Wilms’ Tumor Detection and Treatment

Abstract

Wilms’ Tumors are the most common pediatric renal tumor. The tumors usually present as a palpable mass in the abdomen with little or no other symptoms. There are many different renal tumors and the right differential diagnosis are detrimental to the prescribed treatments for the patient. With the use of medical imaging along with pathology reports it is a precise way to determine the appropriate treatment. It is a combined effort from medical imaging staff, surgeons, medical oncologists, radiation oncologists and diagnosticians. Many different studies have been performed to help provide for a better outcome for children diagnosed with these tumors.

Introduction

Wilms’ Tumors (WT) are the most common pediatric renal malignancy in children with a cure rate of more than ninety percent. This cure rate is substantially better than that of a thirty percent cure rate in the 1930s. They constitute from six to ten percent of all childhood cancers. The tumor usually presents between the ages of one and five without gender discrimination. Some rare cases of WT have been diagnosed in utero. “Ninety-five percent Wilms tumor cases are unilateral, and approximately 10 percent are associated with congenital syndromes including WAGR (Wilms tumor, aniridia, genitourinary, and mental retardation) Syndrome, Beckwith-Wiedemann syndrome, Deny-Drash syndrome, and hemiphypertrophy.” “WT affects 1 in 10,000 children younger than fifteen years of age.” Most WT cases respond well to treatment with only approximately ten percent of cases being unfavorable. Advanced medical imaging could possibly help diagnose if the tumor has the potential to rupture or has already ruptured.

Symptoms

WT is often discovered during a routine examination or incidentally as a palpable abdominal mass. As seen on the patient in Figure 1 this patient’s tumor was discovered during a
routine yearly examination, the patient had a slightly distended abdomen and was otherwise a happy, healthy one-year old. A plain film x-ray was ordered and the mass was clearly seen. After the x-ray an abdominal Computed Tomography (CT) scan was ordered with oral and IV contrast. These images are seen in Figures 1-4. The tumor is usually not tender, but generally is large, firm, or presents clinically as a varicocele that indicates compression of the renal vein by the tumor. Most patients are asymptomatic but some present with abdominal pain, hypertension, hematuria, loss of appetite, weight loss or fever.²

Radiographic Features

Pediatric renal tumors are very difficult to diagnose radiographically. There are several different types of renal tumors that could be presented in a patient. Radiographic features such as: age of the patient, associated disease or syndrome, bilateral involvement, and type or presence of metastasis. As seen in Figure 10, this patient has metastasis of both bone and lungs. The diagnosis of pediatric tumors is very extensive with WT being the most common, but other malignant masses must be considered. Sanchez et al³ has developed a mnemonic WARM N COLD to allow for an easy way to remember the different pediatric renal tumors. The mnemonic WARM N COLD can be broken up into:

W—Wilms’ tumor- Most common pediatric renal mass, bilateral in 5%
A—Angiomyolipoma Fat- containing often multiple, associated with TS, VHL, and NF
R—Renal cell carcinoma- Smaller, more likely to be bilateral, bone metastasis common
R—Renal medullary carcinoma- Sickle cell disease/trait, central/ infiltrating, presents in the second to fourth decade
R—Rhabdoid tumor- Presents within the first year, associated CNS tumor and extensive metastasis
M—Mesoblastic nephroma- Diagnosed within the first year, can mimic Wilms’ but has more benign features (no vascular invasion or lymphadenopathy)
M—Multilocular cystic nephroma- Cystic mass with thin septations, no solid components
N—Nephroblastomatosis- Bilateral multiple masses, enlarged kidney, can present with bilateral Wilms’
C—Clear cell sarcoma- Same age range as Wilms’, bone metastasis are more common
O—Ossifying renal tumor of infancy- Very rare tumor, small calcified mass in pelvis
L—Lymphoma- Unilateral or bilateral with lymphadenoptathy elsewhere
D—Desmoplastic small round cell tumor- Extremely rare to just involve the kidney³ (p. 262)
With the use of this mnemonic radiologists have the ability to differentiate between the different types of tumors. “Although WT peak age is around four years, it has been documented in the neonate and adults as old as ninety-three years.”3 (p.267) This statement demonstrates that it is not only prudent to include this differential diagnosis in pediatric renal tumors but in renal tumors patients of all ages.

