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WILMS TUMOR- A 10 YEAR INSTITUTIONAL REVIEW AT GMCH NAGPUR

Oncology

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ABSTRACT

BACKGROUND- Wilms tumor also known as nephroblastoma has multimodality treatment approach leading to good prognostic outcomes in this disease, still in India the overall survival is poor. Also,there is paucity of data about the epidemiology, pathology, treatment and prognosis of the disease from India, therefore we conducted a retrospective analysis of the multimodality treatment & report the outcomes of Wilms tumor at department of radiation oncology at GMCH Nagpur over 10 yrs

MATERIAL AND METHODS- 104 clinico-radiologically and histopathologically proven patients registered of which 68 were evaluated for Demographic Data,Clinico-pathologic Profile, Treatment related data and Survival registered from 2007-2017 at the dept of radiation therapy and oncology GMCH Nagpur

RESULTS- Total 104 patients of which 53 were males (50.96%) and 51 were females (49.03%) with mean age at the time of diagnosis 4.4±0.84yrs. Radical Nephrectomy was performed in 62% of cases, 25% were metastatic & 13% came in locally advanced stage with poor general condition at the time of presentation. Favourable histology findings were found in 38 (56.71%) and unfavourable were 29 (focal + diffuse + CCK + RTK) (42.85%). 5 yrs overall survival rate stage I 90% stage II 80% stage III 75%stageIV 45%, the 5 yrs overall survival rate was found to be 74.25%.

CONCLUSION- the children who presented at our institute came in late stages; most common presentation was in stage III followed by stage IV. The 5 year &10-year survival rate & event free survival rate was very low compared to the other studies. The probable reason for this may be due to the presentation of patients in late stages and poor general condition causing difficulty in delivering the optimum treatment

KEYWORDS

Wilms Tumour, Histology, Radical Nephrectomy, Outcome.

INTRODUCTION: -

Wilms' tumour was named after a German pathologist and surgeon Carl Max Wilhelm Wilms (1). It is the most common malignant renal tumour of childhood, occurs with an annual incidence of 7 cases per million children < 15 yrs of age (2). Wilms tumour had been considered to be uniformly lethal because of its aggressive nature. With advent of newer chemotherapeutics regimens, Radiotherapy protocols and improvements in surgical techniques the prognosis of Wilms tumour has been consistently improving since last 2-3 decades. Advances in imaging techniques have made it easy to diagnose Wilms tumour at an early stage. Early diagnosis and appropriate management is associated with an excellent 5- year survival rate of more than 90%. Moreover, early diagnosis is also associated with minimal drug related toxicities and adverse reactions (3,4).

It must however be emphasized that the healthcare priorities of developing countries including that of India is different from developed world. In developing countries where majority of deaths in paediatric age groups are due to preventable cause of deaths such as Malaria, respiratory tract infections and diarrhoea the paediatric malignant diseases are low priority amongst policy makers (5). This is mainly because simply 2% of all deaths in the children's less than 12 years are due to cancer (6.) This contrasts with data from western countries where cancer is the most common cause of disease related death in children, a close overall second only to accident and injuries (7,8)

In India, the reported incidence of childhood cancer has raised over the last 25years, But the increase is much larger in females than males (9,10). The staggering increase in malignant diseases in female may have been also due to change in the attitude of the society towards female child. With an increase in literacy and improvements in socioeconomic status of the individuals there is increase in consultations sought for female children also thereby increasing the diagnosis of childhood cancers in female. In other words, increased incidence of childhood cancer may at least partly be due to increase cases of female children being brought for treatment (11).

Inherited susceptibility has possibility in every cancer. However, some develops the tumour and others may not. There are some well-documented associations between the Wilms tumour and aniridia, Over growth syndromes such as Beckwith-Wiedemann syndrome WAGR, Denys-Drash are also associated with Increased predisposition to cancer. (12)

PBCR & HBCR survival data is important in studying the outcome of patients with Wilms tumour. Reports from metropolitan cities such as Chennai and Bangalore suggested that an estimated 5-year survival rate for all childhood malignant diseases is around 35 to 40%. In this regards it is important to note that the highest survival in our country is seen for Wilms tumour where approximately two third of the children survive for five years or more (13, 14). Early diagnosis is one of the most important pre-requisites for a better prognosis. Diagnosis in advanced stages is associated with a uniformly poor outcome (15).

