AAPM WGSBRT
NTCP
Optic Apparatus
(chiasm and nerve)

Michael T. Milano, MD PhD

Department of Radiation Oncology
University of Rochester, Rochester, NY

07/16/15
AAPM WGSBRT
Optic Apparatus NTCP

Issam El Naqa, PhD

Wolfgang A. Tomé, PhD
Vitali Moiseenko, PhD
Jinyu Xue, PhD
Arjun Sahgal, MD
Lijun Ma, PhD
Ellen Yorke, PhD

Scott G. Soltys, MD
Timothy Solberg, PhD
John P. Kirkpatrick, MD PhD
Lawrence B. Marks, MD
John C. Flickinger, MD
Jimm Grimm, PhD
Optic nerves and chiasm

pituitary adenoma

optic chiasm

adenoma
Optic nerves and chiasm

- Toxicity: radiation-induced optic neuropathy (RION)
  - decreased visual acuity
  - visual field deficits/vision loss
    - generally occurs within 3 years after SRS
## Scoring systems for optic nerve/chiasm toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>RTOG/EORTC LENT SOMA</th>
<th>CTCAE version 3</th>
<th>CTCAE version 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>Afferent pupillary defect with normal appearing nerve</td>
<td>Asymptomatic, detected on exam/testing only</td>
<td>Asymptomatic; clinical or diagnostic observations only</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 1/4 pallor with asymptomatic visual field defect</td>
<td>Symptomatic, not interfering with ADL</td>
<td>Limiting vision of the affected eye (20/40 or better)</td>
</tr>
<tr>
<td>3</td>
<td>&gt;1/4 pallor or central scotoma</td>
<td>Symptomatic, interfering with ADL</td>
<td>Limiting vision in the affected eye (worse than 20/40 but better than 20/200)</td>
</tr>
<tr>
<td>4</td>
<td>Profound optic atrophy, complete blindness</td>
<td>Life-threatening; disabling</td>
<td>Blindness (20/200 or worse) in the affected eye</td>
</tr>
</tbody>
</table>

RTOG: Radiation Therapy Oncology Group  
EORTC: European Organisation for Research and Treatment of Cancer  
LENT: Late Effects in Normal Tissue  
SOMA: Subjective, Objective, Management, Analytic  
CTCAE: Common Terminology Criteria for Adverse Events
## Scoring systems for optic nerve/chiasm toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>RTOG/EORTC LENT SOMA</th>
<th>CTCAE version 3</th>
<th>CTCAE version 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>None</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Afferent pupillary defect with normal appearing nerve</td>
<td>Asymptomatic, detected on exam/testing only</td>
<td>Asymptomatic; clinical or diagnostic observations only</td>
</tr>
<tr>
<td>Grade 2</td>
<td>&lt; 1/4 pallor with asymptomatic visual field defect</td>
<td>Symptomatic, not interfering with ADL</td>
<td>Limiting vision of the affected eye (20/40 or better)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt;1/4 pallor or central scotoma</td>
<td>Symptomatic, interfering with ADL</td>
<td>Limiting vision in the affected eye (worse than 20/40 but better than 20/200)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Profound optic atrophy, complete blindness</td>
<td>Life-threatening; disabling</td>
<td>Blindness (20/200 or worse) in the affected eye</td>
</tr>
</tbody>
</table>

RTOG: Radiation Therapy Oncology Group  
EORTC: European Organisation for Research and Treatment of Cancer  
LENT: Late Effects in Normal Tissue  
SOMA: Subjective, Objective, Management, Analytic  
CTCAE: Common Terminology Criteria for Adverse Events
Definitions

• Stereotactic Radiosurgery (SRS)
  • 1 fraction

• Fractionated SRS (fSRS)
  • 2-5 hypofractionated
Methods

- Pooled analysis of studies reporting RION (or absence of RION) after SRS/fSRS
  - Summarize publish data
  - develop NTCP risk model
Methods

- PubMed search
  - 34 studies
  - 1,578 patients
Methods

• PubMed search
  • 34 studies
    • 1990-Jun 2015
    • information on
      • optic apparatus maximal dose exposure
      • RION after SRS/fSRS
  • 1,578 patients
Methods

• PubMed search
  • 34 studies
  • 1,578 patients

• Maximum dose to optic nerve/chiasm
## Optic nerves and chiasm

### Risk of optic neuropathy

<table>
<thead>
<tr>
<th>MAX. dose</th>
<th>&lt;8</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>15</th>
<th>&gt;15 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCRT/U.Pitt</td>
<td>0% (0/35)</td>
<td>24% (4/17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U. Pitt</td>
<td>0% (0/31)</td>
<td>67% (2/3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.Pitt/UAB</td>
<td>1 case ¶</td>
<td>3 cases of 2400 patients treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Franzens U.</td>
<td>0% (0/31)</td>
<td>27%* (6/22)</td>
<td>78%* (9/13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>2% (1/58)¶</td>
<td>1% (1/125)¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>0% (0/67)</td>
<td>7% (2/29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komaki City H.</td>
<td>3% (1/28)¶</td>
<td>0% (0/66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Actuarial incidence @ 3-years
¶ SRS + fract. RT in case of optic neuropathy.
In Mayo series, all had preceding surgery as well

- Pollock _IJROBP_ 70: 1325-9 (2008)
RION: Variables analyzed

• no patient treated after 1997 vs. some/all treated after 1997  
  \[ p = 0.023 \]
  \[ p = 0.019 \] *