**Tumor Staging**

WT are staged from I to V and there are different attributes to each. These stages are determined using various imaging modalities, surgery and pathology. The WT staging is listed below.

- **I** – Unilateral tumor, without capsule extension or lymph node involvement
  - The tumor is completely removed without tumor spill
- **II** – Unilateral tumor, with capsule extension or adherent to adjacent structures
  - No lymph node involvement
  - The tumor is completely removed without tumor spill
- **III** – Unilateral tumor with lymph node involvement, preoperative tumor rupture, intra-operative tumor spill, incomplete resection, or tumor biopsy only
- **IV** – Metastasis to lung, liver, bone, brain, or distant lymph node involvement
- **V** – Bilateral tumors2 (p. 752)

Staging is an important factor in the care plan for patients with WT. It is a combined effort to be able to effectively plan and execute a care plan for each individual patient. According to McDonald et al5, “The European SIOP (International Society of Pediatric Oncology) protocol, imaging of the primary includes ultrasound as mandatory, and CT/Magnetic Resonance Imaging (MRI) abdomen is strongly advised and in the UK it is mandatory.” 5 (p.17) Reduction of the tumor before surgery helps to reduce the risk of tumor rupture during surgery as well as intensity of postoperative chemotherapy. According to the SIOP, chemotherapy is followed by surgery, where as in North America it is advocated as surgery before chemotherapy. **Figure 6** demonstrates a major surgical contraindication because the fact that there is a tumor thrombus extending from the mass in the right kidney and also penetration through the renal vein and inferior vena cava. There is also another small mass in the left kidney.1 (p.651) This tumor needs
preoperative chemotherapy so that the tumor can be shrunk to allow for a more successful surgical removal. These guidelines are set by the National Wilms’ Tumor Study Group and have been found to have the same outcome.

Another great example of the benefits of tumor staging is that of the patient demonstrated in Figure 9. This patient has a substantial mass that originates from the left kidney. This mass has lobulated components that extend outside of the renal capsule. This is suggestive of a perinephric spread. This image also demonstrates a great example of a tumor rupture because it shows fluid adjacent to the bare area of the liver superior and lateral to the upper pole of the right kidney. There is also aneuplopathy encasing the aorta. This patient also has liver metastases. 1 (p.651)

In a study performed by McDonald et al5, 52 patients with histologically proven WT were observed. Each patient had an abdominal ultrasound followed by either a CT or MRI. The radiologists in this study looked for conditions including: tumor origin, size, invasion of adjacent structures, presence of tumor thrombus (surrounding veins, arteries, or right atrium), presence of contralateral tumors, lymph node enlargement, tumor rupture, and metastatic spread to the liver. 5 All images were re-reviewed by a pediatric radiologist and a pediatric radiology fellow after the studies were received. Ultrasound images were not reviewed again. They then noted the differences in the finding between the ultrasound, the cross-sectional images acquired, histology and surgical findings.

The results of this study were conclusive that the combination of ultrasound along with cross-sectional imaging is beneficial to the diagnosis and treatment of WT. Out of those patients 19 patients had additional findings on the CT or MRI images that were not detected with ultrasound that were later confirmed with histology. 5 (p.17) Five of the patients were found to have false negatives in surgery. Figure 8 demonstrates an actual photo of a WT during an operation that was unable to be removed due to the great size and involvement of surrounding tissues. It also has an axial CT image corresponding to the actual mass. 2 (p.751) Those included inferior vena cava thrombus and enlarged lymph nodes. Another five patients were found to have false positives including tumor rupture, liver metastasis, and adrenal invasion. MRI in this study was found to be particularly helpful when the origin of the tumor was unknown and the diagnosis was
in question. This study showed that around half of the patients benefited from the additional imaging when staging.