There is paucity of data about the epidemiology,pathology,treatment and prognosis of the disease from India, therefore we conducted a retrospective analysis of the multimodality treatment & report the outcomes of Wilms tumour at department of radiation oncology at GMCH Nagpur over last 10 yr

AIMS AND OBJECTIVES: - To Study
1. Clinicopathologic profile
2. Overall &Disease-Free survival

MATERIAL AND METHODS

Government medical college and hospital, Nagpur is a tertiary care centre in the region of Vidarbha of Maharashtra. A retrospective review was done at the hospital from 2007 to 2017. 104 clinicoradiologically and histopathologically proven patients registered of which 67 were evaluated for

- Demographic Data
- Clinicopathologic Profile
- Treatment related data
- Survival

Remaining patients either files were missing or not taken the treatment at all. Most patients of the unilateral Wilms tumour were treated with NWTS IV protocol. This regimen includes the upfront surgery, postoperative histopathological confirmation of diagnosis, followed by radiotherapy & chemotherapy based on stage of the disease, after

completion of treatment the follow up was 3-monthly for the initial 2 years and 6 monthly thereafter. Every follow up visit consisted of clinical examination, abdominal ultrasound and chest radiography of all patients. The event free survival and overall survival were evaluated using the Kaplan Meier curve (SPSS 19-SPSS Inc, USA). P value less than 0.05 was taken as statistically significant.

OBSERVATION AND RESULTS

During the period of 2007-2017, 104 patients of Wilms tumour were reported to the to the department of radiation oncology, government medical college Nagpur. Out of these 104 patients there were 53 males (50.96%) and 51 females (49.03%) with a M/F ratio of 1.03:1, the mean age at the time of diagnosis was 4.47 years and associated anomalies are were not reported.

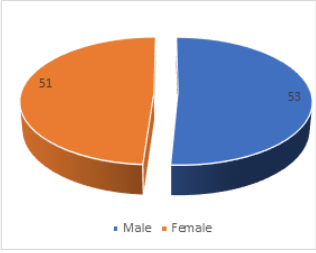

Figure 1: Gender Distribution of the studied cases.

The analysis of the age groups of the patients showed that 43.26% patients were between 2yrs to 5yrs of age,33.65% patients were 6 months-2yrs of age, more than 5 yrs to 10yrs were 18.26% f/b 3.8% more than 10 yrs of age, just one patient were reported with age < 6 months of age

Table 1: Age Distribution of the studied cases.

Age Group	No of Patients	Percentage
< 6 months	1	0.9%
6 months -≤ 2 yrs	35	33.65%
> 2 yrs-≤ 5 yrs	45	43.26%
> 5yrs- ≤ 10 yrs	19	18.26%
> 10- ≤ 12 yrs	4	3.8%

Out of 104 patients 68 patients were evaluable for the data analysis The most common presenting sign/symptom at the time of diagnosis was abdominal mass & distension found by the parents or physician, The left kidney was affected in 52% of cases & right kidney was affected in 47% of cases , only one patient were reported with bilateral kidney involvement at the time of diagnosis.

Table 2: Clinical features in the studied cases.

Sr no	PRESENTING SYMPTOMS (n= 68)	PERCENTAGE
1	Abdominal mass/distension	79%
2	Heamaturia	2%
3	Abdominal pain	13%
4	Fever	2%
5	Weight loss	2%
6	Diarrheoa	1%
7	Hypertension	1%

Most patients (55%) presented in the stage III of the disease followed by stage IV (25%). Stage III was most common stage in males as well as female patients., More female children were present in stage III than male child while male predominance were seen in stage IV.

Table 3: Stage of the disease at presentation and gender distribution.

