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Diagnosis and Management of Wilms Tumor

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ABSTRACT

Wilms Tumor is one of the malignancies frequently found in children under five years old. This tumor is frequently found coincidentally by parents or caregivers who notice a lump in the children's abdomen. The specific factors of Wilms tumor have not been detected yet. However, it is often associated with specific syndromes as a predisposing factor and a mutation of specific genes. The symptoms caused by this tumor are varied, starting from asymptomatic without any symptom to severe symptoms due to the tumor distribution to the lung. In general, Wilms tumor attacks one of the kidneys (unilateral) with different grades and particular histology. Generally, the management encompasses surgery, chemotherapy, and radiotherapy, depending on the tumor grade. The patients' recovery rate and managed survival rate were quite high with a low recurrence rate. Therefore, a clinical approach and skepticism of Wilms tumor become one of the diagnoses in children with an abdominal mass.

1. Introduction

Worldwide, there are around 250,000 reported child abuse cases annually, and around 200,000 cases occur in developing countries.¹ Wilms tumour, also known as nephroblastoma, is the most common renal malignancy in children. Wilms tumour makes up 5% of all malignancies in children² and is the fourth most common malignancy in children after leukaemia, retinoblastoma, and neuroblastoma.³ Around 85% of primary renal malignancies in children are Wilms tumours. In the United States, around 650 children are diagnosed with Wilms tumours every year.⁴ Meanwhile, in Europe, around 1 per 10,000 children is diagnosed with Wilms tumour.⁵ In the UK, there are around 80 cases of Wilms tumours per year.⁶ The incidence of Wilms tumours in Asian countries is relatively low.⁷

The majority of children with Wilms tumours are diagnosed between 1-5 years. Diagnosis is most commonly established at the age of 3 years.⁴ Girls tend to be slightly more affected than boys in some Asian countries (girl to boy ratio = 4:1).⁵ In general, recovery and survival rates vary depending on the type of Wilms tumour. The five-year survival rate is more than 90% in children with a favourable history of Wilms tumour (FHWT) receiving adequate therapy.⁷ This survival rate is lower for children with anaplastic Wilms tumours. Over time, the survival rate has increased from 20% in 1960 to around 90% today in developed countries, and around 80% in middle-income countries.⁸

Etiology

In its development, the definitive kidney from the fetus originates from the ureteric bud, which forms the collecting tubule and from the metanephric mesenchyme/blastema, which forms the proximal tubule glomerulus, distal tubule and loop of Henle. The blastema usually disappears by 36 weeks of gestation. However, approximately 1% of infants still have residual blastema in their kidneys at birth. These residual blastema cells are referred to as the nephrogenic rest. This is a precursor lesion and triggers the formation of Wilms tumor. In 40% of Wilms tumor patients, this nephrogenic rest is observed.⁹

The etiology of Wilms tumor is still unknown. Approximately 10-20% of Wilms tumor patients have predisposing genetic factors.¹⁰ The WT1 gene, an important transcription factor in renal and gonadal embryogenesis, is important in forming a normal genitourinary system. The gene is located in the locus 11p13. The defective WT1 gene will cause abnormalities of the genitourinary system and predisposition to form Wilms tumor. Microdeletion of the WT1 gene results in the WAGR syndrome (>50% risk of Wilms tumor, aniridia, genitourinary system abnormalities, and mental retardation) or developmental delay).^{11,12}

Other predispositions associated with Wilms tumor are Denys-Drash syndrome and Beckwith-Wiedemann syndrome. Denys-Drash syndrome includes male pseudohermaphroditism and progressive renal failure beginning with glomerulopathy in infancy. Children with this syndrome have 90% chance of developing Wilms tumor.¹³ Beckwith-Wiedemann syndrome consists of hemihypertrophy, pancreatic enlargement, renal hypertrophy, omphalocele, ear creases, macrosomia, and macroglossia. Patients with this syndrome carry 5-10% chance of developing Wilms tumor.¹⁴

Other syndromes associated with Wilms tumor include Sotos syndrome, Perlman syndrome, Trisomy 18 (Edward syndrome), Frasier syndrome, Bloom syndrome, and Simpson-Golabi-Behmel syndrome.

