ARROCase: Wilms Tumor

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Clinical Presentation

- 3 year old boy with normal developmental/birth history and no past medical history.
- Presentation:
  - Overall malaise, emesis x 1, diarrhea, low grade fever and colicky abdominal pain x 3 days.
  - Normal activity, appetite, energy
- Physical examination:
  - Awake, alert, oriented and interactive.
  - Pulm: lungs clear to auscultation bilaterally.
  - CV: RRR, no murmurs, gallops, or rubs
  - Abd: soft, nontender. Large palpable mass in the RUQ and RLQ ~7 cm in dimension. No splenomegaly noted. No abdominal ascites.
  - Neuro: CN II-XII grossly normal with normal tone, strength, and gait

- NOTE: Described clinical Syndromes:
  - **WAGR**: Wilms, Aniridia, GU abnormalities, Retardation; WT1 deletion on 11p13, 30% risk of developing Wilms.
  - **Denys Drash syndrome**: WT1 missense mutation; 90% risk of developing Wilms
  - **Beckwith-Wiedemann syndrome**: Hemi hypertrophy, macroglossia, GU abnormalities, abdominal wall defects; WT2 gene, 11p15; 5-10% risk of developing Wilms
Work Up

- **Abdominal Ultrasound**
  - Poorly defined complex heterogeneous mass occupying the right renal bed measuring 6 x 8 x 11 cm. Left kidney is unremarkable.

- **CT c/a/p**
  - Large, heterogeneous mass lesion involving near entire right kidney with complex cystic and solid component. Renal artery, renal vein, and IVC are patent with no evidence of thrombus. There are multiple retroperitoneal and aortocaval lymph nodes with the largest measuring 11 mm in short axis.

- **Labs:**
  - CBC – slightly anemic with hemoglobin at 10.3, otherwise within normal limits.
  - CMP, magnesium, phosphate – within normal limits

- **UA**
  - Within normal limits.

- **Other work up considerations (once pathology is available):**
  - For rhabdoid – brain MRI
  - For clear cell – bone scan and brain MRI
CT findings as described
Treatment Decision Point

• Patient admitted to pediatric oncology. Surgical oncology and radiation oncology consulted.

• Treatment plan:
  – No biopsy as imaging is suggestive for Wilms.
    • NOTE: biopsy of un-ruptured tumor automatically upgrades to stage III and post operative radiation is recommended due to concern of intraperitoneal tumor seeding.
  – Nephrectomy with lymph node dissection planned.

• Review operative report and/or discuss with surgeon regarding evidence of peritoneal implants, tumor rupture, other abnormal findings or difficulties with resection.
Pathology Review

• Intraoperative/Gross:

• Pathology review:
  – Wilms tumor (nephroblastoma) with diffuse anaplasia
  – Tumor with capsule in tact (ie: no evidence of rupture)
  – 3/31 lymph nodes involved noted to be from the right hilum of the kidney without ECE.
  – Margins negative (closest margin posterior, 5 mm).
  – Cytology of peritoneal washing negative for malignant cells.
Example of three classic components of nephroblastoma:

- → = blastemal,
- ← = epithelial, and
- → = stromal
Pathology Review

Example of anaplasia, if found in several samples of the tumor = diffuse anaplasia

Normal lymph node background with small focus of Wilms tumor cells
## Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Limited to the kidney and completely excised without tumor rupture.</td>
</tr>
<tr>
<td>II</td>
<td>Extends beyond kidney but is completely excised without tumor rupture.</td>
</tr>
<tr>
<td>III</td>
<td>Residual gross disease confined to the abdomen, positive lymph nodes, positive margins, peritoneal implants, spillage of tumor, or <em>initial biopsy</em></td>
</tr>
<tr>
<td>IV</td>
<td>Hematogenous metastatic disease (lung, liver, brain, bone) or distant metastatic lymph nodes.</td>
</tr>
<tr>
<td>V</td>
<td>Bilateral renal involvement at diagnosis.</td>
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</tbody>
</table>
Other criteria to consider

- Anaplasia is an aggressive pathological feature.
- LOH 1p 16q is predictive for increased risk of relapse.
- Other unfavorable histologies such as clear cell and rhabdoid of the kidney were included in National Wilms Tumor Study group trials.
- Patient should start adjuvant radiation **NO LATER than 9 days** from surgery date. Coordination of care is crucial.
Treatment Decision Point

