Proton magnetic resonance spectroscopy predicts concurrent chemoradiotherapy response and time-to-progression in high-grade gliomas after surgery

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Received 20 July 2013; accepted 14 September 2013
Available online 11 October 2013

Abstract Introduction: Reliable early prediction response to therapy and time-to progression (TTP) remains an important goal of High-grade glioma (HGG) research. Proton magnetic resonance spectroscopy (H-MRS) has been applied with variable success in clinical application, and we hypothesize that 1H-MRS in predictive value should perform well as a marker of TTP in patients treated with concomitant chemoradiotherapy (CRT) after surgery

Methods: 1H-MRS was performed before surgery on 25 patients who had undergone resection of HGGs and fulfilled the inclusion criteria from 43 patients; then the ratios of lipid/creatine (Lip/Cr) and myoinositol/creatine (mI/Cr) were determined in the solid tumor. CRT response was classified as follows: complete resolution (CR), partial response (PR), stable disease (SD), and progressive disease (PD) by comparison of pre-treatment and post-radiotherapy scans. TTP was defined at the time to radiographic progression by MacDonald criteria. Correlation was evaluated between the ratios of Lip/Cr, mI/Cr and treatment response, TTP. The chi-square test and Pearson correlation test were used for data analyses.

Results: Multivariate analysis revealed that the prognostic value of spectroscopic variables was independent of age, sex, WHO histologic grade, extent of surgery, and Karnofsky score (KPS). The correlation between the ratios of lipid/Cr and TTP was significant (r = 0.894, P = 0.000),

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Peer review under responsibility of Egyptian Society of Radiology and Nuclear Medicine.
1. Introduction

The incidence of primary brain tumors has increased dramatically over the past several decades. The term high grade gliomas (HGG), is usually used to describe HO grade III and IV tumors. Of these, glioblastomas account for 60–70%, anaplastic astrocytomas for 10–15%, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas for about 10%, while anaplastic ependymoma and anaplastic ganglioglioma make up the rest (1). Despite aggressive treatment and research for over half a century, survival for most patients is less than 18 months (2).

Radiotherapy (RT) remains the main adjuvant treatment after surgical resection worldwide, despite significant morbidity including memory impairment, personality change and cognitive decline in as much as two thirds of long-term survivors (3).

Trials of systemic chemotherapy provided mixed results but overall were disappointing (4,5). However, the introduction of temozolomide (TMZ) in the setting of newly-diagnosed GBM and anaplastic astrocytoma has made a substantial impact in the treatment of this disease (6,7).

Preliminary reports have shown that functional magnetic resonance imaging (fMRI) techniques, such as diffusion weighted imaging (DWI), perfusion weighted imaging (PWI), and proton magnetic resonance spectroscopy (1H-MRS), yield structural and metabolic information that may provide better insight into tumor functionality and improve the prognostic stratification of HGG (8). Several studies have evaluated some particular resonances of the spectrum and have found them to be useful for predicting patient outcome in gliomas (9–11). Oh et al. (12) found a significantly shorter median survival time for patients with a large volume of metabolic abnormality, measured by 1H-MRS. Majos et al. (13) demonstrated an inverse correlation between resonance intensities in these regions at both short echo time (STE) and patient survival (a high-intensity value of the peaks of lipid (Lip) and myo-inositol (mI) correlates with low survival), and a direct correlation between mI and patient survival (a high-intensity value of the peak of mI correlates with high survival). However, there are no reports on the relation between the ratios of Lip/Cr or mI/Cr and RT response, time-to-progression (TTP).

The purpose of this study was to determine which of the ratios, Lip/Cr or mI/creatinine (Cr), was the most relevant for predicting CRT response and TTP in HGG after surgery and to analyze the potential of 1H-MRS for discriminating patients with good or poor prognosis.

2. Patients and treatment

A total of 43 consecutive patients with HGG who underwent 1H-MRS between April 2012 and April 2013 were enrolled for the study. In some of the patients, the spectrum was considered to be of poor quality and these patients were excluded. Finally, the definitive dataset of the study included 25 patients. A total of 25 patients with HGG, glioblastoma multiform (n = 19) and anaplastic astrocytoma (n = 6), who underwent subtotal or total resection, were recruited to participate to test the efficacy of 1H-MRS for the assessment of concurrent chemoradiotherapy response. Patients with histologically confirmed HGG who had not received any prior therapy, and who had undergone immediate postoperative computed tomography (CT) or MRI within 24 h of surgery to assess the extent of resection were included. All patients were treated with fractioned RT in daily doses of 2 Gy to a total of 56–60 Gy with concurrent timodal 50mg daily. Patients received timodal concurrent with radiotherapy in dose of 100 mgm half an hour prior to radiotherapy. They underwent 1H-MRS at the time of MRI before concurrent CRT. MRI was performed at follow-up to determine CRT response 4 weeks after completion of the therapy. The patients were subsequently assessed by their neuro-oncologist at 2-month intervals according to the local standard of care (See Case numbers 1 and 2).

2.1. Image acquisition

Data were acquired with a 1.5 T MR imaging scanner (GE – high signal). Single-voxel 1H-MRS was performed as the last sequence of the MR imaging examination. A volume of interest (VOI) between 1.5 and 2.0 cm³ was placed for performing 1H-MRS in HGG. Specifically, the VOI location and size were determined with the aim of positioning the largest possible voxel within the solid brain mass, with minimal contamination from the surrounding non-affected tissue or from non-enhancing areas of the tumor, when possible. One spectrum was acquired from the VOI: STE (TR/TE, 1500/35) (Case 3).

A spectrum was considered to be of poor quality when large peak line width, poor signal intensity-to-noise ratio, or obvious artifacts precluded precise quantification of some areas of the spectrum.

2.2. Response assessment

Radiological assessment of response was carried out according to the current World Health Organization (WHO) 2000 modified MacDonald criteria change in maximal perpendicular tumor diameters 3 months after the conclusion of a therapeutic protocol as follows: (14–16) complete response (CR) is defined as complete disappearance of abnormal contrast enhancement in a patient not on steroids at the time of MRI; partial response (PR) refers to a > 50% decrease in volume measure of enhancing abnormality on MRI performed more than 4 weeks after the end of therapy in a patient on a stable or decreased steroid doses;
stable disease (SD) refers to no change in volume of abnormal enhancement or a change that does not meet PR or PD criteria (<50% decrease or <25% increase) in a patient on stable or decreased steroid dose; and progressive disease (PD) refers to a >25% increase in volume measure of enhancing abnormality in a patient on a stable or increased steroid dose. Patients were classified as responders (CR and PR) or non-responders (SD or PD) by comparison of post-treatment images to the pre-concurrent chemoradiotherapy (baseline) MRI images (17). TTP was defined as the time from diagnosis to recurrence.
2.3. Statistical analysis

Prognostic variables evaluated were both clinical (age, sex, WHO grade, Karnofsky score (KPS), and extent of surgery) and spectroscopic (the ratios of Lip/Cr, mI/Cr). The statistical significance of the differences in the ratios of Lip/Cr, mI/Cr between response groups was analyzed using c2 test. The correlation of ratios of Lip/Cr, mI/Cr with TTP was evaluated by
Pearson correlation test. The association between CRT response and median TTP was evaluated with log-rank tests. Kaplan–Meier curves were constructed by defining TTP as the time from the initial surgical diagnosis to the time of tumor progression. For all statistical tests, a $P$ value less than 0.05 was considered to indicate statistical significance.

3. Results

A total of 25 patients fulfilled the inclusion criteria and were retained in the study. Multivariate analysis revealed that the prognostic value of spectroscopic variables was independent of age, sex, WHO histologic grade, extent of surgery, and KPS (Table 1).

The dataset of 25 patients included four groups, and the ratios of Lip/Cr, mI/Cr, TTP and the correlation are shown in Table 2.

