Historical Review of Retinoblastoma

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Financial Disclosure

I have the following financial disclosures:

<table>
<thead>
<tr>
<th>Clearside Biomedical</th>
<th>patent pending</th>
</tr>
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<tbody>
<tr>
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<td>research support</td>
</tr>
</tbody>
</table>
Seven Eras of Retinoblastoma

- prehistologic
- histologic
- enucleation
- irradiation/chemotherapy
- molecular biology
- targeted therapy
- global health
Prehistologic 1500s-1800s

James Wardrop 1782-1869

fungus haematodes
Histologic 1800s-present
Brenda Gallie

mother and grandmother of patient with retinoblastoma (courtesy B. Hubbard)
Retinocytoma

A Benign Variant of Retinoblastoma

Curtis Margo, MD; Lt Col Ahmed Hidayat, MC, USAF; Joel Kopelman, MD; Lorenz E. Zimmerman, MD

*Arch Ophthalmol* 1983;101:1519

courtesy of C. Margo
retinocytoma

fleurettes
Endophytic retinoblastoma
anterior diffuse retinoblastoma
Trilateral Retinoblastoma
Herman Knapp 1832-1911

Enucleation 1900s-present
1885 pre and post enucleation

prior to mid 1800s

- leeches
- poultries
- purgatives
- bland diet
- venesection
- antimony
- iodide
- vesicants

after mid 1800s

- chloroform as general anesthetic
- ophthalmoscope for earlier diagnosis
Irradiation/chemotherapy 1950s-present

Konrad Röntgen

Hyla Stallard

Gerd Myer-Schwicherath

Carl Kupfer

Algernon Reese

Robert Ellsworth
<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (very favorable)</td>
<td>solitary 4DD at/behind equator</td>
<td>multiple 4DD at/behind equator</td>
</tr>
<tr>
<td>II (favorable)</td>
<td>solitary 4-10 DD at/behind equator</td>
<td>multiple 4-10DD at/behind equator</td>
</tr>
<tr>
<td>III (doubtful)</td>
<td>any lesion anterior to equator</td>
<td>solitary tumor 10DD behind equator</td>
</tr>
<tr>
<td>IV (unfavorable)</td>
<td>multiple, some larger than 10DD</td>
<td>any lesion anterior to ora serrata</td>
</tr>
<tr>
<td>V (very unfavorable)</td>
<td>massive tumor half or more of retina</td>
<td><strong>vitreous seeding</strong></td>
</tr>
</tbody>
</table>
Reese and Ellsworth-bilateral EBRT
The two-mutation hypothesis is consistent with current thought on the mutational origin of cancer.

ALFRED G. KNUDSON, JR.

Graduate School of Biomedical Sciences and M. D. Anderson Hospital and Tumor Institute, The University of Texas at Houston, Houston, Texas 77025
heritable rb

non-heritable rb

germline

1st hit

2nd hit

developing retina

early age multiple bilateral

later age single unilateral
A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma

Stephen H. Friend*†, Rene Bernards*, Snezna Rogelj*, Robert A. Weinberg*‡, Joyce M. Rapaport§, Daniel M. Albert§ & Thaddeus P. Dryja§

NATURE VOL. 323 16 OCTOBER 1986
modified from Harbour IOVS 2006
Proceedings of the Consensus Meetings From the International Retinoblastoma Staging Working Group on the Pathology Guidelines for the Examination of Enucleated Eyes and Evaluation of Prognostic Risk Factors in Retinoblastoma

Xavier Sastre, MD; Guillermo L. Chantada, MD; François Doz, MD; Matthew W. Wilson, MD; Maria T. G. de Davila, MD, PhD; Carlos Rodríguez-Galindo, MD; Murali Chintagumpala, MD; Patricia Chávez-Barrios, MD; for the International Retinoblastoma Staging Working Group

(Arch Pathol Lab Med. 2009;133:1199–1202)
Retinoblastoma Optic Nerve and Choroidal Invasion

surgical margin

35%

choroidal invasion

70%
Gene expression profiling identifies different sub-types of retinoblastoma

G Kapata1,5, M-A Brundler1,2, H Jenkinson3, P Kearns1,3, M Parulekar4, A C Peet1,3 and C M McConville*,1

1School of Cancer Sciences, Vincent Drive, University of Birmingham, Birmingham B15 2TT, UK; 2Department of Histopathology, Birmingham Children’s Hospital, Birmingham B4 6NH, UK; 3Department of Oncology, Birmingham Children’s Hospital, Birmingham B4 6NH, UK and 4Department of Ophthalmology, Birmingham Children’s Hospital, Birmingham B4 6NH, UK

retinocytoma

mild

moderate

severe
retinoblastoma anaplasia vs survival

[Graph showing survival rates for retinoblastoma with different levels of anaplasia: Mild, Moderate, Severe.]

