PROGNOSTIC CLASSIFICATION OF GLIOMAS AS DETECTED BY $^1$H NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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DISCLOSURES

Authors declare not to have any financial or organizational relationships with commercial interests or other entities. They acknowledge that if there is any case where their private interest conflict with the interests of AANS/NREF/NPA, they will indicate that they may have a conflict and abstain from any vote, speaking, engagement, planning related to that issue. This work was supported in part by grants PI2017/00361 from Investigation Institute Carlos III to JMR, grant B2017/BMD-3688 from the Community of Madrid to JMR and grant PI-0143-2016 from the Regional Ministry of Health of the Regional Government of Andalucía to JS.
INTRODUCTION

- Histological, genetic and magnetic resonance imaging (MRI) and spectroscopy (MRS) methods have contributed general criteria for glioma diagnosis and classification. However, prognosis of overall survival (OS) of individual patients after surgical glioma resection remains limited, configuring currently a daunting challenge of modern neurosurgery. In particular, specific patients with poor histopathological prognosis depict sometimes unexpectedly long-OS, while some patients with positive histopathology markers, may suffer unpredictably short-OS. This highlights the need to improve current prognostic criteria.

- We report here a pilot retrospective study of the prognostic value of $^1$H MRS biomarkers on the OS of patients after neurosurgical removal of glioma between 1992 and 1998 comparing the predicted outcome with histopathologic criteria.
METHODS

• $^1$H NMR spectra of glioma, histopathological, clinical and demographic features of 46 selected glioma II-IV patients who underwent surgery for the first time during the period 1992-1998 were retrospectively revised.

• We created two Classification and Regression Trees (CRT), to classify the groups of OS by a multivariate combination of $^1$H MRS metabolic variables, and by the histopathological grade variables. A confusion matrix, summarizing the correct and incorrect classifications produced by the classifier (CRT), and obtaining the global percentage of correct classifications for metabolic and histopathological grade variables was elaborated thereafter.

• Statistical analyses were performed using IBM SPSS Statistics 24 (Windows) with statistical significance threshold $p<0.05$. 
**RESULTS**

Figure 1. Three different OS groups in weeks (w) were identified in the retrospective database. Long-OS (364-731w) and Intermediate-OS (53-364w) or Short-OS (1-52w) groups were clearly separated. Intermediate-OS and short-OS were separated using the median of both groups.

Figure 2. Representative spectra from two young male glioma II patients with the same histopathological diagnosis but very different OS (Figure 2A-OS 149w, Figure 2B-OS 605w), despite both underwent the same therapeutic protocol. Note that MI resonances increased markedly in 2B.
RESULTS

Figure 3. Relationship between OS and metabolomic profile of glioma patients as determined by high-resolution $^1$H NMR analysis of glioma biopsies. OS increased progressively with decreased in Ala, Ac, Glu, fCho, PC and Gly levels and increased tCr, GPC and MI levels.
RESULTS

Figure 4. CRTs based in metabolomic (left) or histopathological (top right) criteria. MI and GPC levels provide the strongest indicators of long- and intermediate-OS, respectively. Histopathological grade only predicts Short-OS, with no Intermediate- or Long-OS predictive capability.
## RESULTS

Classification Confusion Matrix of correct/incorrect classifications of OS using metabolomic or histopathological criteria.

<table>
<thead>
<tr>
<th>Observed OS (n=46)</th>
<th>Predicted OS metabolomic / histopathological</th>
<th>Percent Correct Classifications metabolomic/histopathological</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Short (n=19)</td>
<td>18 / 16</td>
<td>1 / 3</td>
</tr>
<tr>
<td>Intermediate (n=19)</td>
<td>4 / 3</td>
<td>15 / 16</td>
</tr>
<tr>
<td>Long (n=8)</td>
<td>1 / 0</td>
<td>1 / 8</td>
</tr>
</tbody>
</table>

Grey background cells indicate correct classifications. White background cells indicate incorrect classifications.
DISCUSSION

• Glioma treatment represents a daunting challenge of modern neurosurgery, currently based on histopathological criteria. However, additional biomarkers are considered necessary to improve predictive accuracy of current classifications.

• Previous studies provided $^1$H MRS OS markers of glioma mainly using in vivo MRS of high grade lesions over shorter periods of time.

• This study contributes the first CRT with predictive OS value based in individual metabolite levels, revealing a prominent role of increased MI and GPC as robust OS biomarkers.

• In summary, present findings contribute a novel metabolomic decision tree to improve general histopathological classifications with more accurate predictions at the individual level.
SUMMARY POINTS

• We investigated the use of metabolomic markers as prognostic criteria of post-surgical survival in glioma patients, comparing the predictions with those of the classical histopathological method.
• Three groups of patients with Long-, Intermediate- and Short- OS were identified.
• We found increased MI levels predicted adequately Long-OS, and increased GPC levels separated well intermediate- and Short-OS groups.
• Histopathological criteria predicted well the Short-OS group, but could not predict Intermediate- or Short-OS.
• The overall capacity to predict correctly the three OS groups was higher using metabolomic (84,7% correct) than histopathological (69,6% correct) criteria.