Limits of Radical Resection for Low- and High-Grade Gliomas

Nader Sanai, MD, FAANS, FACS
Associate Professor of Neurological Surgery
Director, Division of Neurosurgical Oncology
Director, Barrow Brain Tumor Research Center
Barrow Neurological Institute
Phoenix, Arizona, USA
Disclosures

**EXTRAMURAL RESEARCH SUPPORT**
- American Association of Neurological Surgeons
- American Brain Tumor Organization
- American Cancer Society
- American Society of Clinical Oncology
- Arizona Biomedical Research Commission
- National Cancer Institute
- National Institute of Neurological Disorders and Stroke
- Novartis AG
- The Ben & Catherine Ivy Foundation
- The Pivotal Foundation
- The Thurston Foundation

**ADVISORY BOARDS**
- Caris Life Sciences
- Carl Zeiss AG
- Medtronic, Inc.
- Osteomed L.P.
Distribution of Adult Gliomas

- **7%** Grade I: *Least aggressive*
- **14%** Grade II: *Less aggressive*
- **9%** Grade III: *More aggressive*
- **70%** Grade IV: *Most aggressive*

All Grade II gliomas eventually become high-grade.
Current Glioma Standards of Care

- Surgery
- Radiation Therapy
- Chemotherapy
  - Temozolomide
  - IMRT
  - NovoTTF
## Current Glioma Survival Data from the U.S.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mean Age at Diagnosis</th>
<th>2-Year Survival</th>
<th>5-Year Survival</th>
<th>10-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>17</td>
<td>91%</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>Grade II</td>
<td>40</td>
<td>55%</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>Grade III</td>
<td>42</td>
<td>40%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>55</td>
<td>12%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Source:** 2014 Central Brain Tumor Registry of U.S.
Low-Grade Gliomas: Extent of Resection
LGG Surgery in the Modern Literature

Cumulative Publications

- Favor More Extensive Resection
- No Significant Benefit for Extent of Resection
The Value of Extent of Resection: Low-Grade Glioma Overall Survival

Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas

Smith et al.

$n = 216$

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Point Estimate†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EOR remained significant predictor of overall survival even if only analyzing patients with EOR ≥ 80%

* Adjusted for the effects of patient age, KPS, tumor location and tumor subtype.
† Per unit of measure (e.g. log cm³, cm³, %)
The Value of Extent of Resection: Low-Grade Glioma Transformation

Malignant Progression-Free Survival

$n=190$ patients

$P<0.001$

# Low-Grade Glioma Heterogeneity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tumor Type</th>
<th>Median Age at Diagnosis</th>
<th>2-Year Survival</th>
<th>5-Year Survival</th>
<th>10-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>JPA</td>
<td>17</td>
<td>97%</td>
<td>94%</td>
<td>91%</td>
</tr>
<tr>
<td>Grade II</td>
<td>Astrocytoma</td>
<td>40</td>
<td>61%</td>
<td>47%</td>
<td>35%</td>
</tr>
<tr>
<td>Grade II</td>
<td>Oligodendroglioma</td>
<td>32</td>
<td>90%</td>
<td>79%</td>
<td>64%</td>
</tr>
<tr>
<td>Grade II</td>
<td>Mixed Glioma</td>
<td>35</td>
<td>75%</td>
<td>57%</td>
<td>46%</td>
</tr>
</tbody>
</table>

*Source: 2014 Central Brain Tumor Registry of U.S.*
### Low-Grade Glioma Heterogeneity

<table>
<thead>
<tr>
<th><strong>World Health Organization (WHO) Grade I</strong></th>
<th><strong>WHO Grade II</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile Pilocytic Astrocytoma (JPA)</td>
<td>Diffuse Astrocytoma</td>
</tr>
<tr>
<td>Subependymal Giant Cell Astocytoma (SEGA)</td>
<td>Oligodendroglioma</td>
</tr>
<tr>
<td>Myxopapillary Ependymoma</td>
<td>Oligoastrocytoma</td>
</tr>
<tr>
<td>Subependymoma</td>
<td>Pleiomorphic Xanthroastrocytoma</td>
</tr>
<tr>
<td>Dysembryoplastic Neuroepithelial (DNET)</td>
<td>Pilomyxoid Astrocytoma</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>Ependymoma</td>
</tr>
<tr>
<td>Choroid Plexus Papilloma</td>
<td>Central Neurocytoma</td>
</tr>
</tbody>
</table>
# Low-Grade Glioma Heterogeneity