The correlation between the ratios of lipid/Cr of each group and TTP was significant ($r = 0.894$, $P = 0.000$), and that between the ratios of mI/Cr of each group and TTP was also significant ($r = 0.891$, $P = 0.000$).

As expected, CRT response correlated significantly with TTP ($r = 0.590$, $P = 0.002$). The log-rank test and Kaplan–Meier curves revealed that patients with PD had a shorter median TTP (49.9 days) compared with those with CR (234.5 days). TTP was also significantly longer in the PR group (208.0 days) and SD group (202.7 days) than the PD group, but not quite as long as in the CR group. After concurrent

Figure A before treatment MRI with MRS ---- choline/NAAA=2.9 (more than 1.9 malignant tumor), myoinositol/NAA=0.2, the sum of two ratios=3.1, choline/creatine=2.5---- finding are constent with residual /RECCURRENCE TUMOR

Post fractionated radiotherapy with concomitant timodal ----MRI with MRS ---- choline/NAAA=2.5 (more than 1.9 malignant tumor), myoinositol/NAA=1.1, the sum of two ratios=2.9, choline/creatine=3.2---- finding are constant with marked progression of previously detected.

Case 3  Representative STE spectra from PD group to RT. A 42-year-old man treated for an anaplastic astrocytoma by standard fractionated RT (total dose, 60 Gy) with TTP of 64 days. The main significant differences are seen in the Lip and mI region.
chemoradiotherapy case 1 showed radiation necrosis with MRS. case 2 showed residual or recurrence with MRs. MRS in case 3 showed progressive disease.

4. Discussion

It is important to identify responsive patients with HGG who can take advantage of intensive treatments and non-responsive ones for whom conservative support treatment is a choice. Histopathology remains the reference standard for prognostic assessment, providing an insight into the morphologic cytostructure of the tumor (18). Nevertheless, histopathology has its limitations in providing prognostic value, and additional factors have been defined for stratifying patients into diverse prognostic groups. A recursive partitioning analysis undertaken by the Radiation Therapy Oncology Group identified four risk classes for glioblastoma based on patient age, KPS, neurologic function, mental status, and extent of surgery (19,20). These items provide a prognostic assessment based on factors related to patient status and effectiveness of the surgical approach. Nevertheless, several researchers suggested that there might be some metabolic information in tumors that could help in specifying the prognosis of HGG and that this information could be assessed in a non-invasive way by 1H-MRS (14,20).

Our study has shown that the information provided by 1H-MRS may be of help in the prognostic assessment of patients, and we found two regions of the spectrum that have prognostic value. The regions corresponding to lipids and mI, and these spectroscopy points offer the opportunity to formulate ratios between metabolites at STE to be used in a clinical setting. Using ratios would have the advantage of producing a straightforward quantitative assessment of the spectrum that would not require any additional normalization procedure.

Our study demonstrates that there is an inverse correlation between ratios of lipid/Cr at STE and patient TTP, and furthermore, a direct correlation between ratios of mI/Cr at STE and patient TTP.

Prior studies showed some prognostic value of the major resonances of the spectrum, such as choline-containing compounds, N-acetylaspartate, creatine, lipids, and lactate (11,12). The methodology used in our study provided the opportunity to detect differences in the area around mI, not evaluated in previous studies.

Limitations of our study include the limited number of patients, and more data should be acquired. Since 1H-MRS can be readily performed on most modern scanners in a short time, without added risk or use of contrast, this could be of significant benefit in monitoring patients who are responding well and selecting patients who are not responding well to receive additional chemotherapy or supplementary stereotactic radiation.

In our study, we tried to define the relevant value of 1H-MRS in HGG patients only with surgery and CRT for a prognostic assessment. We found that the ratios of Lip/Cr, mI/Cr at STE provided relevant prognostic information, and may offer an early marker of treatment response. This predictive value of 1H-MRS concerning TTP could be very useful for evaluating whether intensive oncologic therapy is necessary in some patients.

Conflict of interest

No potential conflicts of interests were disclosed.
References