Prognostic value of baseline MRI in Glioblastoma Multiforme patients: a survival analysis of morphological, volumetric and diffusion MRI predictors

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Aims and objectives

Glioblastoma multiforme (GBM) is the most common primary malignant tumor in adults, being characterized by very poor survival rates, despite continuous development of multimodal therapeutic approaches. Pre-treatment robust categorization of GBM patients based on MRI prognostic predictors would be a helpful tool for programming individualized therapeutic strategies.

Several imaging features have been discussed in literature and pointed out as possible prognostic markers. However, we find conflicting results and most studies do not take into account the clinical, technical and economical restraints we face in our medical practice.

We placed emphasis on three main tumor features: size, peritumoral edema (PTE) and apparent diffusion coefficient (ADC) values, adding to a more general characterization of other morphological characteristics (including cyst, necrosis and multifocality).

Size is well established as a significant prognostic factor and is usually included in therapeutic response criteria for most solid tumors. However, in high-grade glial tumors, size does not seem to be a major predictor of overall survival (OS), with inconsistent results on the few studies published so far (1, 2, 3, 4, 5, 6). This is partially justified by the different methods and definition of "size" per se, that is, maximum diameters (used on current assessment protocols in therapy trials) versus true volumetric assessment. Recent studies have shown that 3D measures are more accurate, less subjective and take into account the highly irregular shape of tumors disregarded by 1D and 2D measures. Furthermore, 3D volumetric analysis showed significant prognostic impact on previous studies (5, 7) and, consequently, this was the approach adopted for the present analysis.

Similarly, methodological differences are reflected in the inconsistent reports of peritumoral edema as a prognostic factor, most of them applying qualitative measures for edema classification or quantitative linear metrics, which were either subjective or time-consuming. Recently, a more practical classification based on 1cm cut-off was implemented, showing pre-operative PTE as an independent survival predictor (3, 8), defying previous studies in which PTE have no impact, lost its significance in multivariate analysis or had a quadratic effect on survival (1, 2, 9, 10 11).

Lastly, we explore ADC values as a prognostic feature based on the theoretical concept that increased cellularity, probably associated with higher grade and a more aggressive tumor, constitutes an obstacle to the free motion of water molecules. That is, the impeding effect of membranes underlies restricted diffusion, thus lower ADC values. Ultimately, we
should expect an inverse correlation between ADC values and grade tumor, the latter affecting overall survival.

Confirming this theorization previous studies showed a negative correlation between ADC values and ki-67 (proliferation index), being also correlated to tumor grade, histological category and some other biomarkers, namely 1p19q (12)

Furthermore, a meta-analysis of four studies published between 2006 and 2007 showed that low ADC correlates with poor survival in malignant astrocytomas, independent of tumor grade (13).

We aim to evaluate the predictive value of morphological, volumetric and diffusion MRI parameters in GBM patients' overall survival.

Methods and materials

Patient Population

We selected 214 patients histologically diagnosed with glioblastoma multiforme between January 2012 and December 2014 from the neuropathological database of our institution. Histological diagnosis was based on the modified World Health Organization classification.

Of these, we excluded 147 patients who did not have a pre-operative MRI including a volumetric T1 (MPRAGE), T2 FLAIR and diffusion weighted image with ADC map calculation. Additionally, 11 patients were dismissed for selection errors, multicentric tumors or small diffuse foci, and co-existence of other tumor types.

We retrospectively reviewed the pre-operative MRI of the remaining 56 patients, who were included on this study, and determined the several tumor variables, as following described. Clinical and demographical features including age and sex were also recorded. Survival assessment was last performed in August 1st 2015, with overall survival time being measured from the day of the pre-operative MRI.

Imaging visualization and measurements were performed using Osirix imaging software v5.7.1.

Topographic and morphological features

Tumors were classified according to hemisphere (right, left, both), specific location, corpus callosum involvement (yes, no), necrosis grade visually determined (no necrosis, <25%, 25-50% or >50% of the tumor mass) and cyst presence (yes, no).
Peritumoral Edema Categorization

PTE was defined as a region of increased T2 sign on tumor margin, without contrast-enhancement. We classified edema according to two different parameters:

- 1 cm cut-off, in which minor is inferior to 1cm and major is superior to 1cm (Fig. 1 on page 5)
- four qualitative grades including no PTE, mild, moderate and severe (Fig. 2 on page 5), which took into consideration the proportionality of edema extension to tumor volume.

