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Diagnostic Accuracy and Imaging Appearance Glioblastoma Multiforme on MRI and MRS

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Author`s Contribution

[1]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Final approval of the version to be published. [2,4,5]Drafting the work or revising it critically for important intellectual content, [3]Active participation in active methodology, statistical analysis

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ABSTRACT

Objective: To determine the diagnostic accuracy of contrast-enhanced MRI with conventional sequences and MR Spectroscopy in the diagnosis of Glioblastoma Multiforme, taking histopathology as the gold standard. We also determined the MR imaging appearance of GBM on conventional sequences.

Methodology: This descriptive cross-sectional study was conducted at a tertiary care hospital from August 2019 to August 2020 on 165 adult patients suspected of having an intracranial space-occupying lesion. Informed consent was sought and a questionnaire was filled out for patient data, MRI imaging findings, and MRS results. Histopathology results were subsequently followed and recorded. The diagnostic accuracy of contrast enhanced MRI brain as well as MRS was determined in terms of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy, taking histopathology as gold standard.

Results: In a total of 165 patients selected for the study, the mean age was 56.34±10.04 years with a male to female ratio of 1:1 and the frontal lobe being the most common location (34.5%). In histopathological positive GBM cases, margins of the mass were ill-defined in 55.1%, intralesional low ADC values were observed in 63.3%, signal drop out on susceptibility imaging in 42.8%, and MRS with raised choline and reduced NAA in 75.5%. MRI had a sensitivity of 81.6% and specificity of 94.8%, and MRS has a sensitivity of 75.5% and a specificity of 100%.

Conclusion: Ill-defined margins, necrosis, and hemorrhage are important MRI features suggesting GBM. MRS combined with conventional MR sequences has high sensitivity and specificity in its diagnosis.

Keywords: Glioblastoma multiforme, histopathology, MRI, MR Spectroscopy.

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Introduction

Primary central nervous system tumors have one of the highest cancer incidence rates worldwide as well as in Pakistan; approximately 400,000 cases were reported in USA between 2012 and 2016.[1] Neuroepithelial tumors are commonest tumors- Glioblastoma multiforme is the largest and most aggressive subtype, with a global incidence of <10 per 100,000 people. GBM arises from astrocytes, and is characterized by rapid growth, thus having one of the worst 5 year survival rates amongst all cancer types.[2]

Imaging techniques are being used to track the diagnosis, progression, and recurrence of central nervous system space-occupying lesions. Histopathology, which is performed on a tissue sample obtained by invasive neurosurgery, is the gold standard for diagnosis.[3] According to the World Health Organization (WHO) categorization of brain tumors, necrosis and endothelial proliferation are defining histopathologic features of grade IV tumors.[4]

The standard imaging method for diagnosing and localizing brain tumors, as well as performing stereotactic biopsies, planning operations, and separating post-treatment alterations from recurrence, is magnetic resonance imaging (MRI). [5] T1-weighted, T2-weighted,

T2-based fluid attenuation inversion recovery (FLAIR), DWI with apparent diffusion coefficient (ADC), susceptibility-weighted or gradient echo imaging, and contrast enhanced T1-weighted sequences are all examples of traditional MRI sequences.[6]

Necrosis, enhancement, mass effect, peritumoral tissue, and midline displacement are all essential aspects of the mass that can be detected using standard imaging. On typical MRI sequences, the complicated character of glioblastoma is visible macroscopically. The most common imaging appearance is a single peripherally enhancing lesion, but multiple foci of enhancement within a larger area of T2-weighted signal abnormality (multifocal glioblastoma) or discrete enhancing regions without evidence of connecting tumor (multicentric glioblastoma) are also appreciated.[7]

In pre-and post-operative comprehensive characterization of GBM, advanced MRI sequences such as Functional MRI (fMRI), diffusion techniques such as diffusion tensor imaging generating rich tractography maps, dynamic contrast enhanced sequences (DCE), MR spectroscopy (MRS), and radiomic studies are used.[8]

Diffusion-weighted imaging (DWI) is inversely connected with tumor cellularity and offers information on random microscopic mobility of water protons. Low grade cancers have lower cellularity and higher ADC values than high grade tumors with high cellularity and low ADC values.[9]

Water-soluble brain metabolites are assessed non-invasively using MRS based on their precession frequency. Creatinine (Cr), N-acetyl aspartate (NAA), choline (Cho), lactate, lipids, alanine, glutamine, glutamate, 2-hydroxyglutarate, citrate, and myoinositol are some of the metabolites that are routinely measured on MRS. MRS has a 92 percent specificity for distinguishing neoplastic from non-neoplastic tissue.[10] It has a diagnostic accuracy of 80–97% in distinguishing tumor development from radiation necrosis, which is better than conventional imaging alone in glioma grading.[11]

With the deployment of advanced MR modalities, including novel image processing and machine learning approaches, to aid in early diagnosis and treatment planning in a tailored fashion.[12] The objective of this study is to determine the diagnostic accuracy of contrast enhanced MRI with conventional sequences and MRS in the diagnosis of glioblastoma multiforme taking histopathology as the gold standard. We also determined the morphological appearance of GBM on the MR imaging in different conventional and MR spectroscopy.