The chance of Perlman syndrome patients to develop Wilms tumor is around 75% and 5-10% for Simpson-Golabi-Behmel syndrome.¹³ Several somatic gene variants associated with Wilms tumor other than WT1 include CTNNB1, WTX, MYNC, TP53. Abnormalities of the WTX and CTNNB1 genes are found in 1/3 of Wilms tumor cases, while the TP53 gene is associated with anaplastic Wilms tumors and carries a poorer prognosis.

Diagnosis

The majority of Wilms tumor patients present with complaints of asymptomatic abdominal masses. These masses or lumps are often found incidentally by caregivers or parents bathing the patient. The majority of the patients only have a tumor in one kidney. However, 5-13% of the children have bilateral tumors, and 10% have multiple tumors in one kidney. Approximately 83% of patients present with abdominal masses, 37% with pain, 23% with fever, followed by 25% with hypertension, and 21-25% with hematuria.¹³ Symptoms of hypertension will disappear after nephrectomy. Atypical clinical manifestations are found in less than 10% of cases, including ascites, congestive heart failure, and hepatomegaly due to tumor spread to the renal vein or inferior vena cava in 4%.¹⁵ Sometimes, children may present with an acute abdomen, rapid abdominal mass swelling, anemia, hypertension, pain and fever associated with a ruptured tumor, or other genitourinary disorders such as varicocele. Tumor hormone production can cause paraneoplastic syndromes such as hypercalcemia. Approximately 10% of patients will develop coagulopathy due to von Willebrand disease.¹³

In addition to medical history and physical examination, for initial screening, complete blood counts, blood chemistry, kidney function, urinalysis, and clotting factors are needed. Imaging holds an important role here. Imaging is intended to differentiate primary renal tumors from extra-renal tumors and benign renal tumors. In addition, imaging is also used to see if the tumor is unilateral or bilateral and whether there are metastases. Abdominal

ultrasound examination is the first-line modality option because it is widely available and does not require the patient to be sedated. Ultrasound can differentiate between intra- or extra-renal masses and solid or cystic masses. Wilms tumor is a sizeable hyperechoic area due to central necrosis and cyst formation.¹⁶ In the case of vascular invasion, ultrasound is helpful for viewing tumor thrombi in the inferior vena cava.

CT scan or abdominal MRI can be used to evaluate tumor distribution. If the diagnosis of Wilms tumor is suspected, a CT scan of the thorax is necessary to see if there is any spread to the lungs, which is the most common site of metastases from Wilms tumor. In around 10-20% of cases, the tumor metastasizes to the lungs and 10% spread hematogenously. Wilms tumor follows the rule of ten: 10% with unfavorable histology, 10% bilateral, 10% hematogenous spread, 10% calcified on CT scan, and 10% metastasized to the lungs at the time of discovery.¹⁷ During CT scan examination, “claw sign” may be seen.

The differential diagnosis for children with abdominal masses includes Wilms tumor, renal tumors other than Wilms tumor, and extra-renal tumors. The differential diagnoses include clear cell renal sarcoma, rhabdoid renal tumor, abdominal neuroblastoma, and congenital mesoblastic nephroma. Clear cell renal sarcoma often metastasizes to bone, while it is rare in Wilms tumor. Rhabdoid kidney tumors are very malignant and are often found before the age of 2 years and are rarely found in children over 5 years. These tumors often have metastasized at the time of discovery and have a poor prognosis. Congenital mesoblastic nephroma is usually found in children under one year of age with symptoms of hypertension and a concomitant increase in renin levels. Abdominal neuroblastoma is also one of the extra-renal tumors often found in the abdominal cavity to become the differential diagnosis of Wilms tumor.

