Saga of Wilms’ Tumor: Lessons learnt from the past

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ABSTRACT

Wilms’ tumor (WT) represents 6% of childhood cancers. Recent advances in molecular biology have significant implications for the clinical management. A dramatic improvement in overall cure has resulted from the adoption of multimodality treatment during the past few decades. National Wilms’ Tumor Study (NWTS), and the Société Internationale d’Oncologie Pédiatrique (SIOP) have laid down the guidelines for standardized treatment of WT, though differing in the diagnostic and therapeutic approach. Both these groups currently aim at intensifying treatment for patients with poor prognosticators while appropriating the therapy to reduce long-term complications for those with favorable prognostic features. Challenges faced in developing nations include poverty, malnutrition, ignorance, and presentation in advanced stages coupled with limited facilities that are necessary for total management of these cases. In this article, we have discussed our approach to deal with patients with nephroblastoma, reviewed the literature on the current management strategies and the long-term outcome. Most countries have adopted the NWTS protocols, while others especially in Europe, South America and some Asian countries follow the SIOP regimen. Both have their advantages and weaknesses and may not necessarily be suitable to the setup in developing countries. We have discussed the controversial issues in the management of WT including the timing of biopsy, type of biopsy, investigative approach, role of chemotherapy / radiotherapy, management of bilateral Wilms’ tumor and parenchymal sparing renal surgery. Despite deviating from NWTS at various points, the overall results have remained satisfactory. Thus, developing countries might adopt their own protocols depending on the prevalent situations and facilities available to them to treat such patients.

KEY WORDS: Wilms’ tumor, Nephroblastoma, NWTS, Pediatric malignancy

Wilms’ tumor was first described by Thomas F. Rance in 1814. However, Max Wilms, a German surgeon and pathologist, gave the detailed description, adding seven new patients of his own in 1899 and since then the tumor bears his name.[1]

Wilms’ tumor (nephroblastoma) is an embryonic kidney tumor. It is the most common abdominal tumor in children and represents 6% of childhood cancer. Wilms’ tumor is primarily a disease of the kidney, but occasionally extrarenal locations have been reported, especially in the retroperitoneum, the sacrococcygeal region, testis, uterus, inguinal canal, and mediastinum.[2]

A dramatic improvement in overall survival rates lately has resulted from the coordinated use of modern surgical technique and anaesthesia, multiple drug chemotherapy, and radiation therapy.[3] Large cooperative cancer groups, especially the National Wilms’ Tumor Study (NWTS), and the Société Internationale d’Oncologie Pédiatrique (SIOP) have laid down guidelines for standardized treatment of this tumor and thus achieved a 5-year survival rate of more than 90%.

The median age at diagnosis is 41.5 months for males with unilateral tumor and 46.9 months for females with unilateral tumors.[4] For bilateral tumors the median age at presentation is 29.5 months for males and 32.6 months for females.[4] The male to female ratio is 0.92 for unilateral tumors and 0.6 for bilateral tumors. Most of the patients present before 5 years of age. Wilms’ tumor is bilateral at presentation in 4% to 8% of cases.

ASSOCIATED ANOMALIES

Wilms’ tumor is associated with congenital anomalies in 10% to 13% of cases. Aniridia is present in 10% of children; hemihypertrophy is noted in 2% to 3%. Other genitourinary malformations are present in 5% of cases mainly cryptorchidism, hypospadias, double collecting...
system or fused kidney. Rarely, Wilms’ tumor has been found in a horseshoe kidney.\[^{[5]}\] Congenital abnormalities are seen more commonly in bilateral tumors. The “Denys-Drash Syndrome” is a combination of Wilms’ tumor, male pseudohermaphroditism and glomerulonephritis. The “WAGR Syndrome” is a combination of WT with aniridia, genitourinary malformations and mental retardation. Wilms’ tumor also occurs with increased frequency in the “Beckwith – Wiedemann syndrome” which includes macrosomia, hemihypertrophy, and macroGLOSSIA. Hemihypertrophy is extremely rare and normally seen in only 3 per 100,000 children. Other associated malformations include Septal defects, microcephalus, hyperinsulinism, and von Willebrand’s disease (8%).

**MOLECULAR BIOLOGY**

Nephrogenic rests, potentially premalignant lesions, are found in the kidneys of 30 to 40% of children with Wilms’ tumors.\[^{[6]}\]

In 1984, the loss of heterozygosity (LOH) on chromosome 11p alleles was described in up to 40% of Wilms’ tumors. A “two hit model” similar to that of retinoblastoma was proposed, indicating a recessive mutation in the etiology of Wilms’ tumor.

Wilms’ tumor (hereditary or sporadic) appears to result from changes in one or more of several genes. Specific germ-line mutations in one of these genes (Wilms’ tumor gene-1, WT1) located on the short arm of chromosome 11 (band 11p13) are not only associated with Wilms’ tumor but also cause a variety of genitorinary abnormalities such as cryptorchidism and hypospadias, and the rare Denys-Drash syndrome. A gene that causes aniridia is located near the WT1 gene on chromosome 11p13, and deletions encompassing the WT1 and aniridia genes may explain the association between aniridia and Wilms’ tumor. Patients with aniridia or hemihypertrophy should be screened with ultrasound every 3 months until they are 6 years of age. There appears to be a second Wilms’ tumor gene (WT 2) at or near the Beckwith-Wiedemann gene locus on chromosome 11p15, and children with Beckwith-Wiedemann syndrome are at increased risk for developing Wilms’ tumor. Approximately one-fifth of patients with Beckwith-Wiedemann syndrome who develop Wilms’ tumor present with bilateral disease, primarily at diagnosis, although metachronous recurrence is also observed.