<table>
<thead>
<tr>
<th>Astrocytomas (World Health Organization (WHO) Grade I)</th>
<th>Oligodendrogliomas (WHO Grade II)</th>
<th>Mixed Gliomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile Pilocytic Astrocytoma (JPA)</td>
<td>Diffuse Astrocytoma</td>
<td>Ependymoma</td>
</tr>
<tr>
<td>SEGA</td>
<td>Oligodendroglioma</td>
<td>Others</td>
</tr>
<tr>
<td>Apendymal Giant Cell Astrocytoma (SEGA)</td>
<td>Oligoastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Myxopapillary Ependymoma</td>
<td>Pleomorphic Xanthroastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Subependymoma</td>
<td>Pilomyxoid Astrocytoma</td>
<td></td>
</tr>
<tr>
<td>DNET</td>
<td>Ependymoma</td>
<td></td>
</tr>
<tr>
<td>Embryoplastic Neuroepithelial (DNET)</td>
<td>Subependymoma</td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choroid Plexus Papilloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glioma with Ependymal Differentiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Others
LGG Heterogeneity: Oligodendrogliomas

- Cytoreduction impacts the rate for transformation
- EOR does not predict MPFS for pure oligodendrogliomas*
- Insular LGGs: EOR > 90%: 5-year MPFS of 88% ($p=0.04$)*

- Is the biological impact of EOR driven by histology?

Laura Snyder, MD
Assistant Professor of Neurosurgery
Barrow Neurological Institute

High-Grade Gliomas: Extent of Resection
HGG Surgery in the Modern Literature

- Favor More Extensive Resection
- No Significant Benefit for Extent of Resection

Cumulative Publications

Years: 1990 to 2014
European 5-ALA Study Group

Gross Total Resection
65% (5-ALA)

6-Month Progression-Free Survival
41% (5-ALA)

Overall Survival
16.7 mo (5-ALA)

Table 2: Patients without residual tumour at early postoperative MRI: all patients, and stratified by age, performance status, and eloquent areas
The Value of Extent of Resection: High-Grade Gliomas

New Management Paradigm of High Grade Gliomas

500 Newly-Diagnosed Glioblastoma Patients

Survival benefit seen with $\geq 78\%$ extent of resection

Radiation + Chemotherapy

Sanai et al., J. Neurosurg., 2011 Jul;115(1):3-8
The Value of Extent of Resection: Recurrent High-Grade Gliomas

170 consecutive glioblastoma patients at first recurrence
- All had initial resection and Stupp regimen at first diagnosis
- All underwent repeat resection upon recurrence
- Mean clinical follow-up 22.6 months
The Value of Extent of Resection: Recurrent High-Grade Gliomas

170 consecutive glioblastoma patients at first recurrence
- All had initial resection and temozolamide/RT at first diagnosis
- All underwent repeat resection upon recurrence
- Mean clinical follow-up 22.6 months


Graded Effect of Extent of Resection

Multivariate Cox Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0009</td>
</tr>
<tr>
<td>EOR</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

Survival Benefit Seen Beyond 80%
Extent of resection improves glioma survival in a graded fashion

WHO Grade IV (glioblastoma)

Less tumor = longer survival

WHO Grade III (hemispheric)

