MANAGEMENT OF WILMS TUMOUR-ROLE OF RADIOTHERAPY

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20th ICRO PG TEACHING COURSE, HYDERABAD, 18-19th JULY 2015
EPIDEMIOLOGY

Wilms tumour (nephroblastoma)-embryonic kidney tumor

Most common abdominal tumour in children- 6% of childhood cancer

Incidence rate in children younger than 15 years is 7 per million population


470 to 500 new cases in the US per year

>75% patients present before 5 years of age

Children present with more advanced disease in less developed nations
<table>
<thead>
<tr>
<th>Function</th>
<th>Locus</th>
<th>Syndromic association</th>
<th>Frequency of genetic aberration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour suppressor gene Role in glomerular &amp; gonadal development</td>
<td>11p13</td>
<td>WAGR (WT, aniridia, genito-urinary malformation, mental retardation) Denys-Drash syndrome (pseudohermaphroditism, mesangial sclerosis, renal failure, WT)</td>
<td>Germline mutation: 82% in pts with renal failure/ GU anomalies 10-20% of sporadic WT 4% of familial WT</td>
</tr>
<tr>
<td>Effect on IGF2, the H19 tumor suppressor gene, and the P57 cell cycle regulator</td>
<td>11p15.5</td>
<td>Beckwith-Wiedemann syndrome (somatic gigantism, omphalocele, macroglossia, genitourinary abnormalities, ear creases, hypoglycemia, hemihypertrophy)</td>
<td>LOH 11p15.5 in<del>30%  Loss of imprinting on IGF2 in</del> 40% of sporadic WT</td>
</tr>
<tr>
<td>Tumour suppressor gene</td>
<td>Xq11.1</td>
<td>-</td>
<td>WTX inactivation in~ 50% of sporadic WT</td>
</tr>
<tr>
<td>1 Encodes β-catenin Role in WNT pathway</td>
<td>3p21</td>
<td>-</td>
<td>Gain of function mutation in~ 10% of sporadic WT</td>
</tr>
</tbody>
</table>
Abdominal mass (80-90%)  
Abdominal pain (30-40%)  
Haematuria (20-25%)  
Fever (20-25%)  
Hypertension  
Varicocele  
Metastatic symptoms-rare
DIAGNOSTIC WORK-UP

Record pre-existing conditions, family history of cancer, or congenital defects
Blood pressure, weight, height, presence of abdominal masses, congenital anomalies particularly genitourinary, hemihypertrophy, and aniridia
Hemoglobin, white cell, and differential counts, platelets, urinalysis, serum blood urea nitrogen, creatinine, protein, alanine, and aspartate aminotransferases, alkaline phosphatase, bilirubin
CT or MRI scan of the abdomen and pelvis, abdominal ultrasonography, chest CT scan, chest x-ray
Bone scan and MRI of the brain (CCSK, RTK, and renal cell carcinoma)
STAGING

Stage I: Residual nonhematogenous tumor present following surgery and confined to abdomen. Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are involved by tumor.
- Lymph node involvement in the thorax or other extra-abdominal sites is a criterion for stage IV.
- The tumor has penetrated through the peritoneal surface.
- Tumor implants are found on the peritoneal surface.
- Gross or microscopic tumor remains postoperatively (e.g., tumor found at the margin of surgical resection on microscopic examination).
- The tumor is not completely resectable because of local infiltration of vital structures.
- Tumor spillage occurring either before or during surgery.
- The tumor was biopsied (whether true-cut, open, or fine-needle aspiration) before removal.
- Tumor is removed in more than one piece (e.g., tumor cells are left in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).

Stage II: Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. Note: For a tumor to qualify for certain therapeutic protocols as stage I, regional lymph nodes must be examined microscopically.
The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria:
- There is regional extension of the tumor (i.e., penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus).
- Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.

Stage III: Hematogenous metastases (i.e., lung, liver, bone, brain) or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present.)

