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Archives in Cancer Research
ISSN 2254-6081

2015
Vol. 3 No. 1:1

# Use of Magnetic Resonance Spectroscopy of the Brain to Differentiate Low Grade Glioma and its Clinical Relevance

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## Abstract

**Background and purpose:** Nuclear magnetic resonance (NMR) spectroscopic examination plays an important role in diagnosis of low grade gliomas. We compared the spectroscopic examination with the histopathological results of low grade gliomas concerning its reliability and their clinical relevance.

**Materials and methods:** The charts of 29 patients with low grade gliomas were collected. Only in 19 cases of them an NMR-spectroscopic examination was performed. Due to choline, N-acetylaspartate (NAA) and lipid content the gliomas were classified into astrocytoma WHO II or III or in low or high grade gliomas. After stereotactic biopsy or neurosurgical removal histopathological examination was performed.

**Results:** We found 18 astrocytomas WHO II and 1 oligodendroglioma WHO II at the histopathological examination. In the spectroscopic examination we found 13 low grade gliomas II and 6 high grade gliomas. 68.4% of the 19 low grade gliomas WHO II correspond to the spectroscopic examination. 6 cases showed high choline contents suitable for high grade glioma and one of them with very high choline content which correspond to a glioblastoma. These tumours were classified as low grade gliomas WHO II in the histopathological examination.

**Conclusion:** We compared the NMR-spectroscopic findings with the histopathological results of the tumours. The actual spectroscopical method does not seem to be reliable enough in the diagnosis of low grade gliomas but can play an important role in assessing the clinical condition and follow-up. Whether the NMR-spectroscopic findings correlate with the clinical course better than with the histopathological findings remains to be clarified.

**Keywords:** Low grade glioma; Magnetic resonance spectroscopy; Choline; N-acetylaspartate

**Abbreviations:** Cho: Choline; NAA: N-acetylaspartate; tCr: total Creatine; 1H MRS: Proton Magnetic Resonance Spectroscopy

## Introduction

Accurate histological diagnosis of gliomas is fundamental to optimal treatment of patients and to the interpretation of basic and clinical investigations. Diagnostic accuracy and reproducibility are compromised by the subjective histologic criteria currently used to classify and grade gliomas.

If the histologic features of gliomas were reviewed independently by 4 neuropathologists to determine interobserver diagnostic concordance rates, it will be for all 4 reviewers 69%, any 3 reviewers 75% and 2 reviewers 80% [1].

1H MR-spectroscopy offers a risk free method for the diagnosis of the brain lesions by providing biochemical information related to mitotic cell division (Cho), displacement of neural tissue (NAA), energy metabolism (total creatine (tCr)), and necrotic transformation (lipids) [2-5].

The aim of this study is to evaluate the diagnostic accuracy of 1H MR-spectroscopy in the preoperative evaluation of low grade glioma and compare the results versus postoperative histopathological findings and discuss the clinical relevance.

# Materials and Methods

## Patients population

We performed a retrospective study in 19 patients referred to the Neurosurgery Department of the Neurocenter of the University Clinic of Frankfurt am Main between 1999 and 2003. The age ranged from 24 to 68 years. The mean age was 37.8 (±11.6) years. The clinical, neuroradiological and neuropathological data of the patients were collected prospectively in a data bank. The patient's demographic data are shown in **Table** 1.

## 1H NMR-spectroscopy

All patients underwent 1H MR-spectroscopy before complete or incomplete resection if feasible, otherwise stereotactical biopsy was been performed. The MR-spectroscopical examinations were carried out in the Institute of Neuroradiology at the Neurocenter of the University of Frankfurt. 1H MR-spectroscopical studies were performed with a clinical 1.5 Tesla MR scanner. After acquisition of axial T2 and post contrast T1-weighted axial and coronal MR-tomograms, a single voxel 1H MR-spectroscopy was conducted. After selection of the voxel of interest (VOI), one or two water suppressed metabolite spectra were acquired using double spin-echo localization technique and frequency selective water suppression. Reference data were obtained with the VOI located in the mirror image region of the contra-lateral hemisphere. Depending on the size of selected VOI's, 128 to 512 acquisitions with an echo time of 135 ms and repetition time of 1500 ms were added. Spectroscopic raw data were analyzed with the MRUI tool. The resulting metabolite signal intensities of NAA, total creatine (tCr), choline (Cho), lipids (Lip) and lactate (Lac) from the tumour tissue were quantified (normalized) by calculating their ratio to the signal intensity of tCr measured in the reference spectrum and expressed as ratio of the reference tCr from the tumour tissue. The spectroscopic diagnoses were established by an experienced neuroradiologist before the complete or incomplete resection if feasible, otherwise stereotactical biopsy was been performed.

## Spectroscopical diagnosis

Spectroscopical diagnoses were established using stringent diagnostic criteria [6]. The voxel-positioning, in relation to solid tumour components was controlled in order to exclude considerable partial volume effects. Second, local field homogeneity and signal to noise ratio of the spectra were assessed; the criterion of sufficient field homogeneity was good resolution of the signals at 3.05 and 3.20 ppm originating from Cho and tCr. Adequate signal to noise ratio was considered to be present if the most prominent peak of the spectrum – mostly Cho – yielded a standard deviation of the MRUI fit of 5% or less. Lesions showing a slight decrease (up to 20% decrease as compared with normal white matter) or a moderate increase in Cho signal intensity (50% or less) were rated as low grade tumour, while spectra showing an increase in Cho signal intensity of more than 50% were rated as a high grade neoplasm. Grade III tumours typically showed lower Cho levels than grade IV tumours (150 to 220% for grade III vs. 180% to over 500% for grade IV tumours) [7].

Lesions with imaging features suggestive of a neoplasm but showing clearly reduced Cho signal intensity (lower than 80% of normal) were judged to be non-neoplastic. Differentiation of non-enhancing sub-acute silent infarction from low grade

| Patient | Age | Spectroskopic Diagnosis | Histopathologic Diagnosis | MRI | Contrast Enhancement | Site | Seizures |
|---|---|---|---|---|---|---|---|
| SBA | 26 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | frontal | + |
| BM | 29 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| FP | 38 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| GH | 46 | Astrocytoma WHO III | Astrocytoma WHO II | low grade glioma | NO | frontal | + |
| HM | 29 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| HR | 33 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | - |
| KM | 25 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| KaT | 37 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | frontal | + |
| KT | 31 | Astrocytoma WHO III | Astrocytoma WHO II | low grade glioma | NO | frontal | - |
| MA | 68 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | corpus callosum | - |
| MC | 25 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | + | temporal | + |
| MU | 59 | high grade glioma | Astrocytoma WHO II | low grade glioma | NO | parietal | - |
| RK | 48 | Astrocytoma WHO III | Astrocytoma WHO II | low grade glioma | NO | frontal | + |
| SK | 40 | Astrocytoma WHO III | Astrocytoma WHO II | low grade glioma | NO | parietal | + |
| SP | 28 | Astrocytoma WHO II | Olgodendroglioma II | low grade glioma | NO | basal ganglia | - |
| ST | 39 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| VF | 40 | Astrocytoma WHO III | Astrocytoma WHO II | low grade glioma | NO | temporal | + |
| WoR | 37 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | frontal | + |
| WR | 44 | Astrocytoma WHO II | Astrocytoma WHO II | low grade glioma | NO | temporal | - |

**Table 1** Patient demographics.
(Gray shaded rows show no concordance of spectroscopic diagnosis with the histopathologic findings)

tumours was achieved by high Lac in addition to the reduction in the concentration of the other metabolites, especially NAA. Diagnostic criteria of gliosis were reduced levels of NAA, tCr, and Cho without evidence of Lip and/or Lac. The process of making the final imaging and spectroscopic diagnosis consists of two steps:

1. Assignment of plain MR spectrograms to one of the following groups: non-tumourous-inflammative lesions, non-tumourous-noninflammative lesion, extra-axial high grade tumour, extra axial low grade tumour, intra-axial low grade tumour, intra-axial high grade tumour without necrosis, intra-axial high grade tumour with necrosis.
2. Establishment of the final pre histopathological diagnosis after consideration of information obtained from conventional MRI (location of lesion, signal characteristics, contrast enhancement etc.).

### Histopathological diagnosis

Smear preparations of the biopsy specimens were intra operatively examined by an attending neuropathologist from the Department of Neuropathology (Edinger Institute). The final diagnosis, based on paraffin-embedded tissue specimens with conventional and immunohistochemical analysis, was assessed by an experienced neuropathologist.

### Statistical methods

For the statistical procedures, a commercially available software package (SPSS 10.0) was used. Sensitivity and specificity for 1H MR-spectroscopy were obtained. Patients for whom a definite histopathological diagnosis and MR spectroscopic diagnosis were not achieved were not considered for these calculations.

## Results

The final diagnosis, taking account of 1H MR-spectroscopy and the histopathological findings are shown in Table 2.

There have been in 13 (64.8%) cases an accordance of the 1H MR-spectroscopy with the histopthological findings and no accordance in 6 (31.6%) cases.

The 1H MR-spectroscopy established 13 low grade glioma and 6 high grade glioma. NAA levels were been decreased from 9-86% compared to the mirror image of the contra-lateral hemisphere. Cho signal intensities were increased up to 87-150%. Cho levels more than 160% were considered as high grade gliomas. In the current study the Cho levels of the high grade gliomas ranged from 164 to 441%. Spectroscopically it was not possible to distinguish between Astrocytoma II and III or between Astrocytoma and Oligodendroglioma. Patient demographics are shown in Table 1. The spectroscopically established intensities are shown in Table 3.

| Results of the 1H MR-spectroscopy | | Histopathological findings | |
|---|---|---|---|
| **Diagnosis** | **Number of patients** | **Diagnosis** | **Number of patients** |
| **Low grade** | 13 | **Astrocytoma II** | 18 |
| **High grade** | 6 | **Oligodendroglioma II** | 1 |

**Table 2** Comparison of 1H MR-spectroscopic diagnosis with the histopathological findings

Histopathological there was been established 18 Astrocytoma WHO II and one Oligodendroglioma WHO II.

In one case Cho increase up to 441% was been noted compared to the mirror image of the contra-lateral healthy hemisphere. The spectroscopical diagnosis was been high grade glioma in contrast to Astrozytoma II of the histopathological establishment. The clinical course of the patient showed a rapid deterioration suitably to glioblastoma WHO IV.

## Discussion

The aim of this study was to evaluate the diagnostical accuracy of 1H MR-spectroscopy in the preoperative evaluation of low grade glioma and compare the results versus postoperative histopathological findings and discuss the clinical relevance.

We found accordance in 13 (64.8%) cases of the 1H MR-spectroscopy with the histopthological findings and no accordance in 6 (31.6%) cases.

Nowadays, the diagnosis of glioma is mainly based on an examination of neuroimages, with presence of diffuse infiltration of cerebral parenchyma on MR images, contrast enhancement and on histopathological findings in general acceptance as gold standard.

The wide range of survival times reported for patients with glioma may reflect contamination resulting from misdiagnosis, particularly of oligodendroglial tumours and pilocytic astrocytomas and the limits of these diagnostic criteria.

Indeed, it is sometimes difficult to differentiate low grade gliomas because they have the following characteristics: 1) they may infiltrate large areas of brain parenchyma; 2) most often display a lack of contrast enhancement; and 3) are often indistinguishable during review of stereotactical brain biopsy specimen.

If the histologic features of gliomas were reviewed independently by 4 neuropathologists to determine interobserver diagnostic concordance rates, it will be for all 4 reviewers 69%, any 3 reviewers 75% and 2 reviewers 80% [1].

In view of the known failure rate of stereotactic biopsies of 7-15% [8-11] and the interobserver diagnostic concordance rates [1], information about the progress of the disease, (follow-up clinical examinations, follow-up neuroradiological examinations, results of repeated stereotactical biopsy or repeated open surgery) should be considered in the treatment of patients with low grade glioma.

1H MR-spectroscopy provides additional information to the neuroradiological examination, which also could be used easily in follow up examinations.

There are significant spectral differences between tumour and normal brain tissue shown in 1H MR-spectroscopic studies. These differences in metabolite spectra have been consistently detected, even for different acquisition parameters, as techniques have progressed from obtaining single-voxel spectra within a

tissue volume as large as 2 $cm^3$ [12-18] to present techniques that provide hundreds of contiguous voxels at resolution of 1 $cm^3$ or less [19,20].

