International Journal of Pharmaceutical Drug Design
IJPDD (February, 2025)
ISSN: 2584-2897
Website: https://ijpdd.org/

DOI: 10.62896/ijpdd.2.2.6
Review

Wilms Tumor: A Rare but Aggressive Childhood Cancer

Anki Haritha*[1], Chevuru Baby Shalini[2], Yadala Prapurnachandra[3]

[1]*Ratnam Institute of Pharmacy, Pidathapolur [V&P], Muthukur[M], SPSR Nellore District-524346*

[2,3]*Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Pidathapolur[V&P], Muthukur[M], SPSR Nellore District-524346*

Received: *05-12-2024 /* ***Revised:*** *23-01-2025 /* ***Accepted:*** *10-02-2025*

Corresponding Author: *Anki Haritha*

Email: *aharitha861@gmail.com*

Conflict of interest: *Nil*

ABSTRACT:

Wilms' tumor is also know as nephroblastoma is a rare pediatric kidney cancer that primarily effect children under the age of 5. It originates from immature renal cell and is characterized by its ability to present as a large abdominal mass, often discovered incidentally during routine medical examination .the pathogenesis of Wilms tumor involves complex genetic alteration including mutations in tumor suppressor genes such as Wilms tumor1 and the imbalance in chromosomes . although the prognosis for children diagnosed with Wilms tumor has significantly improved due to advances in treatment including surgery, chemotherapy and radiation challenges persist in managing reccurent metastasized cases the treatment approach is based on the staging tumour with ongoing research focused on optimizing high survival rates .symptoms such as hypertension, hematuria, or abdominal pain. Crucial diagnosis of Wilms tumor is abdominal ultrasound is often the first imaging modality used, followed by computed tomography (CT) or magnetic resonance imaging (MRI) to asses the tumors size location, and potential spread. Is usually not required unless there is ambiguity in diagnosis as Wilms tumor characteristics appearence and imaging is often diagnostic. The main test involves ULTRASOUND OF THE ABDOMEN: a non invasive imaging technique that uses ultrasound waves to create an image of the internal organs it is often used as the first step to detect a kidney mass. The most commonly used drugs in the treatment of Wilms tumor includes: VINCRISTINE, DACTINOMYCIN.

Keywords: Wilms Tumor, VINCRISTINE, DACTINOMYCIN

1. INTRODUCTION:

Wilms' tumor, or Nephroblastoma, is the most common Malignant Renal tumor of childhood. It occurs with an annual incidence of 7 cases per million children aged less than 15 years. Approximately 450 new cases are diagnosed each year in North America. Although at the beginning of this century, most children with Wilms' tumor died of the disease, survival now exceeds 80%[1.]

The total number of new cases of Wilms' tumor in the UK is estimated at about 80 cases per year . The tumor usually arises in a single kidney. Synchronous bilateral or multifocal tumors occur in approximately 10% of patients and tend to present at an earlier age . Wilms' tumor can also be diagnosed in adolescents or adults, but this is extremely rare, representing less than 1% of all renal tumors . The usual treatment approach in most patients is a combination of surgery and chemotherapy, with the addition of radiotherapy in high risk patients. Substantial progress in the treatment of Wilms' tumor over the past few decades has been made by refining risk stratification and by the use of existing chemotherapy schedules. This has improved overall survival for patients with Wilms' tumor in high income countries to greater than 90% for localized disease and 75% for metastatic disease.[2]

It is a relatively rare tumor, and many patients are treated on cooperative group studies. The prognosis for children diagnosed with Wilms tumor has significantly improved in recent decades with a five-year survival of 75% from the time period of 1975-1979 improved to 90% from 2003 to 2009.Current treatment recommendations include upfront

nephrectomy in the Children's Oncology Group (COG) and nephrectomy following chemotherapy in the International Society of Pediatric Oncology (SIOP) studies. The choice of chemotherapy agents and inclusion of radiotherapy are dependent upon risk categorization. In SIOP, for example, renal tumors are classified as low, intermediate, or high risk depending on histology after initial chemotherapy and nephrectome. Staging is based on extension of the tumor beyond the kidney, tumor spillage or rupture, lymph node, peritoneal or hematogenous spread. Distant metastases are present in 10% to 20% of cases, with lungs being the predominant site of spread. Synchronous bilateral disease is detected in approximately 5% of Wilms Tumor patient.[3]

TYPES:

There are two kinds of Wilms tumors, divided by how the cells look under a microscope.

