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Pre- and Post-Operative Imaging Markers and its Relation with Pseudo and Real-Progression According to MGMT Promoter Methylation Status

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Abstract

In addition to tissue indicators, imaging markers also frequently predict the prognosis of certain malignancies. The methylation status at the MGMT Promoter may also affect the imaging markers in high grade gliomas. This study was conducted to investigate imaging biomarkers like CT Attenuation, Apparent Diffusion Coefficient (ADC), and Cerebral Blood Volume (CBV) in High Grade Gliomas, and to search for pseudoprogression and ADC values after a 3-month gap using DSC MRI with reference to MGMT Promoter Methylation status. Forty patients who initially arrived with neurological symptoms and were eventually confirmed to have a primary brain tumor on a regular MRI scan were included in the research. The mean CT attenuation value was 31.4 HU for methylation tumors and 38.1 HU for unmethylated tumors (p value 0.001). Even though the unmethylated group's rCBV ratios were higher than the methylated group's (mean 2.98 vs. 2.49), the difference was not statistically significant (p value = 0.059). The methylation group exhibits pseudoprogression more frequently (7 out of 9, or 77%), compared to the unmethylated group (3 out of 10, or 30%). The MGMT promoter methylation status in these tumor cells can be prophesied by pre-operative imaging, and post-operative imaging can help identify patients who have pseudoprogression in relation to their methylation status, which is crucial for predicting the response to therapy as well as overall outcome and survival.

Keywords: Apparent diffusion coefficient, cerebral blood volume, methylguanine-methyl transferase, Magnetic Resonance Imaging, Computed tomography

Introduction

Gliomas are usually hypointense on T1W imaging and hyperintense on T2W imaging. The probability of a high-grade glial neoplasm is suggested by contrast enhancement, necrosis and hemorrhage, vaguely defined infiltration of the surrounding brain, and significant peritumoral edema, which are frequently regarded as imaging hallmarks of aggressive lesions. There is a lot of research on the relationship between contrast enhancement and tumor grade. Contrast enhancement is a characteristic of high grade gliomas (HGG), however it is still a general observation. For instance, although approximately 50% of low grade oligodendrogliomas show some enhancement, only about a third of HGG tumors do [1]. Enhancement with central necrosis showing central T2 hyperintensity is a typical hallmark of glioblastoma (GBM) (WHO grade IV), but it can also be caused by a number ofotherdiseases,includingabscesses,multiplesclerosis,lymphoma in immunocompromised people, etc. GBMs can enter the opposite cerebral hemisphere through the corpus callosum and are frequently extremely infiltrative tumors. Additionally, common imaging characteristics of these tumors include satellite lesions and intratumoral bleeding. Particularly indicative of GBM is the presence of a ring-enhancing lesion together with regions of cortex- or deep-nucleus-involving hypo- or nonenhancing tumor infiltration.

The concept of diffusion imaging (DWI) has many applications in neuroimaging. The technique makes the use MRI sequences tailored to capture the movement of molecules of water. Pulse sequences are generated so that water molecules that do not start moving between pulse applications are refocused, and are therefore capable of producing signal, whereas the ones that start moving lose their capability to produce signal in the reconstructed image. The diffusional coefficient can be expressed in terms of both magnitude and direction by gathering diffusion data from a wide range of gradient directions. Additional accurate assessment of the direction variations in ADC in three-dimensional space is obtained by employing additional gradient directions. This technique, the diffusion tensor imaging (DTI) enables the visual representation of dominant white matter tracts, in which the degree of diffusive homogeneities can be presented as colour scheme of three-dimensional directional layouts of nerve fibers (tractography) [2]. Diffusion seems to be preferential along the longitudinal axis than transverse to myelinated nerve fibers. Tractographic data may be used to demonstrate the relationship between tumors and major white matter tracts, which is crucial information for preoperative planning. The capability of DTI imaging to diagnose and estimate the aggressive growth patterns of high-grade malignancies like GBM [3] is another promising application. Many other variations of diffusion imaging, including diffusion kurtosis imaging [4], high b value imaging [5}, histogram curve fitting [6], functional diffusion maps [7-8], and restriction spectrum imaging [9], are currently being researched and may give extra data on complex cellular environments. The most commonly used MR technique for assessing brain malignancies is dynamic susceptibility contrast (DSC) perfusion. High temporal resolution T2*W images are acquired when injectable contrast is actively administered with dynamic image acquisition. As the contrast bolus travels through the brain, it retains its integrity, producing a very brief decrease in signal intensity that represents the vascular contrast level. This signal change can be analyzed using a number of algorithmic approaches in order to calculate the relative cerebral blood volume (rCBV), among other metrics.

