Original Article

MRI Characterization and Histopathological Correlation of Primary Intra-axial Brain Glioma

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ABSTRACT

OBJECTIVE: To determine the diagnostic accuracy of magnetic resonance imaging (MRI) in preoperative diagnosis and grading of intra-axial gliomas compared with histopathology.
STUDY DESIGN: Prospective, comparative, study.
PLACE AND DURATION OF STUDY: Radiology Department, Aga Khan University Hospital, Karachi from July 2004 to June 2006.
METHODS: Fifty-three patients having different neurological symptoms referred to Radiology Department Aga Khan University Hospital for MRI examination were included in the study. These patients were provisionally diagnosed radiologically having intra-axial brain tumor or subsequently found to have pathologically proven primary intra-axial brain tumors. MRI scans were evaluated for location, consistency, hemorrhage, necrosis, margins, edema, MRI signals contrast enhancement and any additional features for staging the tumor. Preoperative diagnosis was compared with postoperative pathological diagnosis by using Pearson's Chi square test. Accuracy of magnetic resonance imaging in diagnosing and staging the brain tumors was determined. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of MRI in characterizing the lesion was also calculated.
RESULTS: The study included 53 patients with age ranging from 1-year 10-months to 60 years (mean 32.7 years). Twenty-eight patients had supratentorial tumors (52%) and 25 had infratentorial tumors (47%). Twenty-eight patients had Astrocytoma (52%), 10 had Oligodendroglioma (19%), 6 had Medulloblastoma (11%), 5 had Lymphoma (9%), and 4 had Hemangioblastoma (7%). Preoperative MRI diagnosis was correct in 50 patients with accuracy of 94%. No significant difference was found between preoperative MRI grading and postoperative histopathological grade of intra-axial tumor (p-value>0.05). Sensitivity, specificity, positive predictive value and negative predictive value of MRI in detecting tumor necrosis were 93%, 77%, 80% and 90% while for detecting tumor hemorrhage were 57%, 93%, 57%, and 93% respectively.
CONCLUSION: MRI is very accurate in preoperative diagnosis, staging and assessing the tumor characteristics of primary intra-axial brain tumors. It can be used reliably in our usual clinical practice.

KEY WORDS: Glioma, Intra-axial, Brain tumors, MRI, diagnostic accuracy.

INRODUCTION

Cerebral tumors predominantly occur in adult life with a peak incidence of 13 cases per 100000 population at age of 55-65 year. They are relatively uncommon in infants and children at 2 cases per 100000[1]. They can be classified as intra-axial and extra-axial[1]. Prompt diagnosis and treatment of cerebral neoplasms are critical to decrease both morbidity and mortality[2]. New therapeutic modalities, such as image-guided surgery and anti-angiogenic agents, are becoming increasingly reliant on high quality imaging for diagnostic evaluation, treatment planning and post-treatment follow-up [3]. CT and MRI are the mainstays of imaging in current practice. MR imaging with its multiplanar capabilities and superior contrast resolution is now modality of choice. Most primary intra-axial brain tumors are malignant or potentially malignant. Most common of these include glial tumors, lymphoma, medulloblastoma and hemangioblastoma. Astrocytomas are histologically heterogeneous group, having varying degrees of cellular and nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis[4]. Astrocytomas are classified into three grades, low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme [5]. Accurate grading of astrocytoma is critical for planning therapeutic strategies, assessing prognosis, and monitoring response to therapy[5]. A difficulty in the management of astrocytomas is related to potential sampling errors and improper grading with needle biopsy. This is due to focal areas of more malignant features widespread among regions with a less aggressive histopathological

appearance[6]. Diagnosis and staging mainly rely on imaging features.

Primary CNS lymphoma is extranodal lymphoma confined to the CNS. With an increasing incidence in both the immunocompetent and immunocompromised populations. Primary CNS lymphoma represents 1% of all lymphomas and as many as 16% of all primary brain tumors[7]. Cerebellar medulloblastoma is most frequently seen in children and is uncommon in adults. Medulloblastoma accounts for 15% of all brain tumors in children and only 0.4% of all brain tumors in adults [8]. MRI have significant role in characterizing and staging of these tumors[16]. Data regarding the impact of MRI for diagnosis and staging brain tumor in our population is sparse, therefore, the purpose of this study is to determine the efficacy of MRI in preoperative diagnosis of primary intra-axial brain tumors and to determine its diagnostic accuracy in grading gliomas in our population, compared with histopathological findings taking as gold standard.