Classification and stages

Macroscopically, Wilms tumor is spherical with

well-defined borders and a pseudo-capsule. Wilms tumor is classified according to its histology into favorable and unfavorable. 90% of Wilms tumors show favorable histology, which has a better prognosis. Histologically favorable includes epithelial triphasic blastema layer and stromal tissue. Histologically unfavorable shows a degree of anaplasia and undifferentiated blastema. This is associated with an abysmal prognosis. Confirmation of the diagnosis of Wilms tumor by pathological-histological examination is significant.

Wilms tumor can be classified into several stages. Staging is essential in determining the next step of treatment. In stage I, the tumor is entirely within the kidney (limited to the renal parenchyma) with no spillage of the lesion outside the capsule and no vascular invasion.¹³ This stage makes up 40-45% of Wilms tumor cases. The tumor has developed outside the renal parenchyma in stage II, such as in the renal pelvis or in the renal capsule. Around 20% of Wilms tumor patients are in this stage.

Furthermore, stage III tumor makes up 20-25% of the cases. The tumor has spread outside the kidney in this stage but is still in the abdominal cavity. Some of the conditions included in stage III are tumors that have spread to the lymph nodes, peritoneum, tumors removed separately during the intraoperative period (e.g., in the kidney and adrenal glands), or tumors that “spilled” during the intraoperative period.^{11,13} Patients with evidence of metastatic spread to other organs (mainly to the lungs and liver) seen on radiological imaging are considered stage IV. Ten percent of Wilms tumor cases are in this stage. Stage V means that both kidneys have been affected at the initial diagnosis. Around 5% of Wilms tumor cases are in this stage.

Management

The COG management guidelines recommend that patients undergo surgery before chemotherapy. Meanwhile, in Europe, which adopted the SIOP guidelines, pre-operative chemotherapy is recommended to be performed first. The difference in both protocols is based on the difference in staging.

The staging system in the COG guidelines refers to the pathological analysis results of nephrectomy results in almost all cases, while SIOP is based on the results of pre-operative chemotherapy.¹⁸ Despite this significant difference, the overall survival rate of patients undergoing therapy according to either SIOP or COG guidelines is >90%.¹⁹

Risk assessment

Risk assessment is needed to determine the most appropriate type of therapy to minimize recurrence and the long-term effects of therapy. Tumor histology, tumor stage, tumor biomarkers, presence or absence of metastases, involvement of two kidneys, age of the child, and presence or absence of certain predisposing factors or syndromes need to be assessed for risk stratification. LOH cytogenetic and molecular examination is recommended for all children newly diagnosed with favorable histology Wilms tumor.²⁰ Other factors that indicate the need for intensive therapy are older age at diagnosis, unfavorable/anaplastic histology, and advanced stage.

Surgery

The goal of surgery is to remove Wilms tumor without rupturing it (no gross tumor spill) by taking a sample of lymph nodes for pathological examination as well.²¹ Nephrectomy procedure is the treatment protocol performed in almost all patients with unilateral Wilms tumor. Nearly all children with favorable histology Wilms tumor undergo ureteronephrectomy.¹³ Contraindications to surgery include enlargement of the tumor to surrounding structures, one kidney, spread of tumor thrombus over the hepatic vein, very large tumors, the risk of gross tumor spillage, and the risk of anesthesia-related to pulmonary metastases. Metastasis in itself is not a contraindication to surgery. The surgical method of choice is a transabdominal or thoracoabdominal incision approach to avoid tumor spillage.²² Any spillage found intraoperatively must be documented to determine the right management.

Every patient with spillage falls to stage III category and radiotherapy is indicated.

