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3D-MR Spectroscopic Imaging at 3Tesla for Early Response Assessment of Glioblastoma Patients during External Beam Radiation Therapy

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Abstract

Purpose—To evaluate the utility of 3D-MR proton spectroscopic imaging for treatment planning and its implications for early response assessment in glioblastoma multiforme.

Methods and Materials—Eighteen patients with newly diagnosed, histologically confirmed glioblastoma had 3D-MR proton spectroscopic imaging (MRSI) along with T2 and T1 gadolinium enhanced MR images at simulation and at boost treatment planning after 17-20 fractions of radiotherapy. All patients received standard radiotherapy with temozolomide and follow-up with every two month MR scans. Progression free survival was defined using MacDonald criteria.

MRSI images obtained at initial simulation were analyzed for choline / N-acetylaspartate ratios (Cho/NAA) on a voxel by voxel basis with abnormal activity defined as Cho/NAA ≥ 2 . These images were compared on anatomically matched MRSI data collected after 3 weeks of radiotherapy. Changes in Cho/NAA between pre-therapy and 3rd week RT scans were tested using Wilcoxon matched-pairs signed rank tests and correlated with progression free survival, radiation dose and location of recurrence using Cox proportional hazards regression.

Results—After 8.6 months (median follow-up), 50% of patients had progressed based on imaging. Patients with a decreased or stable mean or median Cho/NAA values had less risk of progression ($p < 0.01$). Patients with an increase in mean or median Cho/NAA values at the 3rd week RT scan had a significantly greater chance of early progression ($p < 0.01$). An increased Cho/NAA at the 3rd week MRSI scan carried a hazard ratio of 2.72 (95% confidence interval 1.10-6.71, $p = 0.03$). Most patients received the prescription dose of RT to the Cho/NAA ≥ 2 volume, which was where recurrence most often occurred.

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Conflict of interest statement:

The authors declare that no actual or potential conflict of interest exists.

Conclusion—Change in mean and median Cho/NAA detected at 3 weeks was a significant predictor of early progression. The potential impact for risk-adaptive therapy based on early spectroscopic findings is suggested.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. (1) The therapeutic outcome in glioblastoma depends on age and the functional status of the patient (2, 3). Studies suggest completeness of resection is prognostic yet the degree of resection also depends significantly on tumor location, the patient's functional status and age (4-6). Radiation offers survival benefit to patients in randomized trials (7, 8) and combining chemotherapy (temozolomide) with radiation further enhances survival (9). Despite progress in surgery, radiation and chemotherapy approaches, the median survival for glioblastoma patients remains poor, approximately 14 months (7,9).

The primary mode of recurrence remains local yet response assessment after therapy is complicated by inflammatory reactions after radiation and chemotherapy (10-13). The differential diagnosis of radiation necrosis versus tumor recurrence has limited sensitivity and specificity with traditional CT and MR imaging (14). Because of this inability to distinguish viable tumor versus therapy reaction, a search for image-based identification of metabolically active tumor has been pursued. Proton MR spectroscopic imaging (MRSI) as well as other functional imaging (dynamic susceptibility contrast DSC MRI, diffusion weighted DW MRI, SPECT-Thallium, FDG-PET, FLT-PET, ^{11}C -choline-PET) have been studied to differentiate these clinical conditions (15-17). MRSI has the advantage of being clinically available, quantitative and has a clinically relevant albeit not ideal voxel resolution of 7-10mm³ for anatomic co-identification of abnormal tumor metabolic activity.

MRSI provides a non-invasive spatially quantifiable measure of cellular metabolites in the brain. Spectral data acquired at long echo times (TE = 135 ms) usually depict key metabolite signals such as choline (Cho), creatine (Cr), N-acetylaspartate (NAA), lactate (Lac) and lipids. The elevated choline signals (3.22 ppm), a marker of membrane turn over and cellular density, are juxtaposed against decreased NAA signals (2.02 ppm), a marker of neuronal function. The increase of this Cho –NAA ratio defines the metabolic abnormality seen in malignant tumors which is associated with a Cho/NAA > 2 (18).