MATERIAL AND METHODS

Data were prospectively collected in the Department of Radiology Aga Khan University Hospital, Karachi from July 2004 to June 2006. We included 113 (68 male and 45 female) patients who underwent MRI brain examination with clinical suspicion of intra-axial space occupying lesion. All patients had different neurological symptoms; most common were headaches and seizures. Inclusion criteria were patients having intra-axial brain lesion and having MRI examination. Exclusion criteria were contraindication to MRI, inappropriate medical/pathological records and follow-up patients. Out of 113 patients 60 patients were excluded from study. For 38 patients no record of surgery or histopathology of 38 patients was available (all patients were outside referrals), 11 patients had previous brain tumor surgery, now they came for follow-up, 2 patients had colloidal cyst on MRI, and 9 patients had known primary tumor came for MRI brain for evaluation of brain metastasis.

Fifty-three patients were finally selected for the study. In all patients surgery or biopsy was performed within two weeks of MR imaging.

All the patients were examined with 1.5 Tesla systems. Head coil was used in all the patients. Before the procedure patients were explained about the procedure including possible risk of contrast material administration and informed consent was taken in all cases. Brief history was obtained and any contraindication to MRI was assessed including cochlear implants, surgical metallic clips, cardiac pacemaker or any metallic foreign body in patient was excluded. A combination of T1 weighted, T2 weighted and FLAIR sequences and post gadolinium T1 weighted was obtained in all the patients. Parameters used were as follows.

For T1 weighted sequence TR = 370–630 ms, TE = 9-15 ms, flip angle = 90/180. For T2 weighted sequences TR = 3859–7200 ms, TE = 91–120 ms, flip angle = 90/160 or 90/180. For FLAIR sequence TR = 10000 ms, TE = 100-ms, TI = 2200 ms and flip angle = 90/160 or 90/180. Matrix size was 160 x 192 or 192 x 256. Slice thickness varied from 5 mm to 6 mm. Images were acquired sagittal, axial and coronal planes. Consent of patient was taken for injection of intravenous gadolinium.

Two radiologists, experienced in reporting brain MRI, interpreted MR images. Final report was made by consensus.

For preoperative diagnosis of intra-axial glioma we used same criteria for grading as described by Bruce et al [6]. MR imaging findings were evaluated for tumor crossing of midline, edema, tumor signal heterogeneity, hemorrhage, border definition, cyst formation or necrosis, and mass effect; each given a weighting of 0,1or 2.

Crossing mid line: Grade 0 indicate no crossing of mid line; Grade 1 is for equivocal cases; Grade 2 indicate tumor has crossed mid line

Surrounding edema: Grade 0 indicate mild edema; Grade 1 is for moderate edema; Grade 2 indicate severe edema

Signal heterogeneity: Grade 0 indicate mild heterogeneity; Grade 1 is for moderate; Grade 2 indicate severe signal heterogeneity

Tumor hemorrhage: Grade 0 indicate no hemorrhage; Grade 1 is for equivocal cases; Grade 2 indicate definitive hemorrhage

Tumor border definition: Grade 0 indicate well circumscribed lesion; Grade 1 is for poorly circumscribed lesion; Grade 2 indicate highly infiltrating lesion

Cystic/ necrotic changes of tumor: Grade 0 indicate no cyst/ necrosis: Grade 1 is for equivocal cases; Grade 2 indicate definite cystic /necrotic changes

Mass effect of tumor: Grade 0 indicate mild mass effect; Grade 1 is for moderate; Grade 2 indicate severe mass effect adjacent to tumor

For low grade glioma including astrocytic glioma and oligodendroglioma the numbers are less than three. For intermediate glioma including anaplastic astrocytoma and intermediate oligodendroglioma the number ranges from 5 to 7. For glioblastoma multiformis the range is 8 to 14. Location of tumor was also recorded. Each observer was asked to give an overall impression as to whether the abnormality represented a low-grade glioma, intermediate glioma, and glioblastic

multiforme or other tumor.

Diagnosis of all the patients was confirmed from biopsy reports, and pathological findings of surgical specimen. Preoperative MRI diagnosis and grading for intra-axial glioma were compared with postoperative pathological diagnosis and grading.

Data were collected in predefined proforma, entered in Microsoft Excel, analysis was done in SPSS version 15. Pearson's chi-square testing was done to see the statistical differences at 95% confidence level. *P*-value up to 0.005 were considered as significant. Sensitivity of MRI in staging of low, intermediate and high grade gliomas was calculated. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of MRI in characterizing the lesion for necrosis and hemorrhage were also calculated.

