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# Recent Advances in the Management of Wilms' Tumour

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The initial pathologic description of nephroblastoma was done as early as 1872<sup>1</sup> and in 1879<sup>2</sup> by Osler, but it was only in 1899 that Max Wilms thoroughly reviewed the literature and gave a detailed description of the tumour. Wilms' tumour or nephroblastoma is the most common primary malignant renal tumour of childhood. The mean age for diagnosis of unilateral Wilms' tumour in boys is 41.5 months and in girls is 46.9 months.<sup>3</sup> The mean age of diagnosis for bilateral tumour is 29.5 months in boys and 32.6 months in girls.<sup>3</sup> Surgical excision was the only treatment available until 1915, when Friedlander<sup>4</sup> added radiation therapy. Chemotherapy with Actinomycin D was begun much later in 1954 and with Vincristine in 1963.<sup>5</sup> In 1969, the National Wilms' Tumour Study Group (NWTSG) was formed in America. Since its inception four NWTSG trials have been completed, and since July 1995 the NWTSG-5 is in progress. At near about the same time randomized controlled trials were conducted in Europe by the SIOP.

The main goals of NWTSG-4 (1986-1994) were to further decrease treatment intensity for patients with favourable prognosis while maintaining their excellent survival. NWTSG-5 is a single arm non-randomised therapeutic trial in which the biological features of the tumour will be assessed. It will attempt to verify that whether loss of heterozygosity (LOH) for chromosome 16q and 1p are useful markers in identifying patients who will relapse.

## Pathology

Wilms' tumour is thought to be derived from primitive metanephric blastema but the tumour is also known to contain tissues not found in the normal metanephros, such as skeletal muscle, cartilage, and squamous epithelium. By

definition, Wilms' tumour is a malignant embryoma of the kidney.<sup>6</sup> Histologically the classic *nephroblastoma (favourable histology)* is made up of varying proportions of three cell types—blastemal, stromal and epithelial, but all the tumours are not triphasic. *Anaplastic tumours* constitute the unfavourable histology in Wilms' tumour. Anaplastic tumours comprise 4.5% of all Wilms' tumours (NWTSG-3) and are rare in the first two years of life.<sup>7</sup> The anaplastic changes may be focal or diffuse. *Clear cell sarcoma of the kidney (CCSK)* is no longer considered a variant of Wilms' tumour, but as it is an important primary tumour of the kidney, associated with higher rate of relapse and death, its treatment is still being evaluated under the NWTSG trials.

*The rhabdoid tumour of the kidney (RTK)*, a highly malignant tumour of the kidney, was described by NWTSG in 1978.<sup>8</sup> It occurs mostly in children less than 2 years of age.<sup>9</sup> This is another tumour, which is no longer considered a variant of the Wilms' tumour. *Congenital mesoblastic nephroma (CMN)*: Congenital mesoblastic nephroma is the commonest renal neoplasm in the newborn and the second most common tumour seen in the neonatal period, after sacrococcygeal teratoma.<sup>10</sup> CMN occurs predominantly in males and in infants (median age of 2 months).<sup>11</sup> A cellular or atypical variant of CMN contains hyperchromatic nuclei and more prominent mitotic figures.<sup>12,13</sup> This cellular variant is associated with a higher risk of recurrence and aggressive biologic behaviour when encountered in children more than 3 years of age. Nephrectomy alone is the treatment of choice for CMN. There are only a few reports of recurrence and/or metastases to the lungs or central nervous system.<sup>10-12, 14,15</sup> Chemotherapy similar to that for stage I Wilms' tumour, may also be considered in children more than 3 years of age, with a highly mitotic cellular variant.