**Diagnostic Imaging Involvement**

Ultrasound, CT, MRI and x-ray can be used to aide in the diagnosis of pediatric renal tumors. X-ray can be a place of accidental finding and is usually a routine procedure for any type of gastrointestinal or urological patient complaints. It can also be used for staging purposes and to look for pulmonary metastases. Ultrasound is a quick and effective way of seeing if the tumor is a solid mass or a fluid filled cyst. Another diagnostic benefit of ultrasound is that of being able to show the presence of intravascular tumor extension. **Figure 5** shows a right upper quadrant ultrasound image which shows that the liver is displaced and this scan was unable to demonstrate a clear fat plane. A CT was done following the Ultrasound and it showed a clear fat plane which suggests no local invasion of the liver.\(^5\) MRI and CT are used to better characterize the mass and detect metastasis. The most common metastases of WT are lymph nodes, lungs, and the liver. A major down side to MRI is that of long scanning time on children can be extremely difficult to have the child maintain completely still without using oral or IV sedation. CT is the most commonly used for diagnosis of WT. The scanning times on these images are much shorter while still producing quality images. The down side of CT scanning is the amount of dose the child receives and will receive throughout repeated studies.\(^2\)

Tumor weight and volume have been used interchangeably throughout the many years of WT research. CT scans prior to surgery can help to predict the final pathological weight of the tumor. The ability to get an estimated tumor volume through an abdominal CT scan can help to determine the possibility of a tumor rupture during resection and help determine the need of possible pre-operative chemotherapy to reduce tumor volume to prevent a possible rupture. WT tumor volume was described to be the total volume of the tumor and was obtained from the pathology report. Weight was defined at weight of the tumor only and was also taken from the final pathology report. The formula for density was used to evaluate the final density of the tumors (Density = Mass/Volume).\(^6\) Pshak et al\(^6\), performed a retrospective study of WT patients from 2003 to 2011 at the Children’s Hospital in Colorado. The patients that were included in this
study had a pathological confirmation of WT, pre-operative CT-scan, final pathological specimen weight and dimensions.

In order to calculate an accurate measurement of tumor volume on the CT scans and pathological measurements the WT were assumed to have a natural ellipsoidal shape. A radical nephrectomy group of patients was used to determine volume estimation from pre-operative CT scans. Each scan was evaluated by a radiologist without the knowledge of final pathological results. The radiologist evaluated the tumor depth (D) and width (W) in centimeters at the largest size comparatively to other slices. Tumor length (L) was obtained from sagittal images. The formula used to find the tumor volume is that of ellipsoid volume \( (\text{cm}^3) = \frac{4}{3}\pi(D/2)(L/2)(W/2) \). Using this formula allowed for tumors of all sizes to be evaluated.\(^6\)

**Figure 7** demonstrates an example of one of the patients CT images being evaluated.

WT Volume and weight were not found to be equivalent to final pathological weight. This is suspected to be because of fluid loss post resection or if extra tissue was involved in the initial estimation. The pre-operative CT scans were found to accurately estimate final pathological specimen weight. In tumors greater than 250 grams the CT estimated tumor volume suggested that the tumors were larger than what was taken to pathology. This is likely due to blood flow through the tumor making it appear larger on the CT images. WT under 250 grams had a result of the pathological tumor weight being greater than estimated but this could be due to the differentiation between benign and actual tumor tissue.\(^6\)

**A Case Study Determining Possible Tumor Rupture**

A main concern of physicians is to determine a care plan for each patient that can help determine the risks of a WT rupture and the side effects of the spillage. “Tumor Spillage of Wilms’ Tumor increases the recurrence to twenty percent. Tumor spillage is considered to be present if there has been preoperative tumor rupture, intra-operative, tumor spill or a tumor, biopsy.”\(^7\) (p.611) Spillage can also occur in cases of trauma. A Chest CT along with a contrast enhanced abdominal CT scan can be used in some cases to help determine rupture. “Recurrence of Wilms tumor is associated with significant mortality. Recurrence in favorable Wilms tumor subtypes has an overall survival rate of fifty percent, whereas recurrence of unfavorable types is associated with much lower survival rates.”\(^2\) (p.754)
A study was conducted by Khanna et al\textsuperscript{7} of 136 patients to discover if CT imaging could help diagnose a possible preoperative WT rupture. Two pediatric radiologists reviewed the exams independently. From the radiologist reports the following conditions were assessed: poorly circumscribed mass, perinephric fat stranding, peritumoral fat planes obscured, retroperitoneal fluid, ascites beyond the cul-de-sac, peritoneal implants, ipsilateral pleural effusion, and intratumoral hemorrhage. The sensitivity and specificity for detection with CT was 54\% and 88\%. The first reviewer had a success rate of 70\% and the second 88\%. The most accurate readings came from a presence of a poorly circumscribed mass, fat stranding around the tumor, retroperitoneal fluid, ascites beyond the cul-de-sac, and ipsilateral pleural effusion. Both reviewers found that the odds of rupture were the greatest in the presence of ascites beyond the cul-de-sac. Subcapsular fluid also increased the odds of rupture by both reviewers, even though it was not statistically significant.