The presence of structural anomalies of chromosome 17 in approximately 15% of tumors and the observation of an individual with Wilms’ tumor in a Li-Fraumeni fam-

ily (a cancer susceptibility syndrome with germ line mutations of p53) suggested a role for the p53 tumor suppressor gene.\[^{[7]}\] The p53-encoded protein appears to act as a cell cycle checkpoint protein that arrests cell growth in G1. Inactivation by mutation or alteration results in genomic instability and cytogenetic aberrations (e.g. aneuploidy, translocations, deletions, and gene amplification).\[^{[8]}\]

Genes on other chromosomes may also have an etiologic role in Wilms’ tumor, and loss of genetic material from chromosome 16 and/or chromosome 1p occurs in some tumors. Many Wilms’ tumors appear to arise from abnormally retained embryonic kidney precursor cells arranged in clusters termed nephrogenic rests. The different genetic lesions are associated with different subtypes of nephrogenic rests.

**DNA CONTENT**

Some studies suggested that flow cytometric evaluation of DNA-ploidy is a useful predictor of outcome and response to therapy. Diploid and aneuploid tumors are reported to have better long-term survival when compared with tetraploid tumors. However, other studies reported that this factor is not superior compared to histology and staging. Ongoing studies will determine the clinical usefulness of DNA-ploidy.

**HEREDITARY FACTORS**

Despite the number of genes that appear to be involved in the development of Wilms’ tumor, hereditary Wilms’ tumor (either bilateral tumors or a family history of the neoplasm) is uncommon, 1% to 2% of patients having a positive family history for Wilms’ tumor. The risk of Wilms’ tumor among offspring of persons who have had unilateral (i.e., sporadic) tumors is quite low (<2%). Siblings of children with Wilms’ tumor have a low likelihood of developing Wilms’ tumor. A second Wilms’ tumor may develop in the remaining kidney of 1% to 3% of children treated successfully for Wilms’ tumor. The incidence of such metachronous bilateral Wilms’ tumors is much higher in children whose original Wilms’ tumor was diagnosed at less than 12 months of age and/or whose resected kidney contains nephrogenic rests. Periodic abdominal ultrasound is recommended for early detection of metachronous bilateral Wilms’ tumor as follows: children with nephrogenic rests in the resected kidney (if < 48 months of age at initial diagnosis) - every 3 months for 6 years; children with nephrogenic rests in the resected kidney (if > 48 months of age at initial diagnosis) - every 3 months for 4 years; other patients - every 6 months for
2 years, then yearly for an additional 1 to 3 years.

Clear cell sarcoma of the kidney and rhabdoid tumor of the kidney are childhood renal tumors unrelated to Wilms’ tumor. Because of their renal location, they have been treated on clinical trials developed by the National Wilms’ Tumor Study Group. The approach to their treatment, however, is distinctive from that of Wilms’ tumor, and requires timely and accurate diagnosis.

CLINICAL PRESENTATION

Patients usually present with a large, smooth and non-tender flank mass on palpation, usually noted by a parent. About a quarter may have associated (microscopic) hematuria, dysuria, malaise, weight loss, anemia, or hypertension. The tumor can rupture with trivial trauma and these patients present with acute abdominal pain. Obstruction of the left spermatic vein by the mass can result in a left-sided varicocele. Few cases of Wilms’ tumor have been diagnosed antenatally with help of ultrasonography. It is usually associated with polyhydramnios. Increased mortality has been reported if associated with fetal hydrops.

LABORATORY TESTS

Recently, urinary basic Fibroblast Growth Factor (bFGF) has been reported to be elevated preoperatively in patients with Wilms’ tumor. Rebhandl et al. described the Tissue Polypeptide Specific antigen (TPS), a cytokeratin-18 derived marker, which might be of clinical value in monitoring the therapy of neuroblastoma. Hypertension may be associated with Wilms’ tumor. Increased plasma proenin and renin levels, found by several investigators, could be the cause. The serum level of neuron-specific enolase (NSE) and urinary catecholamine levels should be routinely measured to exclude neuroblastoma.

IMAGING STUDIES

Advances in radiological techniques are able to detect non-palpable Wilms’ tumors, nephroblastomatosis, and tumor spread much earlier and in a less invasive manner than in the past. An abdominal ultrasound study of the mass and color-duplex investigation of the renal vessels should be performed. Thus, the extent of renal involvement (contralateral kidney), the renal vein, the inferior vena cava (IVC) and the liver can be assessed. Additionally, high-resolution sonography may detect areas of nephroblastomatosis usually presenting as multiple solid, subcapsular, hypovascular and hypoechogenic nodules or cysts.

Skipgram chest, CT scans of the chest and the abdomen should also be done as baseline diagnostic procedures for complete evaluation of the extent of the mass. Following the NWTS-5 recommendations, positive findings seen in chest CT but not on chest radiograph should be ignored. Whether the accuracy of CT or MRI obviates the need for surgical exploration of the contralateral kidney remains controversial. MRI studies have a predominant role in demonstrating the relation of the tumor to other organs. MRI, along with ultrasound is more sensitive than CT for assessing extension of a tumor thrombus into the inferior vena cava (IVC) with the additional possibility of MR-venography. Nephrogenic rests (NRs) as small as 4mm typically appear as homogeneous lesions after Gadolinium enhancement, different from the heterogeneous appearance of Wilms’ tumor. SIOP-investigators strongly recommend a judgement by a reference radiologist because in these studies preoperative chemotherapy without histopathological diagnosis is favored.

If there is no clear discrimination from neuroblastoma, an I (131) metaiodobenzylguanidine (MIBG)-scan may be performed. Patients with clear cell sarcoma or rhabdoid tumor of the kidney additionally need skeletal radiographs, radionuclide bone scans, and MRIs of the cranium.

