Understanding recurrence in glioma

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Authors: T. B. S. Buxi\textsuperscript{1}, M. Gupta\textsuperscript{2}, S. Sud\textsuperscript{2}, A. Sud\textsuperscript{2}, S. S. Ghuman\textsuperscript{3}, K. S. Rawat\textsuperscript{2}, A. Verma\textsuperscript{2}, S. Gupta\textsuperscript{4}, S. Sethi\textsuperscript{2}; \textsuperscript{1}Gurugaoan/IN, \textsuperscript{2}New Delhi/IN, \textsuperscript{3}Noida/IN, \textsuperscript{4}IN
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Learning objectives

Grade III-IV gliomas have a poorer prognosis despite surgical intervention, chemotherapy and radiotherapy. Response to these measures is somewhat non uniform and recurrence is nearly universal. However there is paucity of literature in understanding the recurrence in glioma which have downgraded on treatment or continued to accelerate despite treatment.

- Presented in this study is an attempt to understand recurrence in gliomas. Various parameters on MR were studied in depth. These included DWi, DTi, MRS, DSC-T2*W, \( k^{\text{trans}} \) and \( v_e \) followed subsequently by statistical analysis.

- Since non uniformity of results of perfusion parameters, \( k^{\text{trans}} \) and \( v_e \) have been noted in the past, this study highlights an attempt to understand this subjective variation.

- Correlation of parameters with normal brain tissue in a given case and proportionate variation of low or high order reflects the underlying pathological basis of recurrence.

- The value of this correlation is in prognostication of such cases.
Background

The treatment therapy for patients with gliomas is surgical resection along with external beam radiation therapy (EBRT). It delivers high doses of radiation that along with killing tumor cells within the target also leads to delayed radiation necrosis which manifests as progressive contrast enhancement on follow-up magnetic resonance (MR) images. It may lead to imaging dilemma whether a progressively enhancing lesion is due to recurrent glioma or necrosis due to radiation. (1)

Angiogenesis plays an important role in the growth and aggressiveness of brain tumors. Gliomas have a variable degree of neovascularity and blood brain barrier (BBB) alteration depending on the grade and histologic subtype. The lower-grade gliomas may not have any evidence of angiogenesis or BBB disruption.

Vascular endothelial growth factor (VEGF) is a cytokine which regulates this pathogenesis and stimulates endothelial proliferation and increases transendothelial permeability. (2)

Endothelial permeability of vessels in brain tumors regulates BBB integrity, vascular morphology, and the nature of neovascularization and in turn provides useful information regarding tumor pathophysiology and prognosis. (3)

Recent studies have shown that quantitative estimates of endothelial permeability correlate with brain tumor grade. (3)

This degree of endothelial permeability on MR imaging is represented by the endothelial permeability surface area product or the transfer coefficient, \( k_{\text{trans}} \), which is estimated on the basis of dynamic susceptibility contrast-enhanced (DSCE) MR imaging, and also \( v_e \), which governs the leakage of contrast agent from the vascular to the extravascular compartment.

\( k_{\text{trans}} \) also depends on vascular surface area and flow. Therefore it is an indirect measure of physiologic parameters that vary with vascular attenuation and angiogenic activity. (3)

These measures provide the ability to understand the vascular permeability (leak) which helps to identify the region of interest for biopsy. The future potential benefits also include the targeted EBRT, focal excision at zone of recurrence with manipulation of the BBB for improved drug delivery. (4)

Different grades of gliomas behave differently pre and post operatively.
MR Spectroscopy

Significantly increased ratios of Choline (Cho) upon N-Acetylacetic acid (NAA) and Cho upon Creatine (Cr) are seen in areas of recurrent tumor compared with areas of radiation injury and with normal adjacent brain tissue. Cut off values is 1.8 for either Cho/NAA or Cho/Cr i.e., values more than 1.8 are diagnostic for tumor recurrence.

- The limitations of spectroscopy include (a) Cho and Lipid-Lactate (LL) can be seen in both - radiation necrosis and recurrent glioma, (b) Cho may not be elevated in high grade tumors, (c) Lesions close to skull base cannot be assessed well and (d) Presence of hemorrhage in the lesion causes poor quality spectra. (5)

DSC MR- is a marker for angiogenesis.

(DSC) perfusion MR imaging include the following parameters - relative cerebral blood volume (rCBV), relative peak height (rPH) and percentage of signal-intensity recovery (rPSR).