Stage IV: Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the criteria here on the basis of the extent of disease.
PATHOLOGY

- Soft, homogeneous, tan to grey in colour with occasional foci of haemorrhage & necrosis
- Well circumscribed margin
- Enclosed by renal capsule/fibrous pseudo-capsule
- Bilateral-7% & multifocal -12% of cases
- Tumor can contain a mixture of cells:
  - blastemal cells
  - stromal cells
  - epithelial cells
- High degree of anaplasia associated with poor outcomes
(A) WT with tightly packed blue cells consistent with blastemal component & interspersed primitive tubules, representing the epithelial component. Although multiple mitotic figures are seen, none are atypical in this field; (B) Focal anaplasia present in other areas characterised by cells with hyperchromatic, pleomorphic nuclei & abnormal mitoses
TREATMENT OPTIONS: NWTS VERSUS SIOP

NWTS
Treatment principle: Nephrectomy → adjuvant chemo ± RT
Advantages: Avoidance of
- Administration of chemo to a patient with benign disease
- Administration of chemo to a patient with a different histological type of malignant tumour
- Modification of tumour histology
- Loss of staging information

SIOP
- Treatment Principle: Pre-op chemo → Nephrectomy → adjuvant chemo ± RT
- Advantages:
  - Tumour downsizing thereby making surgery simpler and ↓ing intra-op tumor rupture & intra-abd recurrence
  - Makes nephron sparing surgery possible
Intra-op tumour spillage in NWTS protocol

Tumour downsizing with pre-op chemo in SIOP protocol
### NWTS 1-4 SCHEMA

<table>
<thead>
<tr>
<th>NWTSG study</th>
<th>Disease stage</th>
<th>Treatment protocols&lt;sup&gt;b&lt;/sup&gt;</th>
<th>RT</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>RT vs no RT</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II, III</td>
<td>RT</td>
<td>A vs V vs A + V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>RT</td>
<td>A + V</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>no RT</td>
<td>A + V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II, III, IV</td>
<td>RT</td>
<td>A + V vs A + V + D</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>no RT</td>
<td>A + V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>no RT vs 20 Gy</td>
<td>A + V vs A + V + D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>10 Gy vs 20 Gy</td>
<td>A + V vs A + V + D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>RT</td>
<td>A + V + D vs A + V + D + C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>no RT</td>
<td>A + V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>no RT</td>
<td>A + V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III, IV</td>
<td>RT</td>
<td>A + V + D</td>
<td></td>
</tr>
</tbody>
</table>

- Is post-op RT necessary in group I disease?

- Is single agent chemo with vincristine (VCR) or actinomycin D (AMD) equivalent to combining these drugs for group II and III disease?

- Is preoperative VCR of value in group IV disease?

- Radiation doses adjusted for age
  - Birth – 18 mo: 18 to 24 Gy
  - 18 – 30 mo: 24 to 30 Gy
  - 31- 40 mo: 30 to 35 Gy
  - 41 mo or older: 35 – 40 Gy

NWTS-1 RESULTS

Post-op RT not needed for group I <2 yrs

VA better than either agent alone for group II and III

Pre-op VCR not useful in group IV

4 yr RFS for group I pts >2 yrs treated with AMD +RT- 76%

4 yr RFS for group II/III pts treated with VA + RT- 79%
NWTS-1 RESULTS

2-year RFS:
- Favorable histology- 89%
- Unfavorable histology- 29%

Poor prognostic factors
- Large tumor size
- Lymph node involvement
- Age >2 years

No RT dose response between 10-40 Gy

Delays of ≤ 10 days for post-op RT found acceptable

WAI not necessary for tumor spills confined to the flank
Can VA substitute for RT in older children with Group I disease?

Is protracted period of adjuvant VA helpful for Groups II – IV disease?

Is addition of Doxo to VA of value in Groups II – IV disease?

NWTS-2 RESULTS

VA can substitute for RT in Group I disease

VA x 6 months = VA x 15 months for Group I disease

Addition of Doxo to VA+RT for Group II-IV disease provided benefit

Worse 2-year survival for LN + disease (54% vs 82%) and patients with unfavorable histology (54% vs 90%)
NWTS-3 (1979-85)

Patients stratified by stage instead of group
FH & UH incorporated in the treatment algorithm

Five questions

- Can duration of chemotherapy be shortened for Stage I FH?
- Can RT be eliminated for Stage II FH?
- What is the minimum effective RT dose for Stage III FH?
- Is Doxo clearly beneficial and necessary for Stage II & III FH?
- Will addition of CTX improve survival in Stage I – IV UH and Stage IV FH?

