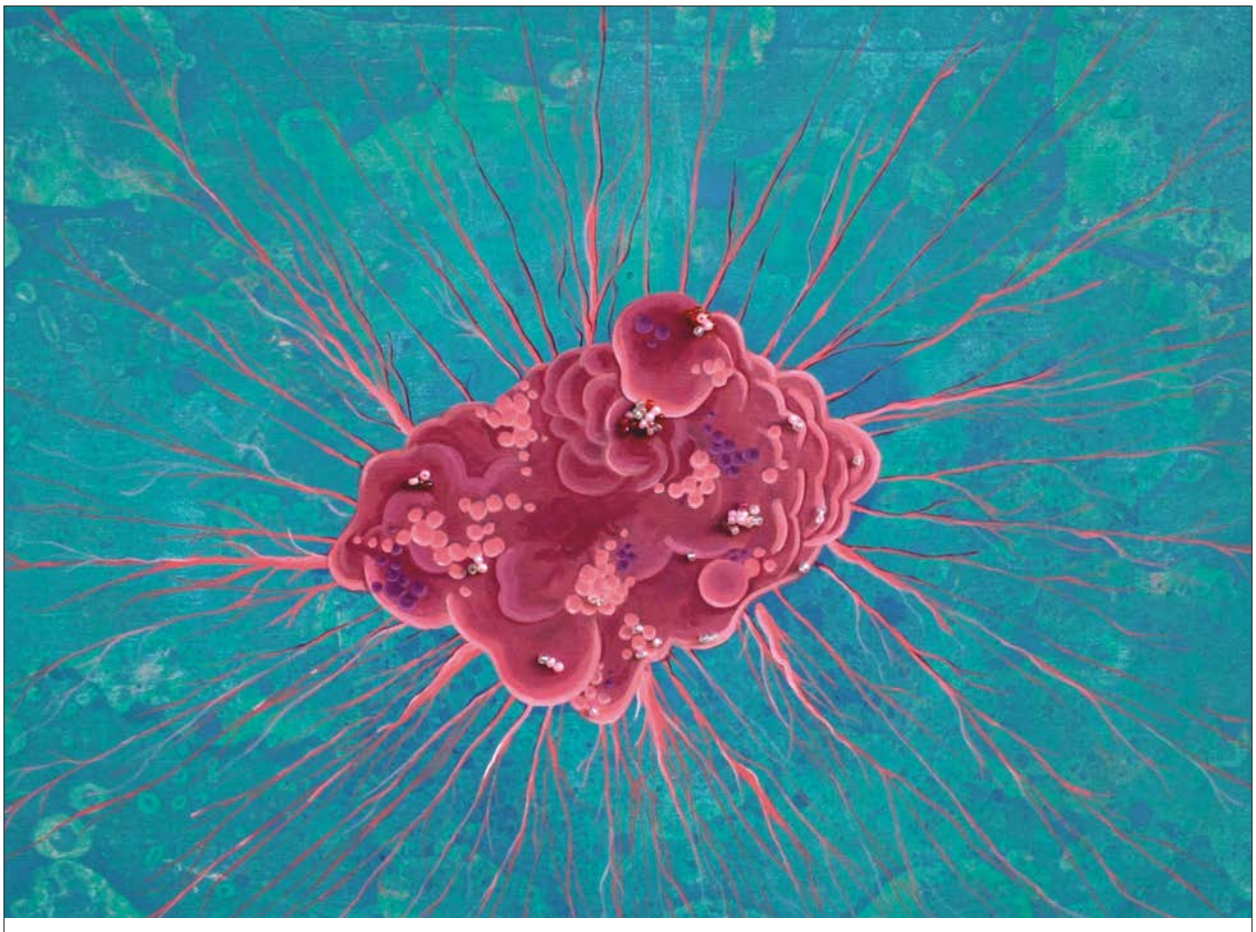

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An Overview and Perspectives of Wilm's Tumor

