ORIGINAL ARTICLE

DIAGNOSTIC ACCURACY OF MAGNETIC RESONANCE SPECTROSCOPY IN DIAGNOSING GLIOBLASTOMA BY TAKING HISTOPATHOLOGY AS A GOLD STANDARD

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ABSTRACT

BACKGROUND: Glioblastoma (GBM) is the most aggressive brain tumor, and despite multimodal treatment with surgery, radiation and chemotherapy patients generally show incurable relapse of disease. The aim of the study was to determine the diagnostic accuracy of magnetic resonance spectroscopy (MRS) in diagnosing glioblastoma by taking histopathology as a gold standard. **MATERIALS AND METHODS:** This cross-sectional descriptive study was conducted from 19-12-2017 to 18-06-2018 enrolling 83 patients. MR Spectroscopy was performed through single voxel technique in all these patients. Initially, post contrast conventional MR imaging was done to localize the lesion and then voxel was placed on volume of interest. Specimens of patients undergoing intracranial biopsy in Shifa international hospital Islamabad were sent for histopathological analysis in pathology department and findings of MRS were compared with histopathology report. **RESULTS:** Patients ranged between 30-70 years of age. Mean age of the patients was 52.2 ± 12.6 years. There were 49 males (59%) and 34 females (51%). Mean duration of disease was 2.0 ± 1.7 year and mean size of lesion was 54.3 ± 26.9 mm. Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma showed sensitivity 90.7%, specificity 94.4%, positive predictive value 98.3%, negative predictive value 73.9% and diagnostic accuracy was 91.5%. Stratification with regard to age, gender, duration of disease and size of lesion was carried out. **CONCLUSION:** In conclusion, present study demonstrated a clear advantage of magnetic resonance spectroscopy for diagnosis of glioblastoma with sensitivity 90.7%, specificity 94.4% and diagnostic accuracy 91.5%.

Key words: Glioblastoma, MR spectroscopy, Histopathology

Introduction

Detecting brain tumors at an early stage is extremely beneficial to patient both in terms of patients health and monitory benefits. A study shows that a total of 57100 new cases of intracranial brain tumors were diagnosed in the year 2012 in Europe alone half of which were glioblastomas. Approximately 45000 deaths occurred in the same year in Europe due to complications related to brain tumors.[1]

Gliomas are the most common primary intracranial lesions representing 81 % of malignant brain lesions.[2] Glioblastoma is the most common glioma (45 % of all gliomas) and has a 5 year survival of 5%.[2] Glioblastoma or grade IV astrocytoma was previously known as glioblastoma multiforme. Currently clinical management of brain tumors and patients survival percentage is directly dependent upon histological

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grading and tissue diagnosis which therefore is the gold standard. However there are some limitations of histopathology, firstly potential sampling error is an inherent error leading to false diagnosis. Secondly any residual tumor cannot be accessed by histopathology.[1]

Advancements in magnetic resonance imaging has made it possible to make appropriate diagnosis of various intracranial lesions including glioblastomas in recent years. However MRI has a high sensitivity and low specificity, as a result of which there are many brain tumors that give rise to differential diagnosis. In order to increase the specificity of magnetic resonance imaging, MR spectroscopy has been included as an auxiliary method to complement the MRI.[3]

Magnetic resonance spectroscopy allows non-invasive measurement of metabolites in tissues. MR spectroscopy enables comparison of chemical composition of normal brain tissue with abnormal tumor tissue. Important metabolites measured in MR spectroscopy are lipids, lactate, choline, N-acetyl aspartate (NAA), amino acids, alanine, creatine and myinositol. The metabolites are measured in units parts per million (ppm). Metabolites having clinical significance in diagnosis of glioblastoma include choline, creatine, Myo-inositol, lipids, lactate and N-acetylaspartate.[4] Number of metabolic peaks seen on the MR spectroscopy varies with TE used. NAA peaks at 2.02 ppm and is a marker of neuronal integrity. Choline which is a marker of cell turn over peaks at 3.22 ppm. Creatine peaks at 3 ppm and is an indicator of cell metabolism. Lipid and lactate peaks at 1.33 ppm.[5,6] Sensitivity and specificity of MRS in detecting tumours are 91.7% and 94.3%, respectively.[7]

The definite diagnosis of a glioblastoma is still based on biopsy which is more favored by clinicians however the MRS does help in narrowing down the differential and to avoid unnecessary biopsies.