- Decisions regarding adjuvant radiation depends upon:
  - Tumor rupture
  - Lymph node involvement
  - Presence of unfavorable histology (diffuse anaplasia, clear cell, rhabdoid)
  - Positive margins/gross residual disease/metastatic disease
  - LOH of 1p and 16q (for consideration of whole lung)

- Final recommendation: treat flank only, dose prescribed to **19.8 Gy** due to evidence of diffuse anaplasia without tumor rupture.
  - NOTE: If diffuse anaplasia was not present, the dose would be reduced to **10.8 Gy** (see table in subsequent slides). If presence of tumor rupture, fields would include whole abdomen.
Radiation Planning (3D)

• Patient supine, in mold for reproducibility.
  – Special attention to removal of undergarments at pelvis (for simulation and treatments) and alignment of spine and pelvis as straight as possible.

• General anesthesia for planning CT and daily treatments due to patient age, though dependent upon clinical judgment.

• Contours*:
  – GTV – recapitulate location of tumor. This contour will now extend into liver or spleen and bowel that was displaced preoperatively.
  – CTV – Expansion of 1 cm three-dimensionally.
  – PTV – Institutional preference and physician comfort with reproducibility of set up. The general range from 0.5 cm to 1.5 cm.

• OAR:
  – Contralateral kidney
  – Femoral heads
  – Heart
  – Lung
  – Spinal Cord

*Adapted from AREN0532
Flank only – 3D field design

- **AP:PA field arrangement**
- **Medial border:**
  1 cm beyond vertebral body on the contralateral side
- **Lateral border:**
  1 cm beyond PTV
- **Superior border:**
  1 cm beyond PTV border, or diaphragmatic crus (due to + LN)
  Block Heart on left side
- **Inferior border:**
  1 cm beyond PTV border ensuring coverage of region lymphatics if applicable
- **MLCs drawn at vertebral body interspaces to limit bone growth abnormalities.**

Adapted from AREN0532

PTV – blue, left kidney – yellow, diaphragmatic crus – green
Radiation Planning (3D)

GTV – red, CTV – green (1 cm expansion, contours adjusted off of bone/anatomic barriers),
PTV – blue (0.5 cm expansion)
20.5 Gy = 104% of prescription dose, 18.8 = 95% of prescription dose.  
Note lateral edges of PTV, often difficult to accomplish 100% dose coverage due to pediatric body habitus and minimal dose build up. 95% covers entire PTV.
Radiation Planning

• Prescription:
  – Flank PTV prescribed to 19.8 Gy in 1.8 per fraction using 6 MV photons.

• PTV coverage goals:
  – 100% of PTV receives ≥ 95% of prescription dose.
  – The maximum dose is ≤ 107% of prescription dose.
Radiation Planning

Dose Volume Histogram

- PTV
- cord
- liver
- L. kidney
- heart

Normalized Volume

Dose (Gy)
Whole Abdomen – 3D field design for comparison

- AP:PA field arrangement
- Lateral border: 1 cm beyond body contour
- Superior border: 1 cm beyond top of diaphragm
- Block Heart as feasible
- Inferior border: Beyond 1 cm beyond obturator foramen
- Draw peritoneal reflection to guide femur block

PTV—blue, right kidney—yellow, Top of diaphragm—green, Heart—pink
Whole Abdomen DVH

Dose Volume Histogram

- Cord
- Acetabuli
- Heart
- Femurs

- Right kidney – yellow,
- PTV and surgical bed – red
Side Effects of Treatment

• **Acute:**
  - Loose stools
  - Nausea – provide prophylactic anti-emetics
  - Fatigue

• **Long term:**
  - Bowel adhesions
  - Infertility (females > males)
    • Greater in females treated with whole abdomen with both ovaries and uterus in the field.
  - Scoliosis/vertebral body foreshortening
  - Hypertension
    • Secondary to fibrosis of contralateral renal artery
  - Renal failure (low incidence if treating flank)
  - CHF – risk is ~4% in patients receiving adriamycin\(^1\)
  - Liver failure (chemotherapy associated)
  - \(2^{nd}\) malignancy (1.6% cumulative risk)