Previous studies have evaluated the association between MRSI derived tumor metabolic activity and patterns of tumor recurrence in GBM patients (19, 20). To date, no studies have investigated the potential value of MRSI derived changes in tumor metabolic status during radiation therapy (RT) to predict tumor response. The purpose of this study wherein patients had MRSI done at the time of initial radiation simulation and again at the time of boost simulation (3-4 weeks into therapy) was to i) evaluate the change in MRSI metabolite values in predicting ultimate tumor response, ii) compare spatial relationships between MRSI defined tumor activity (Cho/NAA > 2) and location of first tumor recurrence, and iii) correlate regions of tumor recurrence with delivered radiation dose. All volumetric MRSI was performed using a 3 Tesla MRI scanner dedicated for RT simulation.

PATIENTS AND METHODS

Patients

Eighteen patients with newly diagnosed, histologically confirmed GBM were included in this study. Patients had biopsy (7/18 patients) or surgery (subtotal or gross total resection, 11/18 patients,) and received radiotherapy between January 2008 to February 2011. Thirteen patients were male and 5 were female. Median age was 56 years (range 24-78 years). Institutional practice includes CT and MRI for initial radiation treatment planning. Patients had T₂ and T₁ weighted MRI with gadolinium as well as volumetric MRSI. After the third week of RT, all MR sequences are repeated for boost radiation planning. Institutional Review Board (IRB) approval was obtained.

MRI and MRSI data acquisition

The MRI and MRSI imaging were performed on a Siemens 3T TIM TRIO scanner (Siemens Medical Solutions, Malvern, PA) with 12 channel head matrix coil. The MRI protocol included the following scans: i). T₂-weighted 3-dimensional (3D) SPACE sequence with TR = 3200, TE = 462 ms, 176 slices at isotropic (1.0 mm × 1.0 mm × 1.0 mm) voxel resolution, parallel imaging (GRAPPA) acceleration factor: PAT = 2. (or) a T₂-weighted 3D axial fluid attenuated inversion recovery (FLAIR) sequence with TR = 5000 ms, TE = 395 ms, Inversion time (TI) = 1800 ms, 160 slices at isotropic (1.0mm × 1.0mm × 1.0mm) voxel resolution, PAT = 2. ii). 3D axial T₁-weighted gadolinium enhanced MRI using ultra-fast magnetization prepared rapid gradient echo (MPRAGE) sequence with TR = 1530 ms and TE = 2.9 ms, Flip angle = 9°, 176 slices at isotropic (1.0mm × 1.0mm × 1.0 mm) voxel resolution, PAT = 2.

All MRSI scans were performed during the same simulation imaging session. A 5 mm thick T₂-weighted anatomical reference image for MRSI covering the entire tumor region in axial, coronal and sagittal planes was reconstructed from the 3D SPACE or 3D- FLAIR sequence described previously. The 3D MRSI data was acquired in 8 min 55 sec using point resolved spectroscopy (PRESS) sequence with TE/TR: 135/1510 ms, number of excitations (NEX)=2, 12×12× 8 matrix at acquisition and 16×16×8 after zero filling, FOV: 16×16×8 cm resulting in MRSI voxel size of 10×10×10 mm³. MRSI data were obtained approximately 1 week prior to start of radiation therapy (RT) and during the third week of RT (after 17 to 20 fractions). Flexible coils were placed over patients immobilized with thermoplastic masks for all imaging studies to improve image registration.

The MRSI excitation volume (PRESS box) was chosen to avoid subcutaneous fat and areas with magnetic susceptibility such as the sinuses and skull, which induce artifacts in spectral data. The PRESS box encompassed as much as the T₂ hyper-intensity area and normal surrounding tissue as possible. During the third week of RT MRSI scan, care was taken to position the PRESS excitation volume to anatomically match the initial MRSI scan. Magnetic field uniformity within the PRESS volume was optimized using the advanced automated shimming routine available with the scanner followed by manual shimming. MRSI scans were acquired immediately after the 3D anatomical T₂- weighted scan to minimize patient movement between the T₂- weighted images and MRSI and T₂- weighted

images served as reference images to overlay the processed MRS spectral array. The MRSI data were intrinsically registered to the T₂- image data set.