Material and Methods

STUDY DESIGN

Cross-sectional descriptive study

SETTING

Department of Radiology, Shifa International Hospital, Islamabad.

DURATION OF STUDY WITH DATES

Study was carried out over a period of six months from 19-12-2017 to 18-06-2018.

SAMPLE SIZE

The sample size of 83 patients was calculated by using 95% confidence level, 45% prevalence of gliomas, 91.7% sensitivity, 94.3% specificity with 9% precision level.

SAMPLING TECHNIQUE

Non Probability, consecutive sampling

SAMPLE SELECTION

Inclusion Criteria

1. All patients with suspicion of glioblastoma on MR (as per-operational definition).
2. Age 30-70 years
3. Both genders

Exclusion Criteria

1. Those patients who were lost to follow up.
2. Pregnant or breastfeeding females
3. Patients with history of previous brain surgery
4. Patients with MRS incompatible prosthesis or cardiac pacemaker holders.
5. Patients with claustrophobia history.
6. Patients not willing to undergo biopsy of intracranial lesions.

DATA COLLECTION PROCEDURE

After approval from ethical review committee, patients presenting with suspicion of glioblastoma on MRS (as per-operational definition) referred from neurosurgical or neurology department and outpatient department fulfilling the inclusion/exclusion criteria were selected. MR Spectroscopy was performed through single voxel technique in all these patients. Initially, post contrast conventional MR imaging was done to localize the lesion and then voxel was placed on volume of interest. After water suppression, a point-resolved spectroscopy (PRESS) technique was used for localization and the studies were obtained with parameters including TE (echo time) and TR (repetition time) of 135 and 1500 respectively. All the images were interpreted by consultant radiologists (with at least 5 years of post-fellowship experience) and looked for presence or absence features of

glioblastoma (as per-operational definition). Specimens of patients undergoing intracranial biopsy in Shifa international hospital Islamabad were sent for histopathological analysis in pathology department and findings of MRS were compared with histopathology report. All findings were compiled on proforma attached as annex-A.

DATA ANALYSIS PROCEDURE

All the data were analyzed with SPSS version 20.0.

Results

A total of 83 patients were included in the study during the study period of six months from 19-12-2017 to 18-06-2018.

Duration (year)	Number	Percentage
≤ 4	72	86.7
> 4	11	13.3
Total	83	100.0
Mean±SD	2.0 ± 1.7	

Table 1: Distribution of patients by duration of disease

Size (mm)	Number	Percentage
≤ 50	41	49.4
> 50	42	50.6
Total	83	100.0

Table 2: Distribution of patients by size of lesion (mm)

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	59 (TP) a	1 (FP) b	60
Negative	6 (FN) c	17 (TN) d	23
Total	65	18	83

Sensitivity :	a/a+c x 100	90.7%
Specificity :	d/d+b x 100	94.4%
Positive Predictive Value	a/a+b x 100	98.3%
Negative Predictive Value:	d/c+d x 100	73.9%
Diagnostic accuracy	a+d/a+d+b+c x 100	91.5%
Likelihood ratio	16.3	

Table 3: Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 83

Patients ranged between 30-70 years of age. Mean age of the patients was 52.2 ± 12.6 years. There were 49 males (59%) and 34 females (51%). Mean duration of disease was 2.0 ± 1.7 year and mean size of lesion was 54.3 ± 26.9 mm. Diagnostic accuracy of MR spectroscopy in diagnosing Glioblastoma showed sensitivity 90.7%, specificity 94.4%, positive predictive value 98.3%, negative predictive value 73.9% and diagnostic accuracy was 91.5%.