NWTS CLASSIFICATION OF PEDIATRIC RENAL TUMORS

Low risk
Mesoblastic Nephroma
Intermediate risk
Favorable histology WT – Classic form of WT
High risk
Anaplastic Wilms’ tumor
- focal
- diffuse
Clear cell sarcoma
Rhabdoid tumor

PROGNOSTIC FACTORS

1. Stage of the disease
2. Favorable or unfavorable histology
3. Metastases at presentation
4. Regional lymph node involvement
5. Hyper-diploidy which correlates well with anaplastic variety
NWTS STAGING

NWTS has pioneered the stage grouping of WT.

Stage I
The tumor is limited to the kidney and has been completely excised. The renal capsule and the tumor were not ruptured. The vessels of the renal sinus are not involved and there is no residual tumor after surgical resection.

Stage II
The tumor extends beyond the kidney but was completely resected. There is regional extension of the tumor (i.e., penetration of the renal capsule, extensive invasion of the renal sinus). Blood vessels outside the renal sinus may contain tumor (tumor thrombus or infiltration). The tumor may have been biopsied, or there was local spillage of tumor confined to the flank. There is no evidence of tumor at or beyond the margins of resection. Free floating inferior venacaval thrombus.

Stage III
Residual nonhematogenous tumor confined to the abdomen or any of the following:
Lymph node involvement in the hilum or pelvis, Diffuse peritoneal spillage either before or during surgery, Peritoneal implants, Tumor beyond the surgical margin either grossly or microscopically Tumor not completely resected because of local infiltration into vital structures, IVC thrombus that is adherent to the venacaval wall, Tumor infiltrating a cuff of bladder.

Stage IV
Hematogenous metastases to lung, liver, bone, brain, or lymph node metastases outside the abdomen or pelvis. Pulmonary nodules seen on CT only must undergo biopsy for definitive diagnosis of stage IV.

Stage V
Bilateral renal involvement at diagnosis. Each side must be staged individually according to the criteria mentioned above. Therapy would be offered based on the higher stage of the two.

HISTOPATHOLOGY

Although most patients with a histologic diagnosis of Wilms’ tumor fare well with current treatment, approximately 12% of patients have histopathologic features that are associated with a poorer prognosis, and, in some types, with a high incidence of relapse and death. Wilms’ tumor can be separated into two prognostic groups on the basis of histopathology:

Favorable histology
Histology mimics development of a normal kidney consisting of 3 components: blastema, epithelium (tubules) and stroma. There is no anaplasia.

Unfavorable histology
Characterized by anaplasia (extreme cellular pleomorphism and atypia, diffuse). Focal anaplasia may not confer nearly as poor a prognosis as diffuse anaplasia. Anaplasia is associated with resistance to chemotherapy and may still be detected after pre-operative chemotherapy.

There are three main cytopathologic features of anaplasia: a) a threefold or greater nuclear enlargement, compared to the nearby nuclei of the same cell type e.g. stromal or epithelial; b) hyperchromatism (indicating that the nuclear enlargement is attributable to gross polyplody and not to hydroptic swelling or poor fixation) and c) enlarged abnormal (usually multipolar) mitotic figures, which is regarded as the most quintessential criterion.

Nephrogenic rests (NR)
These are foci of persistent primitive blastemal cells, which are normally found in neonatal kidneys (approximately 1% of newborn infants have NRs at autopsy) but also in 30 to 40% of adjacent normal renal tissue removed together with a Wilms’ tumor. NRs may be microscopic or grossly visible, single or multiple. Patients with NRs (in particular perilobar NRs), have a significantly increased risk of metachronous bilateral Wilms’ tumor.

According to their position within the lobe, the “perilobar (PLNR)” located at the periphery of the renal lobe are differentiated from the “intralobar (ILNR)” nephrogenic rests. It is of interest that LNR are consistently present in patients with deleted or mutated WT1-associated syndromes (WAGR complex – 11p13 locus, Denys-Drash syndrome), whereas PLNR are usually found in children with BWS (11p15 locus).

MANAGEMENT

Multidisciplinary Treatment planning by a team of cancer specialists (pediatric surgeon or pediatric urologist, pediatric radiation oncologist, and pediatric oncologist) with experience in treating Wilms’ tumor is required to determine and implement optimum treatment.

Therapy consists of surgery followed by chemotherapy
and, in some patients, radiation therapy.

Operative principles have evolved from NWTS trials. The most important role for the surgeon is to ensure complete tumor removal without rupture and perform an assessment of the extent of disease. Radical nephrectomy via a transabdominal incision and lymph node sampling is the procedure of choice. The contralateral kidney must be palpated and inspected through an opening in the fascia. Hilar, peri-aortic, iliac and celiac lymph node sampling is mandatory. Furthermore, any suspicious node should be sampled. Margins of resection, residual tumor, and any suspicious node basins should be marked with titanium clips.

Patients with massive, nonresectable unilateral tumors, bilateral tumors, or venacaval tumor thrombus above the hepatic veins are candidates for preoperative chemotherapy because of the risk of initial surgical resection. In the authors experience, Fine needle aspiration cytology (FNAC) has been practised routinely over decades without any untoward effects. The diagnostic accuracy in expert hands is high. Supplementation with immunocytochemistry helps to rule out other round cell tumors in cases with diagnostic dilemmas. A formal biopsy for histopathological confirmation, though practised by NWTS, is not recommended in cases appearing unresectable clinically. Pre-operative chemotherapy makes the tumor removal easier and may reduce the frequency of surgical complications.