Diffusion weighted imaging.

- Magnitude of change in tumor water diffusion is related to the numbers of cells killed and, hence, to the therapeutic efficacy. Maximal diffusion parameters could be useful as an early predictor of therapeutic response in human brain tumors.

- Diffusion characteristics can vary in a localized area depending on the treatment instituted. (6)

Diffusion tensor imaging

Fractional anisotropy (FA) reflects fibre density, axonal diameter, and myelination in white matter. It is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. (4)
Findings and procedure details

Eight post op glioma patients were evaluated on 3-Tesla MRI machine and following sequences were obtained.

- T1, T2, Flair
- Post contrast T1 fat saturated
- Diffusion & Apparent diffusion co-efficient
- MR pectroscopy
- Perfusion (DSCE T2* )
- $k^{\text{trans}}$ and $v_e$
- DTI
- Sequences of the spine, if required

rPH was calculated with the following equation:

$$rPH = \frac{[S0(ROI) - S\text{min}(ROI)]}{[S0(NAWM) - S\text{min}(NAWM)]},$$

rPSR was calculated with the following equation:

$$rPSR = \frac{[[S1(ROI) - S\text{min}(ROI)]/[S0(ROI) - S\text{min}(ROI)]]/[[S1(NAWM) - S\text{min}(NAWM)]/[S0(NAWM) - S\text{min}(NAWM)]]}. $$
Fig. 44: Fig 1. Calculation of rPSR and rPH.


Where,

- $S_0$ region of interest (ROI) - precontrast T2*-weighted signal intensity of the ROI,
- $S_{\text{min}}$ (ROI) - minimum T2*-weighted signal intensity of the ROI,
- $S_0$ normal appearing white matter (NAWM) - precontrast T2*-weighted signal intensity of the NAWM,
- $S_{\text{min}}$ (NAWM) - minimum T2*-weighted signal intensity of the NAWM.
- $S_1$ (ROI) - postcontrast T2*-weighted signal intensity of the ROI
- $S_1$ (NAWM) - postcontrast T2*-weighted signal intensity of the NAWM. (1)

Since surgery or radiotherapy can treat the tumour in some places, it is important to look for tumour recurrence focally with the help of $K^{\text{trans}}$. Thus multiple measurements are necessary to define the recurrence.

In the past attempt has been made to understand recurrence by several authors, still a definite interparametric correlation has been lacking in literature.
• The understanding of recurrences can be quantified on scoring system based on perfusion and $k^{\text{trans}}$ and preoperative scans if available.

• The current scoring system gives higher rating to CBV, $k^{\text{trans}}$, PSR, PH, MRS in a descending manner. The proximity of values of $k^{\text{trans}}$ and CBV to the normal tissue is suggestive of low grade glioma character while the variability of >50-60% is suggestive of high grade potential.

To develop any scoring system it is mandatory to have biopsy. It is imperative to mention brain biopsy in post treatment cases is usually not possible in majority of cases because of obvious reasons.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>$k^{\text{trans}}$</th>
<th>ve</th>
<th>rCBV</th>
<th>rPSR</th>
<th>rPH</th>
<th>MRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>Minimum</td>
<td>Maximum</td>
<td>Minimum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.161</td>
<td>0.022</td>
<td>0.444</td>
<td>0.004</td>
<td>2.3±1.7</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>0.104</td>
<td>0.011</td>
<td>0.495</td>
<td>0.01</td>
<td>3.0±0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>0.067</td>
<td>0.025</td>
<td>0.071</td>
<td>0.014</td>
<td>1.5±0.7</td>
<td>1.02</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.02</td>
<td>0.045</td>
<td>0.014</td>
<td>2.2±0.9</td>
<td>1.06</td>
</tr>
<tr>
<td>5</td>
<td>0.082</td>
<td>0.032</td>
<td>0.219</td>
<td>0.03</td>
<td>4.1±2.1</td>
<td>0.94</td>
</tr>
<tr>
<td>6</td>
<td>0.034</td>
<td>0.015</td>
<td>0.01</td>
<td>0.004</td>
<td>1.4±0.7</td>
<td>0.94</td>
</tr>
<tr>
<td>7</td>
<td>0.082</td>
<td>0.024</td>
<td>0.052</td>
<td>0.016</td>
<td>2.1+/-.8</td>
<td>1.3</td>
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<tr>
<td>8</td>
<td>0.231</td>
<td>0.078</td>
<td>0.786</td>
<td>0.044</td>
<td>3.1+/-.2</td>
<td>1.32</td>
</tr>
</tbody>
</table>

**Fig. 45**: $k^{\text{trans}}, v_e, \text{CBV }, \text{rPSR}, \text{rPH}, \text{rPSR}$ and MRS findings of eight patients.