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	29 (TP) a	0 (FP) b	29
Negative	5 (FN) c	5 (TN) d	10
Total	34	5	39

Sensitivity :	a/a+c x 100	85.2%
Specificity :	d/d+b x 100	100%
Positive Predictive Value	a/a+b x 100	100%
Negative Predictive Value:	d/c+d x 100	50.0%
Diagnostic accuracy	a+d/a+d+b+c x 100	87.1%

Table 4: Stratification for age 30-50 years Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 39

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	30 (TP) a	1 (FP) b	31
Negative	1 (FN) c	12 (TN) d	13
Total	31	13	44

Sensitivity :	a/a+c x 100	96.7%
Specificity :	d/d+b x 100	92.3%
Positive Predictive Value	a/a+b x 100	96.7%
Negative Predictive Value:	d/c+d x 100	92.3%
Diagnostic accuracy	a+d/a+d+b+c x 100	95.4%

Table 5: Stratification for age 51-70 years Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 44

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	30 (TP) a	1 (FP) b	31
Negative	1 (FN) c	12 (TN) d	13
Total	31	13	44

Sensitivity :	a/a+c x 100	96.7%
Specificity :	d/d+b x 100	92.3%
Positive Predictive Value	a/a+b x 100	96.7%
Negative Predictive Value:	d/c+d x 100	92.3%
Diagnostic accuracy	a+d/a+d+b+c x 100	95.4%

Table 6: Stratification for gender (Male) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 49

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	21 (TP) a	1 (FP) b	22
Negative	3 (FN) c	9 (TN) d	12
Total	24	10	34

Sensitivity :	a/a+c x 100	87.5%
Specificity :	d/d+b x 100	90%
Positive Predictive Value	a/a+b x 100	95.4%
Negative Predictive Value:	d/c+d x 100	75.0%
Diagnostic accuracy	a+d/a+d+b+c x 100	88.2%

Table 7: Stratification for gender (Female) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 34

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	52 (TP) a	1 (FP) b	53
Negative	5 (FN) c	14 (TN) d	19
Total	57	15	72

Sensitivity :	a/a+c x 100	91.2%
Specificity :	d/d+b x 100	93.3%
Positive Predictive Value	a/a+b x 100	98.1%
Negative Predictive Value:	d/c+d x 100	73.6%
Diagnostic accuracy	a+d/a+d+b+c x 100	91.6%

Table 8: Stratification for duration of disease (= 4 year) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 72

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	7 (TP) a	0 (FP) b	7
Negative	1 (FN) c	3 (TN) d	4
Total	8	3	11

Sensitivity :	a/a+c x 100	87.5%
Specificity :	d/d+b x 100	100%
Positive Predictive Value	a/a+b x 100	100%
Negative Predictive Value:	d/c+d x 100	75%
Diagnostic accuracy	a+d/a+d+b+c x 100	90.9%

Table 9: Stratification for duration of disease (> 4 year) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard. n = 11

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	30 (TP) a	1 (FP) b	31
Negative	1 (FN) c	9 (TN) d	10
Total	31	10	41

Sensitivity :	a/a+c x 100	96.7%
Specificity :	d/d+b x 100	90%
Positive Predictive Value	a/a+b x 100	96.7%
Negative Predictive Value:	d/c+d x 100	90%
Diagnostic accuracy	a+d/a+d+b+c x 100	95.1%

Table 10: Stratification for size of lesion (= 50mm) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 41

Magnetic resonance Spectroscopy	Histopathology (Gold Standard)		Total
	Positive	Negative	
Positive	29 (TP) a	0 (FP) b	29
Negative	5 (FN) c	8 (TN) d	13
Total	34	8	42

Sensitivity :	a/a+c x 100	85.2%
Specificity :	d/d+b x 100	100%
Positive Predictive Value	a/a+b x 100	100%
Negative Predictive Value:	d/c+d x 100	61.5%
Diagnostic accuracy	a+d/a+d+b+c x 100	88.1%

Table 11: Stratification for size of lesion (> 50mm) Diagnostic accuracy of MR spectroscopy in diagnosing glioblastoma by taking histopathology as gold standard n = 42

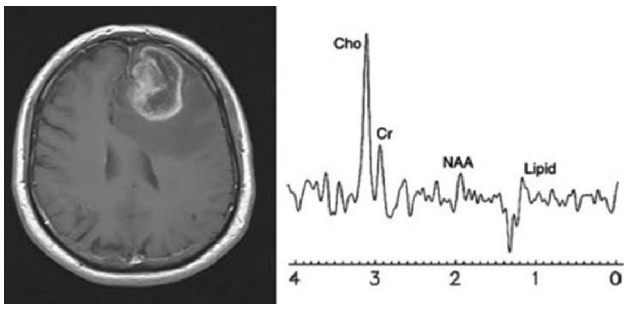

Figure 1: MR spectroscopy in a 32 -year-old man with glioblastoma. Increased choline (Cho)/N-acetyl aspartate and Cho/lipid ratio (4.7 and 5.2, respectively). Histopathologic examination confirmed diagnosis.

