VOLUME-6 | ISSUE-2 | FEBRUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

DYNAMIC SUSCEPTIBILITY CONTRAST ENHANCED MRI PERFUSION IMAGING IN EVALUATION OF POST CHEMO - RADIOTHERAPY TREATED GLIOMAS FOR RECURRENCE – COMPARISON WITH RESPONSE ASSESSMENT CRITERIA

Radiology

KEYWORDS: Glioma, DSC MRI Perfusion, Macdonald Criteria, RANO Criteria, RECIST 1.1

Dr Gurdarshdeep Singh Madan	MD (Radiodiagnosis) Classified Specialist Radiodiagnosis, Military Hospital Namkum Ranchi
Col Giriraj Singh	MD (Radiodiagnosis), DNB(Radiodiagnosis) Senior Advisor Command Hospital (EC) Alipore Kolkata
Brig S Bhatnagar	Consultant Radiology and Radiotherapy Command Hospital (CC) Lucknow Cantonment Lucknow
Dr BK Chakrabarty	Graded Specialist (Pathology) Military Hospital Namkum Ranchi

ABSTRACT

Aim: To compare Dynamic Susceptibility Contrast Enhanced (DSC) Magnetic Resonance Perfusion Imaging with clinicoradiological response criteria in post chemoradiotherapy treated gliomas. **Materials and Methods:** Forty patients of histologically proven gliomas were chosen post chemoradiotherapy and were evaluated with MRI Perfusion The findings were correlated with clinico radiological response criteria. **Results** There was good statistical coorelation of DSC MRI with all the response criteria in complete response and partial response subsets (p value <0.001). However, DSC MRI showed good correlation with RANO Criteria (Pearson Correlation = .642 and 2 tailed significance p value = 0.001). The correlation with other response criteria were not statistically significant. **Conclusion:** RANO Criteria is the presently accepted clinico-radiological criteria which has superseded other response criteria and DSC MRI perfusion imaging shows statistically good correlation among all the subset of responses.

Introduction

Gliomas are most common malignant primary brain neoplasms of the brain in adult patients accounting for four to five per hundred thousand (1,2). According to WHO, low grade Glioma are much less common. Among them the commonest being Grade II Glioma. High grade gliomas are more common with Glioblastoma Multiforme (GBM) (Grade IV Glioma) being the commonest overall (3). In high grade Gliomas, median survival is less than a year and even in best of the circumstances is about two years (4). Even treatment with procarbazine, lomustine, vincristine chemotherapy (PCV) in oligodendroglioma and oligoastrocytoma failed to translate into good survival rates (5,6). However, combination of temozolomide based concomitant and adjuvant radiochemotherapy seems to hold promise and are now standard of care for recently diagnosed gliomas (7). The criteria for assessing response are based on morphological cross-sectional imaging especially Magnetic Resonance Imaging (MRI) along with clinical assessment and corticosteroid use (8). Dynamic Susceptibility Contrast enhanced Magnetic Resonance Imaging (DSC MRI) is a robust modality which provides functional as well as anatomical information about the tumor and can correlate well with the histological grade of the glioma as well as can predates the MR morphological findings in evaluation of recurrence (9). The aim of this study is to compare and correlate DSC MRI findings with clinico-radiological response criteria.

Materials and Methods

The prospective study was done over span of 23 months at tertiary care oncology center in department of Radiodiagnosis and department of radiation oncology. The patients were diagnosed based on clinical assessment and imaging studies with biopsy done for patients with high grade gliomas on imaging studies. It consisted of 43 patients out of which 3 were lost to follow up. The 40 patients (27 males, 13 females; age range – 23 to 67 years, mean age -36.3 years) were subjected to MRI Scan before initiation of therapy and 12 weeks after chemoradiotherapy completion. The MRI Perfusion Cerebral Blood Flow (CBF) images were obtained using leakage correction protocol and the images were analysed by two independent experienced radiologists (GSM,GS) blinded to MRI morphological images and the signal intensity from region of interest (ROI) of the tumor was divided by the signal intensity of the similar ROI from the contralateral side to provide normalized CBF to reference tissue. The arterial Input function (AIF) was also applied. The process was repeated in post chemoradiotherapy MR Perfusion imaging. The ratio of post chemoradiotherapy normalized CBF to pre chemoradiotherapy normalized CBF was used assess response (Table 1). An experienced Radiation oncologist (SB) evaluated clinicoradiological response criteria using Macdonald's Criteria, Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and Response Assessment in Neuro-Oncology Working Group (RANO) Criteria.