Favorable histology. More than 9 out of 10 Wilms tumors fall into this group. It means there isn't a lot of difference among the cancer cells. Children with this type have a good chance of being cured.

Unfavorable or anaplastic histology. This type has a variety of deformed cancer cells. It can be much harder to cure.[4]

Wilms' tumor was first reported by Rance in 1814, and it received its name from Max Wilms, a surgeon who identified nephroblastoma as a mixture of three tissues Multimodal treatment was first used in treating this tumor, and because it has achieved the best results of any tumor group it has become a treatment model for other tumors. With this successful treatment strategy and the creation of cooperative groups in North America and Europe, the survival rate improved from 30 to 90% between 1930 and 2000.[5]

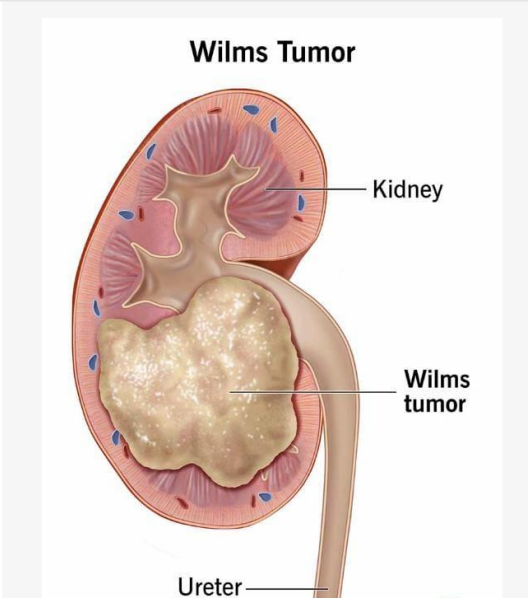

Fig:1 Wilms tumor is a type of kidney tumor that most often effect children.[26]

Wilms Tumor presenting as bilateral disease can be associated with early disruption in renal development, not only because of involvement of both kidneys but due to the fact that in nearly all cases. Bilateral disease can be synchronous (both kidneys affected at the same time) or metachronous (one affected after the other), which occurs in 6.3 and 0.85%. As expected from Knudson's two-hit model, the median age of onset of bilateral WT is younger than for unilateral Wilms Tumor – under 2 years compared with 38 months.[6]

2.EPEDIMIOLOGY:

Wilms' tumor affects one in 10,000 children and accounts for 5% of all childhood cancers . More than 80% of children are diagnosed with Wilms' tumor below the age of five years, and the median age at diagnosis is 3.5 years . The tumor is one of the few childhood cancers with a slight female preponderance among Caucasian patients. In contrast, the disease in Asian children has a peak in the second year of life, and a greater incidence among boys than girls has been observed in the East-Asian population . Although topographic variations in the incidence of this tumor have been shown, the incidence of the tumor varies almost entirely along ethnic groups rather than geographic areas. The highest rates reported are in those of black African descent and the lowest in those of Asian descent. This variation suggests

that genetic factors play the most important role in its etiology.[1].