MRSI data processing and evaluation

MRSI raw data were reconstructed using a vendor supplied spectroscopy processing tool on Syngo software platform (Siemens Medical Solutions, Malvern, PA). Spectral data were quantified using the linear combination (LC) model for determination of metabolite levels (21). Spectral peak parameters-height, width, area for Cho and NAA were estimated on voxel-by-voxel basis within the PRESS excitation volume and a Cho-to-NAA metabolite ratio (Cho/NAA) was assigned to each voxel. Metabolically active tumor regions were defined as voxels with a Cho/NAA ≥ 2 . (19, 20). MRSI voxels with significant tumor activity (Cho/NAA ≥ 2.0) were segmented from the near matching slices of pre-RT and third week-RT scans and used for comparative analysis. Voxel-by-voxel comparison of Cho/NAA values was made for the registered MRSI datasets. Voxels surrounding the active tumor region with borderline metabolic abnormality (i.e., $1.5 > \text{Cho/NAA} > 2.0$) at baseline scan were also included in analysis if they turned out to be metabolically abnormal at the third week of RT. Endpoints analyzed were the magnitude of change in Cho/NAA and the extent of change in metabolically abnormal tumor volume at 3 weeks of RT with respect to pre-RT scans.

The Cho/NAA metabolic maps were generated using 3D MRSI data, which was aligned to the anatomical images using the direction cosines of the acquired volumes. A Cho/NAA metabolic image was created for each assessment time point. For the purpose of defining the tumor extent based on metabolic ratio in 3D space, Cho/NAA images were transferred to a commercial 3D radiation treatment planning system (TPS) (Pinnacle³, Phillips Medical Systems, Fitchburg, WI, USA) and registered with anatomic RT planning image data. Registration of CT and Cho/NAA image maps were accomplished in two steps. First the CT images were registered to T₂ MR images. Second, the transformation matrix of this CT to T₂ MRI registration was applied to register Cho/NAA maps to the CT data set. An automatic local correlation registration algorithm available with TPS registration module (Syntegra) was used to define the correspondence between the two modalities, and was visually verified. Metabolically active tumor contours were created using an automatic threshold approach of (Cho/NAA ≥ 2). For patients with analysis of MRSI scans suggesting progressive, more metabolically active lesions at week 3 of RT, post-RT followup MRI scans (corresponding to the date of anatomic progression) were also fused with the RT planning image sets and the regions of tumor recurrence were contoured within TPS. Spatial correlation of MRSI defined abnormal tumor metabolic activity, extent of gross tumor at the time of boost RT planning (represented by T₁ contrast enhancement) and regions of tumor recurrence were analyzed. The percentage of the recurrent lesion volume that received 100% of the total prescribed dose 61.2 Gy (V_{100}) was calculated from the registered treatment plan. .

Radiation Therapy

All patients received post-operative chemo-radiation therapy. Radiation treatment was delivered with 3D conformal planning or intensity modulated RT technique using a linear

accelerator (Oncor™, Siemens Medical Solutions, Concord, CA). Fifteen out of 18 patients received 61.2 Gy, 1.8 Gy/fraction in 34 fractions. Three patients received 59.4 Gy, 1.8 Gy/fraction in 33 fractions. All patients received temozolomide (TMZ) chemotherapy concurrently. The median follow-up post-radiation therapy was 8.6 months (range 1.6 to 30 months).

Tumor Response Assessment

All patients had follow-up MRI scans at regular intervals (every 2 months) post-treatment. Progression-free survival (PFS) was the primary endpoint for this study. A board certified neuroradiologist (AAC), reviewed the pre-treatment and follow-up MRI scans (blinded to MRSI data) for all 18 patients. The MacDonald criteria were utilized to define and determine the date of progression for each patient (22).

Statistical Analysis

Differences in Cho/NAA values between pre-RT and third week RT for both stable and tumor progression groups were tested for statistical significance using the Wilcoxon matched-pairs signed ranks test. The primary end point, time to disease progression, was analyzed statistically with survival methods. Subjects without progression at their last follow-up were treated as censored observations. To evaluate the prognostic value of MRSI, we compared changes in pre- vs. third week- RT Cho/NAA values with the time of progression-free survival (PFS) using Cox proportional hazards regression (23). Time to progression was modeled as a function of mean, median and 75th percentile tumor Cho/NAA values derived from MRSI at baseline and third week of RT. In addition, the number of MRSI voxels with Cho/NAA ≥ 2 at third week of RT and also the number of voxels which changed from Cho/NAA ≥ 2 at baseline to Cho/NAA < 2 (metabolically inactive) at third week RT were assessed in the Cox proportional hazard model analyses. Hazard ratios are reported, along with 95% confidence intervals, for one standard deviation decrease in each of the MRSI metrics, and represent the associated factors by which the progression rates change. All statistical testing was two-sided and assessed for significance at the 0.05 level.