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\(^{1}\) Review of National Wilms Tumor Studies (NWTS) 1-4
<table>
<thead>
<tr>
<th>Stage</th>
<th>Radiation Treatment</th>
</tr>
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<tbody>
<tr>
<td>Stage I-II, FH</td>
<td>• NONE</td>
</tr>
<tr>
<td>Stage III, FH</td>
<td>• 10.8 to the flank</td>
</tr>
<tr>
<td>Stage I-III, focal anaplasia</td>
<td>• 19.8 if patient is &gt; 16 yr.</td>
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<tr>
<td>Stage I-III, DA, CC</td>
<td>• 19.8 Gy to the flank</td>
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<tr>
<td>Stage I-III, Rb</td>
<td>• 10.8 Gy to the flank if patient is &lt; 12 mo.</td>
</tr>
<tr>
<td>Stage III by virtue of tumor rupture or peritoneal mets.</td>
<td>• 10.5 Gy to whole abdomen if preop tumor rupture</td>
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<td></td>
<td>• 21 Gy to whole abdomen if diffuse peritoneal mets noted at the time of surgery.</td>
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<tr>
<td>Recurrent abdominal disease</td>
<td>• 12.6-18 Gy if &lt; 12 mo.</td>
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<tr>
<td></td>
<td>21.6 Gy if prior dose was &lt; 10.8 Gy</td>
</tr>
<tr>
<td></td>
<td>*Boost of up to 9 Gy to gross residual disease after surgery</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>• 12 Gy to whole lung</td>
</tr>
<tr>
<td></td>
<td>10.5 Gy if &lt; 12 mo.</td>
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<tr>
<td></td>
<td>*NOTE: only treat infant if persistent mets at week 6 of induction chemotherapy</td>
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<tr>
<td>Brain metastases</td>
<td>• 21.6 Gy to whole brain + 10.8 Gy IMRT/stereo boost</td>
</tr>
<tr>
<td></td>
<td>30.6 Gy to whole brain if patient is &gt; 16 yr.</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>• 19.8 Gy to whole liver</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>• 25.2 Gy to the lesion + 3 cm margin</td>
</tr>
<tr>
<td></td>
<td>30.6 Gy if patient is &gt; 16 yr.</td>
</tr>
<tr>
<td>Unresected lymph node metastases</td>
<td>• 19.8 Gy</td>
</tr>
</tbody>
</table>

FH – favorable histology, DA – diffuse anaplasia, CC – clear cell, Rb – rhabdoid, LOH – loss of heterozygosity for 1p 16q

Adapted from Perez and Brady's 6th Edition
NWTS vs SIOP approach

• NWTS (National Wilms Tumor Study Group)/ US approach:
  – Primary surgery
    • Confirms pathological diagnosis
    • Adjuvant treatment based on surgical staging
    • Additional prognostic implication of surgical pathology

• SIOP (International Society of Paediatric Oncology)/ European approach:
  – Pre-operative chemotherapy approach
    • Reduced spillage
    • Tumor downstaging and improved surgical resectability
    • Potentially avoids or reduces intensity of adjuvant therapy

• UK Children’s Cancer Study Group, UKW3 randomized trial: Immediate nephrectomy vs Preoperative Chemotherapy
  – Improved stage distribution with preop. Approach
  – 20% reduced use of radiotherapy or doxorubicin
  – Similar event-free and overall survival

NWTS studies

- **NWTS 1 (1969-74):**
  - Post-operative RT not needed for stage I kids < 2 years age treated with AMD, but needed for older kids
  - Combined AMD and VCR better than either drug alone in stage II/III

- **NWTS 2 (1974-78):**
  - ADR and VCR x 6 months may suffice for older stage I kids, thereby avoiding RT
  - Adriamycin needed for stage II or more

- **NWTS 3 (1979-85):**
  - 10 weeks AMD + VCR is sufficient (not 6 months) in stage I, Favorable histol. (FH)
  - No RT needed for stage II, FH
  - 10 Gy equivalent to 20 Gy for stage III, FH

- **NWTS 4 (1986-94):**
  - No RT randomizations in the study
  - Single dose pulse intensive chemotherapy reduces hematological toxicity and costs (compared to standard course 5 day course)

- **NWTS 5 (1995-2002):**
  - Identified LoH 16 q and 1p as negative prognostic factor
  - Addition of etoposide improved outcomes in stage II or more
AREN 0532 Protocol

- Treatment of very low and standard risk favorable histology Wilms tumor.
- AREN 0533 is reserved for stage IV patients with favorable histology and pulmonary metastases with CR of pulmonary lesions. These patients avoid lung XRT and are treated with DD4A.
- NOTE DD4A chemotherapy: vincristine, dactinomycin, and doxorubicin hydrochloride.
References

• Additional NWTS studies: