Pediatric Abdominal Tumors:
A Focus on Wilms’ Tumor

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General Surgery Grand Rounds
5/25/11
Objectives

• To discuss:
  – The most common pediatric solid abdominal tumors
  – Epidemiology, clinical presentation, and associated congenital syndromes involved in Wilms’ tumor
  – Surgical management
  – Staging and postoperative chemoradiation therapies in Wilms’ tumor
Solid Abdominal Tumor

- 2-year-old boy complains of abdominal pain and loss of appetite. Physical exam is significant for a large palpable abdominal mass.

- Differential diagnosis:
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Hepatoblastoma
  - Nephroblastoma (Wilms’ tumor)
Solid Abdominal Tumors

- **Neuroblastoma**
  - Most common malignant solid abdominal tumor in children
  - Derived from neural crest tissue
    - May arise anywhere along the sympathetic ganglia
    - Most common location is adrenal medulla
  - Average age at presentation is 1-2 years
    - <1 y/o – overall survival >70%
    - >1 y/o – overall survival <35%
  - Commonly extends across midline
  - Ocular involvement may present as “raccoon eyes”
Neuroblastoma

• H&P, labs, imaging
  - LDH >1500
  - Ferritin > 142
  - CT/MRI
  - Bone scan
  - MIBG – one of the single best studies to detect metastatic disease

• Cytogenetics – N-myc
  - Rapid progression, poor prognosis

• Treatment – multimodal: surgery, chemoradiation
Solid Abdominal Tumors

- **Rhabdomyosarcoma**
  - Soft tissue malignant tumor of skeletal muscle origin
  - Accounts for 3.5% of cancer cases among children under 14 years
  - 60% 5-year survival
  - Most common primary sites – head and neck
    - Also: GU tract, GI (liver and biliary) tract
  - Most cases sporadic; however, some associated with congenital abnormality syndromes
    - Li-Fraumeni (p53), NF1, Beckwith-Wiedemann
  - Multimodal therapy – surgery, chemoradiation
    - Basic surgical principle – complete surgical resection with adequate LN sampling
Hepatoblastoma (HBL)
- Liver cancer in children is rare
- Hepatoblastomas usually occur before age 3
- Mainly unifocal and complete resection is often possible
- Seen with gene mutations in the β-catenin gene, the function of which is closely related to the development of FAP
- Also seen with Beckwith-Wiedemann syndrome
- Tumor marker is αFP
- Overall survival is 70%; Stage 1 >90%, Stage 4 20%
- Complete resection is critical, preop chemo can convert an unresectable tumor
Wilms’ Tumor

One of the great successes in oncology
Max Wilms (1867-1914). Professor of surgery in Germany, Wilms was a highly intelligent man with a huge work capacity. He made great efforts to map the pathology and development of tumour cells and after painstaking work concluded that some tumours are initiated already in the development of the embryo.

During World War I, Wilms performed an emergency cricothyroidotomy on a French prisoner of war who had laryngeal swelling due to diphtheria. Wilms acquired the disease in a severe septic form and died a few days later, aged 51 and at the peak of his career. The French officer survived.
Wilms’ Tumor

• Epidemiology
  – Second most common pediatric solid abdominal tumor, most common renal malignancy
  – Incidence of Wilms tumor is 8 cases per million children under age 15
    • About 500 new cases diagnosed per year
    • Accounts for 6% of all childhood malignant tumors
  – Ethnic variability – AA>Caucasian>Asian
  – Presents between age 1-5; most commonly age 3
    • 66% before age 5
    • 95% before age 10
Wilms’ Tumor

• Survival
  – One of the real successes of modern medicine
    • 1930s – 30% survival
    • 2010s – >90% survival
  – Multidisciplinary, multimodality approach
    • Surgery is a critical component
    • The role of the surgeon is central
    • The model for treatment of Wilms tumor has become a paradigm for successful cancer therapy
      – Research now focused on reducing toxicity, i.e. the amount of chemotherapy and radiation necessary
Clinical Presentation