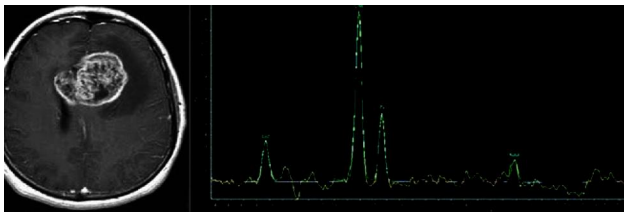

Figure 2: T2-W MRI/ MR spectroscopy shows an increased choline/ decreased NAA in a histopathological confirmed case of midline glioblastoma.

Discussion

Glioblastomas multiforme (GBM), world health organization (WHO) grade IV glioma, is the most common (54% of gliomas) and lethal primary malignant brain tumor in adults, with one-year and five-year survival rates of 33% and less than 5%, respectively. One important prognostic factor of malignant gliomas is histological grade.[9] Stereotactic needle biopsy is a commonly used method for obtaining tissue diagnosis of intracranial lesions.[10] Glioma heterogeneity consist of a complex interface of normal, inflammatory, necrotic, and malignant

tissues. Thus, biopsy from different regions of a glioma may yield different grades. Stereotactic needle biopsy and resection of gliomas have additional challenges due to concern for possible neurologic complications from disturbance in motor and eloquent brain regions.[11] Therefore, given the prognostic implications, developing noninvasive techniques to identify the area with the highest grade potential prior to biopsy or resection is critical.

Reduced NAA level reflects neuronal loss while elevated Cho is an indication of increased cell turnover and is elevated in diseases with increased cellular proliferation like malignant glioma.[12,13]

Studies have shown that a cutoff value of Cho/NAA ratio of 1.6 (NAA/Cho ratio of 0.61) was able to identify neoplasms with sensitivity of 86.1% and specificit y of 81.8% and to distinguish high-grade from low-grade gliomas with sensitivity of 74.2% and specificity of 62.5%.[8,14]

The critical biological characteristic of a glioblastoma (GBM), the most frequent and serious primary brain tumor in adults is an inevitable progression after tandard therapy with the median of 6.9 months.[15]

GBM recurrence, however, has often similar radiologic characteristics on conventional MRI as therapy-related changes, like a pseudoprogression (PsP). Thus, the early and accurate diagnosis of GBM relapse constitutes to be an important clinical need, especially when more and more potentially active drugs are currently being investigated for salvage treatment. In comparison with standard structural MRI techniques, advanced imaging methods, such as diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and the proton MR spectroscopy (MRS), allow much deeper and still non-invasive insight into the interpretation of brain lesions, resulting in greater specificity of diagnostic imaging.[16]

The accurate and timely identification of a tumor relapse is the most essential prerequisite of an efficient salvage therapy emphasizing the importance of precise assessment of the response to the initial treatment. Well-known difficulties with distinguishing between a GBM recurrence and treatment related changes caused by the administration of concomitant RT and TMZ (pseudoprogression) or angiogenesis inhibitors (pseudoresponse)[17] are already expressed in the current RANO (Response Assessment in Neuro-Oncology) criteria.[18]

The MRS seems to be a promising method that is complementary to the widely used structural MRI and can be used to increase the diagnostic accuracy of the brain tumor imaging protocol. The results of present study proved very high sensitivity and specificity of the of MRS in diagnosing glioblastoma (90.7% and 94.5%, respectively). PPV was 98.3%, NPV 73.9% and diagnostic accuracy was 91.5%. These results are comparable with the findings of Naz et al.[7] Two other studies by Alam et al and Majós et al also agree with our findings.[6,19]

Limitations of study

This study didn't correlated MR spectroscopy with the grade of glioblastomas . Anaplastic astrocytomas (WHO grade III) are found to have higher choline levels compared to low grade gliomas. Local studies are required which should correlate Choline levels with grade of glioblastoma.

Conclusion

In conclusion, present study demonstrated a clear advantage of magnetic resonance spectroscopy for diagnosis of glioblastoma with sensitivity 90.7%, specificity 94.4% and diagnostic accuracy 91.5%.

Conflict of Interest: None

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