Volumetry

For volumetric analysis we used a volumetric T1-weighted post-contrast acquisition (1mm isotropic voxel). Volume of interest was drawn manually on each 1mm slice, considering the "solid" component including necrotic centre, peripheral enhancement and cystic areas (Fig. 3 on page 6). Total volume was calculated by Osirix software.

For survival analysis we subdivided considering two different cut-offs: one based on our median and another on the 30cm³ cut-off previously described on literature (4).

ADC evaluation

ADC values were measured in the solid tumor components with highest signal on DWI and correspondent lowest intensity on ADC map (minimum ADC on visual inspection), avoiding necrosis, cysts, large vessels and cerebral spinal fluid. To account for heterogeneity of the ADC values, we place three round ROI’s with 9mm² area on the tumor area selected (Fig. 4 on page 6). For normalization, we also measure ADC values in normal-appearing white matter (NAWM) on contralateral centrum semiovale and calculated an ADC ratio (meanADC tumor/NAWM).

For survival analysis we subdivided the study population considering 1000x10⁻⁶ mm²/s cut-off for ADC values, as described in previous literature (14, 15) and 1 for ADC ratio, that is, tumor area showing more or less diffusion restriction that NAWM.

Statistical analysis

Descriptive statistics, Spearman's correlation and survival analysis with Kaplan-Meier method (with log rank test for curves comparison) and univariate and multivariate Cox regression were performed using SPSS statistics 21.0. Statistical significance was set at p value<0.05.
Fig. 1: Measurement of edema considering major diameter from solid portion limit to outer border of the hypertensity area on FLAIR image.

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Fig. 2: Examples of edema grades, classified by visual inspection.

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Fig. 3: Volume calculation steps.

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**Fig. 4:** Left, tumor ADC ROI's placed on low intensity areas on ADC map. Right, control ROI's on contralateral centrum semioval.

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Results

From the 56 patients enrolled in the study 35 (62.5%) were male and the mean age was 65.45 years (range 33-81). At the time of analysis, 5 patients (8.9%) were still alive. Median overall survival was 193 days (range 60-932).

Although we found a weak negative correlation between age and survival days (Rs=-0.313), survival analysis considering stratification in three groups (<50, 50-69, >69) did not show significant differences.

Morphological and topographical characteristics

Tumours had a similar hemispheric distribution, with 26 (46.4%) located on left and 25 (44.6%) located on right, with the remaining (n=4) being located on posterior fossa. More specific topographic distribution is represented on (Fig. 5 on page 9). Corpus callosum involvement, cyst presence, necrosis grade and multifocality data are summarized in Table 1 on page 10. From those variables only multifocality showed prognostic value, being associated with lower survival (Cox hazard ratio 0.495, p=0.034) especially in those who survive longer than approximately 150 days (Fig. 6 on page 11).

Edema

Patient distribution according to edema classification based on 1cm-cut off and on qualitative grades is represented on Fig. 7 on page 12.

Survival curves by Kaplan-Meier method (Fig. 8 on page 13) and univariate Cox survival analysis for PTE based on 1cm cut-off showed a significant higher survival in patients with major edema Survival distributions for the four qualitative grades were not significantly different (Fig. 9 on page 14).

Volumetry

The tumor volume median was 41,077 cm$^3$ (range 2,246-112,503).

We found no correlation between overall volume (cm3) and survival (days). Survival analysis (Fig. 10 on page 15) did not show significant differences between volume groups considering any of the adopted cut-offs (median and 30cm$^3$).

ADC values
We found a week association between ADCratio and survival (Rs=0.278) and non-significant when analyzing non-normalized ADC values.

However, when we dichotomized patient population considering $1000 \times 10^{-6}$ mm$^2$/s cut-off for minADC values and 1 for ADC ratio, survival curves were significantly different being lower for low ADC values (Fig. 11 on page 16). This was particularly notorious for minADC, but also for ADC ratio except on extreme cases of early death or longer survivals.

Univariate Cox also showed a significant lower survival for minADC<$1000 \times 10^{-6}$ mm$^2$/s ($p=0.018$) and ADC ratio<1 ($p=0.045$) groups.

