completely necrotic (low risk group)
- Blastemic (high risk group)
- Others (Intermediate group)

Complete Resection of the tumour at the time of initial surgery has significant prognostic value in our observation. Among the 25 cases, 20 cases were completely resectable, and mortality rate in this group was only 30% as compared to 80% mortality rate when the tumour is inoperable.

Early mortality in Wilms tumour occur in 7 of our cases. Tumour bed recurrence occur in 2 of our cases. Out of the 9 cases, tumour spillage occur in 7 cases and surgical margin positivity in 3 cases.

Tumour spillage and surgical margin positivity were the attributed causes for early mortality and tumour bed recurrence in our observation.

As per recent NWTs report 10% of patients has poor prognostic variable including

- Unfavourable histology
- Chromosome loss in 1p and 16q (loss of Hetrozygosity)
- Diploidy

However, gene mapping facilities are not available in our hospital, the prognostic significance of these factors are not able to study.

Tumour thrombus in IVC found in 3 of our patients, in all patients tumour thrombus was removed enblock. All 3 patients were survived. So the tumour thrombus involvement below the hepatic veins has not affect the survival of the patients.

In our series, one patient had syndromic association with manifestations of aniridia and nystagmus who survived more than 5 years.

One patient had horse shoe kidney with tumour confined to one pole of the kidney (Stage I). This patient was treated with nephrectomy and chemotherapy. He is surviving for more than 3 years.

Two of our patients had bilateral tumours. One patient had Stage III on right side and Stage II on left side. This patient was treated with right nephrectomy followed by chemotherapy and radiotherapy who expired after 6 months. In another patient both side Staged tumour treated with chemotherapy and radiotherapy, surviving more than 3 years. 2 patients had recurrent Wilms tumour treated with salvage chemotherapy (ICE Regimen – Ifosfamide, Cisplatin, Etoposide).

One patient had liver metastasis after completion of the chemotherapy who was also treated with salvage chemotherapy. She survived more than 2 years with secondaries.

To summarize our experience, tumour staging and histopathology were the two main prognostic indicators that determines the survival of Wilms tumour.

Higher mortality rate was found in less than 24 months age group and older children.

Resectability of the tumour at the time of initial diagnosis had significant prognostic value. Tumour spillage and lymph nodal involvement are the causes for early mortality in Wilms tumour.

## V. Conclusion

- Stage I tumours had 100% survival rate.
- The mortality rate was higher in Stage III and Stage IV tumours (more than 75%).
- The unfavourable histology group had 80% mortality rate.
- Higher mortality rate was observed in less than 24 months age group.
- Resectability of the tumour at the time of initial diagnosis has significant prognostic value.
- Tumour spillage and lymph nodal involvement are associated with early mortality and recurrent tumour.
- Considering the constraints of the size of the study, it needs further follow-up to assess the long term prognostic variables..

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R P Dharmendra. "Etiopathological and management profile of Wilms tumour – A single centre experience.." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, vol. 17, no. 10, 2018, pp 48-53.-