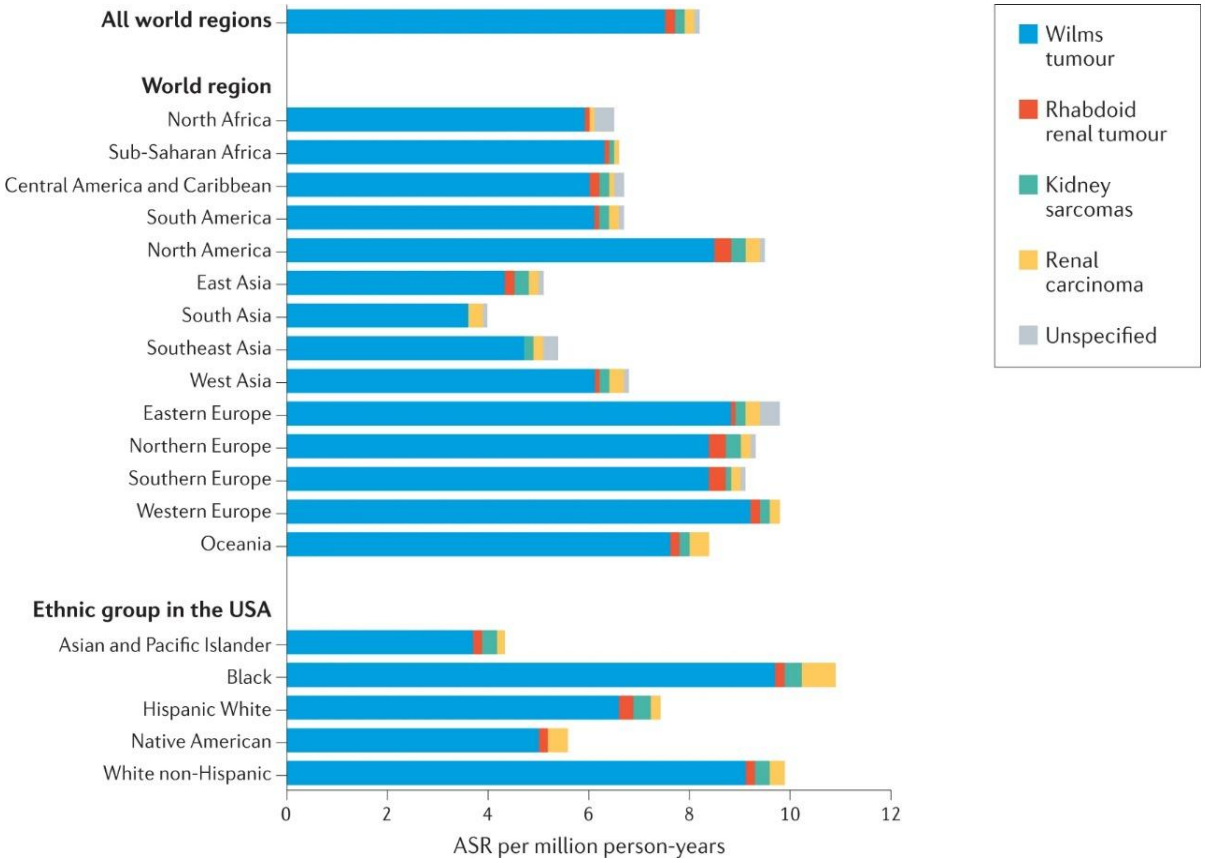

Fig:2 the incidence of Wilms tumor according to geographical area and ethnicity[27].

Wilms tumor is the most common abdominal cancer in childhood and typically presents between ages 3 to 5 years. There are approximately 650 new cases in the United States every year. Girls are slightly more likely to have Wilms than boys .Wilms is more common in Africans and African Americans while it is least common in East Asians. Asian patients also had fewer unfavorable histology tumors, tend to have lower-stage disease, and enjoy better survival outcomes. Europea tumors are diagnosed before six years of age with the median age of diagnosis being 3.5 years .With marked improvements in chemotherapy, the over whelming majority of affected children now survive.5-year survival in the US is 92% but in poor parts of the world with fewer resources, the survival rate is only 78%. Wilms tumor is associated with a number of specific syndromes including WAGR syndrome. WAGR syndrome refers to the presence of Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.[7.]

3.ETIOLOGY

There are a number of recognized syndromes associated with an increased predisposition towards developing Wilms tumor. They can be divided into overgrowth and non-overgrowth syndromes. Common overgrowth syndromes include Beckwith–Wiedemann syndrome (BWS) and isolated hemihypertrophy. The most recognized non-overgrowth syndromes include WAGR (WT, aniridia, genitourinary anomalies, mental retardation) syndrome and Denys–Drash syndrome (DDS) . Aniridia is found in 1.1% of Wilms tumor.[8]

CAUSES:

The abnormal cells multiply in their primitive state and become a tumor, which is usually detectable at the age of 3 to 4 years.

Genetic factors: Genes that control cell growth mutate, or change, allowing cells to divide and grow in an out of control manner.

Family history: Wilms tumors may stem from a genetic anomaly that a parent passes for most Wilms' tumors. In. Most Wilms tumors occur by chance. They are sporadic, resulting from genetic mutations that affect cell growth in the kidney. These changes usually start after birth.

Beckwith-Wiedemann Syndrome: This syndrome is associated with macroglossia, visceromegaly, omphalocele and gigantism . WAGR Syndrome: The components of this syndrome are WT, aniridia, genitourinary_abnormalities and mental retardation. Cardiopulmonary problems, head anomalies, neurobehavioral disorders, musculoskeletal defects and metabolic problems have also been reported . The Wilms tumor risk is 30% in this syndrome.