CT imaging is an adequate way of diagnosing a possible preoperative WT rupture, but more research needs to be performed to decide what type of diagnostic imaging best suits this situation.\textsuperscript{7} This will help to make a more fitting care plan for each patient and in return help reduce the reoccurrence from ruptures. A more detailed image could potentially increase the success rate of a positive diagnosis. Better detail could be achieved through a 256 slice CT scanner or MRI. MRI was not included in this study due to the protocol of the facilities that were participating using CT as the main diagnostic route for WT diagnosis.

**Late Recurrence of Wilms’ Tumor Incidence and Outcomes Case Study**

Although tumor recurrence is rare, there is a chance of metastases or even a reoccurring WT. “Approximately fifteen percent of patients with favorable-histology WT and fifty percent of patients with anaplastic or post-chemotherapy blastemal type WT experienced recurrence. About ninety-five percent of first recurrences occur within two years of initial diagnosis, with the most frequent sites being lung/plura, tumor bed, and liver.”\textsuperscript{4} (p.1612) A case study was performed by Malogolowkin et al that looked at available records on children with WT that were enrolled onto 10 national or international clinical trials looking for late recurrence of WT. Late recurrence meaning that of recurrences after more than five years of initial diagnosis.
There are many different factors that were taken into consideration for this study. The first information that was evaluated for these WT patients was gender, stage at the time of diagnosis, histology, initial treatment information, and those who had reoccurrence before five years post diagnosis. All patients’ information was gathered again at the time of recurrence, the site or recurrence was recorded, and outcome was reviewed. The histology and therapy for the new tumors were included in this analysis. A total of 13,330 patients were reviewed for this study. Out of those patients, seventy of them had late recurrence tumors. Thirty-five of them were alive and the other thirty-five had succumbed to the disease at the time of the last follow-up data collection performed. The median age for reoccurrence was around thirteen years old. The patients of this study were at all different stages if the disease. Fifteen patients were initially staged as I, nineteen stage II, fourteen stage III, eight in stage IV, and fourteen in stage V. Thirty-two percent (22 patients) received three or more initial chemotherapy drugs and thirty-seven percent (26 patients) received radiation therapy treatments. Common chemotherapy drugs used in treatment of WT are Cincristine, and Dactinomycine with or without the use of Doxorubicin.⁸(p. 1210)

Varying sites for reoccurrence were discovered in the patients. The most common sites were the abdomen (21 patients), lungs (20 patients), and contralateral kidney (15 patients). “Patients with lower stages (I and II) had more lung recurrences (41%), while those with higher stages (III, IV, and V) had more local recurrences (41%) in the area of the original WT. The frequency of contralateral recurrences was similar for all patients regardless of their tumor stage.”⁴(p.1613) Eighty-seven percent of patients with contralateral recurrence were living without any evidence of the disease and were long time survivors. The opposing factor to this is that only forty-five percent of the patients that did not have contralateral involvement were long time survivors.⁴

This information gathered from this study helps to better determine a plan of action in those patients that do have a reoccurring cancer. “Researchers from the Childhood Cancer Survivor Study have reported that the cumulative incidence of recurrence more than five years after the primary diagnosis of a childhood cancer is 6.2%.⁴(p.1613) This data suggests that most patients that clear the five year mark are very unlikely to have a late recurrence WT and that most reoccurrences are linked with earlier reoccurrence before the five year benchmark.
Conclusion