The COG guidelines recommended surgery before chemotherapy. Radical nephrectomy and lymph node sampling are performed with a transabdominal incision.²³ Nephron-sparing surgery is not recommended by the COG guidelines, except for children with one kidney, children with bilateral Wilms tumor, children with genetic predispositions, and children with a high risk of kidney failure. The SIOP guidelines recommend radical nephrectomy after pre-operative chemotherapy.⁷ samples of regional lymph nodes were required for pathology examination. Nephron-sparing surgery may be performed in children with unilateral Wilms tumors with no genetic predispositions or certain syndromes or children with small tumors (<300mL).⁵

Chemotherapy

The SIOP guidelines recommend chemotherapy in all Wilms tumor cases. For patients with unilateral tumors, pre-operative chemotherapy is given for 4 weeks with vincristine (1 time a week) and dactinomycin (every 2 weeks). For patients with bilateral tumors, 9-12 weeks of vincristine-dactinomycin is recommended and doxorubicin may be added. Furthermore, for patients with metastasis, regimen of vincristine-dactinomycin for 6 weeks and doxorubicin in the first week and the fifth week is administered.^{5,24} In the COG guidelines, chemotherapy is performed postoperatively for all Wilms tumor patients except children aged less than 2 years with a favorable histology stage I tumor and tumor weight <550 grams. Pre-operative chemotherapy is indicated for children with inoperable Wilms tumor, with one kidney, with bilateral Wilms tumors, with tumor thrombus in the inferior vena cava above the hepatic vein, with tumor spreading to other organ structures where if it is removed the structure/organ will also be lifted (such as pancreas, spleen, or colon). In these cases, pre-operative neoadjuvant chemotherapy is needed to shrink the tumor. The chemotherapy regimen is given for 6

weeks, then the response to therapy is re-evaluated.

Chemotherapy regimens after nephrectomy include EE4A (vincristine and dactinomycin), DD4A (vincristine, dactinomycin, and doxorubicin), VAD (vincristine, dactinomycin, and doxorubicin), regimen M (vincristine, dactinomycin, doxorubicin, cyclophosphamide), regimen I, and etoposide (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide). For the EE4A regimen, 13 doses of vincristine and 7 doses of actinomycin are administered over 18 weeks. For the DD4A regimen, 15 doses of vincristine (1x weekly for 10 weeks and 5 doses every 3 weeks), 5 doses of dactinomycin, and 4 doses of doxorubicin are administered (for a total cumulative dose of 150mg/m²). This regimen is administered for a total of more than 24 weeks with alternating doses of dactinomycin and doxorubicin every 3 weeks. In the VAD regimen, 6 to 12 doses of vincristine, 2-4 doses of dactinomycin, and 2-4 doses of doxorubicin (cumulative total 7-140mg/m²) are administered for 6-12 weeks based on response to therapy and time of surgery. This regimen should only be given to patients undergoing nephron-sparing surgery, and dactinomycin is administered concurrently with doxorubicin.

Regimen M includes 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose of 150mg/m²), 4 cycles of once daily cyclophosphamide dose for 5 days, and 4 cycles of 1x daily dose of etoposide for 5 days, with the total regimen administered for more than 24 weeks.²⁵ Dactinomycin and doxorubicin are given concurrently and cyclophosphamide and etoposide are also given concurrently. The M regimen is initiated at week 7 for tumors requiring augmentation therapy based on molecular markers or response to lung metastases to 6 weeks of DD4A chemotherapy regimen. Regimen I contains 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose of 180mg/m²), 7 cycles of 3-5x daily doses of cyclophosphamide, and 3 cycles of 1x daily dose of etoposide for 5 consecutive days.²⁶ Doxorubicin and 1x daily dose of cyclophosphamide

for 3 days are given concurrently and 1x daily dose of cyclophosphamide with etoposide is also given concurrently. Depending on when the surgery is performed, regimen I is initiated at week 7, 9 or 12.