- No tumor-specific symptoms
  - 1/3rd patients may have anorexia, vomiting, malaise
- Most common presentation is painless abdominal mass
- Physical Exam
  - Smooth, palpable large abdominal mass
  - May reveal HTN in 25% of patients
  - Hematuria – 30%
  - Associated congenital abnormalities – 25%
  - Check labs – associated with vonWillebrand’s Disease in up to 10% of cases
Associated Congenital Abnormalities

- **WAGR Syndrome** – Chromosome 11p13, WT1 gene
  - **Wilms’ tumor** (30%)
  - **Aniridia**
  - **Genitourinary malformations**
  - **Mental Retardation**

- **Denys-Drash Syndrome** – Chromosome 11p13, WT1 gene
  - Progressive renal disease – diffuse mesangial sclerosis -> proteinuria -> nephrotic syndrome -> ESRD
  - Male Pseudohermaphroditism
  - Wilms’ tumor (90%)

- **Beckwith-Wiedemann Syndrome** – Chromosome 11p15, WT2 gene
  - Macroglossia, hemihypertrophy, visceromegaly, omphalocele
  - Wilms’ tumor (5%)
Screening in Congenital Syndromes

• Serial renal ultrasonography has been recommended in children with aniridia, male pseudohermaphroditism, hemihypertrophy, and BWS
• Every 3-4 months until age 5
• Tumors detected by screening will generally be a lower stage
Genetics

- Wilms’ tumor was one of the original examples in Knudson’s two-hit model of cancer development.
- Tumor suppressor genes
  - WT1 – 11p13 – WAGR, DDS
  - WT2 – 11p15 – BWS
  - FWT1 and FWT2 – 11p17 and 11p19
    - Rare (1-5%)
    - Familial predisposition to Wilms’
- However, >90% of Wilms’ are sporadic mutations.
Tumorigenesis

- Wilms tumor is thought to rise from a foci of persistent metanephric cells called **nephrogenic rests**
  - These normally occur in 1% of newborn kidneys and regress in early childhood
- Multiple foci of nephrogenic rests is called **nephroblastomatosis**
  - Present in 35% of kidneys with unilateral Wilms and almost 100% of bilateral Wilms
  - Need for continued surveillance after nephrectomy
Nephrogenic Rest Histology

- **A – Intralobar**
  - Earlier presentation
  - Seen with WAGR, DDS
- **B – Perilobar**
  - Later presentation
  - Seen with BWS

<table>
<thead>
<tr>
<th>Table 130–7. Approximate Prevalence of Nephrogenic Rests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
</tr>
<tr>
<td>Infant autopsies</td>
</tr>
<tr>
<td>Renal dysplasia</td>
</tr>
<tr>
<td>Unilateral Wilms’ tumor</td>
</tr>
<tr>
<td>Synchronous bilateral Wilms’ tumor</td>
</tr>
<tr>
<td>Metachronous bilateral Wilms’ tumor</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome, hemihypertrophy</td>
</tr>
<tr>
<td>Aniridia</td>
</tr>
<tr>
<td>Drash syndrome</td>
</tr>
</tbody>
</table>
Wilms’ Tumor Histology

- Wilms’ tumor consists of three cell types
  - (a) Tubular
  - (b) Blastemal
  - (c) Stromal
- All three are present in Wilms’ tumor and considered Favorable Histology
Wilms’ Tumor Histology

- Anaplasia
  - Nuclei with diameters at least 3x those of adjacent tumor cells
  - Hyperchromasia
  - Presence of multipolar, polyploid mitotic figures

- Considered Unfavorable Histology
2-year-old with painless abdominal mass

H&P, labs, etc...
Imaging

- Abdominal ultrasonography first
  - Solid nature of the lesion, confined to kidney
- Doppler US is particularly helpful to exclude intracaval tumor extension
  - If indeterminate, MRI
Imaging

- MRI with tumor thrombus extending into IVC
Imaging

- CT Chest/Abdomen/Pelvis can further define the extent of the lesion, pulmonary metastasis
High index of suspicion of Wilms’ Tumor

Now what?
Herein lies a debate between US and Europe…
NWTSG and SIOP

• National Wilms’ Tumor Study Group
  – North American, started in 1969
  – 5 sequential NWTSG trials
  – Surgical therapy first