Modern medical advances and studies performed since the 1930s have greatly increased WT survival rates. These advances are not only in medical imaging, but in histology, surgery, chemotherapy, and radiation treatments. The use of better scanners in both MRI and CT have had a great contribution in the staging of the WT and helping to determine metastases or possible tumor rupture. Radiologists being more informed in the different appearance of renal tumors through the use of the mnemonic of WARM N COLD will help people of all ages to get the right differential diagnosis. Medical imaging and the radiologist report is usually a first line of defense in the diagnostic process for the patients. The combined efforts of the staff that perform these necessary tests and treatments have greatly influenced the families and children who are affected by WT.
References


Figures and Captions

Figure 1. Example of a localizing image on a CT scan, note that the tumor can be visualized on the left side. There are abnormal gas patterns as well. Images used by permission, courtesy of a local hospital.
Figure 2. A localizing lateral CT image that visualizes distention of the abdomen and the bowel gas being pushed anterior. Images used by permission, courtesy of a local hospital.
Figure 3. This image shows an axial image showing contrast in the right kidney with a large tumor on the left with some vascular attributes to the tumor. The contrast used in these images was intravenous Isovue 370 and orally taken Isovue mixed with juice. Images used by permission, courtesy of a local hospital.
Figure 4. This sagittal CT image shows the large extent of this Wilms’ Tumor and the extent of the other abdominal organs being forced out of the way. The contrast used in these images was intravenous Isovue 370 and orally taken Isovue mixed with juice. Images used by permission, courtesy of a local hospital.
Figure 5. A 4–year old male patient with a large, right sided mass. (a) Transverse ultrasound of the right upper quadrant showing the large heterogeneous mass, which displaces the liver, but a clear fat plane was difficult to demonstrate. (b) Contrast-enhanced axial CT-image of the upper abdomen. A clear fat plane, suggesting no local invasion, is present between the large right-sided mass and the liver, which is displaced to the left. The findings were confirmed at the time of surgery. Imagery courtesy of: McDonald K, Duffy P, Chowdhury T, et al. Added value of abdominal cross-sectional imaging (CT or MRI) in staging of Wilms’ tumours. Clin Radiol. 2013 Jan;68(1):16-20. doi: 10.1016/j.crad.2012.05.006.
Figure 6. This image shows an example of Wilms’ Tumors that up front contradict surgery. (a) bilateral tumors as marked by arrows. In fact, a smaller tumor shown by the short arrow is also seen at the upper pole of the left kidney. (b) A tumor thrombus extending from the mass in the right kidney (arrow head), upwards into the right atrium (short arrow) through the renal vein (not shown in this image) and inferior vena cava (arrows) Images courtesy of: Kembhavi SA, Qureshi S, Vora T, et al. Understanding the principles in management of Wilms' tumour: can imaging assist in patient selection? *Clin Radiol.* 2013 Jul;68(7):646-53. doi: 10.1016/j.crad.2012.11.012.
Figure 8. (A) CT scan of the abdomen shows a large right-sided Wilms’ Tumor. (B) The tumor was not primarily resected secondary to size and adherence to surrounding structures. Images courtesy of: Davenport KP, Blanco FC, Sandler AD. Pediatric malignancies: neuroblastoma, Wilm's tumor, hepatoblastoma, rhabdomyosarcoma, and sacroccygeal teratoma. Surg Clin North Am. 2012 Jun;92(3):745-67, x. doi: 10.1016/j.suc.2012.03.004.
Figure 9. This image shows an example of a patient who would benefit from preoperative chemotherapy. (a) A coronal reformatted image showing a large tumor on the left kidney. This mass has lobulated components (arrows) extending outside the renal capsule and abutting the other abdominal viscera suggestive of peri-nephric spread. (b) A localized retroperitoneal rupture with fluid (arrow) adjacent to the bare area of the liver supero-lateral to the mass in the upper pole of the right kidney. (c) A left renal mass with extensive abdominal adenopathy encasing the aorta. (d) Post contrast T1W axial scan showing liver metastases. Images courtesy of: Kembhavi SA, Qureshi S, Vora T, et al. Understanding the principles in management of Wilms’ tumour: can imaging assist in patient selection? Clin Radiol. 2013 Jul;68(7):646-53. doi: 10.1016/j.crad.2012.11.012.