Table 1: Criteria to assess post chemoradiotherapy response on MRI perfusion images.

Ratio of normalized CBF in post chemoradiotherapy to prechemo-radiotherapy scan	Additional features	Response assessment	Remarks
<0.5	Total disappearance of lesion on rCBF perfusion images. No new lesions visualized on rCBF images	Complete Response	All of the following required
0.5 to 1.2	> 50% decrease in the sum of products of perpendicular diameters of all measurable lesions on rCBF images with no new lesions as compared with pre chemoradiotherapy images	Partial Response	All of the following required
1.2 to 2.5	Does not qualify for complete response, partial response or progression.	Stable disease	
>2.5	>25 % increase in the sum of products of perpendicular diameters of all measurable lesions on rCBF images as compared with pre chemoradiotherapy images. Any new lesion	Progressive disease	Any of the above

The results obtained were statistically analysed using IBM SPSS ver 20.0(BKC).

Results

Out of the forty patients evaluated in this study, histological diagnosis was obtained in 37 patients. 35%(n=14) of patients were graded as WHO Grade IV astrocytoma, 20% (n=8) as WHO grade III astrocytoma. The rest had low grade gliomas (37.5% WHO Grade II astrocytoma (n=15). Average time for obtaining MRI Scan post completion of chemoradiotherapy was 12weeks 6 days (range 12 weeks 0 days to 14 weeks 2 days). The response assessed by clinico clinic- radiological scores are described in Table 2.

On exclusive analysis of DSC MRI perfusion images, there were 30% patients showed complete response(n=12) and 35% patients showed progressive disease(n=14). Partial response (n=7) and stable disease(n=7) were seen in fourteen patients.

Table 2 – Results of evaluation of patients on various clinico-radiological response criteria

	MacDonald's Criteria	RECIST 1.1	RANO
Complete Response	16 (40.0%)	16 (40.0%)	13 (32.5%)
Partial Response	15 (37.5%)	7 (17.5%)	7 (17.5%)
Stable Disease	7 (17.5%)	11 (27.5%)	3 (7.5%)
Progressive Disease	2 (5.0%)	6 (15.0%)	17 (42.5%)

DSC Perfusion images showed overall good correlation with all response criteria (Table 3). However, the statistical analysis was skewed by extremely good correlation in complete response and partial response subset. Even on overall analysis correlation was best between DSC MRI and RANO criteria.

Table 3 – Overall correlation and significance of paired sample correlation between DSCMRI and clinicoradiological response criteria.

	Correlation	p value (significance)
DSC MRI & Macdonald criteria	.851	<.001
DSC MRI & RECIST 1.1	.901	<.001
DSC MRI & RANO	.964	<.001

On exclusion of complete and partial responses, DSC MRI showed statistically relevant correlation with RANO criteria using Pearson correlation and 2 tailed significance (Table 4).

Table 4 – Correlation and significance on Pearson sample correlation and 2 tailed significance between DSCMRI and clinicoradiological response criteria in patients excluding complete and partial response.

	Pearson Correlation	2 tailed significance
DSC MRI & Macdonald criteria	.558	0.009
DSC MRI & RECIST 1.1	.542	0.011
DSC MRI & RANO	.640	0.001

Discussion

Malignant gliomas are infiltrative and extremely vascular tumors. Their growth is dependent on proangiogenic cytokines like vascular endothelial growth factor (VEGF). High grade gliomas inherently have poor prognosis due to infiltration of the surrounding brain parenchyma by tumor cells which is compounded by blood brain barrier, that hampers the delivery of the chemotherapy agents. In addition to these, refractory nature of tumor cells and rapid mutation leads to early development of drug resistance (10).

Conventional MRI studies have been used to define tumor volume for over two decades but the studies are suboptimal as tumor cells extends beyond the signal intensity changes of conventional T1 and T2 weighted images(11). This is further complicated in post chemo radiotherapy patients where tumor necrosis and use of antiangiogenic therapy such as Bevacizumab and Cediranib can produce reduced contrast enhancement (12).