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ABSTRACT

Wilm's tumor or nephroblastoma is a tumor of the kidneys that typically occurs in children, rarely in adults. Most cases are not part of a genetic malformation syndrome and have no familial history; however, familial Wilms tumor arises with high frequency in certain families. Genetic syndromes that predispose to and may include Wilm's tumor. Nephroblastomatosis is a condition in which abnormal tissue grows on the outer part of one or both kidneys. Children with this condition are at risk for developing a type of Wilm's tumor that grows quickly. Frequent followup testing and the child is treated radiation therapy and chemotherapy will often be started after surgery, depending on the stage of the tumor. Staging is determined by combination of imaging studies and pathologic findings if the tumor is operable. With treatment, the disease has a high cure rate. Children with a localized tumor have a 90% cure rate when treated with surgery and chemotherapy; or with surgery, radiation and chemotherapy combined. This study gives a broad perspective of occurrence, causes, symptoms, stages, treatment and prevention of Wilm's tumor.

Key words: Nephroblastoma, eponym, malignant tumor, nephrectomy, chemotherapy

INTRODUCTION

Wilm's Tumor (WT) is the fifth most common pediatric malignancy and the most common renal tumor in children. When an unborn baby is developing, the kidneys are formed from primitive cells. Over time, these cells become more specialized (Breslow *et al*., 1988). The cells mature and organize into the normal kidney structure. Blood vessel formation is important for normal organ development and tumour growth. A highly specialised developmental program of vessel formation exists in the heart and is essential for normal cardiogenesis (Scholz *et al*., 2009). WT1s unique role during organ formation, particularly development of the genitourinary system and mesothelial tissues, sets it apart from other tumor suppressors (Scholz and Kirschner, 2005). Sometimes, clumps of these cells remain in their original, primitive form. If these cells begin to multiply after birth, they may ultimately form a large mass of abnormal cells. This is known as a Wilm's tumor. Wilm's tumor is a rare kidney cancer that primarily affects children. Also, known as nephroblastoma, it's the most common malignant tumor of the kidneys in children. The peak time of Wilm's tumor occurrence is at age 3 (Boglino *et al*., 2004; Coppes and Pritchard-Jones, 2000) and it occurs only rarely after age 8. Wilm's tumor may arise in either or both kidneys. The condition is named after 19th century German surgeon who recognized that the cancer develops from immature kidney cells. It is made up of cells that are significantly immature and abnormal. These cells are also capable of invading

nearby structures within the kidney and traveling out of the kidney into other structures. Malignant cells can even travel through the body to invade other organ systems, most commonly the lungs and brain. These features of Wilm's tumor make it a type of cancer that, without treatment, would eventually cause death. However, advances in medicine during the last 20 years have made Wilm's tumor a very treatable form of cancer. Treatment is a living example of success achieved through a multidisciplinary collaboration of the National Wilm's Tumor Study Group (NWTSG) and the Societe Internationale d'Oncologie Pediatrique (SIOP) (Coppes and Egeler, 1999; Davies-Johns *et al*., 1999). Approximately 500 cases are diagnosed in the US annually. The majority (75%) occurs in normal children, a minority (25%) is associated. With other development abnormalities. It is highly responsive to treatment; with about 90% of patients surviving at least 5 years. Incidence is approximately 0.8 cases per 100,000 persons. Approximately 500 new cases are diagnosed each year in the United States, with 6% of cases involving both kidneys (Egeler *et al*., 1999; Goske *et al*., 1999).

Causes: The exact cause of this tumor in most children is unknown. The tumor is associated with certain birth defects, including urinary tract abnormalities, absence of the iris (aniridia) (Wagner *et al*., 2002b) and hemihypertrophy (enlargement of one side of the body). It is more common among some siblings and twins, which suggests a possible genetic cause (Coppes and Pritchard-Jones, 2000). The tumor may become quite large, but usually remains encapsulated (self-enclosed). It may spread to other body tissues, especially the lungs. The disease is estimated to occur in about 1 out of 200,000 to 250,000 children. Because 15% of all patients with this type of tumor have other heritable defects, it seems clear that at least some cases of Wilm's tumor are due to an inherited alteration. A genetic defect known as WT1, the Wilm's tumor suppressor gene has been identified in some patients on chromosome 11. It appears that the tendency to develop a Wilm's tumor can run in families. In fact, about 1.5% of all children with a Wilm's tumor have family members who have also had a Wilm's tumor. The genetic mechanisms associated with the disease are unusually complex (Coppes and Egeler, 1999). It is thought that the tumor develops because the defective WT1 gene fails to stop its growth. Other genes that have been linked to Wilm's tumor are located on chromosomes 16q, 7p15 and 17q12 (Coppes and Egeler, 1999; Davies-Johns *et al*., 1999). Less than 2% of cases will have an affected relative. Most cases of Wilm's tumor are considered sporadic (occur by chance) and are the result of genetic mutations that affect cell growth in the kidney. These mutations generally arise after birth, but, in some cases, children are born with a genetic alteration that predisposes them to cancer (Emerson *et al*., 2004; Glick *et al*., 2004).