The apparent diffusion coefficient (ADC) histogram analysis in a study found that MGMT promoter methylation was associated with a low median ADC of the lower curve [10]. Conversely, higher average ADC values are associated with MGMT promoter methylation [11-12]. One study found higher rCBV in unmethylated versus methylated tumors [13] although another study found no significant association [11]. A study of 43 GBM patients using DCE MRI found that MGMT methylated tumors had increased permeability (higher K trans) compared to unmethylated tumors [12]. The preliminary area underneath the time-to-signal intensity curve from DCE imaging too was revealed from the same team to categorise longevity in promoters unmethylated MGMT GBM, but not in methylated tumors [14]. An accurate marker for the state of the MGMT promoter methylation in patients with GBM was recently developed using a combination of structural and physiological MR imaging. Based on the research, MGMT promoter methylation was linked to increased ADC and decreased rCBF. Following the first biopsy or tumor removal, the diagnostic and prognostic molecular characteristics of GBM are often determined by histological investigation.

However, throughout the course of therapy, GBM may modify its molecular characteristics, for example by down-regulating MGMT expression. [15] A subacute treatment-related re-

sponse with or without clinical worsening may present as "pseudo progression" of the illness in the years and months after therapy. Nevertheless, the rise in radiologic alterations is clinically asymptomatic in the bulk of pseudo-progression cases [16]. Most probable explanations of pseudo progression are a localized cellular response with only an inflammatory component, oedema, and aberrant vascular permeability that results in new or enhanced contrast enhancement on MR imaging studies. Obtaining a non-invasive assessment of molecular state could provide valuable data on disease condition potentially influencing treatment recommendations, as re-biopsy in the majority of these cases is not realistically possible. Keeping this in view, the aim of this study was to evaluate imaging markers such as CT Attenuation, Apparent Diffusion Coefficient (ADC), and Cerebral Blood Volume (CBV) in High Grade Gliomas, and to search for pseudo progression and ADC values after a 3-month gap using DSC MRI with reference to MGMT Promoter Methylation status. These parameters can also predict the Chemosensitivity of methylated gliomas thus improving survival rates. Also, this helps in assessing the response of alkylating agents as treatment modalities

Materials and Methods

From May 2019 to May 2021, the investigation was carried out at the Sher-e-Kashmir Institute of Medical Sciences (SKIMS), Soura, in the Department of Radiodiagnosis & Imaging. On a standard MRI scan, those patients who were found to have primary brain tumors (high grade gliomas) were encouraged to take part in the study. Patients with secondary brain tumors, such as metastatic brain tumors, and patients having claustrophobia were excluded. Study participation was approved by 40 consenting patients. High Grade Glioma patients underwent CT, pre- and post-contrast MRI evaluations, and ADC values were calculated and compared between methylated and non-methylated Gliomas. DNA was extracted for MSP using standard techniques. By chemically converting cytosines that were either methylated or unmethylated to uracil, methylation patterns on the CpG island of MGMT were identified.Using primers made specifically for methylation or unmethylated DNA, MSP was carried out.

Statistics: Microsoft Excel spreadsheets were used to enter the data, which were subsequently exported for analysis into SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Using the Student's t-test, continuous variables were compared and represented as Mean + SD. Statistical significance was defined as a p-value< 0.05.