Newborns and all infants less than 12 months of age require a reduction in chemotherapy doses to 50% of those given to older children. This reduction diminishes toxic effects reported in children in this age group enrolled in NWTS studies while maintaining an excellent overall outcome. Liver function tests in children with Wilms’ tumor should be monitored closely during the early course of therapy based on hepatic toxic effects (veno-occlusive disease) reported in these patients. Dactinomycin should not be administered during radiation therapy. Children treated for Wilms’ tumor are at increased risk for developing second malignant neoplasms. This risk depends on the intensity of their therapy, including the use of radiation and doxorubicin, and on possible genetic factors. Congestive heart failure has been shown to be a risk in children treated with doxorubicin. Efforts, therefore, have been aimed toward reducing the intensity of therapy where possible.

The approach for treating clear cell sarcoma of the kidney is different from Wilms’ since the overall survival of children with CCSK remains considerably lower than patients with favorable histology Wilms’ tumor. In the NSTS-3 study, the addition of doxorubicin to the combination of vincristine, dactinomycin, and radiation therapy resulted in an improvement in disease-free survival for patients with clear cell sarcoma of the kidney.

Under the current NWTS study, children with stage II-IV diffuse anaplasia and stage I-IV clear cell sarcoma of the kidney are treated with a new chemotherapeutic regimen combining vincristine, doxorubicin, cyclophosphamide, and etoposide (Regime I) in an attempt to further improve the survival of these high-risk groups. All these patients will receive radiation therapy to the tumor bed.

Patients with rhabdoid tumor of the kidney continued to have a poor prognosis on NWTS-4 regimens. In the study currently open, children with all stages of rhabdoid tumor of the kidney are being treated with carboplatin, cyclophosphamide, etoposide, and abdominal irradiation.

Chemotherapy
1. Neoadjuvant chemotherapy indications include
   - Bilateral Wilms’ tumor
   - Inoperable tumor
   - Intravascular extension into IVC above hepatic veins
   - Tumor in solitary kidney
2. Adjuvant chemotherapy
   Regimen EE4A • 18 week course
     • Actinomycin D and Vincristine
     • Stage I/II FH WT
     • Stage I focal or diffuse anaplasia WT
   Regimen DD4A • 24 week course
     • Actinomycin D, Vincristine, Doxorubicin
     • Stage III/IV FH WT
     • Stage II – IV Focal anaplasia
   Regimen I • 24 week course
     • Vincristine, Doxorubicin,
       Cyclophosphamide, Etoposide
     • Stage I – IV diffuse anaplasia

Surgical Principles
A. Standard procedure
   Radical nephrectomy + lymph node sampling through a transperitoneal approach
   Surgery helps in
   - Assessing Tumor extent involvement
   - Lymph node sampling
   - Any liver metastasis biopsy
   - Any peritoneal seeding biopsy
   Formal retroperitoneal lymph node dissection is not in-
dicated but lymph node sampling in the hilar, periaortic, pericaval, iliac and celiac lymph node regions are manda-

tory.

The incidence of post-operative complications in the NWTSG was 11%. The most serious complication intra-
operatively is tumor embolus into pulmonary artery and sudden death.

Common post-operative complications are Hemorrhage, Intestinal obstruction and Intestinal obstruction which
in first post-op week is mostly due to intussusception and after that is due to adhesive obstruction.

B. Role of contralateral exploration
Contralateral exploration is mandatory according to NWTSG with formal opening of Gerota’s fascia and in-
spe ction of anterior and posterior surface of kidney and biopsy of any suspicious lesion. The chance of missing a
bilateral WT after imaging studies is 0.35%. Hence, the routine practice of contralateral exploration is controver-
sial.

C. Intravascular tumor extension
Neoadjuvant chemotherapy will be helpful in avoiding a tumor embolus during mobilization.

An infradiaphragmatic infrahepatic non-adherent caval
vein thrombus generally can be removed by cavotomy or
using a Fogarty or Foley balloon catheter. Patients with intravascular extension above the level of the hepatic veins
should receive preoperative chemotherapy. Recent reports showed that preoperative therapy in patients with supra-
hepatic caval or atrial extension led to a marked decrease in size of tumor thrombus and even complete regression
of thrombus without embolization. As an alternative in adverse cases, embolectomy under cardiopulmonary by-
pass is required.

D. Parenchymal sparing surgery
- Partial nephrectomy
- Enucleation
The above procedures can be done if following criteria
are satisfied:

a. Tumor involving one pole and less than one-third
of kidney
b. Normal functioning remaining kidney
c. No tumor extension into renal collecting system
and renal vein
d. Clear demarcation between tumor and kidney and
adjacent structures

Parenchymal sparing surgery is indicated in

- Bilateral WT
- Renal insufficiency as in Denys-Drash syndrome.
- Solitary kidney WT
- Syndromes associated with increased incidence of
nephrogenic rests

BILATERAL WILMS’ TUMORS

In the NWTS studies, approximately 4 to 6% of children
registered, presented with synchronous bilateral tumors.
The male-to-female ratio was 1.2, and the patients were
usually younger at diagnosis. It was found that more bi-
lateral or multifocal tumors occur at an earlier age (2 years
versus 3.6 years in sporadic tumors). Also, the frequency
of genitourinary anomalies (16%) and hemihypertrophy
(5.4%) was higher compared to unilateral disease.

The presence of synchronous bilateral disease requires
alteration of management. It is not recommended to per-
form unilateral nephrectomy and contralateral biopsy or
heminephrectomy as was the approach earlier. Initial
unilateral nephrectomy may predispose patients with bi-
lateral disease to late renal failure. Furthermore, studies
demonstrate no difference in survival for children who
undergo initial bilateral biopsy followed by chemotherapy
and then surgical resection compared to those patients
who had initial resection followed by chemotherapy. Sur-
geical strategy therefore attempts to preserve renal mass
to minimize the risk of late renal failure. The initial pro-
cedure is usually bilateral biopsies with lymph node sam-
ping. Surgical stage should be assigned to both kidneys.
Preoperative chemotherapy (vincristine and actinomycin-
D in case of FH) may facilitate the subsequent second
look. Following 6 weeks of chemotherapy the patient is
reassessed.