• International Society of Pediatric Oncology
  – European
  – Pre-operative chemoradiation therapy
    • Shrink tumor, easier resectability, less tumor spillage, less vascular complications

• Pts who receive pre-op chemo and those who have primary resection have an equal rate of complications, but more major complications occur in the primary resection group
Treatment

We’re in North America…
Let’s go to the OR first
Surgical Resection Principles

- Adequate exposure
  - Generous transverse, transperitoneal incision
- Check for peritoneal spread
- NOT necessary to examine contralateral kidney due to quality of preop imaging.
- Check for vascular extension prior to division of renal vein
  - 10% of cases have tumor involvement renal vein
  - COG recommends chemotherapy for those with extension to above the level of the hepatic veins
- During tumor resection, the ureter is ligated and divided as low as possible, but complete removal of the ureter down to the bladder is NOT necessary
- Adequate LN sampling critical despite imaging
  - FN – 31%, FP – 18%
The main responsibility of the surgeon is to:
- Remove the tumor completely, without spillage
- Accurately assess the extent to which the tumor has spread
- Pay particular attention to adequately assessing the lymph node involvement
Radical Nephrectomy
Radical Nephrectomy

Tumor spillage associated with recurrence
Role of Laparoscopy

- Laparoscopic Unilateral Nephrectomy or Partial Nephrectomy described for treatment of Wilms’tumor.
- Case reports, particularly performed in Europe where children get neoadjuvant chemotherapy.
- Currently not endorsed in US.
Surgical Complications

- Overall complication rate 13%
  - 5% bowel obstruction
  - 2% extensive intraoperative hemorrhage
  - 2% wound infection
  - 1.5% extensive vascular injury
- Factors associated with increased complications
  - advanced local stage
  - intravascular extension
  - resection of other organs
Who gets chemotherapy first in US?

- Solitary kidney
- Tumor in a horseshoe kidney
- Bilateral Wilms’ tumors
- Tumors with IVC and intra-atrial involvement
- Patients with massive tumors considered to be unresectable by operating surgeon
- Respiratory distress from extensive pulmonary metastasis
- Size of tumor alone is NOT an indication for preop chemoradiation therapy
Surgery complete, now what?

Chemo- and Radiation Therapy protocols based on tumor histology and stage.
Staging

Table 2 Wilms’ Tumor Staging System

I. Tumor limited to kidney and completely excised. The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of excision.

II. Tumor extends beyond the kidney, but is completely excised. There is regional extension of the tumor; i.e., penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopsied or there has been local spillage of tumor contained to the flank. There is no residual tumor apparent at or beyond the margins of excision.

III. Residual nonhematogenous tumor confined to abdomen. Any one or more of the following occur:
1. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond.
2. There has been diffuse peritoneal contamination by tumor such as by spillage of tumor beyond the flank before or during surgery, or by tumor growth that has penetrated through the peritoneal surface.
3. Implants are found on the peritoneal surfaces.
4. The tumor extends beyond the surgical margins either microscopically or grossly.
5. The tumor is not completely resectable because of local infiltration into vital structures.

IV. Hematogenous metastases. Deposits beyond Stage III; i.e., lung, liver, bone, and brain.

V. Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy.
## Table 3: Risk Stratification and Treatment Study Assignment for patients with favorable histology Wilms’ tumor

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Tumor weight</th>
<th>Stage</th>
<th>LOH</th>
<th>Rapid response</th>
<th>Final risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>&lt;550 g</td>
<td>I</td>
<td>Any</td>
<td>N/A</td>
<td>Very low</td>
</tr>
<tr>
<td>Any</td>
<td>≥550 g</td>
<td>I</td>
<td>None</td>
<td>N/A</td>
<td>Low</td>
</tr>
<tr>
<td>≥2 years</td>
<td>Any</td>
<td>I</td>
<td>None</td>
<td>N/A</td>
<td>Low</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>II</td>
<td>None</td>
<td>N/A</td>
<td>Low</td>
</tr>
<tr>
<td>≥2 years</td>
<td>Any</td>
<td>I</td>
<td>LOH</td>
<td>N/A</td>
<td>Standard</td>
</tr>
<tr>
<td>Any</td>
<td>≥550 g</td>
<td>I</td>
<td>LOH</td>
<td>N/A</td>
<td>Standard</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>II</td>
<td>LOH</td>
<td>N/A</td>
<td>Standard</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>III</td>
<td>None</td>
<td>Any</td>
<td>Higher</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>III</td>
<td>LOH</td>
<td>Any</td>
<td>Higher</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>IV</td>
<td>LOH</td>
<td>Any</td>
<td>Higher</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>IV</td>
<td>None</td>
<td>Yes</td>
<td>Standard</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>IV</td>
<td>None</td>
<td>No</td>
<td>Higher</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>V</td>
<td>Any</td>
<td>Any</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>
Wilms' tumor