Less morbidity = longer survival

McGirt et al., Neurosurgery, 2009

Smith et al., J. Clin Oncol., 2008

Keles et al., J. Neurosurg., 2006

Sanai et al., J. Neurosurg., 2009

Sanai et al., J. Neurosurg., 2011

Is There Value to Extent of Resection?
<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor Location</th>
<th>Tumor Grade/Type</th>
<th>Recurrence? (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>Yes (5.0)</td>
</tr>
<tr>
<td>38</td>
<td>Insular</td>
<td>Grade II Oligo</td>
<td>No (16.5)</td>
</tr>
<tr>
<td>31</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>No (13.0)</td>
</tr>
<tr>
<td>39</td>
<td>Parietal</td>
<td>Grade II Oligo</td>
<td>No (12.5)</td>
</tr>
<tr>
<td>45</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>No (12.4)</td>
</tr>
<tr>
<td>32</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>Yes (8.1)</td>
</tr>
<tr>
<td>63</td>
<td>Insular</td>
<td>Grade II Astro</td>
<td>Yes (8.8)</td>
</tr>
<tr>
<td>39</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>No (10.9)</td>
</tr>
<tr>
<td>41</td>
<td>Frontal</td>
<td>Grade II Astro</td>
<td>Yes (4.0)</td>
</tr>
<tr>
<td>48</td>
<td>Temporal</td>
<td>Grade II Oligo</td>
<td>No (10.0)</td>
</tr>
<tr>
<td>35</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>Yes (2.7)</td>
</tr>
<tr>
<td>43</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>Yes (4.0)</td>
</tr>
<tr>
<td>59</td>
<td>Frontal</td>
<td>Grade II Oligo</td>
<td>No (8.4)</td>
</tr>
<tr>
<td>27</td>
<td>Temporal</td>
<td>Grade II Astro</td>
<td>No (8.2)</td>
</tr>
<tr>
<td>54</td>
<td>Insular</td>
<td>Grade II Oligo</td>
<td>Yes (6.7)</td>
</tr>
<tr>
<td>41</td>
<td>Frontal</td>
<td>Grade II Astro</td>
<td>Yes (7.5)</td>
</tr>
</tbody>
</table>

### Glioma Rates of Gross-Total Resection: Results in the Modern Literature

#### 2000-2010

<table>
<thead>
<tr>
<th>Grade of Glioma</th>
<th>Reported Rates of Gross-Total Resection</th>
<th>Disaggregated Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Grade Glioma</strong></td>
<td>33% - 76%</td>
<td>1412 of 2266 Tumors = 62.3% GTR</td>
</tr>
<tr>
<td><strong>Low-Grade Glioma</strong></td>
<td>14% - 46%</td>
<td>399 of 1462 Tumors = 27.3% GTR</td>
</tr>
</tbody>
</table>
Maximizing Glioma Extent of Resection

**Fundamental Techniques**

- **Operative Corridor Selection:** using gravity & arachnoidal planes
- **Intraoperative Mapping Techniques:** minimizing morbidity
- **Fluorescence-Guided Surgery:** visualizing cellular infiltration
Maximizing EOR: Optimizing Exposure

Arachnoidal Dissection

Entry-Point Selection

Gravity-Retraction
Maximizing Glioma Extent of Resection

Fundamental Techniques

- Operative Corridor Selection

- Intraoperative Mapping Techniques: minimizing morbidity

- Fluorescence-Guided Surgery
Intraoperative Stimulation Mapping: Resect to the Boundaries of Function
Maximizing EOR: Intraoperative Mapping
Maximizing EOR: Intraoperative Mapping

- Meta-analysis of 6095 low- and high-grade glioma cases
- Stimulation mapping improved gross-total resection in eloquent areas
- Two-fold reduction in late severe deficits with stimulation mapping (8.3% vs. 3.4%)

DeWitt et al., J Clin Oncol. 2012 Jul 10;30(20):2559-65
Maximizing Glioma Extent of Resection

Fundamental Techniques

✓ Operative Corridor Selection
✓ Intraoperative Mapping Techniques

□ Fluorescence-Guided Surgery: visualizing cellular infiltration
5-Aminolevulinic Acid (5-ALA)

- Oral administration: essentially nontoxic, $t_{1/2} = 45$ min
- Visible macroscopically in WHO Grade III / IV gliomas
- Visible microscopically in WHO Grade II gliomas

Isihara et al., Neurol Med Chir (Tokyo) 2007

5-ALA HGG Fluorescence

White Light

Diagram:
- Mitochondrion
  - Glycine + Succinyl CoA $\rightarrow$ Negative Feedback $\rightarrow$ Hemoglobin
  - 5-Aminolevulinic Acid
  - Protoporphyrin IX
  - Protoporphyrinogen IX
  - Coproporphyrinogen III
  - Uroporphyrinogen III
  - Porphobilinogen

Intensities: $\times 10^{-3}$

Barrow Neurological Institute
5-ALA: High-Grade Glioma Visualization

- Necrotic Center
  - No Fluorescence
  - Will not enhance on postoperative MRI
- Border of Necrosis
  - Deep Red
  - Will enhance on postoperative MRI
- Marginal Tissue
  - Lighter Pink
  - Will not enhance on postoperative MRI

5-ALA fluorescence is more sensitive than gadolinium for high-grade gliomas.