Tumour spectra have been characterized in part by reduction in signal intensity of the NAA resonance at 2.0 ppm (NAA and other NAA-containing compounds), which has been shown to be present in millimolar concentrations, mainly within neurons [21]. Although the majority of studies have reported increased choline levels (measured at 3.1 ppm) in tumours compared with normal brain tissue, the measured levels can be highly variable presumably because of differences in tumour cell proliferation and averaging tumour tissue with normal or necrotic tissues [5,16,19,22].

The practical application of 1H MR-spectroscopy has a poor appraisal. The spectroscopically established diagnosis before operative intervention is mostly considered to be incorrect as soon as the histopathological finding emerges.

In general the site of biopsy and the site of spectroscopy did not correlate, so it could represent another reason for iscordance between the histopathology and spectroscopy results, the biopsy of a hot spot in the spectroscopy in suggestive low-grade gliomas may help to identify focal points of higher tumour malignancy and offer advantages as compared to conventional stereotactic biopsy.

The spectroscopy findings needed to be correlated with clinical outcomes data to state significant discordance between the histopathology and spectroscopy results.

1H MR-spectroscopy offers a risk free method for the diagnosis of the brain lesions by providing biochemical information related to mitotic cell division (total cholin compounds) displacement of neural tissue (N-acetylaspartate), energy metabolism (total creatine), and necrotic transformation (lipids) [2,3,5,7].

Furthermore 1H MR-spectroscopy provides considerable advantages. It is reported to predict accurately the response of therapy in vivo [23], to identify the border between viable tumour and brain parenchyma shown on conventional MR images [24,25] and to differentiate between tumour and post radiation necrosis [26].

Recent studies of Shao using 1H NMR spectroscopy reveal metabolic heterogeneity of glioma cell lines with different degrees of malignancy [27].

Other spectroscopically methods like $^{31}P$ Phosphorus spectroscopy using metabolites inorganic phosphates and Phosphocreatine seem to be an additional tool in assessing grades of gliomas [28].

Pulsed arterial spin-labeling and diffusion tensor imaging as additional method to MR spectroscopy seem to be very useful for predicting glioma grade [29].

However 1H MR-spectroscopy will never replace the gold standard of histopathological diagnosis, but it can give additional information beyond morphology and help better understanding glioma in their appearance and clinical course.

## Conclusion

It is not possible to distinguish with spectroscopical methods between Astrocytoma II and III or between Astrocytoma and Oligodendroglioma.

1H MR-spectroscopy provides objective and quantitative metabolic diagnostic criteria and offers new insights into pathophysiology of low grade gliomas and provides additional aspects to histopthological considerations. 1H MR-spectroscopy could be used routinely in follow up of patients in particular with low grade gliomas.

| Patient | Spectroscopical Diagnosis | Cholin in % | Cr/Cr-P in % | NAA in % | Removal | Biopsy |
|---|---|---|---|---|---|---|
| BA | Astrocytoma WHO II | 110 | 36 | 86 | + | |
| BM | Astrocytoma WHO II | 131 | 103 | 63 | + | |
| FP | Astrocytoma WHO II | 91 | 68 | 11 | + | |
| GH | Astrocytoma WHO III | 199 | 89 | 21 | | + |
| HM | Astrocytoma WHO II | 150 | 70 | 111 | | + |
| HR | Astrocytoma WHO II | 103 | 93 | 24 | | + |
| KM | Astrocytoma WHO II | 93 | 32 | 9 | + | |
| KaT | Astrocytoma WHO III | 169 | 28 | 36 | + | |
| KT | Astrocytoma WHO II | 100 | 54 | 70 | + | |
| MA | Astrocytoma WHO II | 91 | 102 | 39 | | + |
| MC | Astrocytoma WHO II | 129 | 27 | 30 | + | |
| MU | high grade glioma | 441 | 174 | 43 | + | |
| RK | Astrocytoma WHO III | 187 | 136 | 49 | | + |
| SK | Astrocytoma WHO III | 169 | 28 | 36 | | + |
| SP | Astrocytoma WHO II | 134 | 82 | 34 | | + |
| ST | Astrocytoma WHO II | 78 | 102 | 45 | | + |
| VF | Astrocytoma WHO III | 184 | 56 | 23 | + | |
| WoR | Astrocytoma WHO II | 144 | 75 | 46 | | + |

**Table 3** Spectroscopically established metabolite compounds of gliomas considered WHO II in histopathological assessment.
(Gray shaded rows show no concordance of spectroscopic diagnosis with the histopathological findings)

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