Stage at Presentation	Stage I	7 (10.29%)	
	Stage II	5 (7.35%)	
	Stage III	38 (55%)	
	Stage IV	17 (25%)	
	Stage V	1 (1.47%)	
Stage Distribution Among Sexes		Male	Female
	Stage I	5	2
	Stage II	3	2
	Stage III	15	23
	Stage IV	9	8
	Stage V	1	0

The analysis of histology reports of the patients showed that amongst both males and female patients 38 (56.71%) patients had favourable histology and of 27 (39.7%) had anaplasia (FA+DA), 2 (2.98%) patients had CCK and RTK was present in 1 (1.49%) patient.

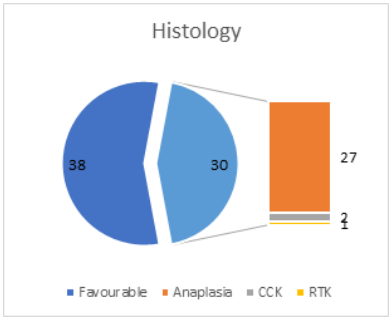

Figure 2: Histology of the tumour in the studied cases.

The most common investigational modality was used CECT-abdomen &pelvis, USG-abdo pelvis, chest radiography & IVP to access the patients disease burden. CT-abdomen pelvis was performed to evaluate the origin of the tumour within the kidney, assess IVC extension, and rule out hepatic metastasis. This assessment revealed 16 patients with lung metastasis,10 patients with liver metastasis, no brain metastasis was reported in this study. Also, the inferior vena cava involvement was seen in 3 patients while renal vein involvement was in 5 patients.

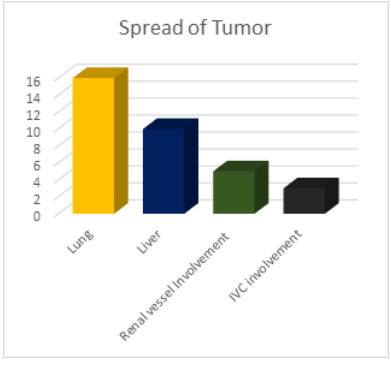

Figure 3: Spread of Tumour in the studied cases.

Surgery was performed in 42 (61.76%) of cases. It consisted of radical nephrectomy in all cases except partial contralateral nephrectomy in one case of Bilateral Wilms tumour,15 (22.05%) were metastatic &11 (16.17%) came in advanced stage(Non-Metastatic) with poor general condition at the time of presentation.

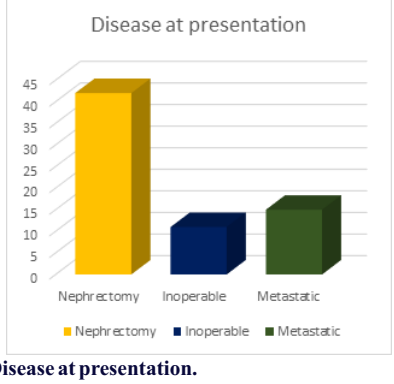

Figure 4: Disease at presentation.

Preoperative chemotherapy was received by 20 patients was according to SIOP93-01 and adjuvant chemotherapy was given to 20 patients according to NWTS-5 protocol, adjuvant radiotherapy was received by 22 patients, delivered by cobalt 60 with dose 10.8 Gy whole abdomen .the indications for the post-operative radiotherapy was stage III &stage IV disease, also metastasis, 2 patients received whole lung irradiation with lung metastasis radiotherapy was delivered with average time of 35 days post surgery. Remaining 6 patients didn't receive any treatment post surgery.

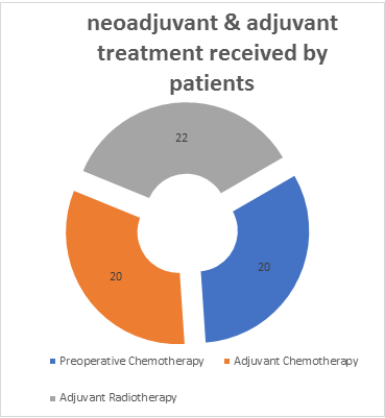

Figure 5:Neoadjuvant and Adjuvant treatment received by Patients.