Results

Using routine sequences like T1, T2, Diffusion sequence and MR perfusion values like ADC, rCBV are calculated Using ROI based measurement of attenuation of most enhancing portion on CT

Preoperatively, the mean CT attenuation value in the methylated tumours was 31.4 HU and that of the unmethylated tumours was 38.1HU (p value <0.001) [Figure 1]. The pre-operative ADC values were significantly higher in the methylated gliomas (mean 1009.1 x 10-6m2/sec) compared to that of the unmethylated gliomas (mean 723.3 x 10-6 m^2/sec) with a p value of <0.001. The rCBV ratios were not significantly associated with methylation or non-methylation (p value 0.059), although increased rCBV ratios were seen in the unmethylated group (mean 2.98) than in the methylated group (2.49) [Table 1].

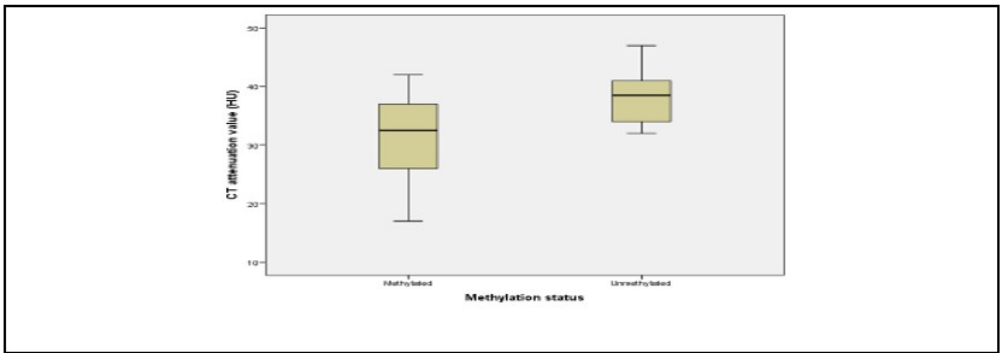

Figure 1: Box and Whisker plots of preoperative CT attenuation

Table 1: Comparison of Preoperative values of imaging markers according to methylation Status

Methylation status		No. of patients	Mean	SD	95% CI	P-value
CT Attenuation Value (HU)	Methylated	18	31.4	7.09	27.9-34.9	<0.001
	Unmethylated	22	38.1	4.35	36.2-40.1	
ADC Value	Methylated	18	1009.1	225.34	897.1-1121.2	<0.001
	Unmethylated	22	732.3	105.98	685.3-779.2	
rCBV Value	Methylated	18	2.49	0.923	2.03-2.95	0.059
	Unmethylated	22	2.98	0.587	2.72-3.24	

The post-operative ADC values between the methylated (mean ADC value 1101 x 10-6m2/sec) & unmethylated (mean ADC value 890.3 x 10-6m^2/sec) gliomas had a significant difference with a p value of 0.002%. The post-operative rCBV values did not significantly differ between the methylated (mean value 1.73) and unmethylated (mean value 2.48) groups with a p value of 0.081 [Table 2].

Table 2: Comparison of Postoperative imaging markers according to methylation Status

Methylation status		No.ofpatients	Mean	SD	95% CI	P-value
ADC Value	Methylated	9	1101	150.1	985.7-1216.3	0.002
	Unmethylated	10	890.3	68.6	841.2-939.4	
rCBV Value	Methylated	9	1.73	0.669	1.21-2.25	0.081
	Unmethylated	10	2.48	1.028	1.75-3.21	

The methylated group showed significant differences in the ADC values between pseudoprogression (mean ADC 1167x 10-6m2/sec) and true progression (mean ADC 870 x 10-6m2/sec) with a p value of 0.002. No significant difference was seen in the rCBV values of methylated tumour between pseudoprogression (mean rCBV 1.46) and true progression (mean rCBV 2.47). Significant difference was noted in rCBV values in patients with unmethylated tumours between pseudoprogression (mean rCBV 1.09) & true progression (rCBV 3.08) with a p value of < 0.001[Table 3].