Roberts et al., J Neurosurg. 2011 Mar;114(3):595-603
5-ALA in Non-Enhancing Gliomas

- Focal PpIX fluorescence observed in 46% of nonenhancing gliomas
- 85% of PpIX(+) nonenhancing gliomas had WHO grade III histology
- Proliferation index, cell density, and nuclear pleomorphism were significantly higher in areas of focal PpIX fluorescence

Widhalm et al., PLOS One 2013; Oct 18
Limitations of Wide-Field Microscopy

- Image intensity of wide-field microscopy is subjective, particularly at the diffuse margins of a glioma

- Poor sensitivity when detecting sparse tumor cell populations

Liu JT et al., Neurosurgery 2014 Jul;75(1): 61-71
Intraoperative Confocal Microscopy: Cellular Resolution
BALANCE Trial: Low-Grade Gliomas

BARROW ALA INTRAOPERATIVE CONFOCAL EVALUATION

High Expected EOR
Low Expected EOR

Intraoperative Fluorescence
Intraoperative Confocal

All Gliomas

Pl: Nader Sanai / NCT01502280
5-ALA Visualization of Low-Grade Gliomas

Sanai et al.,
## 5-ALA Visualization of Low-Grade Gliomas

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Tumor Location</th>
<th>Tumor Grade</th>
<th>Macroscopic Fluorescence</th>
<th>Initial Encounter</th>
<th>Mid-point Resection</th>
<th>Cavity Margin</th>
<th>Volumetric EOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>M</td>
<td>Frontal</td>
<td>Grade I</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
</tr>
<tr>
<td>37</td>
<td>F</td>
<td>Frontal</td>
<td>Grade II/III</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>Frontal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>98%</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>Temporal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>87%</td>
</tr>
<tr>
<td>39</td>
<td>F</td>
<td>Parietal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>99%</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>Frontal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>94%</td>
</tr>
<tr>
<td>38</td>
<td>F</td>
<td>Temporal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>92%</td>
</tr>
<tr>
<td>49</td>
<td>M</td>
<td>Insular</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>93%</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>Temporal</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>97%</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>Insular</td>
<td>Grade II</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>90%</td>
</tr>
</tbody>
</table>

Sanai et al., *J. Neurosurg*. 2011; 115(4): 740-8
Intraoperative Dual-Axis Confocal Microscopy

- Superior Optical Sectioning
  - Dual-Axis Confocal (DAC) architecture improves rejection of out-of-focus light
- Short working distance
  - More background noise from scattered light

Enhanced Sensitivity & Contrast
- Light scattered along the illumination path (blue) is less likely to be collected

Improved Optical Clarity
- Low numerical aperture (NA) lenses
- Off-axis path traversed by photons eliminates noise due to back reflections
- Long working distance
  - Less noise from scattered light

Liu et al., Neurosurgery 2014
Intraoperative Dual-Axis Confocal Microscopy

NCI 1R01CA175391 (PI: Sanai)

Normal Vasculature

Glioma Vasculature
Quantification of Microscopic Tumor Burden

PpIX(+) Human Glioma

Real-Time Cell Density Heat Map

WHO Grade II

WHO Grade III
Conclusions

- Extent of resection matters for all grades of gliomas.
- Cytoreduction can delay malignant transformation and alter the natural history of low-grade gliomas.
- 80% is the extent of resection threshold for newly-diagnosed and recurrent high-grade gliomas.
- Intraoperative stimulation mapping is a critical tool to maximize extent of resection and minimize morbidity.
- In the near future, extent of resection will be measured by microscopic tumor burden at the cavity margins.
Thank you for your attention

Email: Nader.Sanai@bnaneuro.net