### Work-up of a case of Wilms' tumour

The investigations in any case of suspected Wilms' tumour fall into two basic categories: those done to establish the diagnosis and the extent of disease and the others, which are baseline investigations for any major surgical procedure. Initially an ultrasound is done as screening investigation in a child with an abdominal mass. Ultrasound is quick, cheap, easily available, non-invasive, does not require any preparation and easily confirms the presence of a solid renal mass. Further imaging studies are performed to establish the presence of a renal mass and a normally functioning contralateral kidney, document patency of inferior vena cava (IVC), and demonstrate the presence or absence of pulmonary or hepatic metastases. A contrast enhanced CT scan (CECT) is currently the investigation of choice. MRI scan may soon replace the CECT as the investigation of choice but is at present more expensive. A CECT is performed to evaluate the nature and extent of the mass and the involvement of adjoining structures such as the liver, spleen, or colon. CECT also gives information on the presence and function of the contralateral kidney and whether the tumour is bilateral. A simultaneous CECT scan of the chest should also be done, to detect pulmonary secondaries as this is the commonest site of secondary in Wilms' tumour. Though IVC thrombus can at times be picked-up on CECT scans (Fig. 1), it is best identified by using Dop-

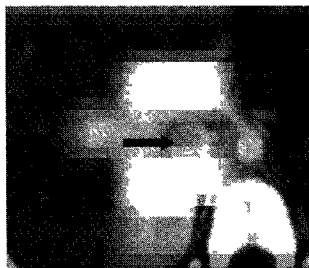


Fig1: CECT scan of a child with right sided Wilms' tumour showing an IVC thrombus.

pler studies. The identification of IVC thrombus is important as it up-stages the tumour (stage II or III) and will change management. As the in-

formation obtained on a CECT is much more than on an intravenous pyelography (IVP), IVP is now not a routine in the work-up of a patient with Wilms' tumour (WT). Radio-nuclide bone scan and x-ray skeletal survey are needed in those with pulmonary and/or hepatic metastases and also in those who have suggestive symptoms like bony pains. It is also mandatory in those diagnosed to have clear cell sarcoma of kidney (CCSK). Brain imaging by MRI or CT scan should be obtained in all patients with CCSK and rhabdoid tumour of kidney (RTK) as both may be associated with intracranial secondaries.<sup>16,17</sup> The baseline investigations should include a complete blood count and differential count, liver and kidney function tests, serum calcium, and urine analysis.

A fine needle aspiration cytology (FNAC) of the tumour to confirm diagnosis before nephrectomy is not mandatory and should probably be done only in those cases that are being planned for preoperative chemotherapy. Doing a FNAC does not upstage the tumour but doing a needle biopsy does. A needle biopsy is considered as a local spill and so the tumour will be staged as minimum stage II. Needle biopsy also carries a potential risk of tumour seeding along the needle tract. Thus needle biopsy is not recommended.

In those trials where preoperative chemotherapy is given to all patients, like SIOP, the diagnosis of WT is made on CT only, and at most with an additional fine needle aspiration cytology. The incidence of wrong diagnosis when imaging is the only modality used was reported to be 6.8% in NWTs and 9.9% in SIOP.<sup>18</sup> These were actually other pathologies like neuroblastoma, CMN, renal cell carcinoma, multicystic dysplastic kidney etc. In such cases, though it would be preferable to obtain a tissue diagnosis by a needle biopsy most centers do not advocate this because of the fear of needle tract recurrences.

### Staging and Prognostic Considerations

As more effective regimens are developed, the significance of previously determined prognostic factors changes and the older variables

may no longer pertain. Tumour size, age of the patient, histologic features, lymph node metastases, and certain local features, namely capsular and vascular invasion have all been used to predict outcome. The tumour histology, stage of disease, and lymph node involvement still remain the most important predictors of treatment outcomes. However, recent research has favored identification of additional prognostic factors that may be employed for further stratification

of therapy. These include loss of heterozygosity of chromosome 16q, and tumour cell DNA content. Histological prognostication on fine needle aspiration samples has also been attempted.<sup>19</sup>

The staging of Wilms' tumour has also changed over the years and the current surgico-pathologic staging used in NWTS-5 is shown in table-1 and the stage wise distribution of patients as reported in NWTS-3 is shown in table-2.