RESULTS

In this study glioma was the most common tumor. According to histopathological diagnosis, 22 out of 53 patients had adult astrocytic series gliomas, 6 patients had pilocytic astrocytomas, 10 had oligodendro series gliomas, 6 had medulloblastomas, 5 had lymphoma and 4 had hemangioblastoma. Twenty-seven tumors were supratentorial and 26 were infra-tentorial in location.

Preoperative radiological diagnosis was correct in 50 cases (94% accuracy). No significant difference was found between preoperative MRI grading and postoperative histopathologic grade of intra-axial tumor (p-value >0.05).

For low grade and high grade gliomas sensitivity of MRI was 100% while for intermediate grade gliomas sensitivity was 95% **(Table I)**. Two false positive cases diagnosed as intermediate grade glioma, in which one turned out to metastases and other was lymphoma on histopathology. One false negative case preoperatively diagnosed as lymphoma proved to be an anaplastic astrocytoma (Intermediate grade glioma) on histopathology.

All patients with glioblastoma multiforme (GBM), pilocytic astrocytoma, medulloblastoma and hemangioblastoma were correctly diagnosed by magnetic resonance imaging.

There were total 37 gliomas including astrocytic series and oligodendro series. Out of these 37 cases 27 were astrocytic gliomas and 10 were oligodendrogliomas. Out of 27 astrocytomas there were 6 pilocytic astrocytomas, 1 was low grade astrocytoma, 16 were anaplastic astrocytomas, and 4 were glioblastoma multiformis. Out of 10 oligodendrogliomas, 4 were low grade and 6 were intermediate grade gliomas.

We found 5 low grade gliomas with score range of 2-3 including one low grade astrocytoma and 4 low grade oligodendrogliomas. None of the lesion were crossing mid line, 4 lesion had mild edema, all showed equivocal signal heterogeneity. None of the lesion had hemorrhage, 3 lesions had well defined margins and 2 had poorly defined margins, none of the lesion showed cystic or necrotic changes. Low grade astrocytoma had not showed mass effect but low grade oligodendrogliomas had moderate to severe mass effects **(Table II-III)**.

There were 22 intermediate gliomas with score range of 6-7, in which anaplastic astrocytomas were 16 and intermediate oligodendrogliomas were 6. None of the anaplastic astrocytomas were crossing mid line, 2 intermediate oligodendrogliomas were also not crossing mid line but 4 did so. Eleven lesions were associated with moderate edema and 11 lesions had severe edema effect. Seventeen lesions were showing severe signal heterogeneity and 5 had equivocal signal heterogeneity. Only 5 lesions had hemorrhage. Only 1 anaplastic astrocytoma had infiltrative appearance and rest of 21 lesions had poorly defined margins. Only 1 lesion had well defined cystic/necrotic changes, 12 had equivocal changes and 9 lesions had showed no cystic/necrotic changes. All lesions had mass effect in which 10 had severe mass effect.

Out of 4 glioblastoma multiformis, score range was 11 -12, 2 showed equivocal mid line crossing but two had definitive mid line crossing. Two lesions had mild edema and 2 had severe edema, all lesions showed severe signal heterogeneity. Two had equivocal hemorrhage and remaining 2 had definite hemorrhage, again 2 lesions had poorly defined margins and remaining 2 had infiltrative borders. All lesions had cystic or necrotic changes and severe mass effect. Sensitivity, specificity, positive predictive value and negative predictive value of MRI in detecting tumor necrosis were 93%, 77%, 80% and 90% while for detecting tumor hemorrhage were 57%, 93%, 57%, and 93% respectively.

The range of score for low grade astrocytoma was 2, low grade oligodendroglioma was 3, anaplastic astrocytoma was 6-7, intermediate grade oligodendroglioma was also 6-7 and glioblastoma multiformis had score range of 11-12.

Pilocytic astrocytoma was in the range of 3-6, it means they have some low grade and intermediate grade score overlapping. Pilocytic astrocytoma's were all diagnosed pre-operatively on MRI without confusion because of age, typical location in cerebellum with predominant cystic changes and mural enhancing nodule.