In view of these, various clinico-radiological criteria were developed to assess response in post chemo-radiotherapy patients. In 1990, Macdonald et al published a Computed Tomography (CT) Scan based objective criteria measuring enhancing tumor area. It also considered neurological status of the patient and use of corticosteroids. The Macdonald criteria was subsequently extrapolated to MRI (13,14). Among the various limitations of Macdonald Criteria was its use of increase in size by 25% of enhancing lesion as surrogate for disease progression warranting change of treatment. However, contrast enhancement is nonspecific and reflects breach of blood brain barrier. In addition, abnormal enhancement is also seen in post-surgical changes, ischemia, and post radiotherapy changes such as acute radiation effects and radiation necrosis. These are even prominent in patients receiving Temozolomide and other anti angiogenic therapies. Twenty to 30% of patients undergoing radiotherapy show increased contrast enhancement on MRI that eventually subsides without any change in therapy. This is called Pseudo progression. This phenomenon is even more enhanced with use of temozolomide. Hence, the need was felt for a revised criteria.

RECIST was first introduced in 2000 and was revised to RECIST version 1.1 in 2009. Numerous studies have shown good concordance in assessing response using one dimensional, two dimensional, three dimensional, volumetric measurements in freshly diagnosed and recurrent high grade gliomas with exception of three dimensional method which proved to be inferior to one and two dimensional methods. However, till date adequate studies to validate RECIST version 1.1 criteria in high grade gliomas have not been performed.

In 2010, Response assessment in Neuro- Oncology (RANO) working group proposed updated response criteria for high grade glioma. Pseudo response, contrast enhancement reduction with subsequent increase in T2 and FLAIR signals suggesting infiltrative tumor, in patients who had received antiangiogenic therapy with or without therapy was recognized by the group. Hence, appearance of these T2 and FLAIR signals were included in progressive disease. (8)

DSC MRI is a robust technique which uses T2* - weighted echo planar MR sequences and calculates relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF) and Mean Transit Time (MTT). Local alteration in these parameters in region of the tumor reflect changes in tumor vascularity. As tumor – mimicking changes in pseudo progression lack angiogenesis, MR perfusion studies hold promise in distinguishing pseudo progression from true progression. Assessment of r CBF has been highly predictive of treatment outcomes. (19)

In our study we used small – flip- angle echo planar GRE imaging as leakage correction method. The effect of leakage of contrast media through damaged blood brain barrier was further offset by employing rCBF as a method of evaluation. There was good overall correlation in DSC MR Perfusion based response criteria and other clinicoradiological criteria. This was skewed due to extremely high degree of correlation in patients showing complete response.

We also evaluated correlation between the DSC MRI and other criteria in stable disease and disease progression subsets. There was statistically relevant correlation between RANO and DSC MRI with kappa value of 0.640 and p value of 0.001. No other clinicoradiological criteria had good correlation with either DSC MRI or RANO.

The cases number 24, 29 and 37 in which the patients received antiangiogenic treatment (bevacizumab) along with radiotherapy, they showed disease progression on RANO but stable disease on DSC

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perfusion images. The rCBF images showed relative increase of 17%, 21.4% and 23.8% in size in cases 24, 29 and 37 respectively. However, there was significant increase in T2 and FLAIR white matter changes. This reflects that the T2 and FLAIR signal intensity changes antecedes significant changes in perfusion indices.

Although DSC perfusion imaging was suboptimal in detecting progression of disease, especially in patients who had received antiangiogenic treatment, it can be of immense value addition to convention MRI imaging techniques in RANO criteria. It is still superior to contrast enhancement in evaluating the size of the tumor and assessing tumor response.

The authors believe that more research is needed before MR perfusion imaging is used as a criteria for assessing therapy response in high grade glioma, especially in patients who have received antiangiogenic treatment. However, this modality holds promise for increasing our knowledge and understanding of tumor progression, pseudo response and pseudo progression.

Conclusion

We propose that DSC MRI perfusion study holds significant promise in increasing understanding of tumor angiogenesis and its blood flow alteration. With more detailed studies and research DSC MRI can augment the clinico radiological criteria for assessing response of chemo radiotherapy in high grade gliomas.

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