FOLLOW UP &SURVIVAL: -

With median follow up of 64 months, in our study, 41 patients have complete response, 9 patients were having partial response. tumour relapse was reported in 17 patients, of which stage I 2, Stage II 2, Stage III 12 & 1 were reported in stage IV, of which 60% were unfavourable histology & 40 % were favourable histology, site of relapses was abdomen in 8 cases & lung in 9 cases. The mean time after relapse of surgery 1.67 years, the sites of metastasis post treatment were lung (12 cases), liver(7 cases)

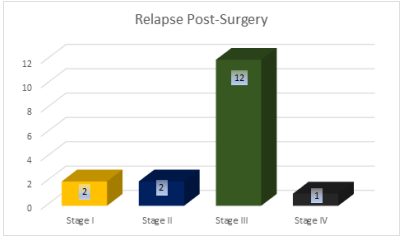

Figure 6: Relapse after surgery in the studied cases.

For the cohort of 68 patients the 2 year & 5-year overall survival rate achieved after 24 &60 months were 84.69%, 74.25% respectively and the event free survival at 5 years were 69% in this study.

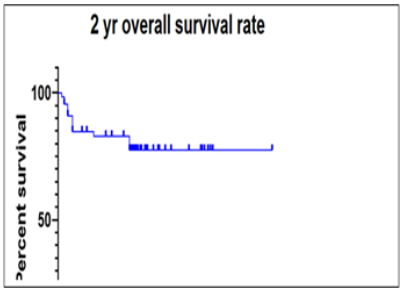

Figure 7: 2 Year Survival Rate in studied cases.

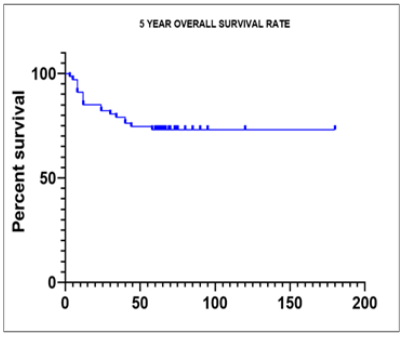

Figure 8:5 Year Survival Rate in studied cases.

The 5-year overall survival rate in our study is stage I 90%, stage II 80%, stage III 75% and stage IV were 45% and the 5-year overall survival and disease-free survival were 74.25% and 69%.

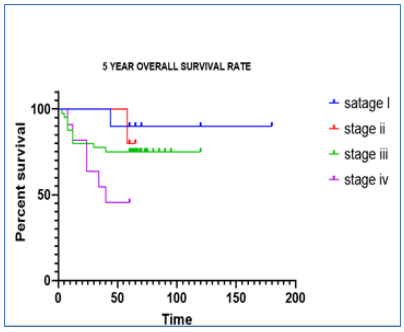

Figure 9:5 Year Survival Rate in studied cases.

The five-year survival rate stratified according to the histology, regardless of staging, was 74% for patients with FH, 60% for patients with FA and the log-rank test showed highly significant statistical differences between the curves ($p<0.0001$) and that the patients with CCK & RTK had the worst survival rate.

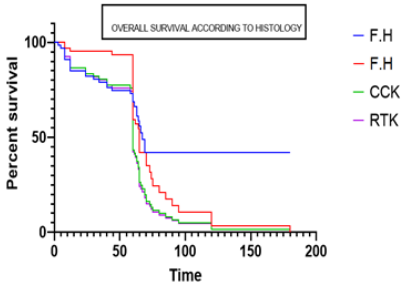

Figure 7 : Overall Survival Rate according to histology in studied cases.

DISCUSSION-

The M/F ratio was 1.03 & mean age at diagnosis was 4.47 yrs as compared to a study which is approximately equal compared to Taiwan Paediatric oncology group study (TPOG-W-9)(16).Most frequent presenting feature was abdominal mass 79% compared to a study in UK which is 74%,seems patients presents in late stages(17). The stage distribution in our study stage I 10.29%, stage II 7.35%, stage III 55.85%, stage IV 21%, stage V 1.49% as compared to TPOG-W-9 in which stage distribution was: I, 43.2%; II, 19.3%; III, 23.9%; IV, 6.8%; and V, 6.8% suggesting patients presents in advance stages (16).

