Sodium fluorescein guided resection of malignant glioma
Muhammad Waqas, Muhammad Shahzad Shamim

Abstract
The average rate of gross total resection (GTR) for malignant gliomas (MGs) is reported to be around 36%. One of the major challenges to GTR is the recognition of tumour margins. Sodium fluorescein is a freely available fluorophore used to recognize the boundaries of MGs. It accumulates in tumour areas with disrupted blood brain barrier that can then be visualized under a microscope with dedicated filters. No randomized controlled trial or meta-analysis is available that reports the impact of fluorescein use on the extent of tumour resection. Several prospective studies and a phase II trial prove it to be safe and helpful in achieving GTR rates of 68.42-100%. At higher doses i.e., 15-20 mg/Kg, sodium fluorescein can even be used under white illumination. The dye is safe even at high doses and has helped achieve GTR rates of 80-84.4%.

Keywords: Gross total resection, Malignant gliomas, Sodium fluorescein.

Introduction
Gross total resection (GTR) increases the progression free survival and overall survival of patients with malignant gliomas (MG).1 GTR is however, difficult to achieve despite the availability of neuronavigation, intraoperative MRI and intraoperative ultrasound. One of the major challenges to GTR is the recognition of tumour margins for at times the brain-tumour interface is less distinct. This has led to the use of fluorophores like 5-ALA (5-aminolaevulinic acid) that highlight the tumour and its margins.2 The use of 5-ALA showed a significant increase in the rate of GTR for MGs.2 However, its use remains limited due to lack of availability and a high cost. An alternate compound, sodium fluorescein, also highlights the tumour and its margins, by accumulating in areas of disrupted blood brain barrier.3,4 Its fluorescence can be detected with the help of Yellow 560 nm and Blue 400 nm filters on Pentero (Carl Zeiss™) and Leica™ operative microscopes respectively. The purpose of this evidence-based review is to summarize the literature and find out if sodium fluorescein improves the extent of resection of MGs.

Review of Evidence
Studies on the use of fluorescein for tissue identification date back to 1947. The largest study that explored the sensitivity and specificity of fluorescein was done by Murray et al.5 They performed biopsies on 186 patients and calculated a sensitivity of 96% and specificity of 81%. Studies on determining the extent of resection are only recent.

There are no systematic reviews to support the use of fluorescein for MG resection. We found only one phase II trial that explored the safety and efficacy of fluorescein sodium in the resection of GBM. The initial results of the trial were published in 2014 and comprised of 20...
patients, and the complete results were published just recently, in 2018. No adverse reaction was seen with fluorescein and the rate of GTR was 75% in the initial results, and 80% in the final paper. The 6-month survival was 71.4%. There was however, no control or comparison group.

Three prospective non-randomized studies described the use of high dose fluorescein (20mg/kg, before dural opening) and white light illumination, for the microsurgical resection of MG (total sample size of 101). The rate of GTR was 80 - 84.4%. One of these studies by Koc et al., involved 47 patients divided in two groups (with and without fluorescein). The rates of GTR were 83% and 55% respectively. Another study by Chen et al., studied 22 patients. The rates of GTR were 80% (fluorescein) and 33.3% (control group).

Five studies have reported the use of microscope integrated filter to measure the extent of resection. Kuroiwa et al., described the use of fluorescein with OPMI microscope (Carl Zeiss™) and published three studies using fluorescein at 8mg/kg. The sample sizes were 10, 30 and 20 patients with GTR rates of 100%, 83.3% and 95% respectively. Okuda et al., studied 10 patients with 100% GTR rate. Since 2012 a dedicated filter is available with Pentero (Carl Zeiss™) microscope i.e., yellow 560 nm. Smaller doses (5-10mg/Kg) of fluorescein have been tried by Acerbi et al., with the yellow 560 filter. Results of various studies are summarized in Table. A descriptive review by Koneko et al., reported GTR of HGG from 36% using standard surgery, to 74.5 and 84.4% using ALA and fluorescein. Neira et al., and Hamamcioglu et al., also studied the use of low dose fluorescein with GTR rates of 84% and 68.42%.

### Table: Rate of gross total resection of malignant glioma using sodium fluorescein, in chronological order.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Dose and Timing</th>
<th>Percentage of patients with GTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acerbi et al. (2018) (FLUOGLIO study)</td>
<td>57</td>
<td>5-10 mg/Kg</td>
</tr>
<tr>
<td>2</td>
<td>Hamamcioglu et al. (2016)</td>
<td>19</td>
<td>2-4mg/Kg after induction</td>
</tr>
<tr>
<td>3</td>
<td>Neira et al. (2017)</td>
<td>32</td>
<td>3 mg/Kg</td>
</tr>
<tr>
<td>4</td>
<td>Acerbi et al. (2013) (FLUOGLIO initial results)</td>
<td>20</td>
<td>5 mg/kg before skin incision</td>
</tr>
<tr>
<td>5</td>
<td>Okuda et al. (2012)</td>
<td>10</td>
<td>20 mg/Kg upon durotomy</td>
</tr>
<tr>
<td>6</td>
<td>Chen et al. (2012)</td>
<td>22</td>
<td>15-20 mg/Kg before durotomy</td>
</tr>
<tr>
<td>7</td>
<td>Koc et al. (2008)</td>
<td>47</td>
<td>20mg/Kg before durotomy</td>
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<tr>
<td>8</td>
<td>Shinoda et al. (2003)</td>
<td>32</td>
<td>20mg/Kg before durotomy</td>
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<tr>
<td>9</td>
<td>Kuroiwa et al. (1999)</td>
<td>20</td>
<td>8mg/Kg before durotomy</td>
</tr>
<tr>
<td>10</td>
<td>Kuroiwa et al. (1999)</td>
<td>30</td>
<td>8mg/Kg upon durotomy</td>
</tr>
<tr>
<td>11</td>
<td>Kuroiwa et al. (1998)</td>
<td>10</td>
<td>8mg/Kg upon durotomy</td>
</tr>
</tbody>
</table>

### Conclusion
Fluorescein sodium guided resection of malignant gliomas is safe. Available evidence consists of descriptive reviews and non-randomized prospective studies that suggest a large variation in the GTR rates, from 68.4 to 100%. The authors would like to emphasize that the usefulness of any of the available modalities is merely complimentary, and depends upon several factors, especially the surgeons’ experience and expertise.

### References