Approximately 10% of patients with bilateral tumors have
unfavorable (anaplastic) histology and may benefit from
more aggressive chemotherapy (addition of doxorubicin
and cyclophosphamide) and radiation therapy and an
aggressive surgical approach at the second-look operation.
Salvage chemotherapy regimens using Cis-platinum,
ifosfamide and VP-16 have been found to be helpful.[16]

After chemotherapy, the patient is reassessed with ab-
dominal CT to determine the feasibility of resection. If
serial imaging studies show no further reduction in tumor,
a second look surgical procedure should be performed.
For small synchronous bilateral lesions at the poles, bi-
lateral partial nephrectomies or wedge resections can be
performed. Excisional biopsy or partial nephrectomy is
regarded as appropriate only if radical tumor resection is
not compromised, negative margins are obtained and if
two thirds of the renal parenchyma can be preserved. The goal is to achieve survival and at the same time to preserve an adequate amount of renal parenchyma. In case of a large tumor on one side and a contralateral small one, radical tumornephrectomy on the extensively involved site and partial nephrectomy on the opposite side is done.

If conditions are not favorable for any surgical intervention, another biopsy is taken to confirm viable tumor. Chemotherapy and/or radiation therapy following the second-look operation is dependent on the response to initial therapy, with more aggressive therapy required for patients with inadequate response to initial therapy observed at the second procedure.

A third look may be indicated; bilateral nephrectomy and subsequent renal transplantation remain the last issue. Unfortunately, due to immunosuppression, recurrence of disease occurs frequently. Before considering bilateral nephrectomy, bench surgery with autotransplantation and intraoperative radiotherapy may be performed. The cumulative survival rate for infants with bilateral tumors is approximately 65 to 70% at 10 years. However, one series reported overall survival of metachronous bilateral Wilms’ tumor to be 49.1% and 47.2% at 5 and 10 years, respectively.17

Metachronous bilateral tumors were reported in about 1.5% of NWTS patients (58 of 4669 registered children). Since many of these lesions appear to be overlooked at initial laparotomy, a thorough investigation of the opposite kidney remains crucial. Children younger than 12 months diagnosed with Wilms tumors, who also have multicentric disease or NRs, in particular perilobar NRs, have a markedly increased risk of developing contralateral disease and require frequent and regular imaging of the contralateral kidney for several years. The median interval of diagnosis of metachronous Wilms’ tumor ranges from 1.37 (NWTS) to 3.29 (SIOP) years.17

Lung metastases
Pulmonary nodules seen on chest CT and not on chest radiograph (“CT only” metastases) do not mandate treatment with whole-lung irradiation in NWTS-5. NWTS-4 data raise the possibility that children with CT-only pulmonary nodules who receive whole lung irradiation have fewer pulmonary relapses than those who were treated less aggressively (based on the extent of locoregional disease with 2 or 3 drugs), but a greater number of deaths due to treatment toxicity (4-year event-free 89 vs. 80%, overall survival 91 vs. 85%). The role of whole lung irradiation in the treatment of this group of patients cannot be definitively determined as yet. The nodules should be removed to confirm diagnosis.

Inoperable tumors
Since imaging studies alone carry the risk of overstaging, NWTS recommends determining “inoperability” at surgical exploration. Tumors with caval extension above the hepatic veins or so massive in size that are considered risky to remove surgically should be biopsied and treated with preoperative chemotherapy. If surgery is performed in a patient with caval or atrial extension, care should be taken to ensure that appropriate resources are available for pediatric cardiopulmonary bypass. In rare cases, advanced right-sided tumors may extend into the liver and wedge resection en bloc or even hepatic lobectomy may be necessary in these patients. If the diaphragm has been infiltrated by tumor, it should also be partially excised en bloc. Patients considered to have unresectable tumor based on imaging studies only should be considered stage III and treated accordingly. On the NWTS-5, these patients are treated after biopsy by initial chemotherapy with vincristine and daetinomycin with or without doxorubicin. If no reduction in tumor size has occurred after using 3 drugs, then radiation therapy should be used. Surgery is performed as soon as sufficient tumor shrinkage has occurred, generally within 6 weeks of diagnosis. Patients are subsequently treated as for stage III tumors, which includes postoperative radiation therapy. Because of the 5% to 10% error rate in preoperative diagnosis of renal masses after radiographic assessment, confirmation of the diagnosis by Fine needle aspiration cytology (FNAC) should be obtained prior to chemotherapy.

Recurrent Wilms’ Tumor
The prognosis and selection of further treatment for patients with recurrent Wilms’ tumor depend on many factors, including the site of recurrence, tumor histology, length of initial remission, and initial chemotherapy regimen (2 versus 3 drugs).