TABLE I: CORRELATION BETWEEN MRI AND HISTOPATHOLOGY CORRELATION FOR GRADING INTRAAXIAL BRAIN GLIOMAS

Tumor	MRI Diagnosis	Histopathology	Sensitivity of MRI	p-value
Low	5	5	100%	1.00
Intermediate	24	22	95%	0.136
High	4	4	100%	1.00

TABLE II: RELATIONSHIP OF MRI DETECTABLE NECROSIS, HEMORRHAGE, IRREGULAR MARGINS AND MASS EFFECT WITH THE HISTOPATHOLOGICAL GRADE OF GLIOMAS

Tumor characteristic	Glioblastoma Multiforme	High grade Astrocytoma	Low grade Astrocytoma	Oligodendroglioma	Anaplastic Oligodendro glioma
Necrosis	100%	33%	0%	0%	100%
Hemorrhage	50%	22%	0%	0%	67%
Irregular margins	100%	33%	0%	0%	100%
Mass Effect	100%	100%	67%	50%	100%

TABLE III: ASSOCIATION OF DEGREE OF EDEMA WITH GRADE OF GLIOMAS

Degree of Edema	Glioblastoma Multiforme	High Grade Glioma and Anaplastic Oligodendroglioma	Low Grade Glioma and Oligodendroglioma
No Edema	-	8%	60%
Mild Edema	-	17%	40%
Moderate Edema	-	67%	-
Severe Edema	100%	8%	-

DISCUSSION

Purpose of Imaging in patients with brain tumors is the determination of the location, extent, type, and malignancy of the tumor. Imaging is used for primary diagnosis, planning of treatment including biopsy, resection, radiation, and delineation of tumor from functionally important neuronal tissue[9]. Brain tumors are not uncommon in our set up[10]. Common clinical manifestations are headache, vomiting, seizures, visual disturbances, personality change, vertigo and hemiparesis[10]. Similar to our study gliomas are reported to be most common in another local study[10].

The grading of gliomas is needed for deciding clinical management and assessment of prognosis. The histologic classification of astrocytomas is complicated and inherent in all grading systems[6]. Inadequate sampling of tumor at biopsy introduces error into classification of astrocytomas. MR imaging can be used to classify astrocytic-series tumors into a three-tiered system of low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme; and to evaluate MR imaging features that may aid in this classification[6]. MR imaging may serve as an adjunct in management when the clinical course and MR findings appear to be at odds with the neuropathologic diagnosis. Low grade astrocytoma is the most benign of astrocytomas. Grossly the borders are difficult to define. Cellularity may only minimally exceed that of normal white matter, which makes diagnosis of tumor difficult on frozen sections and at times at permanent sections. Postoperative survival ranges from 3 to 10 years[11].

Anaplastic astrocytoma usually occur a decade later in life. The degree of hypercellularity, differentiation and pleomorphism vary and overlap with gliobastoma multiforme at one end and with low grade astrocytoma at

FIGURE I: GLIOBALSTOMA MULTIFORME. POST GADOLINIUM T1 WEIGHTED IMAGE SHOW HETEROGENEOUSLY ENHANCING MASS WITH NON-ENHANCING NECROTIC AREAS IN THE LATERAL VENTRICLES PREDOMINANTLY ON LEFT SIDE. CORPUS CALLOSUM IS ALSO INVOLVED BY THE MASS

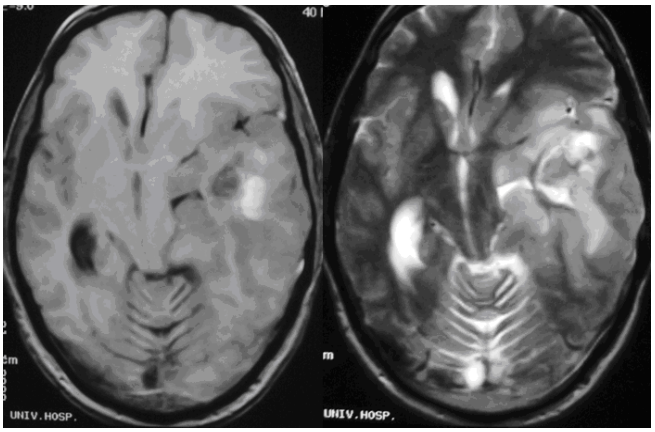
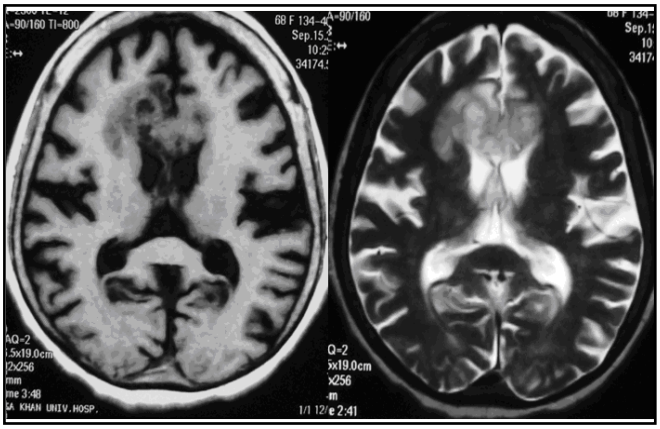