**Table-1: National Wilms' Tumour Study-5: Staging System**

<i>Stage</i>	
I	Tumour limited to the kidney and completely excised. The surface of the renal capsule is intact. Tumour was not biopsied before or ruptured before or during removal. Vessels of the renal sinus are not involved. There is no residual tumour apparent beyond margins of resection.
II	Tumour extends beyond the kidney but is completely resected. There is regional extension of the tumour (i.e. penetration of the renal capsule or extensive invasion of the renal sinus). The blood vessels outside the renal parenchyma, including those of the renal sinus, contain tumour. The tumour was needle biopsied (except for FNAC), Or there was tumour spillage before or during surgery that is confined to the flank, and does not involve the peritoneal surface. There is no evidence of tumour at or beyond the margins of resection, IVC thrombus.
III	Residual non-hematogenous tumour present confined to the abdomen. Lymph nodes in the abdomen or pelvis are involved. IVC thrombus adherent to the IVC wall. The tumour has penetrated through the peritoneal surface. Tumour implants are found on the peritoneal surface. Gross or microscopic tumour remains at the margin of resection. The tumour is not completely resectable because of local infiltration into vital structures or biopsy only done. Gross tumour spill either before or during surgery.
IV	Hematogenous metastases (lung, liver, bone, brain etc) or lymph node metastases outside the abdomino-pelvic region are present.
V	Bilateral renal involvement present at diagnosis. (Each side to be staged separately).

**Table-2: Wilms' Tumour Distribution by Stages**

Stage	NWTS-3
I FH	42%
II FH	19.3%
III FH	20.3%
IV FH	9.1%
I-III UH	7.1%
IV UH	2.2%

## THERAPY FOR WILMS' TUMOURS

Surgery is the cornerstone in the treatment of Wilms' tumour and all patients will need surgical removal of the tumour. When the surgical removal is done, may be debated upon. While the NWTS group recommends surgery as the initial modality of treatment, the European trials (SIOP) recommends pre-operative chemotherapy for all patients, which is followed by surgery. Since the recommendations of the NWTS are what most workers in India follow, this will be discussed in details.

Nephroureterectomy for WT is done through a large incision so as to avoid excess of tumour manipulation which has a higher incidence of tumour spill in addition to the possibility of a tumour thrombus getting dislodged and causing pulmonary embolism.<sup>20, 21</sup> A complete exploration of the abdomen is done. The contra-lateral kidney's Gerota's fascia should be opened and the anterior and posterior surfaces should be palpated and visualized to exclude bilateral tumour. This should be done prior to nephrectomy of the involved kidney. The renal vein and IVC should be palpated carefully before ligation to rule out tumour extension. Routine lymph node sampling from the iliac, para-aortic and celiac areas must be done for accurate staging. Any suspicious lymph nodes must also be sampled. The surgeon should assign "loco-regional stage" to the tumour based solely on the

operative findings. Knowledge that distant metastases are present does not influence this staging. Titanium clips should be used to identify residual tumour, margins of resection, and suspicious areas. The clips are useful in planning subsequent RT. Tumour spill during surgery must be prevented as this will upstage the tumour to stage III, thereby increasing the cost of treatment and the subsequent morbidity. Tumour spill also increases the rate of local recurrence.

Following nephroureterectomy for unilateral Wilms' tumour, the subsequent chemotherapy and radiotherapy is dependent upon the stage of the tumour (Table-3 & 4). While the treatment of stage I and II disease requires the administration of two drugs, namely Actinomycin D (ACD) and Vincristine (VCR) for a period of 18 weeks, it does not require any radiotherapy to be given. The treatment of stage III and IV involves the third drug, Adriamycin (ADR), for a period of 24 weeks. Treatment of stage III and IV tumours also require radiotherapy (RT) which consists of 1080 cGy for the tumour bed and varying doses for all the sites of metastatic disease. This addition of ADR and RT increases the morbidity as well as the cost of treatment. It is therefore important to detect WT early so that more and more children are in the earlier stages of the disease that can be treated with minimum morbidity and at a much lower cost and with better final outcome.