Denys-Drash Syndrome: It is a combination of Male_pseudohermaphroditism, glomerulonephritis and WT. There is also an association with a defect on the WT1 gene.

Perlman Syndrome: This syndrome can be associated with WT and includes macrosomia, islet cell hyperplasia, renal hamartomas and an atypical face shape.[9]

"paternal pre conceptional exposures may play a more important role in the etiology of Wilm's tumor than maternal factors"(8,p.943). Pathologic and molecular biologic studies have shown that Wilm's tumor arises from nephrogenic rests that represent renal stem cells, the development of which has been arrested before normal differentiation occurs (2,44). Exposures that occur during intrauterine life are likely to be relevant to this process; these can be studied with epidemiologic methods, and clues have emerged (7,86,89). It is important to realize, however, that the fetus may be exposed in utero to substances to which the mother was exposed prior to conception, if these substances are excreted slowly or not at all, such as the persistent organochlorine pesticides.[10]

4.PATHOPHYSIOLOGY:

Histology is the most important prognostic indicator for Wilms Tumor. The majority of Wilms Tumor patients have tumors with FH. Several tumor types are associated with an increased risk of tumor recurrence, or resistance to standard Wilms Tumor chemotherapy. These include patients with anaplastic Wilms Tumor, which can be focal or diffuse.[8]

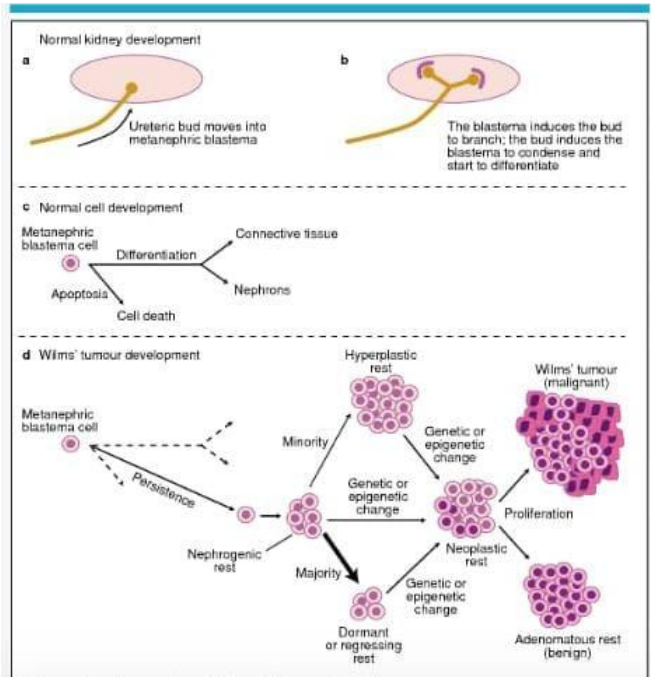

Fig:3 Kidney development and Wilms tumourigenesis[28]

Wilms tumor is renal embryogenesis and is composed of a variable mixture of stromal, blastemal, and epithelial elements. Nephrogenic rests, generally considered to be precursor lesions of the WT, are foci of the embryonic metanephric tissue that persist after the completion of renal embryogenesis. These are classified as perilobar and intralobar based on their location and maybe present as single or multiple foci. Intralobar and perilobar rests and the tumors arising from these rests differ morphologically and are characterized by 2 different sets of genetic abnormalities

involving 2 adjacent foci, *WT1* and *WT2*, on the *short* arm of chromosome 11. WTs arising in the intralobar rests tend to be stromal predominant and have a mutation or deletion of *WT1*. Germline mutation in *WT1* may be associated with syndromic conditions such as WAGR and Denys-Drash syndromes.[11]

5.CLINICAL MANIFESTATION

Most of the patients present with an abdominal mass. The tumor is often detected by the parents or caregivers while bathing the child. Hematuria is seen in 30% of patients and 25% have hypertension. In addition, malaise, fever, weight loss, anorexia, or a combination of these symptoms can be seen. 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 hormones, such as erythropoietin and ACTH, can be secreted in WT. In addition, hypercalcemia and hemorrhagic conditions caused by reduced von Willebrand factor can be Seen Physicians must be cautious for other associated findings, such as hemihypertrophy, aniridia and genitourinary malformations.[12]