AREN03B2 Classification study (Central review)

Favorable histology
AREN0532
1. Very low risk
2. Standard risk
AREN0533
1. Higher risk
2. Standard risk
AREN03B2
1. Low risk

Anaplastic
AREN0321
1. High risk

Bilateral
AREN0534

Patients being treated for low-risk disease (Stages I–II, favorable histology, without 1p and 16q LOH) are treated with regimen EE-4A and are followed on AREN03B2.
Figure 2: Treatment outline for patients with favorable histology Wilms' tumor on AREN0532: treatment for very low and standard risk favorable histology Wilms' tumor

- **AREN0532**
  - **Stage I+II**
    - **Stage I**
      - <2 yr
      - <550g
    - **Stage I+II**
      - No LOH
      - 1p and 16q
    - **Stage I+II**
      - LOH 1p and 16q
    - **Low risk**
      - Off Protocol
      - Follow on AREN03B2
      - EE-4A
      - No XRT
    - **Standard risk**
      - DD-4A
      - No XRT
  - **Stage III**
    - **No LOH**
      - 1p and 16q
    - **LOH**
      - 1p and 16q
    - **Standard risk**
      - DD-4A + XRT
    - **High risk**
      - Switch to AREN0533

- **Very low risk**
  - Nephrectomy and observation
Figure 3  Treatment for patients enrolled on AREN0533: treatment of newly diagnosed higher risk favorable histology Wilms’ tumor

Stage IV FH Wilms' tumor

- 2-drug chemotherapy (VCR, AMD, DOXO)
  - Per DD4A for 2 cycles

Week 6 evaluation

Stage III FH (found to have LOH 1p and 16q, transferring from AREN0532)

Stage IV pulmonary lesions only 'rapid complete responders (RCR)'
- No LOH

Stage IV or IV patients with LOH of both 1p and 16q
- Stage IV pulmonary lesions only 'slow incomplete responders (SIR)'
- Stage IV patients with metastases other than lung or in combination with lung

Complete regimen DD4A
- without pulmonary XRT
- with abdominal XRT for local (abdominal) Stage III patients
- with XRT to non-lung metastases

Change regimen M
- with whole lung XRT for Stage IV pulmonary lesions only (no LOH) 'slow responders’ (SIR)
- with whole lung XRT for patients with LOH and lung lesions, regardless of pulmonary nodule response to therapy.
- with abdominal XRT for all local (abdominal) Stage III patients
- with XRT to non-lung metastases
### Table 4. Treatment regimens used in NWTS-5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Radiotherapy</th>
<th>Chemotherapy regimen</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II</td>
<td>Favourable</td>
<td>No</td>
<td>EE4A</td>
<td>18</td>
</tr>
<tr>
<td>I</td>
<td>Anaplastic</td>
<td>No</td>
<td>EE4A</td>
<td>18</td>
</tr>
<tr>
<td>III–IV</td>
<td>Favourable</td>
<td>Yes</td>
<td>DD4A</td>
<td>24</td>
</tr>
<tr>
<td>II–IV</td>
<td>Focal anaplasia</td>
<td>Yes</td>
<td>DD4A</td>
<td>24</td>
</tr>
<tr>
<td>II–IV</td>
<td>Anaplastic</td>
<td>Yes</td>
<td>I</td>
<td>24</td>
</tr>
<tr>
<td>I–IV</td>
<td>CCSK</td>
<td>Yes</td>
<td>I</td>
<td>24</td>
</tr>
<tr>
<td>I–IV</td>
<td>RTK</td>
<td>Yes</td>
<td>RTK</td>
<td>24</td>
</tr>
</tbody>
</table>