Symptoms: Some patients with Wilm's tumor experience:

- Abdominal pain
- Nausea
- Vomiting
- Fever
- Loss of appetite
- Constipation
- Increased growth on only one side of the body (hemihypertrophy)
- High blood pressure or blood in the urine

However, the parents of many children with this type of tumor are the first to notice a firm, rounded mass in their child's abdomen (Green, 2004). This discovery is often made while bathing or dressing the child and frequently occurs before any other symptoms appear. Rarely, a Wilm's tumor is diagnosed after there has been bleeding into the tumor, resulting in sudden swelling of the abdomen and a low red blood cell count (anemia) (Levien and Bringelsen, 1999). Abnormal urine color may also be associated with this disease. A missing iris of the eye (aniridia) is a birth defect that is sometimes associated with Wilm's tumor (Wagner *et al*., 2002a).

Screening: Special emphasis is placed on the history and physical exam looking for a family history of cancer and for associated birth defects in the child. The physical examination reveals an abdominal mass. High blood pressure may also be present (Green, 2004). Initial diagnosis of Wilm's tumor is made by looking at the tumor using various imaging techniques. Ultrasound and computed tomography scans (CT scans) are helpful in diagnosing Wilm's tumor. Intravenous pyelography, where a dye injected into a vein helps show the structures of the kidney, can also be used in diagnosing this type of tumor. Final diagnosis, however, depends on obtaining a tissue sample from the mass (biopsy) and examining it under a microscope in order to verify that it has the characteristics of a Wilm's tumor. This biopsy is usually done during surgery to remove or decrease the size of the tumor. Other studies (chest x rays, CT scan of the lungs, bone marrow biopsy) may also be done in order to see if the tumor has spread to other locations (Neville and Ritchey, 2000; Weirich *et al*., 2004).

Lab studies

- Complete blood count
- Basic metabolic panel
- Coagulation abnormalities (to rule out acquired von Willebrand disease) (Li *et al*., 2005)

Imaging studies

- Ultrasound
- Initial diagnosis of a renal or abdominal mass, possible renal vein or Inferior Vena Cava
- (IVC) thrombus
- Information regarding liver and other kidney
- Computed tomography scan of the chest and abdomen
- Differential diagnosis of a kidney tumor versus adrenal tumor (neuroblastoma)
- Liver metastases
- Status of opposite kidney
- Lymph node assessment
- Status of chest with respect to metastases
- Chest x-ray-as a baseline for pulmonary metastases
- Bone scan-necessary for children with clear cell sarcoma of the kidney
- Magnetic resonance imaging

Other tests

- Chromosomal analysis and gene mapping
- Analysis for LOH on chromosomes 1p and 16q (Ross and Kay, 1999)

Histologic findings

- Wilm's tumor arises from the primitive embryonal renal tissue (Wagner *et al.*, 2001) and contains epithelial, stromal and blastemal elements (Vujanic *et al.*, 2002b)

Staging the disease: NWTSG recommends surgical staging in every case.

- **Stage 1:** The tumor is limited to the kidney and is excised completely
- **Stage 2:** The tumor extends beyond the kidney but is excised completely. Capsular penetration, renal vein involvement and renal sinus involvement also may be found. A biopsy of the tumor is performed and local spillage occurs
- **Stage 3:** Residual intra-abdominal tumor (nonhematogenous) exists after the completion of surgery. Lymph node findings are positive, or peritoneal implants are found. The resected specimen has histologically positive margins, or the tumor has been spilled into the abdominal cavity (De Kraker and Jones, 2005)
- **Stage 4:** Hematogenous or lymph node metastasis has occurred outside the abdomen orpelvis
- **Stage 5:** Synchronous bilateral involvement has occurred. Each side is assigned a stage from I to III and histology is based on biopsy findings

Treatment: Clinical staging of the tumor is done to determine the extent of the tumor and to maximize the effectiveness of treatment plans. Surgical exploration and removal of the tumor is scheduled as soon as possible.