SYMPTOM

- Most kids show symptoms around the ages of 3 or 4, and these symptoms are similar to many other childhood ailment Some symptoms include:
- constipation
- abdominal pain, swelling, or discomfort
- nausea and vomiting
- weakness, fatigue
- loss of appetite, fever
- blood in urine or discolored urine
- high blood pressure
- A swollen spot or hard lump in your child's abdomen (stomach area). [13]

6.DIAGNOSIS

Wilms Tumour has been a success story, and currently in excess of 80% of children diagnosed with Wilms Tumour can look forward to long-term survival, with less than 20% experiencing serious morbidity at 20 years from diagnosis.[13]

early age at diagnosis, a male predominance, and an association with ILNR. Loss of IGF2 imprinting is associated with PLNR more commonly seen in Wilms tumors from white children than tumors from children of Asian descent. Therefore, this epigenetic difference and the higher frequency.[14]

Diagnosis of malignant renal tumors does not mostly create difficulties. Although micro metastases may be encountered during postmortem examination, kidney is not a preferred organ for clinically detected metastases of malignant tumors. Therefore, almost all renal tumors in adults and children are primary tumors. When primary renal tumors are encountered, most of the cases pose a diagnostic simplicity. Indeed, diagnosis of malignant kidney tumors in children is Wilms tumor (WT) in 80–90% of the cases, while it is renal cell carcinoma in adults. In fact, a typical WT contains tissue components in three different morphologies. .[15]

ULTRASONOGRAPHY:

Abdominal ultrasonography is the first diagnostic choice to confirm a renal mass. To differentiate a WT from other renal masses (e.g., kidney malformations) or masses in close proximity to the kidney (e.g., neuroblastoma), abdominal MRI- and CT-scans are the current standards of imaging. Urine analysis for catecholamines and metaiodobenzyl guanidine scintigraphy can also help to discriminate neuroblastoma from WT.[16]

Staging

A medical team uses staging to assess how far a Wilms' tumor has grown or spread.

- **Stage 1**: The cancer stays within the kidney, and surgical removal is possible.
- **Stage 2**: The cancer has reached tissues and structures close to the kidney, such as blood vessels and fat. However, a surgeon can still completely remove the tumor at this stage.
- **Stage 3**: The cancer has spread further and has reached nearby lymph nodes or other parts of the abdomen. Complete surgical removal may not be possible.

- **Stage 4**: The cancer has spread to distant parts of the body, such as the brain, liver, or lungs.
- **Stage 5**: Both kidneys have cancer cells.[17]

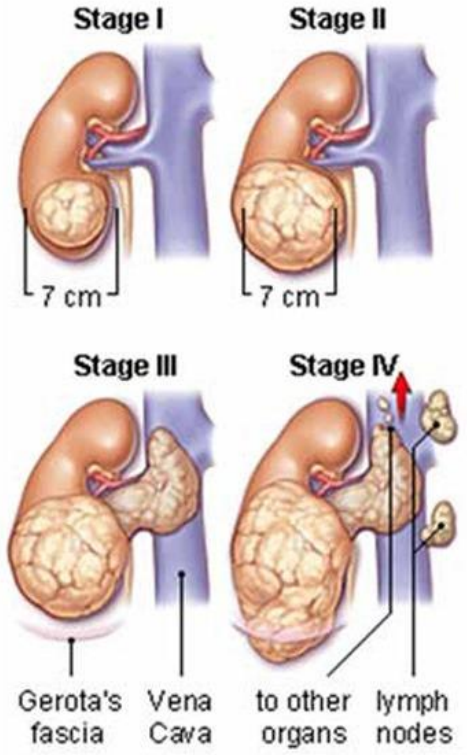

Fig 4: pediatric cancer of Wilms tumor[30]

7.TREATMENT :

Treatment includes surgical resection and chemotherapy for virtually all affected children and additional radiotherapy for those with advanced disease or adverse prognostic features. This approach leads to cure rates exceeding 80%.[18] Specific treatment recommendations are based on the current National Wilms' Tumor Study IV schema. Stages I and II favourable histology patients do not receive radiotherapy, but are treated postoperatively with 'pulsed' or 'conventional' dactinomycin and vincristine; stage III favourable histology requires postoperative abdominal radiotherapy followed by triple agent, 'conventional' or 'pulsed' chemotherapy (dactinomycin, doxorubicin and vincristine). Patients with stage IV favourable histology, stages II to IV anaplastic, clear cell or rhabdoid histology, are treated similarly with aggressive triple-agent chemotherapy, with the addition of radiotherapy to selected sites. Recurrent and adult Wilms' Tumours have poor prognoses and are treated with aggressive surgery, radiotherapy and chemotherapy.[19]