FIGURE II: PRIMARY BRAIN LYMPHOMA. POST GADOLINIUM T1 WEIGHTED IMAGE SHOW MASS WITH PATCHY ENHANCEMENT INVOLVING THE RIGHT BASAL GANGLIA, THALAMUS AND INTERNAL CAPSULE



the other end. The average postoperative survival is approximately 2 years[11]. Glioblastoma multiforme is the most malignant astrocytoma. Peak incidence occurs in 5th and 6th decades. Necrosis is the microscopic hallmark. Diagnosis is easily made when necrosis is present in microscopic specimens. A diagnosis of anaplastic astrocytoma will be considered if a limited tissue specimen does not contain necrosis. This leads to under grading of Glioblastoma multiforme in surgical series compared with autopsy series. Survival is approximately less than 1 year[11]. Pilocytic astrocytoma is the most common pediatric central nervous system glial neoplasm and the most common pediatric cerebellar tumor. This tumor has a noteworthy benign biologic behavior that translates into an extremely high survival rate of 94% at 10 years, by far the best of any glial tumor[12].

In our series anaplstic Astrocytoma was the most common tumor, followed by Pilocytic Astrocytoma and GBM. This is in contrast to international literature, which describes GBM to be most common of astrocytomas[11]. All the oligodendrogliomas were supratentorial.

All diffused astrocytomas tend to progress to glioblastoma multiforme (GBM)[13]. The most common imaging appearance of GBM is a large heterogeneous mass in the supratentorial white matter that exerts considerable mass effect. Less frequently, GBM can occur near the dura mater or in the corpus callosum, posterior fossa, and spinal cord. GBM typically contains central areas of necrosis, has thick irregular walls, and is surrounded by extensive, vasogenic edema. GBMs most commonly metastasize from their original location by direct extension along white matter tracts; however, cerebrospinal fluid, subependymal, and hematogenous spread can also occur.

MRI features of tumor in predicting grade included crossing mid line, edema, signal heterogeneity, hemorrhage, border definition, cystic formation or necrosis and mass effect.

Corpus callosum involvement was an additional feature seen in 4 tumors, 2 in GBM and 2 in lymphoma.

Necrosis was seen in 100% of GBM and intermediate grade oligodendrogliomas, and in 44% of anaplastic astrocytomas. Irregular margings are seen in 100% of GBM, intermediate grade oligodendrogliomas and anaplastic astrocytomas. Mass effect is seen in all GBM, intermediate gliomas including oligodendroglioma and astrocytomas, but it is also seen in low grade oligodendroglioma. Hemorrhage is most commonly seen in GBM followed by intermediate grade oligodendrogliomas in 50% and anaplastic astrocytoma in 16%. Gross edema was seen most commonly with GBM (100%). Moderate edema is most common in intermediate grade oligodendrogliomas then anaplastic astrocytoma. So, tumor necrosis, irregular margins and peritumoral edema are most important markers for tumor grade. Corpus callosum involvement, if present, almost always indicate high grade tumor.

Medulloblastoma is the most common primitive neuroectodermal tumor of CNS[14]. In our series 5 tumors were located in fourth ventricle arising from cerebellar vermis and one tumor was eccentric arising from right cereballar hemisphere. This eccentric tumor proved to be desmoplastic medulloblastoma. The pattern of enhancement of desmoplastic tumor was homogenous. This is different from reported by Meyers et al[14] who reported only few small foci of enhancement. In our study all tumors showed marked enhancement with nonenhancing necrotic areas. Necrosis was confirmed on histopathology. Medulloblastoma is also reported in lateral ventricles and recurrent medulloblastoma may not show enhancement[15]. In our study two lymphomas showed mild patchy enhancement with enhancing and non-enhancing areas. This is atypical and in contrast to described homogenous pattern of enhancement[7]. Finally our study have some limitations; sample size is small, interobserver agreement was not calculated between two radiologists and more sophisticated MRI techniques like spectroscopy were not used.

CONCLUSION

MRI is accurate in preoperative diagnosis and assessing the characteristics of primary intra-axial brain tumors. It is very accurate in assessing the grade of gliomas. Tumor necrosis, irregular margins and peritumoral edema are most important indicators of tumor grade.

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