Regional lymph nodes, abdominal organs and other tissues are examined and removed if the tumor has spread to those areas. Radiation therapy and chemotherapy will often be started after surgery, depending on the stage of the tumor (Call *et al.*, 1990; Huff, 1998).

Staging is determined by combination of imaging studies and pathologic findings if the tumor is operable (adapted from www.cancer.gov). Treatment strategy is determined by the stage.

Side effects of treatment: Treatment for Wilm's tumour often causes side effects:

- Feeling sick (nausea) and being sick (vomiting)
- Hair loss
- An increased risk of infection
- Bruising and bleeding
- Tiredness
- Diarrhea
- Late side effects

A small number of children may develop side effects many years later, because of the treatment they have received for a Wilm's tumour. These include possible reduction in bone growth, infertility,

a change in the way the heart and the lungs work and a slight increase in their risk of developing another cancer in later life. There is more detailed information about these late side effects in the general information on children's cancers (Lapunzina, 2005).

Prognosis: With treatment, the disease has a high cure rate. Children with a localized tumor have a 90% cure rate when treated with surgery and chemotherapy; or with surgery, radiation and chemotherapy combined (Coppes and Egeler, 1999).

Possible complications: Spread of the tumor to the lungs, liver, bone, or brain is the most worrisome complication. High blood pressure and kidney damage may occur as the result of the tumor or its treatment. Removal of Wilms tumor that is present in both kidneys may leave the patient with orderline kidney function.

Prevention: For children with a known high risk of Wilm's tumor, screening with ultrasound of the kidneys may be recommended. There are no known ways to prevent a Wilm's tumor, although it is important that children with birth defects associated with Wilms' tumor be carefully monitored. Most children with Wilm's tumour are cured. If the cancer comes back, it is usually within the first two years. When one kidney is removed, the other will be able to work normally and can take over the work of the other kidney. Very few children have long-term kidney problems. Your child will have regular follow-ups to check for any recurrence. If you have specific concerns about your child's condition and treatment, it is best to discuss them with your child's doctor, who knows the situation in detail (Lapunzina, 2005). The factors for determining the prognosis and long-term survival of children with Wilm's tumor include the following:

- Histology, favorable or unfavorable
- Extent of the disease
- Age and overall health of the child at diagnosis
- Size of the primary tumor
- Response to therapy
- Your child's tolerance of specific medications, procedures, or therapies
- New developments in treatment

Prompt medical attention and aggressive therapy are important for the best possible prognosis. Continued follow-up care is essential for the child diagnosed with Wilms tumor. Side effects of chemotherapy and radiation, as well as second malignancies can occur in survivors of cancer. New methods are continually being discovered to improve treatment and to decrease side effects.

CONCLUSION

Wilm's tumor is a curable disease in the majority of affected children. Approximately 500 cases are diagnosed in the United States annually. More than 90% of patients survive 4 years after diagnosis, which is an improvement over the 80% survival observed from 1975 to 1984. The prognosis is related not only to the stage of disease at diagnosis, the histopathology features of the tumor, patient age and tumor size, but also to the team approach to each patient by the pediatric surgeon, radiation oncologist and pediatric oncologist. Previous clinical trials have, in part,

evaluated with some success whether reduced therapy is sufficient to control disease in patients with early-stage, favorable-histology Wilm's tumor. Information about the tumor cell type and the spread of the tumor is used to decide the best kind of treatment for a particular patient. Treatment is usually a combination of surgery, medications used to kill cancer cells (chemotherapy) and x rays or other high-energy rays used to kill cancer cells (radiation therapy). These therapies are called adjuvant therapies and this type of combination therapy has been shown to substantially improve outcome in patients with Wilm's tumor. It has long been known that Wilm's tumors respond to radiation therapy. Likewise, some types of chemotherapy have been found to be effective in treating Wilm's tumor. These effective drugs include dactinomycin, doxorubicin, vincristine and cyclophosphamide. In rare cases, bone marrow transplantation may be used.

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