Patients with anaplastic/unfavorable histology tumors, tumor recurrence in the abdomen after treatment with radiation therapy, recurrence within 6 months of nephrectomy, or recurrence after initial 3-drug therapy, have a poor prognosis. The risk factors associated with relapse in the authors series was unfavorable histology, lymph node involvement, age more than 6 years, diffuse spill, capsular and vascular invasion, and aneuploidy.18

The 2-year survival rate for children after local recurrence is 43%. The combination of ifosfamide, etoposide and carboplatin has demonstrated efficacy in this group of patients, but significant hematologic toxic effects have
been observed. While very high-dose chemotherapy followed by autologous bone marrow has been utilized in the past, a recent POG/CCG intergroup study used a salvage induction regimen of cyclophosphamide and etoposide (CE) alternating with carboplatin and etoposide (PE) followed by delayed surgery. Disease-free patients were assigned to maintenance chemotherapy with 5 cycles of alternating CE and PE, and the remainder of patients to ablative therapy and autologous marrow transplant. All patients received local radiation therapy. The 3-year survival was 52% for all eligible patients, while the 3-year survival was 64% and 42% for the chemotherapy consolidation and autologous marrow transplant subgroups, respectively. Patients in whom such salvage attempts fail should be offered treatment on available phase I or phase II studies.

Radiotherapy
Wilms’ tumor is a highly radiosensitive tumor. The radiotherapy dose has varied from 10Gy to 40Gy. However, the use of radiation has now been reduced due to the awareness and documentation of radiation related late effects (growth disturbances, second cancer) in growing children of WT. The NWTS group has redefined the role of radiotherapy and has provided specific recommendations so that the minimum possible RT dose is administered. The NWTS-3 has documented that there is no survival difference at doses of 10Gy or 20Gy in stage III, FH group. The recommended dose per fraction is 1.2 to 1.5 Gy and it should not exceed 1.8Gy per fraction with concomitant chemotherapy.

The current indications of RT are:
1. Stage II, III, IV with unfavorable histology
2. Stage III & IV with favorable histology
3. Metastatic disease

The postoperative radiotherapy is started within 10 days of surgery because delay beyond 10 days leads to tumor cell repopulating and increase in relapse rate. It has been shown that appropriate adjuvant RT reduces the postoperative recurrence to 0%-4% in children with favorable histology. The dose of radiotherapy has decreased to approximately 10 Gy from the doses of 25-30 Gy that were recommended in the past.

Though radiotherapy has been recommended in bilateral Wilms’ tumor in reduced doses, the author advocates avoiding radiotherapy in Bilateral Wilms’ tumor and preferring salvaging chemotherapy schedules to prevent radiation nephritis and glomerulosclerosis. It has been seen by a long term evaluation of renal function in patients with irradiated bilateral Wilms tumor that 34.6% have deranged renal functions with elevated urea and creatinine levels.[19]

Partial nephrectomy
The role of partial nephrectomy (nephron-sparing surgery) remains controversial.[20] Several studies reported an increased incidence of hypertension, proteinuria and decreased renal function, even renal failure, in patients who underwent unilateral nephrectomy for Wilms’ tumor. Total tumor nephrectomy might potentially be harmful to the patient due the substantial risk of renal function loss of a solitary kidney caused by the consecutive hypertrophy of the remaining contralateral kidney as well as to the probability of a primary malformation, metachronous tumor occurrence (1.5% in NWTS, 2-3% in SIOP studies), accidental damage, or other superimposed renal injury. The currently reported poor evidence of a marked risk of renal failure following unilateral nephrectomy however might be due to the lack of long-term follow-up studies. Surgical (radiological and pathological) selection criteria for partial nephrectomy should include functioning kidney, tumor confined to one pole occupying less than one third of the kidney, no invasion of the renal vein or collecting system, and clear margins between tumor, kidney, and surrounding structures. Most studies concur that safe partial nephrectomy is applicable in approximately 5% of tumors at diagnosis (10% of patients after preoperative chemotherapy) without violating oncological principles. The local recurrence rate for partial nephrectomy in patients with bilateral tumors was found to be 8.2% (NWTS-4, [21]).

LONG-TERM COMPLICATIONS

Fortunately Wilms’ tumor is a curable malignancy in most patients, so limiting iatrogenic sequelae is essential wherever possible. Paulino et al. reported late effects of therapy in more than two thirds of children treated for Wilms’ tumor.[22] Beside morbidity from chemotherapeutic agents, potential side effects of radiotherapy like intestinal strictures, ulceration, perforation, hematochezia, growth arrest and osteonecrosis have to be considered.[23]

1. Renal function
NWTS and SIOP studies showed that the risk of renal failure for patients with unilateral Wilms’ tumor and a normal opposite kidney is very low (0.25%). Most of these children had unrecognized renal disease (Denys-Drash syndrome) followed by radiation nephritis. In patients with nephrectomy and abdominal irradiation, renal dysfunction is more common. However, the development of compensatory postnephrectomy hypertrophy of the contralateral kidney is obvious and proteinuria and hypertension may occur long after tumornephrectomy. Most
of these patients have either synchronous or metachronous bilateral disease. “Renal failure” in these patients is most often caused by bilateral nephrectomy followed by radiation nephritis and surgical complications. The DTPA clearance after unilateral nephrectomy for Wilms’ tumor was found to be normal. However, microalbuminuria in 24-h urinary collections has been detected in 84% of the patients, indicating evidence of hyperfiltration injury.\[24\] This highlights the need for close monitoring of the renal function of long-term follow-up patients after Wilms’ tumor in addition to the routine monitoring for tumor recurrence.

2. Lung damage

Both chemotherapeutic agents and total lung-irradiation can cause severe changes in pulmonary function. Prophylaxis against Pneumocystis carinii is recommended for patients receiving pulmonary irradiation.