Methodology

This is a descriptive cross-sectional study performed at the Department of Radiology, Dow University of Health Sciences, Karachi from August 19th August 2019 to 18th August 2020. Patients of either gender with ages between 40 – 80 years clinically suspected of having a space-occupying lesion were included in the study. The exclusion criteria were (i) post-operative/post treatment patients and (ii) non availability of histopathological reports Sample size was calculated by using the WHO sample size calculator, taking the expected sensitivity and specificity of contrast enhanced MRI in determining GBM as 74.7% and 94.7% respectively[13] prevalence is taken as 54%[14], desired precision for sensitivity as 0.09 and for sensitivity 0.05. The estimated sample size was 165.

After taking IRB approval, all patients with clinically suspected intracranial space occupying lesion referred to the Radiology department of Dow University of Health Sciences for contrast enhanced MRI were included. Informed written consent was taken; patients' Performa were filled for demographic characteristics and patient registration number. Contrast enhanced MRI brain was performed according to the departmental protocol on Siemens MRI 1.5 Tesla scanner. T1-weighted, T2-weighted, T2- weighted fluid attenuation inversion recovery (FLAIR), susceptibility weighted (SWI) and diffusion-weighted imaging (DWI) as well as fat sat T1W post contrast sequences was obtained. The slice thickness was 8 mm. MRS was performed using single voxel technique in all patients.

Images were analyzed by a senior radiologist having at least 5 years post fellowship experience. Relevant patient data was recorded on the performa by the principal investigator (PI). MRI findings in terms of signal intensity on T1W, T2W, SWI, DWI, and ADC as well as imaging appearance in terms of location, margins, and enhancement pattern was recorded. MRS findings were recorded in terms of Choline and NAA. MRS was considered positive for GBM if it demonstrated raised choline and reduced NAA values. Histopathology results were then followed by the principal investigator and recorded on the same performa.

A database was developed on SPSS version 21.0 and mean and standard deviation were calculated for quantitative variables including age, duration of symptoms, and diameter of mass on MRI. Percentages for qualitative variables, including gender, were calculated. The diagnostic accuracy of contrast enhanced MRI brain and MRS was determined in terms of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy, taking histopathology as the gold standard. Effect modifiers were controlled through stratification of age, gender, duration of symptoms, and diameter of mass to see the effect of these on outcome variables. A post-stratification 2 x 2 table was used to calculate sensitivity, specificity, PPV, NPV and diagnostic accuracy.

Results

In a total of 165 patients selected for the study, the mean age was 56.34±10.04 years with a male to female ratio of 1:1. The mean diameter of the mass on MRI was 3.75±0.99cm. TIW was low in most of the cases The mass margins of 158 (95.8%) were well defined in 60 (36.4%) and ill-defined in 105 (63.6%). The frontal lobe was the most common location, seen in 57(34.5%) of cases. Enhancement was peripheral in 97 (58.8%) and diffuse in 66 (40%) cases, respectively. Signal drop out on susceptibility weighted imaging was observed in 75(45.5%) cases. Magnetic Resonance Spectroscopy observed atypical features in 127(77%) cases and typical in 38(23%) cases. (Table I).

In histopathologically positive GBM cases, margins of the mass were ill defined in 27(55.1%) and well defined in 22(44.9%). Frontal lobe was the commonest location 51.0%, followed by parietal lobe (22.4%), occipital (14.3%) and temporal lobes (12.2%). Intralesional low ADC values were observed in 63.3% of GBM cases, signal drop out on susceptibility imaging in 42.8%, and MRS with raised choline and reduced NAA in 75.5%.

The cross tabulation between the findings of histopathology and MRI showed that 40 (81.6%) of the total 49 cases found to be positive by histopathology were labeled as positive by MRI while 110 (94.8%) of the total 116 cases found to be negative by histopathology were labeled as negative by MRI. The study results therefore revealed that while keeping histopathology as gold standard for the diagnosis of glioblastoma multiforme, MRI has a sensitivity of 81.6% and specificity of 94.8%.