**Table-3: NWTS-5 protocol after nephro-ureterectomy for unilateral Wilms Tumour.**

Stage/ Histology	RT	Chemotherapy
I, II FH and I anaplastic	None	EE-4A
I FH(age< 2years, tumours < 550 gms)	None	None
III, IV FH and II-IV Focal anaplasia	1080cGY*	DD-4A
II-IV Diffuse anaplasia and CCSK	1080cGY	Regime I
I-IV RTK	1080cGY#	RTK regime

FH = favourable histology; CCSK = Clear cell sarcoma of kidney; RTK = Rhabdoid tumour of kidney; EE-4A, DD-4A, Regime I and RTK regime are as shown in table-6

\* Stage IV tumours: Tumour bed RT only if the lo-

cal stage is III. In addition the stage IV patients receive RT to all metastatic sites in recommended doses.

# = no abdominal radiation for stage I and II RTK

**Table-4: Various regimes used in NWTS-5**

<b>EE 4A: ACD –</b>	week 0,3,6,9,12,15, and 18 VCR – week 1,2,3,4,5,6,7,8,9, and 10 VCR*- week 12,15, and 18
<b>DD 4A: ACD –</b>	week 0,6,12,18, and 24 VCR – week 1,2,3,4,5,6,7,8,9, and 10 VCR*- week 12,15,18,21,and 24 ADR – week 3, and 9 ADR* - week 15, and 21
<b>RTK regimen:</b>	Carboplatin and Etoposide – week 0,3,9,12,18, and 21 Cyclophosphamide and Mesna – week 6,15, and 24 G-CSF – to start 24 hours after last dose and continue until absolute neutrophil count is more than 10,000.
<b>Regimen I:</b>	VCR – week 1,2,4,5,6,7,8,10, and 11 VCR* - week 12,13,18,and 24 ADR – week 0,6,12,18, and 24 Cyclophosphamide and Mesna – week 6,12,18, and 24 Cyclophosphamide and Mesna* - week 3,9,15, and 21 Etoposide – week 3,9,15,and 21 G-CSF - to start 24 hours after last dose and continue until absolute neutrophil count is more than 10,000.
<b>Drug doses and administration:</b>	which includes Cyclophosphamide and Etoposide (VP-16).
NWTS-5 recommendations for treatment of anaplastic WT is shown in table 3 & 4. Only for stage II to IV tumours with diffuse anaplasia a different regime (Regime I) is recommended	Therapy for bilateral Wilms' Tumour (BWT) Four to seven percent of children with Wilms tumour have synchronous BWT <sup>22, 23</sup> and

approximately 10% of those found to have bilateral tumours on laparotomy are not identified/using CT.<sup>24</sup> Most of the lesions missed on preoperative investigations were generally 1 cm or less in size but early identification of BWT is essential as the therapeutic approach differs, in that they should not undergo nephrectomy at diagnosis.<sup>22, 25</sup> The NWTs indicates that these patients have a good prognosis for survival,<sup>22,23,26</sup> but are at a risk for renal failure. The treatment of these children must be individualised with the goal being eradication of all tumour and preservation of as much renal tissue as possible.<sup>27</sup> Partial nephrectomy should be used at the initial operation only if all tumour can be resected with preservation of two thirds or more of the parenchyma on both sides. Otherwise it is recommended to do laparotomy with bilateral renal biopsies and lymph node sampling for staging of each kidney. The child is then put on initial treatment depending on the stage and the histology. The response to these therapies should be evaluated after 5 weeks. After clinical reduction in size, radiologic re-evaluation is done and the patient taken up for second look surgery, usually in 8-10 weeks time (ie. after completion of the chemotherapy), and bilateral partial resection or wedge resection is done if feasible. Further chemotherapy and radiotherapy should be done as per recommendations for the stage. Cases in which adequate renal parenchyma can't be left and both kidneys have to be removed for complete excision of the tumours would require renal transplantation. In such cases renal transplantation is recommended after two years of completion of therapy if there is no recurrence and during this time the child is to be maintained on regular hemodialysis.