TARGETED THERAPHY

Anti-tumor targeted therapies focus on the specific characteristics of tumor cells, which are essential for the initiation and maintenance of tumors. Because of their specificity, targeted therapies generally cause fewer side effects than chemotherapy and radiotherapy . In terms of action mechanism, the current research on targeted drugs is mainly focused on the following four aspects[15]

SYRGERY

In unilateral WT, the role of surgery includes primary tumor rection, complete nodal staging, and providing tissue for completion of risk stratification. Given that adrenalectomy and en bloc resection of surrounding organs have not shown to benefit survival, radical nephroureterectomy sufficient to optimize local control.7 Patients otherwise classified as stage I-II may be undertreated if complete nodal staging is not completed. Although no specific recommendation exists for the number of lymph nodes required for complete staging, Zhuge et al. demonstrated a five-year overall survival (OS) benefit with the progressive increases in lymph nodes removed.[20]

CHEMOTHERAPY:

chemotherapy was tried to be administered according to schedules, with an effort to minimize delays. However, 34 (21.8%) patients did not complete their adjuvant treatment either because they abandoned the treatment (23) or died during the first few months of chemotherapy. Of 122 patients who completed treatment, 32 patients (3 in Stage I, 12 in Stage II, and 17 in Stage III) did not follow a strict chemotherapy regimen and had a delay of more than 8 weeks in schedule completion. The course of RT was irregular due to long waiting in the RT department and poor compliance by the patients. Only 12 patients (28.6%) completed RT as per schedule, whereas others had delayed patient turn-up (24, 57.1%) or delay due to long RT waitings (14.3%). None of the patient could be started on RT within 14 days of surgery as it was not fesible in our setup.[21]

SIDE EFFECTS OF TREATMENT:

Advancements in surgery, radiotherapy, and chemotherapy have greatly improved the cures rates for children with Wilms tumor. However, a number of therapy-related late effects have been observed in long-term survivors. Generally, late complications are a consequence of treatment type and intensity; the use of radiotherapy and anthracyclines increases the risk of these complications. This commentary highlights some clinically significant late sequelae musculoskeletal effects, cardiac toxicity, reproductive problems, renal dysfunction, and the development of second malignant neoplasms. Careful medical and epidemiological monitoring of survivors can provide critical information to further optimize therapy while minimizing long-term sequelae.[22]

8.DRUGS:

A study was begun in 1971 at St. Bartholomew's Hospital with a combination of 4 drugs, dactinomycin (actinomycin D), adriamycin, vincristine and Endoxan (cyclophosphamide) (D.A.V.E.), together with surgery and radiation, in the treatment of stage III and stage IV Wilms' tumour. Seventy-one percent of the children treated achieved complete response. This four-drug combination was well tolerated and effective, and confirms recent experience suggesting that intensive multiple-drug regimens may be curative even in advanced disease[23]

DACTINOMYCIN

Wilms' tumor treated at eight institutions, 45 received conventional therapy (surgery and irradiation) alone, 59 received conventional therapy and "early" administration of dactinomycin (actinomycin D), and 18 received conventional therapy and "late" administration of dactinomycin. In 102 children without metastasis at operation, life-table analysis revealed a decreased frequency of metastasis and increased survival after dactinomycin therapy. Children starting drug therapy the day of operation had a clearly improved survival experience at four years after operation over those not receiving drug therapy. Patients with metastasis had an improved survival experience even if dactinomycin therapy was started late, as compared with patients who received no drug therapy. Dactinomycin therapy improved survival experience even when metastasis was evident at operation.[24]

VINCRISTINE:

Metastatic Wilms' tumor was temporarily controlled by vincristine (leurocristine) sulfate in 9 of 13 children. The responses to the drug were prompt, becoming apparent within 3 weeks in 75% of the patients .[28] Although some of the patients had two or more toxic manifestations, i.e., alopecia, nausea, vomiting, increased irritability, pain in the abdomen and in the jaws, disturbances of gait, and hematuria, only two patients required a temporary alteration of the dosage regimen. No deleterious effects upon the body weight or blood count of any of the patients were detected. The potential usefulness of vincristine sulfate as a palliative treatment for patients with Wilms' tumor is discussed. [25]

9.FUTURE PLANE:

The future trend will increasingly be driven by two principles: (1) de-escalation of therapy with the aim to define the appropriate level of treatment to achieve the best outcome while minimizing secondary side effects, and (2) identifying tumor-related and personal risk factors justifying escalation of therapy. To address these principles, the two large WT consortia of the COG and SIOP have designed new prospective studies.