NWTS-3

- Stage I FH: VA (no RT) 24 vs 10 weeks
- Stage II FH: 3 vs. 2 drugs (VA±D) ± RT 20 Gy
- Stage III FH: 3 vs. 2 drugs (VA±D) + RT 10 vs. 20 Gy
- Stage IV FH and all UH: RT + 3 drugs ± CTX
NWTS-3 RESULTS

Stage I: VA x 10 wks vs. VA x 24 wks equivalent
  • 4-year RFS 89% & OS 96%

Stage II: no difference between 2 or 3 drugs with or without RT
  • 4-year RFS 87% & OS 91%

Stage III: No stat sig difference in abdominal relapse between 10 and 20 Gy of RT; trend favored use of Doxo or 20 Gy of RT
  • 4-year RFS 82% & OS 91%
NWTS-3 RESULTS

Stage IV FH: 4 drugs equal to 3 drugs (both included flank RT/WAI + WLI)
  • 4-year RFS 79% & OS 80%

Anaplasia
  ➢ 4 drugs better than 3 drugs for stage II-IV
  ➢ Trend toward improved outcome with 4 drug regimen for CCSK
  ➢ 4 yr OS -25% for RTK in both arms

Addressed issues of minimization of therapy and customization by stage & histology

Evaluate the role of pulse dosed intensive chemotherapy

NWTS-4 SCHEMA

FIG. 6. NWTS-4 simplified schema. Stage IV anaplastic tumors continued the randomization as per NWTS-3. (From ref. 59, with permission.)
NWTS-4 RESULTS

Pulse-intensive chemotherapy feasible, produce less hematologic toxicity and allow for increased drug dose-intensity

Cost analysis showed savings of $790,000 a year in the US if all Wilms' patients were treated on pulse-intensive regimens
# NWTS-5 SCHEMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>FH</th>
<th>ANAPLASTIC (UH)</th>
<th>CCSK</th>
<th>RTK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Focal</td>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>(VA&lt;sub&gt;pi&lt;/sub&gt;)&lt;sub&gt;18wk&lt;/sub&gt; No XRT</td>
<td>(VA&lt;sub&gt;pi&lt;/sub&gt;)&lt;sub&gt;18wk&lt;/sub&gt; No XRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>(VA&lt;sub&gt;pi&lt;/sub&gt;)&lt;sub&gt;18wk&lt;/sub&gt; No XRT</td>
<td>(VAD)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(VD, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(Carbo, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
</tr>
<tr>
<td>III</td>
<td>(VAD)&lt;sub&gt;24wk&lt;/sub&gt; 10.8 Gy flank&lt;sup&gt;a&lt;/sup&gt; 10.8 Gy boost&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(VAD)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(VD, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(Carbo, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>(VAD)&lt;sub&gt;24wk&lt;/sub&gt; 10.8 Gy flank&lt;sup&gt;a&lt;/sup&gt; 10.8 Gy boost&lt;sup&gt;b&lt;/sup&gt; 12 Gy lungs&lt;sup&gt;c&lt;/sup&gt; 19.8 Gy liver 30.6 Gy brain 30.6 Gy bone</td>
<td>(VAD)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(VD, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
<td>(Carbo, VP-16, CY)&lt;sub&gt;24wk&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Focal</td>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.8 Gy flank&lt;sup&gt;a&lt;/sup&gt; 10.8 Gy boost&lt;sup&gt;b&lt;/sup&gt; 12 Gy lungs&lt;sup&gt;c&lt;/sup&gt; 19.8 Gy liver 30.6 Gy brain 30.6 Gy bone</td>
<td></td>
</tr>
<tr>
<td>Relapsed WT</td>
<td>12.6-18 Gy (&lt;12 mo of age) and 21.6 Gy in older children if previous XRT is &lt;= 10.8 Gy 9 Gy boost to residual s/p surgery 30.6 Gy max dose (&lt;1 y of age) and 39.5 Gy max dose in older children</td>
<td></td>
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</tr>
</tbody>
</table>

FH = Favorable Histology, UH = Unfavorable Histology, V = Vincristine, A = Actinomycin-D, D = Doxorubicin, VP-16 = etoposide, CY = cyclophosphamide, Carbo = carboplatin, PI = pulse intensive, wk = weeks

*Whole-abdomen XRT for diffuse peritoneal implants, preoperative anterior rupture or diffuse abdominal operative spillage
*Boost to gross (>3cm) disease residual after surgery
*In patients with FH disease, if pulmonary nodules are visible on CT scans but are not detected on chest x-ray, then whole-lung irradiation is not mandatory