Percent survival vs Months
Retinoblastoma

Moderate Anaplasia

Severe Anaplasia
Photoreceptor and Nucleoporin Genes are Expressed Differentially in Severely Anaplastic Retinoblastoma
Cell free DNA (cfDNA) obtained from Aqueous in RB
**Alkylating agent**

*Melphalan*

Intrastrand linking and cross-linking

DNA damage: no transcription

**Topoisomerase inhibitor**

*Etoposide, Topotecan*

1. Topoisomerase
2. + Drug
3. Capped DNA double strand break

DNA damage: no repair/apoptosis

**Platinum based antineoplastic**

*Carboplatin*

DNA damage: no repair/apoptosis

**Vinca alkyloid**

*Vincristine*

1
2
3

Drug
vinca-bound tubulin dimers
Sprindle formation arrested

mitosis inhibition
<table>
<thead>
<tr>
<th>Group</th>
<th>General</th>
<th>Specific Features</th>
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<tbody>
<tr>
<td>A</td>
<td>Small tumor</td>
<td>retinoblastoma ≤ 3mm in size</td>
</tr>
<tr>
<td>B</td>
<td>Larger tumor</td>
<td>retinoblastoma &gt; 3mm in size or</td>
</tr>
<tr>
<td>C</td>
<td>Focal seeds</td>
<td>seeds ≤3mm from retinoblastoma</td>
</tr>
<tr>
<td>D</td>
<td>Diffuse seeds</td>
<td>seeds &gt;3mm from retinoblastoma</td>
</tr>
<tr>
<td>E</td>
<td>Extensive retinoblastoma</td>
<td>retinoblastoma occupying &gt;50% globe</td>
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Murphree, Desjardins, Shields, Shields and others
Retinoblastoma International Classification

- Group A
- Group B
- Group C
- Group D
- Group E
Retinoblastoma-chemoreduction

pre-treatment

post 3 cycles VEC
Targeted Therapy 1990s-present

Akihiro Kaneko

David Abramson
IAC before  IAC after

Courtesy David Abramson MD
Vitreous Seeds Remain a Problem

Courtesy of Jasmine Francis MD
Intravitreal Chemotherapy

Intravitreal chemotherapy

Carol Shields

Francis Munier
intravitreous Melaphalan before

intravitreous Melaphalan after
courtesy Carol Shields MD
Rabbit Model of Retinoblastoma with Vitreous Seeds

J Biomed Biotech 2011; PMID 21253494
Intravitreal topotecan liposomes for vitreous seeds of retinoblastoma
Enucleation is a good option for Group D and Group E eyes.
5 Year Survival

- USA: 96.50%
- Europe: 93%
- Upper income developing: 79%
- Middle income developing: 77%
- Lower income developing: 40%

modified from Chanturk et al Br J Ophthalmol 2010
Pre-meeting Visits

Menelik

TAPCCO
### Stage at presentation

<table>
<thead>
<tr>
<th>ICRB Group Classification</th>
<th>Number, n</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Group A</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Group B</td>
<td>6</td>
<td>6.3%</td>
</tr>
<tr>
<td>Group C</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Group D</td>
<td>28</td>
<td>29.2%</td>
</tr>
<tr>
<td>Group E</td>
<td>62</td>
<td>64.6%</td>
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29 patients (30.2%) presented with fungating mass
Ethiopia Retinoblastoma Symposium and National RB Program Planning Meeting May 12-13, 2018
• retinoblastoma-ophthalmology success story
• ophthalmologists, ophthalmic pathologists, research scientists
• cure of fatal disease, preservation of eye and vision
• future challenges-global health
- prehistologic
- histologic
- enucleation
- irradiation/chemotherapy
- molecular biology
- targeted therapy
- global health
Grossniklaus lab
Max Griffin BS
Lauren Hudson MD, PhD
Shin Kang MD, PhD
Pia Mendoza MD
Thonnie Rose See MD
Gustav Stålhammar MD, PhD
Hua Yang MD, PhD

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