3. Congestive heart failure

The administration of anthracyclines has improved the survival of stage III and IV Wilms’ tumor patients because of its significant single-agent activity against Wilms’ tumor. Congestive heart failure is typically seen after administration of anthracyclines. Reported cardiototoxicity includes electrocardiographic changes, changes in myocyte morphology (necrosis and fibrosis), decreased cardiac function, and congestive heart failure. Dose related cardiomyopathy caused by doxorubicin is a well-known complication, reported for approximately 5% of patients receiving a cumulative dose of 400 to 500 mg/m². MUGA scans can be used to assess left ventricular ejection fraction (LVEF) and myocardial movements and thus timely discontinuation of doxorubicin can prevent congestive heart failure.\[25\]

4. Liver damage

NWTS-4 studies reported a dose-related incidence of hepatotoxicity in patients receiving chemotherapy (especially vincristine and actinomycinD). Irradiation also increases the risk for hepatotoxicity and veno-occlusive disease as characterized by hepatomegaly, elevated liver enzymes, hyperbilirubinemia, and ascites.\[26\]

5. Infertility

Damage to the reproductive systems may represent one of the main late sequelae of both, gonadal radiation or chemotherapeutic agents. Radiation effect even on pre-pubertal germ cells may lead to hormonal dysfunction (hypogonadism) or infertility.\[27\] Vincristine is a major risk factor for azoospermia.

6. Second malignant neoplasms

NWTS studies reported that the risk of developing a second malignant neoplasm in patients with successfully treated Wilms’ tumors is 1.6 to 5.6%.\[28\] Tumors mainly seen in the irradiated field are hepatocellular, bone, breast and thyroid malignancies. The NWTS group cohort of patients have shown the associated risk factors for the occurrence of a SMN as radiation therapy, doxorubicin & in a small proportion of patients the causative agents were also AMD and VCR.

7. Musculoskeletal function

Scoliosis & musculoskeletal abnormalities have been found more frequently in irradiated patients than in those patients who did not receive radiotherapy including - lower rib hypoplasia and limb length inequality. Abdominal radiation can also produce significant reduction in sitting height and a more modest decrease in standing height. These effects are more pronounced the younger the patient is at the time of radiotherapy. Flank and abdominal radiotherapy doses of 20-30 Gy produce a height loss calculated by age at treatment. For a child aged 1 year this was 9 cm, aged 5 years – 7 cm and aged 10 years 5.5 cm. Ionizing radiation has well been documented to interfere with epiphyseal growth.

PROGNOSIS

At our institute the outcome of the 202 cases in last 17 years, the survival rate was 95% for stage I and II tumors, 75% for stage III tumors, 62% for stage IV tumors and 40% for stage V tumors. The number of cases stage-wise was stage I -19.3%, stage II -15.8%, stage III-43.0% stage IV -15.3% and stage V -6.4%. Contrary to the literature, we have seen bilateral WT, not only in much advanced stages but also in bulk, precluding residual effective renal parenchyma after surgical resection.\[16\]

FOLLOW UP

After completion of therapy, the frequency of imaging is dependent on the stage and histology of the tumor and physical and laboratory tests coincide with the schedule for imaging.\[29\] In general, all patients are reviewed every 3 months for the first year, and then every 6 months for another 2 years. During each of the follow-ups in the first three years it is recommended to get a radiological evaluation. This may be an ultrasound or CECT scan in addition to a chest x-ray. The likelihood of recurrence after the first three years is less, however these patients should be followed up every year for various long-term compli-
OTHER PEDIATRIC RENAL TUMORS

Clear Cell Sarcoma of the Kidney
CCSK accounts for about 3% of renal tumors reported to the NWTS. Since CCSK displays the same location, clinical presentation, gross appearance and age at diagnosis as Wilms’ tumor, it was formerly regarded as an unfavorable histologic variant of Wilms’ tumor with poor prognosis and was called “bone metastasizing renal tumor”. Its incidence peaks during the second year of life (NWTS Mean age at presentation: 36 months, Range: 2 months - 14 years). The male to female ratio is 2:1. It has distinctive histopathologic features, a much higher rate of relapse and death than in favorable histology Wilms’ tumor. The histopathologic characteristics include a wide diversity of features, ranging from spindle cell to epithelioid patterns. Most tumors show the classic histologic picture, i.e. multiple blended patterns. The following histopathologic variants were described: myxoid, sclerosing, cellular, epithelioid, palisading, spindle cell, storiform, and anaplastic pattern. Bone metastases is the most common mode of relapse, followed by lung metastases, local (abdominal/tetroperitoneal) recurrence, and brain metastases. It is of note that CCSK metastases were frequently encountered in unusual soft tissue (e.g. scalp, epidural, nasopharynx) and other sites (orbital). The time interval to relapse in the NWTS patient group ranged from <16 months to 4 years. Although the overall relapse rate is significantly lower for patients treated with doxorubicin, the risk of recurrence is prolonged.

Currently (NWTS-5), patients with CCSK are treated with initial nephrectomy regardless of stage, abdominal radiation (10.8 Gy) and combined chemotherapy with actinomycin D, vincristine, and doxorubicin. The main prognosticators for favorable outcome in CCSK are revised stage 1, age at diagnosis (2-4 years), therapy with doxorubicin and absence of tumor necrosis.[30] Except for the presence of necrosis, which seems to be a feature of aggressive high-grade sarcomas, no other histopathologic pattern in CCSK appears to be of prognostic significance.

Rhabdoid tumor
It was initially regarded as a solid monophasic, or rhabdomyosarcomatoid variant of unfavorable histology Wilms’ tumor. It is now recognized as a separate highly malignant entity. RTK represents only 1.8% of cases entered into NWTS since 1969, with a median age at presentation of 17 months and a slight male preponderance (male-to-female, 1.5:1).[31]

Some of the patients have hypercalcemia. In about 15% of RTK, patients develop other primary embryonal tumors in the midline posterior fossa, particularly medulloblastoma. These intracranial tumors are histologically distinct from the primary renal lesion. In contrast to Wilms’ tumor, about 80% of RTKs have stage III or IV disease at presentation. Grossly, RTK typically appears as a bulky, solid, and relatively well-circumscribed lesion. The histiogenesis remains controversial, the tumor may not even be renal-specific since morphologically indistinguishable rhabdoid tumors occur in many other sites (e.g. pelvis, soft tissue, bladder) and deletion of the hSNFS5/INI1 gene on chromosome 22 has been found in all these tumors.[37] Light-microscopic and ultrastuctural features have been defined. The tumor behavior is extremely aggressive and clinical management (triple chemotherapy) has not proven successful. So far, male sex and high tumor stage are the only identified unfavorable prognostic indicators. Metastases occur most frequently in the lung (70%) and most patients with relapse die from tumor progression (NWTS 96%). The reported survival rate at 3 years is less than 20%.