The cross tabulation between the findings of histopathology and MRS showed that 37 (75.5%) of the total 49 cases found to be positive by histopathology were labeled as positive by MRS while all 116 (100%) of the cases found to be negative by histopathology were labeled as negative by MRS. The study results therefore revealed that while keeping histopathology as gold standard for the diagnosis of glioblastoma multiforme, MRS has a sensitivity of 75.5% and a specificity of 100%. (Table II)

Discussion

Glioblastoma is an incurable, notorious primary brain tumor of adult despite of aggressive treatment. The inherent heterogeneity is a major hurdle to its diagnosis and treatment, resulting in disparity in response to treatment. This heterogeneous nature of GBM makes

Table I: MRI Imaging appearance of clinically suspected cases of intracranial space occupying lesions (GBM).

Margins	Well Defined	60(36.4%)
	Ill Defined	105(63.6%)
Location	Parietal	54(32.7%)
	Frontal	57(34.5%)
	Temporal	19(11.5%)
	Occipital	27(16.4%)
	Posterior Fossa	8(4.8%)
Enhancement	Peripheral	97(58.8%)
	Diffuse	66(40.0%)
	None	2(1.2%)
Susceptibility weighted imaging (SWI) Drop out signals	Yes	75(45.5%)
	No	90(54.5%)
Diffusion weighted imaging	High	60(36.4%)
	Low	105(63.6%)
Apparent diffusion coefficient.	High	44(26.7%)
	Low	121(73.3%)
Magnetic Resonance Spectroscopy	Atypical	127(77.0%)
	Typical	38(23.0%)

Table II: Cross Tabulation between MRI and MRS Findings and Histopathology n=165)

	Histopathology			Histopathology	
MRI Findings	**Positive** Count (%)	**Negative** Count (%)	**MRS Findings**	**Positive** Count (%)	**Negative** Count (%)
	40 (81.6)	6 (5.2)		37 (75.5)	**Nil**
	9 (18.4)	110 (94.8)		37 (75.5)	116 (100)
Sensitivity: 81.6%, Specificity 94.8%, PPV =86.9%, NPV=92.4%			**Sensitivity: 75.5%, Specificity: 100%, PPV=100%, NPV=90.6%**		

histological analysis limited and ineffective in determining complete genotypic and phenotypic characteristics. This is particularly true when a single biopsy is performed. [15] These factors have led to the rapid evolution of non-invasive diagnostic approaches such as advanced MRI techniques, nuclear imaging, liquid biopsy, and new integrated approaches including radiogenomics and radiomics.[16] Advancement in noninvasive tests is pivotal to the success of patient tailored treatment regimes. MRI is the preferred imaging modality for GBM, both for diagnosis and post-treatment monitoring.[8]

Equal gender distribution was observed in this study in contrast to some local and international studies by Ahmed et al[17] and Ghangoria et al[18] which showed a male predominance in CNS tumours (more than 60% of all cases). However, a study from Nepal by Aryal G[19] reports equal distribution of CNS tumors in both genders. In this study, the mean age was 56.34±10.04 years, which correlates with another study conducted in Pakistan by Ayaz et al[20] in 2011 and by Darlix at el from France between 2006 to 2011.[21] They also reported the most patients in the 5th decade.

The frontal lobe was the most common site of GBM in this study, followed by the parietal, occipital, and temporal lobes. A number of other researches, notably Larjavaara et al[22] and Ostrom QT et al[23], have identified the frontal lobe as the most common site of malignant intracranial tumors. However, these studies found that the temporal and parietal lobes were the next most prevalent sites, which contradicts this study finding. The difference could be due to difference in the studied population and small sample size of our study. (Figure 1)

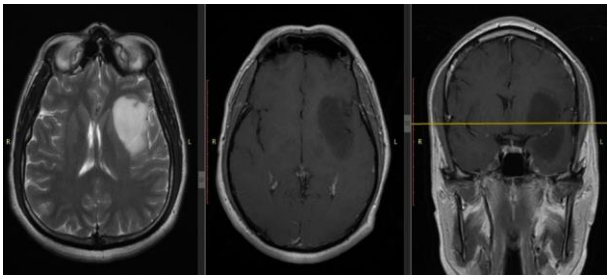

Figure 1. MRI (a)T2WI axial, (b) and (c) T1 axial and coronal post contrast images showing abnormal signal intensity lesion in the left inferior frontal and anterior temporal lobes appearing hyperintense on T2W without significant post contrast enhancement.