**References**: radiology, sir gangaram hospital, sir gangaram hospital - New Delhi/IN

We analysed the difference of $k^{\text{trans}}$ between normal and abnormal tissue in 8 patients and found that there was significant variation of $k^{\text{trans}}$ between recurrent disease and radiation necrosis ($p = 0.016$) and this has correlated well with the rCBV values.

Perfusion MR imaging measurements in recurrent tumour and radiation necrosis.Barajas et al (1)
Fig. 46: Perfusion MR imaging measurements in recurrent tumour and radiation necrosis.(1)


Bajaras et al obtained these measurements in surgically proven cases and measurements obtained by us in our case coincides with these measurements. It is inferred though a larger study may be required in coming to a definite comparison and conclusion, yet our data correlates these measurements despite no post treatment biopsy.

Perfusion MR imaging measurements in recurrent tumour and radiation necrosis. Buxi et al.

<table>
<thead>
<tr>
<th></th>
<th>rPH</th>
<th>rCBV</th>
<th>rPSR</th>
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<tbody>
<tr>
<td>RECURRENT TUMOUR</td>
<td>1.88±0.57</td>
<td>2.6±1.12</td>
<td>104±0.15</td>
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<tr>
<td>RADIATION NECROSIS</td>
<td>1.47±0.50</td>
<td>2.38±0.59</td>
<td>116±0.13</td>
</tr>
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</table>
Images for this section:

**Fig. 1:** CASE 1. 34/f, known case of recurrent glioma. Status post treatment. The tumour shows heterogenous signal intensity on T1W and T2W MRI images.

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**Fig. 2:** CASE 1. The tumour shows areas of heterogenous enhancement on post contrast scan.

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**Fig. 3:** CASE 1 DTI and corresponding ADC map. Low FA values were obtained in the region of interest.

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**Fig. 4:** CASE 1. CBV and CBF perfusion maps which reveal area of increased perfusion.

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Fig. 5: CASE 1. Perfusion graph was obtained and the rPSR, rPH were calculated.

Fig. 6: CASE 1. ktrans and ve values were obtained at multiple points
**Fig. 7**: CASE 1. MR spectroscopy was performed. Choline peaks were obtained.
**Fig. 8:** CASE 1. MRS showing a high choline to creatinine ratio.

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**Fig. 9:** CASE 2. Known case of glioma. Post treatment. An encephalomalacic area is noted in the left high frontal region with hyperintensity on T2W images seen posteriorly

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Fig. 10: CASE 2. $K_{trans}$ and $V_e$ were obtained at multiple points adjacent to the region of interest and from the contralateral normal white matter.
Fig. 12: CASE 2. MR spectroscopy was performed. NAA peak and choline peak were obtained.

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<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Pos./ppm</th>
<th>Integral</th>
<th>Ratio</th>
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<tbody>
<tr>
<td>NAA</td>
<td>2.02</td>
<td>3.25</td>
<td>1.53</td>
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<tr>
<td>Cr</td>
<td>3.04</td>
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<tr>
<td>Cho</td>
<td>3.22</td>
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<tr>
<td>Cr2</td>
<td>3.93</td>
<td>1.79</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Fig. 11: MRS table showing a high NAA to creatinine ratio.

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Fig. 13: CASE2. CBV mapping was done. DSC study was performed. rPSR and rPh were calculated.

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**Fig. 14:** CASE 3.53/f, Known case of glioma. Status post treatment. Area of hyperintense signal on T2W images and hypointense signal on T1W images is noted in the right temporal region. Blooming is noted on susceptibility weighted images suggestive of haemorrhage.

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**Fig. 15:** CASE 3. CBF and CBV mapping were done. rPSR and rPH were calculated from the curve.

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Fig. 16: CASE 3. MRS was performed and a high NAA and choline peak was obtained.

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Fig. 17: CASE3. DTI and ADC mapping was done from multiple points.