• SRS delivery system  
  LINAC, Gamma knife, Cyberknife  
  \[ p = 0.42 \]
  \[ p = 0.31 \] *

• Prior resection  
  \[ p = 0.66 \]

• Prior radiotherapy  
  \[ p = 0.004 \]

* For patients with no prior radiotherapy
RION: Variables analyzed

- no patient treated after 1997 vs. some/all treated after 1997: p=0.023, p=0.019 *

- SRS delivery system: LINAC, Gamma knife, Cyberknife
  - p=0.42
  - p=0.31 *

- Prior resection: p=0.66

- Prior radiotherapy: p=0.004
  - 10-fold increased risk
  - * For patients with no prior radiotherapy
Studies with *some or all* patients treated after 1997
Methods

• NTCP modelling

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{u^2}{2}} \, du \]

\[ t = \frac{D-TD_{50}}{m \cdot TD_{50}}, \quad m = \frac{1}{\gamma_{50} \sqrt{2\pi}} \]

• \( \alpha/\beta \) ratio = 1.6 Gy for dose conversions
<table>
<thead>
<tr>
<th></th>
<th>EQD2_{1.6}</th>
<th>1-fraction SRS</th>
<th>3-fraction fSRS</th>
<th>5-fraction fSRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NTCP model including all studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46.0 Gy</td>
<td>12.1 Gy</td>
<td>20.0 Gy</td>
<td>25.1 Gy</td>
</tr>
<tr>
<td><strong>2% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.1 Gy</td>
<td>13.8 Gy</td>
<td>23.0 Gy</td>
<td>28.9 Gy</td>
</tr>
<tr>
<td><strong>5% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.8 Gy</td>
<td>15.6 Gy</td>
<td>26.1 Gy</td>
<td>32.9 Gy</td>
</tr>
<tr>
<td><strong>NTCP model including only single-fraction SRS studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33.0 Gy</td>
<td>10.1 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>2% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41.0 Gy</td>
<td>11.4 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>5% risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52.1 Gy</td>
<td>12.9 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NTCP model including all studies</td>
<td>1-fraction SRS</td>
<td>3-fraction fSRS</td>
<td>5-fraction fSRS</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>1% risk</td>
<td>46.0 Gy</td>
<td>12.1 Gy</td>
<td>20 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 Gy</td>
<td></td>
</tr>
<tr>
<td>2% risk</td>
<td>59.1 Gy</td>
<td>13.8 Gy</td>
<td>23.0 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28.9 Gy</td>
<td></td>
</tr>
<tr>
<td>5% risk</td>
<td>74.8 Gy</td>
<td>15.6 Gy</td>
<td>26.1 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32.9 Gy</td>
<td></td>
</tr>
<tr>
<td>NTCP model including only single-fraction SRS studies</td>
<td>1-fraction SRS</td>
<td>3-fraction fSRS</td>
<td>5-fraction fSRS</td>
<td></td>
</tr>
<tr>
<td>1% risk</td>
<td>33.0 Gy</td>
<td>10 Gy</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2% risk</td>
<td>41.0 Gy</td>
<td>11.4 Gy</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5% risk</td>
<td>52.1 Gy</td>
<td>12.9 Gy</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Limitations

- Limited data in high-dose range ($P_{\text{max}} > 13 \text{ Gy/1Fx}$)
- Uncertainties in a/b ratio
- Uncertainties in EQD2/BED calculations
- Error bars in NTCP curves
- NTCP calculations do not account for magnitude of toxicity (i.e. grade)
- Optic apparatus not uniformly defined/delineated
Future studies should ...

• Detail prior therapy (surgery/RT)
• Clear define how OAR was defined
  • Image modalities/MRI sequences
  • Slice thickness
• Clearly describe planning algorithm and
treatment system used
Future studies should …

- Define point ‘volume’ (i.e. 0.03 ml) for maximal dose
- Define small volume exposure (i.e. $D_{0.2\text{ml}}$)
- Describe mean dose
Future studies should...

- Describe patient follow-up
- Describe post-SRS visual assessment
- Standardize RION grade reporting
QUESTION 1

The incidence of grade 3+ radiation induced optic neuropathy (RION) for patients receiving modern cranial SRS is

A. Less than 0.1%
B. Less than 3%
C. More than 3%
D. More than 10%
E. More than 25%
a. Less than 0.1%
b. **Less than 3%**
c. More than 3%
d. More than 10%
e. More than 25%

**EXPLANATION:** Reported RION risks are on the order of <1-2% in modern series.

**Provided Reference:**
QUESTION 2

The safest (with respect to vision preservation) dose-volume delivery to the optic nerve in a single fraction radiosurgery plan would be:

A. Median dose of 7.8 Gy to optic nerve

B. Maximal dose of 7.8 Gy to optic nerve

C. Maximal dose of 13 Gy to optic nerve with 95% receiving 10 Gy or less

D. Minimal dose of 7.8 Gy to optic nerve

E. Average dose of 7.8 Gy to the optic nerve
a. Median dose of 7.8 Gy to optic nerve
b. **Maximal dose of 7.8 Gy to optic nerve**
c. Maximal dose of 13 Gy to optic nerve with 95% receiving 10 Gy or less
d. Minimal dose of 7.8 Gy to optic nerve
e. Average dose of 7.8 Gy to the optic nerve

EXPLANATION: While maximal doses in excess of 10 Gy to the optic nerve are presumably safe, the plan delivering the lowest dose to the optic nerve is the safest.

Provided Reference:
THANK YOU FOR YOUR ATTENTION