Rare Tumors at COG

Jeff Buchsbaum
Retinoblastoma (RB)

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https://commons.wikimedia.org/wiki/File%3ARb_whiteeye.PNG
RB Background

- Less than 3% of US children under 15 diagnosed with cancer have RB
- In the first year of life in makes up 11%
- 2/3’s of cases occur in those under 2
- 95% of cases occur in those under 5
- Incidence remains unchanged in the US over the 1975 to 1995 period
  - Balanced between whites and blacks
  - Balanced between males and females
  - 3.7 cases per million children
  - That means about 350 cases in the US per year (of 5-8k worldwide per year)
RB History

- Peru sculpture of about 2000 years ago may show RB
- Greek sculpture shows a lesion of the right eye (Meyer-Steineg collection from the Island of Kos)
- Western written: Peter Pauw’s notes from 1597 about a 3yo boy with a large ocular tumor that was rapidly growing.
- First published bilateral case: Hayes in 1767.
- Around the same time James Wardrop championed enucleation (London).
- The first likely use of radiation was by Hilgartner in Austin, TX in 1903.

RB – Early RT Cases

• Hilgartner – 1903 – Bilateral. Treated with 84 fractions. LTFU.
• Schonberg – Three papers looking at a 2yof with bilateral disease
  • Advanced- enucleation
  • Less advanced eye- radiation
    • At 10 years – useful vision
    • At 15 years - useful vision
    • At 25 years, a secondary sarcoma that spread and killed her
• Verhoeff – bilateral treated in 1917
  • The child did well until 1977, a basal cell developed on the lid, later a squamous cell (that date is not a typo)
RB- Pathway

- Part of the classic “two hit hypothesis” (not covered here).
- Genetic pathway is relatively simple.

Figure kindly provided by Carlos Rodriguez-Gallindo
Image is in the public domain via Wikipedia:
https://commons.wikimedia.org/wiki/File%3ASchematic_diagram_of_the_human_eye_en.svg
# Reese-Ellsworth Staging System

## Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Likelihood of Globe Salvage</th>
<th>Features</th>
</tr>
</thead>
</table>
| I     | Very favorable              | a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator  
|       |                             | b) Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator |
| II    | Favorable                   | a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator  
|       |                             | b) Multiple tumors, 4 to 10 disc diameters in size, at or behind the equator |
| III   | Doubtful                    | a) Any lesion anterior to the equator  
|       |                             | b) Solitary lesion larger than 10 disc diameters behind the equator |
| IV    | Unfavorable                 | a) Multiple tumors, some larger than 10 disc diameters in size  
|       |                             | b) Any lesion extending anterior to the ora serrata |
| V     | Very unfavorable            | a) Massive tumors involving over half of the retina  
|       |                             | b) Vitreous seeding |
The International Classification (Staging) System for Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
<th>Features</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>Small Tumor</td>
<td>Small tumors ≤ 3 mm in basal diameter or thickness and without Group B features.</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Larger Tumor</td>
<td>Tumors &gt; 3mm in basal diameter or thickness.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Near Disc (Juxtapapillary)</td>
<td>Distance to disc ≤ 1.5 mm.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macular (near fovea)</td>
<td>Distance to fovea ≤ 3 mm.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subretinal Fluid</td>
<td>Clear subretinal fluid ≤ 3 mm to margin.</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>Focal Seeds</td>
<td>Tumor with:</td>
</tr>
<tr>
<td></td>
<td>C1</td>
<td>Subretinal seeds ≤ 3 mm away.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>Vitreous seeds ≤ 3 mm away.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C3</td>
<td>Both C1 and C2.</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>Diffuse Seeds</td>
<td>Tumor with:</td>
</tr>
<tr>
<td></td>
<td>D1</td>
<td>Subretinal seeds &gt; 3 mm away.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D2</td>
<td>Vitreous seeds &gt; 3 mm away.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D3</td>
<td>Both D1 and D2.</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>E</td>
<td>Extensive Disease</td>
<td>Occupying over 50% of the globe. Neovascular glaucoma. Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space. Invasion of postlaminar optic nerve, choroid (&gt; 2mm), sclera, or anterior chamber.</td>
</tr>
</tbody>
</table>
### International Classification of Retinoblastoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Likelihood of Globe Salvage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Treated Conservatively</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Eye enucleated, completely resected histologically</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Eye enucleated, microscopic residual tumor</td>
<td></td>
</tr>
</tbody>
</table>
| III   | Regional extension          | a) Overt orbital disease  
          | b) Preauricular or cervical lymph node extension |          |
| IV    | Metastatic Disease          | a) Hematogenous metastasis (without CNS involvement)  
          | b) CNS extension (with or without any other site(s) of regional or metastatic disease) | 1. Single lesion  
          |                                           | 2. Multiple lesions  
          |                                           | 1. Prechiasmatic lesion  
          |                                           | 2. CNS mass  
          |                                           | 3. Leptomeningeal and CSF disease |

RB – Treatment (super condensed)

- Surgery
- Non-radiation local therapies (cryo, laser, etc.)
- Chemotherapy
  - IV (see COG trials over the last two decades)
  - Intra-arterial (Japan, MSKCC, now COG)
- RT (historic dose has been 45 Gy at 1.8 Gy/fx)
  - EBRT
    - Photon
    - Particles
  - Plaques (brachytherapy)
- Nuances: Stage II-IV, see ARET0321. Even CSI is used in some cases (trilateral...).
RB-Brachytherapy

• Seeds (LDR)
  • Please see the Khan Treatment Planning Textbook (chapter by JB) for details regarding planning.

• HDR is used in some places (outside of US more than in the US)
  • Please see the Pediatric Radiation Oncology Textbook by Kortman and Merchant (in press)
  • Copyright prevents sharing those images. Step by step images of HDR placement is shown in images.

Above, radioactive plaque with Iodine-125 seeds (c) and silicone shell (b). A gold foil prevents collateral radiation damage (a). Below, tumor before (d, showing plaque indentations) and after irradiation (e).

RB – External Beam Therapy

Photo from https://www.floridaproton.org/cancers-treated/pediatric-cancer/retinoblastoma