10.CONCLUSIONS:

At present, more than 85% of children with Wilms' Tumour are being cured and in our current treatments about 75% do not require radiotherapy or doxorubicin chemotherapy. Despite this success, several challenges remain. For patients

with low-risk disease, acute and long-term toxicities of treatment must be limited. For patients with high-risk disease, such as Tumour with anaplastic histology, novel therapies must be identified to improve survival.

11.REFERENCE:

1. max.coppes , kathy pritchard-jones.principle of wilms tumor biology 2000;27(3):423-434
1. elwira szychot,johnapps kathy pritchard-john.wilms rumor:biology,diagnosis, and treatment 2014;3(1);12-24.
2. luke pater,patrick melchior, christian rube.wilms tumor:2020;68(52)
3. shruthn.wilmstumor2024
4. ali varan .wilms tumor in children :an over view:2008;108(2) :c83-c90
5. Jocelyn Charlton, sabine irtan, Christophe Bergeron and Kathy Pritchard-jones. Bilateral wilms tumor: a review of clinical and molecular features2017; 19:
6. stephen w.leslie,hussain sajjad,patrick b. murphy.wilms tumor 2024
7. edmund y. ko,michaell.ritchey.current management of eilms tumor in children2009;5(1);\:56-65
8. namita bhutani,pradeep kajal,urvashi sharma .many faces of wilms tumor:recent advancees and future directtons 2021;64
9. montreal,Quebec.etiology of wilms tumor1995;17(2):415-432
10. al-hussain,turki md ,ali afshan md, akhtar.wilms tumor an update 2014;21(3):166-173 12.akzhol karim,kundyz shaikhyzada,
11. brett barlow md,jaime herndon.wilms tumor:2022
12. sc kaste js dome,ps baby,nm graf.wilms tumor: prognostic factor , staging, therapy and late effect2007;38:2-7
13. fukuzawa,ryujimd,reeve,anthony.commentaries molecular pathology and epidemiology of nephrogenic rests and wilms tumor2007.journal of pediatric hematology oncology 29(9):589-594
14. izmir ,turkey. histopathological and molecular characteristic of wilms tumor 2016;
15. till martin theilen, yannickbraun,konrad bochen multidisciplinary treatment strategies for wilms tumor:recent advances,technical innovation and future direction2022:10
16. christina chun,adam felman.what to know about wilms tumor 2019
17. maxj.coppes,Johannes,e.a wolff and Michael,ritchet.wilms tumor 2021:1:251-262
18. minesh p.mehta, kenneth t.bastin,susan r.wiersma : treatment of wilms tumor 2012;42;766-780
19. luke pater,patrick melchior, christion rube, benjemin:wilms tumor2020
20. agrawal, vikesh; mishra, arpan;yadav, sanjay kumar;sharma . 10-years study of the outcome of wilms tumor in central india and identifying2022;27(1):42-52
21. karen d.wright,md,daniel m.green.late effects of treatment for wilms tumor 2009;26(6):407-413
22. monika l. metzger ,jeffrey s.dome . current therapy for wilms tumor2005:10(10);815-826
23. d.b dunger,j.s.malpas,j.freeman.the use of four-drug combination chemotheraphy (d.a.v.e)in the treatment of advanced wilms tumor.1981;5:211-215
24. omer jr,md;oliver glidewell.dactinomycin in wilms tumor1967;199(7) :464-468
25. christopher p. houk md phda leuan .vincristine leurocristine sulfate in the treatment of children with metastatic wilms tumor1963;32(5):880-887
26. clevaland clinic 2021
27. Filippo spreafico, conrad v. Fernandez , jesper brok, kayo Nakata, gordan vujanic, james I, geller, Manfred gassier, mariana maschietto, sam behjati, angela Polanco, Vivian Paintsil, Sandra lina- fineman and Kathy Prichard-jones.wilms tumor2021;7(75)
28. k.brown,k malik. the molecular biology of wilms tumor2001

*****