Table 3: Postoperative ADC and rCBV values between pseudo and real progressions

Methylation status		Pseudoprogression			Real progression			P-value
		MeanADC	SD	95% CI	MeanADC	SD	95% CI	
ADCValue	Methylated	1167	82.7	1090.5-1243.5	870	42.4	488.8-1251.2	0.002
	Unmethylated	923.3	25.17	860.7-985.9	876.1	77.92	804.1-948.2	0.348
rCBVValue	Methylated	1.46	0.439	1.05-1.86	2.7	0.141	1.43-3.97	0.007
	Unmethylated	1.09	0.115	0.81-1.38	3.08	0.445	2.67-3.49	<0.001

Discussion

In our research, we found a statistically significant positive correlation between pre-operative unenhanced CT attenuation value and tumour non-methylation. In the methylated tumors, the mean CT attenuation value was 31.4 HU, whereas it was 38.1 HU in the unmethylated tumors (p value 0.001). This is consistent with the research done in 2012[11] by Moon WJ et al. The electron density and atomic number of the tissue composition in a given volume are directly correlat-

ed with the CT attenuation value, and the cellularity of a tumor is correlated with its CT attenuation. The latter is also somewhat correlated with the tumor's level of heterogeneity. Compared to lymphoma, highly cellular tumors like High Grade Gliomas have a more diverse texture. When contrasted to unmethylated gliomas, methylated gliomas might exhibit a more heterogeneous or less cellular tumor appearance, which may be reflected by a lower CT attenuation number. It is well documented that methylating the MGMT promoter in HGGs leads to decreased MGMT expression, which in turn slows the restoration of DNA damage carried on by chemotherapy and radiation treatment. According to our observations, a majority of past research has revealed that tumors with unmethylated promoters had substantially lower ADC values or ADC ratios, and that the mean ADC was positively correlated with the methylation status of the MGMT promoter. These include research projects carried out by Moon W [11] in 2012 and Romano A, et.al [17] in 2013. ADC has previously been proposed as a promising substitute biomarker for the methylation of MGMT's promoter [18–19]. The apparent diffusion coefficient (ADC), that represents physiological diffusion at the microscopic level, suggests that a tissue with much more cells will usually have less free mobility of water molecules, which would convert to a lower ADC. ADC therefore has been designated a tumor cellularity imaging marker. The minimal ADC on pre-treatment MRI can be considered as a valuable clinical indicator for predicting the survival of patients with malignant gliomas, as per Murakami et al. The rCBV proportions between the methylated and unmethylated groups were greater in the unmethylated group (mean 2.98) than in the methylated group (2.49) in our study, while the result was not statistically significant (p value 0.059). Contrarily, Han et.al [21] and several other studies have found a favourable relationship between both the tumour unmethylation as well as the rCBV or rCBF ratios. One reason for this is because studies have shown that rCBV adjusted for contrast agent extravasation relates better with the grade of tumor in High Grade Gliomas [22], which explains why we did not adjust the T1 shortening effect by preload contrast injection. 19 out of 40 patients experienced new or enlarged enhancing lesions seen on follow-up post-operative imaging. Nine patients out of them had methylation gliomas, while ten patients had unmethylated gliomas. Out of 19 patients, we later discovered that 10 (52.6%) had pseudoprogression, whereas 9 (47.3%) had gradually worsening clinical outcomes and were classified as having actual disease progression, which was later verified on histology.

However, only a small number of studies have looked at the value of combining these two procedures; the majority of them have looked at these two techniques separately in individuals with suspected treatment-related alterations. Our work compared the obtained parameters across methylation and unmethylated MGMT tumors and evaluated the contribution of DWI and perfusion imaging in detecting pseudoprogression. [Figure 2 a-d]