A local study conducted by Danish et al from 2009 to 2018 reported the temporoparietal region to be the most common location, followed by the frontal lobe.[24] However, their study included all CNS tumors and all age groups, which may account for the difference in results.

Another important imaging parameter that was recorded in our study was tumor margin. We found that the majority of GBM have ill-defined margins. It is considered to be one of the most important parameters to differentiate GBM from brain metastases by study conducted by Abd-Elghany. GBM is frequently misdiagnosed due to its infiltrative growth pattern and peritumoral edema, which is comprised of peritumoural infiltrating neoplastic cells.[25]

Signal drop out on SWI sequences was observed in 42.8% of GBM cases in our study. Micro hemorrhages and neoangiogenesis can be sensitively detected by SWI sequences and are graded according to the intratumoral susceptibility signals (ITSS). ITSS is directly proportional to tumor grade. Moreover, studies are utilizing SWI sequences to determine the molecular subtype of glioma, that is, IDH1 mutations and MGMT methylation are related to ITSS grading. Thus opening new horizons in non-invasive prediction and preoperative personalized surgical treatment based on molecular pathology.[26]

Advanced MRI techniques are utilized to determine the pathophysiologic characteristics of brain tumors. These specialized techniques include perfusion- weighted imaging (PWI), MR spectroscopy (MRS), diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI).[27]

The DWI technique is also used to grade gliomas which is not possible with conventional MRI sequences. In solid tumor tissue, there is increased cell density limiting diffusion thus resulting in lower ADC values.[28] Intralesional low ADC values were observed in 63.3% of GBM cases in our study. It correlates with previously conducted studies, including a study by Al-Agha et al. which also showed that ADC values were negatively correlated with glioma grade.[29]

DWI imaging is used not only in the diagnosis and grading of tumors but is also considered useful in (i) estimating the extent of tumor infiltration, (ii) post intervention follow up for residual or recurrent disease (iii) improving neurosurgical approach, (iv) evaluating early treatment response or progression, and (v) in

differentiating between true and pseudoprogression.30 However, on the other hand, the SPECTRO GLIO trial has advocated that PWI and DWI do not have distinct specificity in predicting recurrences. Additional studies into the use of these advanced MRI sequences is required.[31]

Metabolic changes in brain tumors are non-invasively studied with Magnetic Resonance Spectroscopy (MRS). Increased levels of Choline and reduced levels of NAA are detected in malignant tumors. These signify increased cellular membrane turnover and breaking of neuronal integrity respectively. In our study MRS had a sensitivity of 75.5% and specificity of 100%. Another local study by Amin UA et al showed sensitivity of 90.7% and specificity of 94.4%.[32] (Figure 2)

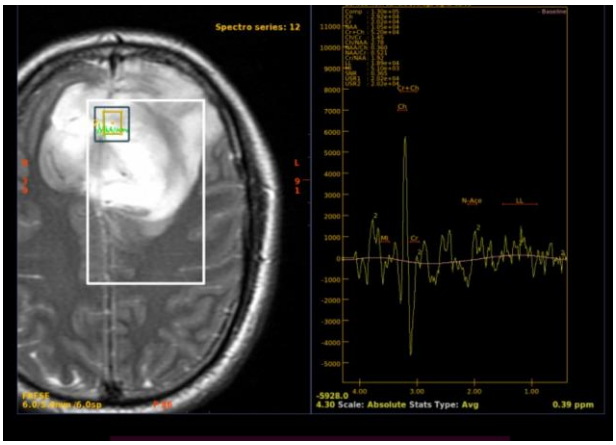

Figure 2. MRI Spectroscopic study shows an abnormal signal intensity lesion involving bilateral frontal lobes. MRS shows raised choline and reduced NAA peaks with Cho/NAA of more than 5, favoring the diagnosis of high grade glioma

It is one of few local studies in our population to describe MRI features of GBM including MRS findings. However major limitation is that it is a single center study with small sample size.

Conclusion

MRI is the imaging modality of choice for diagnosis and management of intracranial space occupying lesions particularly GBM. This study shows that GBM has equal prevalence among both genders in this study; it is most commonly located in the frontal lobe; necrosis and hemorrhage are important conventional MRI features. On advanced MRI sequences, diffusion restriction is seen on DWI and ADC sequences. MRS combined with conventional MR sequences has high sensitivity and specificity in its diagnosis. Further studies focusing on advanced MRI techniques are required to better determine tumor margins and post-operative recurrence.

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