#### THERAPY FOR INOPERABLE WILMS' TUMOUR

Tumours can be inoperable because of massive size, extension into supra-hepatic IVC and/or other reasons, which pose too great a surgical risk (Fig. 2a). That preoperative chemotherapy almost always reduces the tumour size rendering it resectable, thus reducing the frequency of surgical complications has been clearly shown both by NWTs and SIOP.<sup>28,29</sup> All patients who are clinically thought to be inoperable should undergo an initial exploration to assess operability and a biopsy as the error rate in the preop-

erative diagnosis of renal masses after radiologic assessment is 5-10%.<sup>30</sup> Patients who are staged by imaging studies alone are at a risk of both under and over staging. If suspicious lymph node or other metastatic deposits are found, these should also be biopsied. If it is decided not to do an exploration but give preoperative chemotherapy based on imaging alone, with or without a needle biopsy, the tumour should be considered stage III. After initiating preoperative chemotherapy, repeat radiographic evaluation is done in 5 weeks (Fig. 2b) and if considered re-

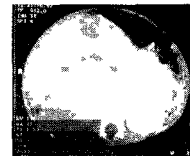


Fig 2: (a) CECT scan showing a massive right sided Wilms' tumour in a child who presented with stage 4 Wilms' with bilateral lung secondaries.



Fig 2: (b) CECT of the same child after 4 weeks of chemotherapy showing reduction in size of the tumour.

sectable, the tumour is removed and the post-operative chemotherapy continued. Some of the patients who fail to respond to preoperative chemotherapy are considered for pre-operative irradiation. The primary tumour must be considered stage III regardless of the findings at surgery and post-operative irradiation to the tumour bed is given to all who did not receive it pre-operatively. NWTSG advocates pre-excision chemotherapy only for cases of Wilms' tumour which are unresectable (after attempt at resection), have supra-hepatic IVC thrombus, bilateral Wilms' tumour and tumour in solitary kidney.

#### THERAPY FOR RECURRENT WILMS' TUMOUR

The factors reported to be associated with relative risk of local recurrence in NWTs-4 are:

**Table-5: Wilms' Tumour: Results of Treatment as reported by NWTs-4**

Stage	Survival
I FH	95.6%
II FH	91.1%
III FH	90.9%
IV FH	80.9%

stage III disease; diffuse anaplasia; tumour spill; and absence of lymph node biopsy specially in stage I disease.<sup>31</sup> The prognosis of children with FH Wilms' tumour who relapse is variable and depends on the initial stage, site of relapse, time from initial diagnosis to relapse and their previous treatment. The favourable prognostic factors in this group of patients include no prior treatment with ADR, relapse more than 12 months after diagnosis, intra-abdominal relapse in a patient not previously treated with abdominal irradiation.<sup>32</sup> These children with relapse who have favourable prognostic factors should be treated aggressively and have a good response to retrieval therapy (Fig. 3a,b,c,d). Surgical excision, if feasible, should be done at the outset to confirm relapse, accurately document sites of relapse and debulk the tumour prior to abdominal irradiation or combination chemotherapy. Though the optimum regime has not been defined but it should probably include drugs not used previously (Adriamycin, Cyclophosphamide, Ifosfamide, Etoposide and Carboplatin). Relapses in children who have already received ADR and tumour bed irradiation have a poor prognosis and a combination of etoposide and ifosfamide<sup>33</sup> have sometimes provided prolonged responses.

#### SPECIAL CONSIDERATIONS IN WILMS' TUMOUR IN NEONATES AND INFANTS

Neonatal Wilms' tumour is rare.<sup>34,35</sup> Chemotherapy is reduced by 50% in all neonates and infants. Children under 18 months of age with pulmonary metastases should be given lung irradiation only if complete resolution does not

take place with 4 weeks of ACD+VCR. These children with residual pulmonary nodules are given 900cGy in daily fractions of 150 cGy. Surgical excision of the residual nodules is another alternative to RT.

#### FOLLOW-UP AFTER COMPLETION OF THERAPY

After completion of the therapy, the frequency of imaging examinations is dependent on the stage and histology of the tumour and physical and laboratory tests coincide with the schedule for imaging. In general all patients are reviewed every 3 months for the first year, and there after every 6 months for another 2 years. After the first three years the likelihood of recurrence is less, however these patients must be reviewed at least once every year for various long term complications. Relevant radiological investigations are done in the initial three years as per recommendations.