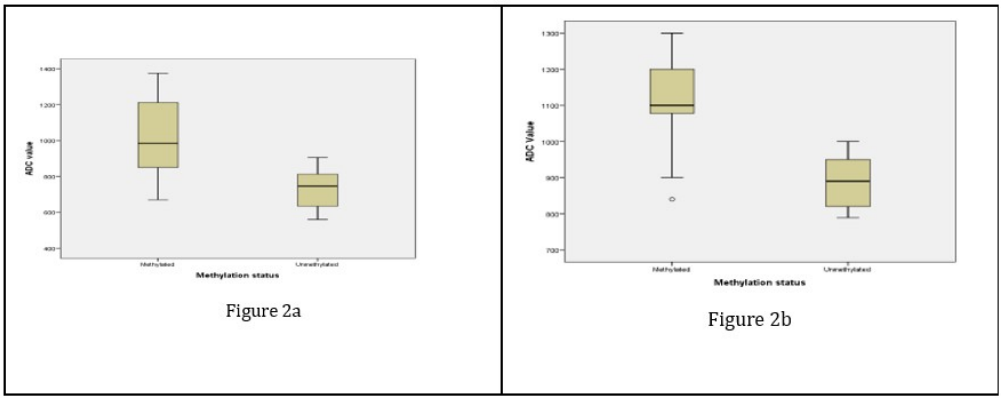

Figure 2a: Box and Whisker plots of the pre-operative ADC values

Figure 2b: Box and Whisker plots of the post-operative ADC values

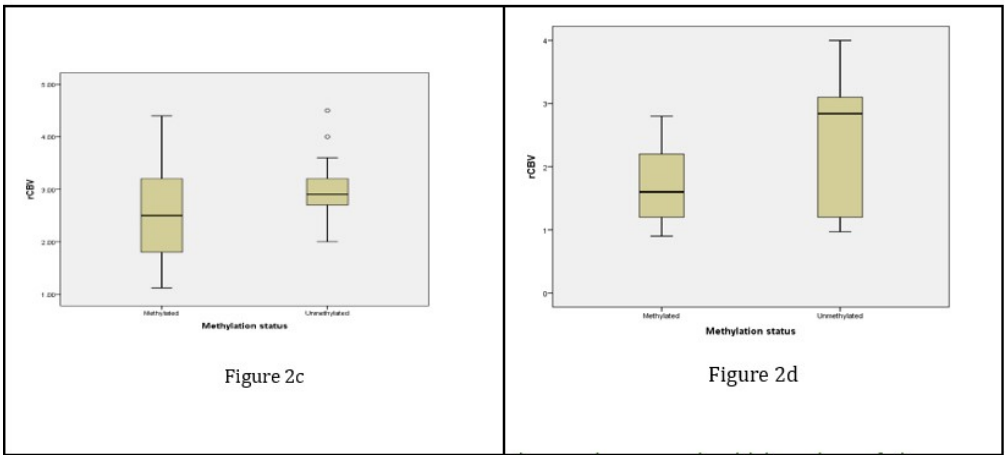

Figure 2c: Box and Whisker plots of the pre-operative rCBV values

Figure 2d: Box and Whisker plots of the post-operative rCBV values

Conclusions

The MGMT promoter methylation status in high grade gliomas can be predicted by pre-operative imaging, and post-operative imaging can help identify patients who have pseudoprogression in relation to their methylation status, which is crucial for predicting the response to therapy as well as overall outcome and survival. Thus, we draw the conclusion that high ADC values and pseudoprogression can serve as stand-in indicators of promoter methylation in high grade gliomas.

Author Contributions

"Conceptualization, Prof. Feroze Shaheen; methodology, Prof Feroze Shaheen.; validation, Zahoor Ahmed.; formal analysis, Zahoor Ahmed; investigation, Dr Gowhar Nazir., Dr Minsha Hameed.; data curation, Dr Gowhar Nazir; writing—Dr Inzamam Wani.; writing—review and editing, Dr Minsha Hameed.; supervision, Prof Feroze Shaheen. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

"This study was conducted in accordance with the Declaration of Helsinki, and approved by

the Institutional Review Board (or Ethics Committee) of SKIMS Soura Srinagar Kashmir" for studies involving humans.

Informed Consent Statement

Not applicable

Conflicts of Interest

The authors declare no conflict of interest.

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