Congenital Mesoblastic Nephroma
Congenital mesoblastic nephroma (CMN), the most common benign renal tumor in neonates, is a low grade spindle cell tumor originating in the renal medulla. It is also known as fetal renal hamartoma, leiomyomatous hamartoma, and mesenchymal hamartoma of infancy. With the increasing experience of antenatal ultrasonography, many cases of CMN have been detected in uterus.[32] An increased association with prematurity and polyhydramnios has been found. Nearly all solid renal tumors presenting in the first week of life are mesoblastic nephromas. However, a few cases of mesoblastic nephroma have been reported in older children. NWTS reported a mean age of diagnosis of 3.4 months with a male preponderance (male-to-female ratio 1.8:1).[33] About 2.8% of all renal neoplasms in children are CMNs. Hypertension and increased renin concentration and skeletal fibromatosis have been reported. On ultrasound, mesoblastic nephroma is an evenly echogenic mass with concentric echogenic and hypoechoic rings resembling uterine fibroids. It may in time form a heterogeneous mass with hemorrhage and cyst formation secondary to central regions of necrosis. Calcification is rare. Grossly, the tumor is usually of a light tan, fleshy with a whorled configuration and has ill-defined peripheral borders, blending into the adjacent renal parenchyma and even the peri-
renal fat. Most are centered near the hilus of the kidney.

Microscopically CMN consists of monomorphic spindle-shaped cells, resembling fibroblasts with scant interstitial collagen. Two morphological subtypes are distinguished: the classical or leiomyomatous type and the atypical or cellular type. Mixed forms have also been described.

In a series of 51 cases, 50 patients survived and only one patient experienced local recurrence.[35] Despite this excellent prognosis, local recurrence and even tumor-related death have been described and were always related to the cellular (atypical) form or to the mixed form, particularly in patients aged more than 3 months and in those cases where surgical removal was not complete.

Cytogenetic studies have reported common trisomies in cellular CMN, particularly of chromosome 11 and t (12; 15) (p13; q25)-associated ETV6-NTRK3 gene fusions.[34] Total surgical excision independent of histological type without further therapy is recommended for most patients as the treatment of choice. Tumor rupture and difficulties in achieving clear surgical margins have been frequently reported but did not affect the excellent prognosis.

Intrarenal neuroblastoma and intrarenal teratoma
Occasionally, neuroblastomas may be clinically and radiologically undistinguishable from Wilms tumors. Intrarenal neuroblastomas are rare tumors and pose diagnostic challenges.[35] Elevated urinary vanillin mandelic acid levels and serum NSE should allow a differential diagnosis before surgery. The prognosis has been found to be very poor.

While sacrococcygeal teratomas can contain elements of Wilms tumors and Wilms tumors have been found to produce Alpha-fetoprotein, few cases of intrarenal teratomas have also been described.[36, 37] The diagnosis depends on histological examination. Teratoid Wilms tumor is defined as an unusual variant of nephroblastoma, in which there is a significant diversity of cell types and tissues along with areas of classic nephroblastoma. After complete resection, the prognosis should be excellent provided the tumor does not contain yolk sac elements.

CHALLENGES FACED IN DEVELOPING COUNTRIES

1. Poverty
2. Ignorance
3. Malnutrition

4. Huge tumors
5. Stage 3-5 comprising 65% cases
6. Noncompliance with schedule
7. Limited facilities for advanced surgery and supportive services
8. Huge population with large number of cases.

WE FOLLOW NWTS V IN

1. Staging
2. Initial surgical management in stage 1 and 2
3. Neo-adjuvant chemotherapy in unresectable tumors and
4. Chemotherapy schedules.

However, we differ in the management strategies as follows –
1. We do not consider laparotomy and biopsy mandatory for preliminary staging
2. FNAC is considered reliable in expert hands. Immunohistochemistry is done for cases with diagnostic dilemmas to rule out other round cell tumors.
3. We rely on clinical examination and radiology for deciding resectability based on lateral mobility in a calmed child.
4. Try and shrink very huge tumors with chemotherapy before attempting resection even though there is no evidence of stage 3 on imaging but clinically there is restricted mobility.
5. Avoid radiotherapy in bilateral Wilms’ tumor
6. Gerota’s fascia is not opened for contralateral exploration during surgery for unilateral Wilms tumor. However, every care is taken to exclude synchronous tumor and nephrogenic rests using advanced and detailed imaging preoperatively and a thorough clinical palpation is performed during surgery. A strict follow up is done to detect any metachronous tumor.

FUTURE

Recent advances in understanding the molecular biology of the tumorigenesis of Wilms’ tumor have provided significant implications for the clinical management. Thus, both large study groups currently aim to intensify treatment for patients with poor prognosticators while reducing therapy and subsequent long-term complications, for those with favorable prognostic features.

Parenchymal sparing renal surgery for patients with small unilateral Wilms’ tumor remains controversial. Treatment of children with Wilms’ tumor should certainly involve a team of specialized pediatric surgeons, oncologists, radiologists, pathologists, and radiotherapists.
REFERENCES