LOH 1p associated with significantly worse RFS in Stage II but not Stage III/IV

Suggests that adverse effects of LOH 1p can be overcome by more aggressive chemotherapy

NWTS-5 SELECTED RESULTS - FH

Stage I FH: 4 y RFS 92% & OS 98%

Stage II FH: 4 y RFS 83% & OS 92%

Stage III FH: 4 y RFS 85.3% & OS 93.9%

Stage IV FH: 4 y EFS 74.6% (most of these patients ↓WLI)
NWTS-5 SELECTED RESULTS UH

Diffuse Anaplasia: 2 yr EFS-
- Stage I - 64.3%
- Stage II - 79.5%
- Stage III - 62.7%
- Stage IV - 33.6%

CCSK: 4 yr RFS-
- Stage I –IV - 77.6%
- 6/9 Stage IV pts relapsed

• RTK
  - Stage I - 50%
  - Stage II - 33.3%
  - Stage III - 33.3%
  - Stage IV - 21.4%
  - Stage V - 0%
## NWTS Treatment Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I FH/UH</td>
<td>VA x 18 wks</td>
</tr>
<tr>
<td>Stage II FH</td>
<td>VA x 18 wks</td>
</tr>
<tr>
<td>Stage III + IV FH</td>
<td>VAD x 24 wks; RT to tumour bed ± metastatic site</td>
</tr>
<tr>
<td>Stage II-IV UH</td>
<td>V, A, CTX, VP-16 x 24 wks; RT to tumour bed ± metastatic site</td>
</tr>
</tbody>
</table>
CURRENT PROTOCOLS

AREN 0532
• FH Stage I through FH Stage III Standard Risk
AREN 0533 & AREN 0321

AREN 0533
- FH Stage III High Risk
- FH Stage IV

AREN 0321
- UH Wilms’
- CCSK
- RTK
- RCC
**AREN 0533**

- **Stage IV FH Wilms Tumor**
  - 3 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 III 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
### COG RISK STRATIFICATION

<table>
<thead>
<tr>
<th>Tumor Weight</th>
<th>Stage</th>
<th>LOH</th>
<th>Rapid Response</th>
<th>Risk Group</th>
<th>COG Study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;550 g</td>
<td>I</td>
<td>Any</td>
<td>N/A</td>
<td>Very Low</td>
<td>AREN0532</td>
<td>Surgery</td>
</tr>
<tr>
<td>≥550 g</td>
<td>I</td>
<td>None</td>
<td>N/A</td>
<td>Low</td>
<td>AREN0532</td>
<td>EE4A</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>None</td>
<td>N/A</td>
<td>Low</td>
<td>AREN0532</td>
<td>EE4A</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Yes</td>
<td>N/A</td>
<td>Standard</td>
<td>AREN0532</td>
<td>DD4A</td>
</tr>
<tr>
<td>≥550 g</td>
<td>I</td>
<td>Yes</td>
<td>N/A</td>
<td>Standard</td>
<td>AREN0532</td>
<td>DD4A</td>
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<td>None</td>
<td>Any</td>
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<td>AREN0532</td>
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<td>III</td>
<td>Yes</td>
<td>Any</td>
<td>Higher</td>
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<td>M</td>
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<td>Higher</td>
<td>AREN0533</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>None</td>
<td>Yes</td>
<td>Standard</td>
<td>AREN0533</td>
<td>DD4A</td>
</tr>
</tbody>
</table>