Table 4 : Comparison of our study with TPOG-W-9 Study

STAGE	OUR STUDY	TPOG-W-9 STUDY
I	10.29%	43.2%
II	7.35%	19.3%
III	55.85%	23.9%
IV	21%	6.8%
V	1.49%	6.8%

THEY SEE EARLY STAGES AND WE SEE LATE STAGES

The preoperative chemotherapy is generally recommended to reduce the tumour bulk and to prevent intraoperative tumour rupture also the intraoperative tumour haemorrhage, the NWTS group also reported that the frequency of occurrence of extensive haemorrhage in Wilms tumour with tumour thrombosis becomes less when preoperative chemotherapy was administered to patients compared to immediate nephrectomy (18,19). At our institute the patients are treated with NWTS protocol, so preoperative chemotherapy is given to those patients which seems inoperable at the time of presentation and the chemotherapy was given according to SIOP 93-01 protocol.

Radical nephrectomy is the standard treatment for Wilms tumour(20), in our study surgery was performed in 52 patients, also NWTS 4 & 5 suggests that it is lymph node sampling at hilar region is adequate for accurate staging & extensive lymph node dissection is not mandatory(21,22), in our study 27 patients underwent lymph node dissection and 13 were found to be positive for metastasis. The presence of anaplasia has been most commonly presented as the

important predictor of poor prognosis marker in children in both NWTS and SIOP studies. The 5-year survival rate in NWTS & SIOP studies with anaplasia cases accounts more than 60% death in our study Unfavourable histology 43.28% which is a poor prognostic marker in our study. (23,24,25).Wilms tumour is one of the most radiosensitive tumours, but nowadays it is indicated only in advance disease i.e. stage III & IV. Post-surgery radiotherapy should be given within 10 days,NWTS studies have suggests that delay of more than 10 days of surgery associated with significantly higher abdominal relapse rate(26,27),also COG studies shows that RT should be preferably given by day 9 but not later than day 14 after surgery(28) in our study the radiotherapy is delivered with average delay of 35 days.

In our study 2-year overall survival is 84.69% similar to some western studies as the UKW-2 and the SIOP-9 which reported 83% and 85%, respectively(29,30). The 5-year survival rate regardless of histology is in stage I 90%, stage II 80%, stage III 75%, stage IV 45% compared to a 10 yrs retrospective study done at Rio De Janero having stage I 100%, stage II 94.2%, stage III 83.2%, stage IV 31.3%

Table 5 : Comparison of our study with Rio De Janero Study.

STAGE	OUR STUDY	Rio De Janero study
I	90%	100%
II	80%	94.2%
III	75%	83.2%
IV	45%	31.3%

The Results Are Not Comparable Suggesting Poor Survival Rate

Also, the five-year survival rate according to the histology, regardless of staging, was 74% for patients with FH, 60% for patients with anaplasia (focal plus diffuse) the results were less in comparison to above study of whom the FH survival were 89.4% and focal anaplasia were 66.70% suggesting the unfavourable histology have poor prognosis (31)

in a review study done by Faria et al of 165 cases of Wilms' tumour with anaplasia in the NWTSG, observed 59 cases of death among 126 patients with Diffuse anaplasia, and 22 of 23 children who presented in stage IV were among these deaths. On the other hand, only one out of the 39 patients with FA died. (32) In a more recent study carried out by SIOP, the patients with stage IV treated with chemotherapy prior to nephrectomy and who presented Wilms' tumour found to be completely necrotic via histology, achieved excellent survival. This again confirms that DA is a predictor for worse prognosis (33). The 5 yrs overall survival & event free survival is 74.25% & 69% respectively which is less than a study done in south India(34).

CONCLUSION-

The children usually presented in late stages in our institute. Most common presentation was in stage III followed by stage IV. The 5-year survival rate& event free survival rate was very low compared to the other studies because of the presentation of patients in late stages and poor general condition responsible for difficulty to deliver the optimum treatment. Also, other causes such as poor socioeconomic status, inability to comply with treatment, inability to afford travel expenses and reach centers offering cancer treatment, lack of knowledge about the excellent prognosis with this cancer were the other contributing factors for sub optimum outcome.

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