We considered for multivariate Cox regression variables with significant correlations with survival, even if weak, and/or suggestive of having prognostic impact on univariate analysis, including age, edema, multifocality and minADC (Table 2 on page 17). ADC value was the only independent predictor of survival.

Images for this section:
**Fig. 5:** Spacial distribution of glioblastomas included in the study. Operc/ins - opercular/insular; TPJ - temporoparietal junction; >1 - more than 1 lobe involved; CC - centered on corpus callosum

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### Table 1: Categorization by tumor morphology

<table>
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<tr>
<th>Characteristic</th>
<th>n</th>
<th>Percent</th>
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<tr>
<td>Corpus callosum involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>55.4</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>44.6</td>
</tr>
<tr>
<td>Cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>17.9</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>82.1</td>
</tr>
<tr>
<td>Necrosis Grade</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>12</td>
<td>21.4</td>
</tr>
<tr>
<td>25-50%</td>
<td>15</td>
<td>26.8</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>28</td>
<td>50.0</td>
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<tr>
<td>Multifocality</td>
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<td>Yes</td>
<td>16</td>
<td>28.6</td>
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<tr>
<td>No</td>
<td>40</td>
<td>71.4</td>
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</table>
Fig. 6: Kaplan-Meier survival curves for multifocality (isolated focus, grey; multifocality, yellow), p=0.024.

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Fig. 7: Patient distribution according to edema classification based on 1cm-cut off (left) and on qualitative grades (right)

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**Fig. 8:** Kaplan-Meier survival curves for edema based on 1cm cut-off (<1cm, light blue; >1cm, dark blue), p=0.026

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Fig. 9: Kaplan-Meier survival curves for edema based on qualitative categorization, p=0.299

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Fig. 10: Kaplan-Meier survival curves for volume based on 30 cm³ cut-off (left) and median (right), $p<0.05$

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**Fig. 11:** Kaplan-Meier survival curves for minADC with $1000 \times 10^{-6}$ mm$^2$/s cut-off value (left) and ADC ratio with 1 cut-off value (right), $p=0.03$ and $0.042$ respectively.

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<table>
<thead>
<tr>
<th></th>
<th>$p$</th>
<th>HR</th>
<th>95.0% CI Lower</th>
<th>95.0% CI Upper</th>
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<tr>
<td>minADC</td>
<td>0.026</td>
<td>2.928</td>
<td>1.136</td>
<td>7.550</td>
</tr>
<tr>
<td>Age</td>
<td>0.129</td>
<td>0.615</td>
<td>0.328</td>
<td>1.153</td>
</tr>
<tr>
<td>Edema (1 cm cut-off)</td>
<td>0.052</td>
<td>1.910</td>
<td>0.994</td>
<td>3.670</td>
</tr>
<tr>
<td>Multifocality</td>
<td>0.347</td>
<td>0.726</td>
<td>0.372</td>
<td>1.415</td>
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</tbody>
</table>
Table 2: Multivariate analysis of specific prognostic predictors. HR - hazard ratio, CI-confidence intervals

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Conclusion

Our study suggests most morphological parameters and precise volume measure of glioblastoma are not significant predictors of patients' overall survival, with exception of multifocality.

Furthermore, with results in strict contradiction with previous reports using 1cm cut-off, our study does not support the reliability of this method for pre-operative evaluation of PTE as a survival predictor. Applying a qualitative classification PTE was not a significant prognostic factor, in accordance to other studies.

Notably, ADC was the only independent predictor for overall survival. Diffusion parameters allow pre-operative exploration of tumor microstructure *in vivo*, providing prognostic value that may help planning more effective surgical strategies.

Limitations

Our study has several limitations mainly relating to its retrospective nature. Those are somehow similar to the ones we face in our daily practice, when trying to use published cut-off values and classification models. MR protocols vary slightly, although they always include the aforementioned sequences (T1 MPRAGE, T2 FLAIR and DWI with ADC map from \(b_0\) and \(b_{1000}\)) in 5 patients images were acquired on a 3T magnetic field. Despite previous reports of no differences on ADC values for the same b values on 1,5 and 3T (16), this is still a matter of debate.

We also did not control for clinical factors that may influence the results, namely Karnofsky Performance Status scale and time since symptomatic presentation.

Therapeutical approaches were not taken into consideration, since the study question was specifically about the independent predictive power of pre-operative MRI, however, we intend to include this variable on further analysis.

Personal information

References