- Loss of heterozygosity at both 1p and 16q; N/A, not applicable; DD4A (V [vincristine] A [dactinomycin], D [doxorubicin]); M (V [vincristine] C [cyclophosphamide], E [etoposide]); EE4A (VA).
<table>
<thead>
<tr>
<th>Abdominal Tumor Stage and Histology</th>
<th>RT Dose/RT Field[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and II FH Wilms tumor</td>
<td>None</td>
</tr>
<tr>
<td>Stage III FH, stage I–III focal anaplasia</td>
<td>10.8 Gy to the flank[^b]</td>
</tr>
<tr>
<td>Stage I–II DA, stage I–III CCSK[^c]</td>
<td>10.8 Gy to the flank[^b]</td>
</tr>
<tr>
<td>Stage III DA, stage I–III RTK</td>
<td>19.8 Gy flank[^b] RT, infants ≤12 months 10.8 Gy</td>
</tr>
<tr>
<td>Recurrent abdominal Wilms tumor</td>
<td>12.6–18 Gy (&lt;12 months)[^b]</td>
</tr>
<tr>
<td>Lung metastases (favorable histology)</td>
<td>21.6 Gy (older children, previous RT ≤10.8 Gy) Boost dose of 9 Gy to gross residual tumor</td>
</tr>
<tr>
<td>Lung metastases (unfavorable histology)</td>
<td>12 Gy WLI in 8 fractions[^d]</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>12 Gy WLI in 8 fractions</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>30.6 Gy whole brain in 17 fractions, or 21.6 Gy whole brain + 10.8 Gy IMRT or stereotactic boost</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>19.8 Gy whole liver in 11 fractions</td>
</tr>
<tr>
<td>Unresected lymph node metastases</td>
<td>25.2 Gy to the lesion plus 3-cm margin</td>
</tr>
<tr>
<td></td>
<td>19.8 Gy</td>
</tr>
</tbody>
</table>

[^a]: Treatment field should include all lesions. Field size is adjusted based on extension of disease into adjacent structures.
[^b]: Dose to flank may be increased to 15.0 Gy in infants ≤3 months of age.
[^c]: CCSK: Clear cell sarcoma of kidney.
[^d]: WLI: Whole liver irradiation.
COG-TREATMENT GUIDELINES

Low-Risk FH Wilms Tumor
- Stage I, tumor weight <550 g
  - Nephrectomy without adjuvant therapy, if node sampling and central pathology review has been performed.

Risk FH Wilms Tumor
- Stage I, tumor weight 50 g, stage II without LOH
  - Nephrectomy, no RT, regimen EE4A

Hard-Risk FH Wilms Tumor
- Stage I and II with LOH
  - Nephrectomy, no RT, regimen DD4A
- Stage III without LOH
  - Nephrectomy, RT, regimen DD4A
- Stage IV FH: rapid responders of lung metastases at week 6 with regimen DD4A, without LOH

Higher-Risk FH Wilms Tumor
- Stage III with LOH
  - Nephrectomy, RT, regimen M
- Stage IV slow responders (lung) and nonpulmonary metastases, with LOH
  - Nephrectomy, RT, regimen M, WLI and RT to metastases

High-Risk UH Renal Tumors
- Stages I-IV focal anaplasia
  - Nephrectomy, RT, regimen DD 4A
- Stage I diffuse anaplasia
  - Nephrectomy, RT, regimen DD 4A
- Stage I-III CCSK
  - Nephrectomy, RT, regimen DD 4A
- Stage II-IV diffuse anaplasia
  - Nephrectomy, RT, regimen DD 4A
- Stage IV CCSK
  - Nephrectomy, RT, regimen DD 4A
- Stage I-IV RTK
  - Nephrectomy, RT, regimen DD 4A

EE4A-VA; DD4A-VAD; M-VAD/CyE; I-VDCy/CyE; UH1-VDCy/CyC(Carboplatin)E
## SIOP Treatment Guidelines