#### RESULTS OF TREATMENT OF WILMS' TUMOUR

The ultimate outcome of patients with WT has gradually and progressively improved over the past few decades and this is basically attributable to the use of multimodality treatment and the development of better understanding of the pathology and the molecular biology. The delineation of the prognostic factors has led to the reduction of chemotherapy and avoidance of radiotherapy for the lower stage disease and the intensification of therapy for higher stage and unfavourable histology disease. This has led to

a decrease in the chemotherapy and radiotherapy related complications and their morbidity and mortality without compromising on the treatment of the tumour itself. The current recommendations are all basically the result of well planned multicenteric studies involving a large number of centers like those in America (NWTs) and Europe (SIOP). The current results of treatment of favourable histology WT as reported by NWTs-4 are shown in Table: 5. With increasing number of survivors reaching adulthood there has been some concern regarding the late effects of nephrectomy, chemotherapy and radiotherapy in terms of growth and development, fertility, development of skeletal deformities and renal failure, and the development of second malignancies. The general growth and development of these survivors has been shown to be normal in the long run.<sup>36</sup> Though there has been some concern on the long term effects of nephrectomy, specially in terms of hyperfiltration injury of the remaining kidney<sup>36</sup> and the gradual onset of renal failure after two or three decades, the last word has yet to be said in this aspect. With such good outcome and overall excellent long term survival of children with WT a chance must be given to all children with this disease and all attempts must be made to save each one of them.

**Dactinomycin (ACD):** 0.045 mg/kg/dose IV push (maximum dose – 2.3 mg), beginning within 5 postoperative day (week 0). The dose will be 1.35 mg/m<sup>2</sup> IV push for all patients who weigh more than 30 kilograms, but no single dose to exceed 2.3 mg. The dose of ACD administered at week 6 should be decreased by 50% if whole lung or whole abdomen radiation therapy has been given.

**Vincristine (VCR):** 0.05 mg/kg IV push (maximum dose – 2.0 mg), beginning day 7 post ne-

phrectomy i.e. week 1. The dose of VCR is 1.5 mg/m<sup>2</sup> IV push for all patients who weigh more than 30 kilograms, but no single dose to exceed 2.0 mg.

**Doxorubicin (ADR):** 1.5 mg/kg IV push . The dose is 45 mg/m<sup>2</sup> IV push for all patients who weigh more than 30 kilograms. The dose administered at 3 week (week 6 in regime I) is reduced by 50% if whole lung or whole abdomen radiation therapy has been given.

**Carboplatin:** 16.7 mg/kg/day x 2 days. The dose is 500mg/m<sup>2</sup> /day x 2 days, IV push for all patients who weigh more than 30 kilograms.

**Etoposide (VP-16):** 3.3 mg/kg/day x 3days in 200 cc/m<sup>2</sup> of N/2 saline as an IV infusion over 60 minutes daily. The dose is 100mg/m<sup>2</sup> /day x 3 days, IV push for all patients who weigh more than 30 kilograms.

**Cyclophosphamide:** Prehydration with 200 cc/m<sup>2</sup>/hr of N/2 saline for two hours then 14.7 mg/kg/day x 3 days in 200 cc/m<sup>2</sup> of N/2 saline as an IV infusion over 60 minutes daily. Continue hydration with 150 cc/m<sup>2</sup> /hr of N/2 saline for 6 hours. The dose is 440mg/m<sup>2</sup> /day x 3 days, IV push for all patients who weigh more than 30 kilograms. \*Note: in weeks 3,9,15 and 21 cyclophosphamide is given for 5 days.

**Mesna:** 3mg/kg/dose x 4 doses in 10 ml IV over 15 minutes x 3 days given. The first dose with cyclophosphamide. The dose should be 90mg/m<sup>2</sup> /dose x 4 doses x 3 days, IV push for all patients who weigh more than 30 kilograms. \*Note: in weeks 3,9,15 and 21 Mesna is given for 5 days.

**G-CSF:** 5 micrograms/kg/day subcutaneously.



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