CCSK = clear-cell sarcoma of the kidney; RTK = rhabdoid tumour of the kidney. EE4A = vincristine plus pulse-intensive dactinomycin; DD4A = vincristine plus pulse-intensive dactinomycin and doxorubicin; I = vincristine, doxorubicin, cyclophosphamide, and etoposide; RTK = carboplatin, etoposide, and cyclophosphamide.
Stage V Disease

Bilateral Wilms’ Tumor
Stage 5 disease – Bilateral Wilms’

- Delayed resection to preserve renal parenchyma
- Biopsy first
- Primary therapy with triple agent chemotherapy x 6 weeks
- Re-image with CT/MRI after 6 weeks.
- If feasible, bilateral partial nephrectomy at week 6.
- If partial nephrectomy not feasible, how much reduction in tumor?
  - >50% - 6 more weeks chemotherapy, then bilateral partial nephrectomy
  - <50% - bilateral open biopsies at week 6
Bilateral Wilms’ Tumor

• Bilateral nephrectomy and dialysis may rarely be required when the tumor fails to respond to chemotherapy and radiation therapy

• The recommended interval between successful treatment of Wilms’ tumor and renal transplant varies.
  – 1-2 years to ensure metastatic disease does not develop
### Survival Outcomes

<table>
<thead>
<tr>
<th>Histology</th>
<th>Stage</th>
<th>10-year RFS (%)</th>
<th>10-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>I</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>65</td>
<td>78</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>I</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>II–III</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

OS, overall survival; RFS, relapse-free survival.
### Table 130-8. Recommended Follow-up Imaging Studies for Children with Renal Neoplasms of Proven Histology Who Are Free of Metastases at Diagnosis

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Study</th>
<th>Schedule after Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable-histology Wilms’ tumor</td>
<td>Chest films</td>
<td>6 wk and 3 mo postop, then q3mo ×5, q6mo ×3, yearly ×2</td>
</tr>
<tr>
<td>Stage I anaplastic Wilms’ tumor</td>
<td>Irradiated bony structures*</td>
<td>Yearly to full growth, then q5yr indefinitely†</td>
</tr>
<tr>
<td>Irradiated patients only</td>
<td>Abdominal ultrasound</td>
<td>Yearly ×3</td>
</tr>
<tr>
<td>Without NRs, stages I and II</td>
<td>Abdominal ultrasound</td>
<td>As for chest films</td>
</tr>
<tr>
<td>Without NRs, stage III</td>
<td>Abdominal ultrasound</td>
<td>q3mo ×10, q6mo ×5, yearly ×5</td>
</tr>
<tr>
<td>With NRs, any stage‡</td>
<td>Abdominal ultrasound</td>
<td>As for favorable histology</td>
</tr>
<tr>
<td>Stage II and III anaplastic</td>
<td>Chest films</td>
<td>q3mo ×4, q6mo ×4</td>
</tr>
<tr>
<td></td>
<td>Abdominal ultrasound</td>
<td></td>
</tr>
</tbody>
</table>
Recurrent Wilms’ Tumor

• The historical long-term survival for recurrent Wilms’ tumor is <30%
• The addition of cyclophosphamide, ifosfamide, carboplatin, etoposide has improved survival to 50-60%
• Favorable prognostic factors:
  – Initial stage I or II
  – Treatment with vincristine and dactinomycin only
  – No previous radiotherapy
  – Favorable histology
  – Relapse >6 months after initial diagnosis
• New frontier – high dose chemotherapy followed by autologous bone-marrow stem cell rescue
Future Goals

• 90% cure rate, 75% do not require radiotherapy or doxorubicin therapy
  – Defining further subsets of pts to lower toxicity of treatment
• Novel strategies for patients with high-risk, anaplastic disease
• Future clinical trials to define genetic markers to provide therapeutic targets
Questions?
References

- **Textbooks:**
  - Sabiston Textbook of Surgery, 18th Ed., *Childhood Solid Tumors*, pg 2080-2086
  - Campbell-Walsh Urology, 9th Ed., *Pediatric Urologic Oncology*, pg 3870-3899

- **Primary Literature**