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Histological subtype after preoperative chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Mesoblastic nephroma*</td>
</tr>
<tr>
<td></td>
<td>Cystic partially differentiated nephroblastoma</td>
</tr>
<tr>
<td></td>
<td>Completely necrotic nephroblastoma</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Nephroblastoma:</td>
</tr>
<tr>
<td></td>
<td>• Mixed subtype</td>
</tr>
<tr>
<td></td>
<td>• Regressive subtype</td>
</tr>
<tr>
<td></td>
<td>• Epithelial subtype</td>
</tr>
<tr>
<td></td>
<td>• Stromal subtype</td>
</tr>
<tr>
<td></td>
<td>• Focal anaplasia</td>
</tr>
<tr>
<td>High</td>
<td>Diffuse anaplasia</td>
</tr>
<tr>
<td></td>
<td>Blastemal-type Wilms’ tumor</td>
</tr>
<tr>
<td></td>
<td>Clear cell sarcoma of the kidney*</td>
</tr>
<tr>
<td></td>
<td>Rhabdoid tumor of the kidney*</td>
</tr>
</tbody>
</table>
### SIOP Treatment Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre-operative Treatment</th>
<th>Post-nephrectomy Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Localised tumor</td>
<td>VCR + Act D ×4 wks</td>
</tr>
<tr>
<td></td>
<td>Metastatic tumor</td>
<td>VCR + Act D + Doxo ×6 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Act D, VCR (4 wks)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Act D, VCR, DOX (27 wks)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Low</td>
<td>Act D, VCR (27 wks)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Act D, VCR, DOX* (27 wks)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>CPM, DOX, VP16, CARBO (34 wks) + RT (anaplastic Wilms’ tumor only)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Low</td>
<td>Act D, VCR (27 wks)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Act D, VCR, DOX** + RT (8-27 wks)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>CPM, DOX, VP16, CARBO + RT (34 wks)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Low, intermediate risk histology and good metastatic response</td>
<td>Act D, VCR, DOX (27 wks) without whole lung RT providing complete response of lung metastases to chemotherapy +/- surgery</td>
</tr>
<tr>
<td></td>
<td>High risk histology or poor metastatic response (any histology)</td>
<td>CPM, DOX, VP16, CARBO + RT* (34 wks)</td>
</tr>
<tr>
<td>Stage V</td>
<td>Low and intermediate</td>
<td>Act D, VCR +/- DOX +/- RT* (duration depends on response)</td>
</tr>
</tbody>
</table>
FLANK RT

- RT vol to encompass the entire pre-op tumour bed
- Upper border-upper margin of tumour+1cm margin
- Lower border-lower margin of tumour+1cm margin
- Medial border-across the midline to include the entire width of the vertebral body & para-aortic LN chain
- Lateral border-abdominal wall
WHOLE ABDOMINAL IRRADIATION

- Upper border- dome of diaphragm
- Lower border-lower border of obturator foramen
- Lateral border-abdominal wall
- Femoral head & acetabulum to be shielded
- Hepatic dose <15 Gy
- Renal dose< 12-15 Gy

Appropriate shielding
CONFORMAL PLANNING

GTV ➔ Pre-op tumour volume using co-registered MR-CT scans

CTV ➔ GTV+1 cm isotropic expansion

PTV ➔ CTV+SM+IM

AP-PA beam arrangement with MLC shaping

Aim ➔ Adequate target coverage with symmetrical irradiation of vertebrae, avoidance of contralateral kidney & minimisation of whole body dose

IMRT rarely needed & conformal treatment adequate
CONFORMAL PLANNING
WHO LUNG IRRADIATION

- Upper border- to include both the lung apices
- Lower border- to include the pleural reflection infero-laterally
- Lat border-chest-wall
- Humerus & shoulder joint to be shielded bilaterally
CONFORMAL WLI

Coronal DRR

AP-PA beam arrangement
WLI + FLANK RT
LONG TERM TREATMENT OUTCOME (NWTS 3 & 4)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
<th>10-Year RFS (%)</th>
<th>10-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I FH</td>
<td>1,582</td>
<td>91.4</td>
<td>96.6</td>
</tr>
<tr>
<td>Stage II FH</td>
<td>1,006</td>
<td>85.5</td>
<td>93.4</td>
</tr>
<tr>
<td>Stage III FH</td>
<td>1,038</td>
<td>84.2</td>
<td>89.5</td>
</tr>
<tr>
<td>Stage IV FH</td>
<td>592</td>
<td>75.2</td>
<td>80.7</td>
</tr>
<tr>
<td>Stage V FH</td>
<td>344</td>
<td>65.1</td>
<td>77.9</td>
</tr>
<tr>
<td>All FH</td>
<td>4,562</td>
<td>84.4</td>
<td>90.8</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>170</td>
<td>67.1</td>
<td>77.1</td>
</tr>
<tr>
<td>Stage II–III anaplasia</td>
<td>128</td>
<td>43.0</td>
<td>49.2</td>
</tr>
<tr>
<td>Stage IV anaplasia</td>
<td>55</td>
<td>18.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>88</td>
<td>27.3</td>
<td>28.4</td>
</tr>
</tbody>
</table>

-In Perez & Brady’s Principles & Practice of Radiation Oncology, 6th edition, 2013
TREATMENT OF RELAPSE

Children with relapsed FH WT can have favorable outcome based on

- Initial stage
- Time from initial diagnosis
- Site of relapse
- Previous therapy