Adjuvant chemotherapy includes regimens EE4A, DD4A, regimen M and regimen I. This chemotherapy is given after nephrectomy. Based on the recommendation, the adjuvant chemotherapy is given to all children with FHWT unilateral and must be started no later than 14 days after surgery.¹³ If radiotherapy is required, the timing of chemotherapy should be coordinated to avoid the administration of full doses of actinomycin or doxorubicin at the same time as radiation. All patients with stage 3 Wilms tumor should undergo a combination of chemotherapy and radiation.¹² For stage III Wilms tumor with favorable histology, both COG or SIOP guidelines recommend post-operative radiation. Second, both guidelines also recommend pre-operative chemotherapy before nephrectomy in bilateral Wilms tumor (stage V).⁵

Complication and prognosis

The prognosis of Wilms tumor varies depending on the stage and histology. Favorable histology tumor shows better prognosis and higher survival rate compared to unfavorable histology/anaplastic. The recovery rate after initial therapy is around 90% for stage I and II, 85% for stage III, and 66% for stage IV.⁷ The recurrence rate for Wilms tumor is 15%, occurring mostly within the first 2 years postoperatively, which increased to 50% for anaplastic tumor. The most common sites for tumor recurrence include the lung, abdomen/flank and liver. In favorable Wilms tumor that relapses, the mortality rate is 24-40%.⁵ Periodic monitoring is needed for Wilms tumor patients post-operatively and post-therapy, which is every 3 months for the first 2 years after the diagnosis, then every 6 months for the subsequent 2 years, and then once every 2 years.²⁷

2. Conclusion

Wilms tumor is the most common primary renal tumor found in children especially under 5 years old. This tumor affects one kidney (unilateral), and has favorable histology where the recovery rate and survival rate are higher than the anaplastic type (unfavorable). There are 5 stages of Wilms tumor that have different criteria according to the SIOP and COG guidelines. The management approach in the two guidelines also differs slightly, where SIOP recommends pre-operative chemotherapy while COG recommends nephrectomy surgery first for all cases of unilateral Wilms tumor followed by chemotherapy, and if needed, radiotherapy. Types of chemotherapy drugs commonly used include vincristine and actinomycin D for stage I and II tumors, with the addition of doxorubicin for stage III, and etoposide, carboplatin, and cyclophosphamide for stage IV and V. For stage III Wilms tumor, a combination of operative therapy-chemotherapy-radiation is recommended. Periodical monitoring of Wilms tumor patients is required to assess the response and side effects of chemotherapy radiation. The prognosis of Wilms tumor depends on various factors, such as stage and histology. Along with the development of therapeutic modalities and early detection of Wilms tumor, the recovery rate and life expectancy of Wilms tumor patients have also increased.

3. References

1. Kellie SJ, Howard SC. Global child health priorities: what role for pediatric oncologists? *Eur J Cancer* 2008; 44:2388-96.
2. Rabeh W, Akel S, Eid T, et al. Wilms tumor: Successes and challenges in management outside of cooperative clinical trials. *Hematol Oncol Stem Cell Ther.* 2016; 9:20-5.
3. Ali K, Sutaryo S, Purwanto I, Mulatsih S, Supriyadi E, et al. Yogyakarta pediatric cancer registry: An international collaborative project of University Gadjah Mada, University of Saskatchewan, and the Saskatchewan Cancer Agency. *Asian Pac J Cancer Prev.*2010; 11:131-6.
4. Gadd S, Huff V, Walz AL, et al. A children's oncology group and TARGET initiative exploring the genetic landscape of Wilms tumor. *Nat Genet.* 2017; 49:1487-94.
5. Wang J, Li M, Tang D, et al. Current treatment for Wilms tumor: COG and SIOP standard. *World Journal Pediatric Surgery.* 2019; e000038.
6. Scott RH, Walker L, Olsen ØE et al. Surveillance for Wilms tumor in at-risk children: pragmatic recommendations for best practice. *Arch Dis Child.* 2006; 91:995-9.
7. Friedman AD. Wilms tumor. *Pediatrics* in review. 2013; 34:328.
8. Charlton J, Irtan S, Bergeron C, et al. Bilateral Wilms tumor: a review of clinical and molecular features. *Expert Rev Mol Med.* 2017; 19:e8.
9. Breslow NE, Beckwith JB, Perlman EJ, et al. Age distributions, birth weights, nephrogenic rests, and heterogeneity in the pathogenesis of Wilms tumor. *Pediatr Blood Cancer.* 2006; 47: 260-7.
10. Hillen LM, Kamsteeg EJ, Schoots J, et al. Refining the diagnosis of congenital nephritic syndrome on long term stored tissue: WT1 mutation causing Denys Drash Syndrome. *Fetal Pediatr Pathol.* 2016; 35:112-9.
11. Szychot W, Appa J, Pritchard-Jones K. Wilms' tumor: biology, diagnosis and treatment. *Transl Pediatr.* 2014; 3(1):12-24.
12. Leslie SW, Sajjad H, Murphy PB. Wilms Tumor. [Updated 2021 Aug 12]. In: StatPearls [Internet]. StatPearls Publishing; 2021.
13. Balis F, Green D, Anderson C, et al. Wilms tumor (Nephroblastoma), version 2.2021. *Journal of the National Comprehensive Cancer Network.* 2021; 19(8).
14. MacFarland SP, Duffy KA, Bhatti TR, Bagatell R, Balamuth NJ, et al. Diagnosis of Beckwith-Wiedemann syndrome in children presenting

- with Wilms tumor. *Pediatr Blood Cancer*. 2018; 65(10):e27296.
15. Davidoff AM. Wilms tumor. *Adv Pediatr*. 2012; 59: 247-67.
 16. Dumba M, Jawab N, McHugh K. Neuroblastoma and nephroblastoma: a radiological review. *Cancer imaging*. 2015; 15: 5.
 17. Dahnert W. Urogenital tract. In: *Radiology Review Manual 7th edition*, Lippincott Williams & Wilkins. 2011: 895-1012.
 18. Kieran K, Ehrlich PF. Current surgical standards of care in Wilms tumor. *Urol Oncol*. 2016; 34:13–23.
 19. Lopes RI, Lorenzo A. Recent advances in the management of Wilms' tumor. *F1000Res*. 2017; 6.
 20. Cone EB, Dalton SS, Van Noord M, et al. Biomarkers for Wilms tumor: a systematic review. *J Urol*. 2016; 196:1530–5.
 21. Gow KW, Barnhart DC, Hamilton TE, et al. Primary nephrectomy and intraoperative tumor spill: report from the Children's Oncology Group (COG) renal tumors committee. *J Pediatr Surg*. 2013; 48:34-8.
 22. Kalapurakal JA, Li SM, Breslow NE, et al. Intraoperative spillage of favorable histology Wilms tumor cells: influence of irradiation and chemotherapy regimens on abdominal recurrence. A report from the National Wilms Tumor Study Group. *Int J Radiat Oncol Biol Phys*. 2010; 76:201-6.
 23. Dome JS, Fernandez CV, Mullen EA, et al. Children's Oncology Group's 2013 blueprint for research: renal tumors. *Pediatr Blood Cancer*. 2013; 60:994–1000.
 24. Vujančić GM, Gessler M, Ooms AHAG, et al. The umbrella SIOP- RTSG 2016 Wilms tumour pathology and molecular biology protocol. *Nat Rev Urol*. 2018; 15:693–701.
 25. Dix DB, Seibel NL, Chi YY, et al. Treatment of stage IV favorable histology Wilms tumor with lung metastases: a report from the Children's Oncology Group AREN0533 Study. *J Clin Oncol*. 2018; 36:1564-70.
 26. Seibel NL, Chi YY, Perlman EJ, et al. Impact of cyclophosphamide and etoposide on outcome of clear cell sarcoma of the kidney treated on the National Wilms Tumor Study-5 (NWTS-5). *Pediatr Blood Cancer*. 2019; 66: e27450.
 27. Mullen EA, Chi YY, Hibbitts E, Anderson JR, Steacy KJ, et al. Impact of surveillance imaging modality on survival after recurrence in patients with favorable-histology wilms tumor: a report from the children's oncology group. *J Clin Oncol*. 2018; 18:JCO1800076.