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Fig. 18: CASE 3. Low FA and corresponding low ADC values were obtained from the region of interest.

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Fig. 19: CASE4. Known case of glioma. Status post treatment. Area of hyperintensity on T2W images are seen in left frontal region which show enhancement on post contrast scan. Blooming is seen on SWI images suggestive of hemorrhage. Restricted diffusion with corresponding low ADC values are noted.

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**Fig. 20:** CASE 4. \( rPSR \) and \( rPH \) were calculated from the perfusion graph.

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**Fig. 21:** CASE4. rCBV and rCBF were calculated.

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**Fig. 22:** CASE5. Known case of glioma. Status post treatment. Area of hyperintensity is noted in the right frontal region with peripheral enhancement on post contrast scan. Blooming is noted on SWi images suggestive of haemorrhage with restricted diffusion and corresponding low ADC.

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Fig. 23: CASE 5. DTI and ADC mapping were done. Low FA values were obtained from the region of interest with raised ADC values.

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Fig. 25: CASE 5. MRS was performed and high lactate and NAA peaks were obtained.
Fig. 24: CASE5. High lactate peak was obtained.

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**Fig. 26:** CASE 5. CBV and CBF mapping were done. rPSR and rPH were calculated.

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**Fig. 27:** CASE 5. ktrans and ve were calculated at multiple points and from the contralateral normal white matter.

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**Fig. 28:** CASE 6. Known case of glioma. Status post treatment. area of volume defect with adjacent hyperintensity is noted in the right frontal region. Mild peripheral enhancement is seen. Restricted diffusion is noted with corresponding low ADC value.

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**Fig. 29:** CASE 6. MRS was performed and high lactate peak was obtained.

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**Fig. 30:** CASE 6. Ktrans and Ve were calculated from multiple points and from the contralateral white matter.

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**Fig. 31:** CASE 7. Known case of glioma. Status post treatment. Area of hyperintensity on T2W images is noted in the left temporal region with hypointensity on T1W images. Minimal peripheral enhancement is seen on post contrast scan.

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**Fig. 32:** CASE 7. MRS was performed and a high NAA peak was obtained.

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<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Pos./ppm</th>
<th>Integral</th>
<th>Ratio</th>
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<td>NAA</td>
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<tr>
<td>Cr</td>
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<td>11.18</td>
<td>1.00</td>
</tr>
<tr>
<td>Cho</td>
<td>3.23</td>
<td>17.26</td>
<td>1.54</td>
</tr>
<tr>
<td>Ins 1</td>
<td>3.59</td>
<td>7.98</td>
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<tr>
<td>Cr2</td>
<td>3.93</td>
<td>10.44</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Fig. 33:** CASE 7. A high NAA to creatinine ratio was obtained.

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Fig. 34: CASE 7. DTI and ADC mapping was done from multiple points. Low FA value were obtained from the region of interest.

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Fig. 35: CASE 7. Low FA value were obtained from the region of interest..

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Fig. 36: CASE 7. rPSR and rPH were calculated.
**Fig. 37:** CASE 7. ktrans and Ve were calculated from multiple points around the region of interest and contralateral white matter.
**Fig. 38:** CASE 8. Known case of glioma. Status post treatment. Substance defect is noted in the occipital region on the right side with adjacent hyperintensity on T2W images.

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**Fig. 39:** CASE 8. Post contrast scan shows minimal peripheral hyperintensity.
Fig. 41: CASE 8. CBV and CBF mapping was done.

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**Fig. 40:** CASE 8. MRS was done. NAA peak was obtained with a high NAA to creatinine ratio.

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**Fig. 42:** CASE 8. DTI and ADC mapping was done. Low FA value were obtained with corresponding raised ADC value.

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Fig. 43: CASE8.ktrans and ve were calculated at multiple points from the region of interest and contralateral white matter.

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Conclusion

• The principal parameters that provide useful information about tumour diagnosis, grade, tumour heterogeneity and therapeutic response and can guide the surgeon regarding stereotactic radiation therapy are $k_{\text{trans}}$ and CBV.

• A post-operative interval of 3-6 months showing this higher value of $k_{\text{trans}}$ and CBV compared to that of normal tissue is suggestive of recurrence.

• Reproducibility of parametric imaging in brain tumours is more than adequate to support longitudinal and multicentre studies.
References