- Adverse factors for relapsed WT
  - Prior use of Doxorubicin
  - Relapse < 12 months from initial diagnosis
  - Intra-abdominal relapse after previous abdominal RT
RESTAGING

Stage 1R – Localized disease, completely excised

Stage 2R – Gross total resection with evidence of regional spread

Stage 3R – Residual non-haematogenous tumor present and confined to abdomen

Stage 4R – Haematogenous mets present

Stage 5R – Bilateral renal involvement
RT is administered at site of relapse

Dose to infradiaphragmatic sites

- CR after surgery (1R/2R) who have either received no previous RT or have received 10.8 Gy
  - Birth – 12 months – 12.6 - 18 Gy
  - 13 months or older – 21.6 Gy
- Gross residual disease after Sx
  - Should get an additional boost (9Gy)
  - Total dose including boost should not exceed 30.6 Gy

- Dose to infradiaphragmatic sites
  - Total nominal dose (including previous RT)
    - <36 months – should not exceed 30.6 Gy
    - >36 months – should not exceed 39.6 Gy
  - Total spine dose < 41.4 Gy
  - Total liver dose < 30.6 Gy
  - Total remaining kidney dose < 19.8 Gy
Lung Irradiation

- Complete remission & no previous RT
  - ≤ 18 months: 9 Gy; 1.5 Gy/fraction
  - > 18 months: 12 Gy, 1.5 Gy/fraction

- Gross residual disease after surgical resection & no previous RT
  - Can boost gross disease with additional 7.5 Gy

Liver, Brain, Bone mets

- Follow guidelines from NWTS 5
CLEAR CELL SARCOMA OF KIDNEY (CCSK)

Primitive mesenchymal neoplasm of kidney
Constitutes 4% of childhood renal tumours
Cell of origin unknown
Propensity for bone mets (In NWTS 4 study incidence of bone mets 23% in CCSK versus 0.3% in other tumours)

• In NWTS 1-4 study, 351 pts of CCSK included
• OS rate-69%
• On MVA, independent prognostic factors:
  ➢ Age
  ➢ Tumour stage
  ➢ Tumour necrosis
  ➢ Use of Doxorubicin

RHABDOID TUMOUR OF KIDNEY (RTK)

Highly malignant renal tumour
Unrelated to WT or RMS
Probably of neural crest origin
Usually detected in first 2 yrs of life
Associated with CNS lesion

- NWTS 1-5 study, 142 pts of RTK included
- 4 yr OS-23%
- Prognostic factors:
  - Age
  - Tumour stage
  - Higher dose of RT (>25 Gy)

LATE EFFECTS OF TREATMENT

Scoliosis-54% in patients treated with a median dose of 30Gy

CHF-4.4% at 20 years (NWTS1-4)

End stage renal disease (ESRD)-20 year cumulative incidence
- 74% in children with Denys-Drash syndrome
- 36% in children with WAGR syndrome
- 7% in children with GU abnormalities
- 0.6% in children without any syndrome/ abnormality
LATE EFFECTS OF TREATMENT

Second malignant neoplasm (SMN)-15 year cumulative incidence 1.6%
- Leukaemia/ lymphoma incidence 0.4% at 8 years with no case thereafter
- Solid malignancy incidence continued to rise sharply with time
- 73% of the solid malignancies arose in previous RT field
- Associated factors: higher dose of RT, use of Doxorubicin & Rx of relapse

Adverse pregnancy outcome-
- Foetal malposition
- Premature labour
- LBW baby
- Congenital malformation
FUTURE DIRECTION

Deintensification of Rx in LR pts & intensification of Rx in HR pts

Refinement of tumour risk stratification using molecular signature

IMRT- cardiac & renal sparing in whole lung & liver RT respectively

Re-evaluation of the necessity of RT in all pts receiving pre-op chemo

Re-evaluation of the current recommendation of WAI in localised pre-op tumour rupture limited to the flank

Biochemotherapy in pts of RTK & WT with DA
CONCLUSION

WT- highly curable childhood neoplasm

The prognosis of children with WT has dramatically improved from a very high mortality rate at the beginning of the 20th century to the current cure rate of >90%

The management of WT- paradigm for successful interdisciplinary treatment of solid tumours of childhood to maximize cure rates and minimize treatment-related complications