RESULTS

Patients Follow-up

Patient demographics and clinical follow-up are listed in Table 1. Among 18 patients, 9 (50%) showed tumor progression and the remaining 9 (50%) had stable disease, based on MacDonald criteria at the time of last follow-up (14). Median follow-up time for all patients was 8.6 months

Pre-RT vs third Week RT MRSI Comparison

Figures 1 and 2 show anatomical MR and spectroscopic images of two patients obtained at pre-RT simulation and at the third week of RT. Variations in Cho/NAA ratios, both the degree and spatial extent of tumors in a single patient and between patients reveal the imaging heterogeneity of GBMs. Similarly, the metabolic response of these tumors during RT is also different between these patients. A voxel-to-voxel comparison of Cho/NAA

values from matched MRSI data sets obtained at pre-RT and third week RT for all 18 patients are summarized graphically in Figures 3a & b. Cho/NAA values between pre-RT and third week RT change differently in patients with stable disease on initial follow-up scans (stable group) compared with those having early progressive disease (progressive disease group). Most patients in the stable group (Figure 3a), at 3 weeks of RT, showed either a decrease or no change in mean ($p < 0.01$) and median ($p < 0.05$) tumor Cho/NAA values. Those in the progressive disease group (Figure 3b), showed an increase in mean ($p < 0.01$) and median ($p < 0.01$) tumor Cho/NAA values during the third week of RT scan. This was observed in 7 out of 9 patients with progression. The remaining two patients showed a marked decrease in Cho/NAA at third week of RT yet they still progressed using the MacDonald criteria. One of these 2 patients (patient 16) remained free of further tumor progression for 10 months after RT (consistent with pseudo progression) and relapsed later. The other patient (patient 18) was a complete outlier with respect to her tumor metabolic status. In this patient, there were two lesions: a large tumor mass and small satellite lesion and each revealed different pattern of response to treatment. The satellite lesion showed no detectable metabolic abnormality both at pre-RT and third week RT but demonstrated a clear radiological progression. This discrepancy could reflect partial volume effects in the small satellite lesion. The larger lesion, which showed a marked decrease in the metabolic status at the third week of RT, remained metabolically and radiologically stable at the time of last follow-up (19 months).

Cox regression analysis results are listed in Table 2. For the 18 patients included in this study, greater decreases in mean Cho/NAA values at the third week RT scan (hazard ratio, 0.37; 95% confidence interval: 0.15-0.91; $p = 0.03$) as well as mean percent decrease (hazard ratio, 0.49; 95% confidence interval: 0.27-0.89; $p = 0.02$) were significant predictors of progression-free survival. Decreases in the median Cho/NAA value and the percent decrease in Cho/NAA value as well as the decrease in the 75th percentile tumor Cho/NAA were moderately significant ($p = 0.07$, 0.06 and 0.06 respectively). Percent difference in median tumor Cho/NAA, number of voxels with Cho/NAA ≥ 2 at third week RT, and number voxels changing from Cho/NAA ≥ 2 at pre-RT to Cho/NAA < 2 at 3rd week RT were not ($p = 0.15$, 0.08 and 0.79 respectively) significant.

Location of tumor recurrence

Spatial locations of tumor recurrence with respect to the MRSI derived abnormal tumor metabolic activity were analyzed for the 9 patients with progressive lesions. The follow-up T₁-weighted contrast enhanced MR images, on which tumor progression was confirmed, were fused with the RT planning image sets within our TPS. Contrast enhanced regions were contoured and overlaid with pre-existing fused MRSI Cho/NAA color maps as shown in Figure 4. Among the 9 patients with progressive disease, the locations of recurrent lesions coincided with the areas of pre-RT or third week RT MRSI metabolic abnormality in 6 patients. For two of the remaining 3 patients, due to technical limitations, the PRESS excitation volume was not able to cover a portion of the T₂-abnormality, where part of the recurrent lesions were located. In one patient MRSI results were negative for a small satellite lesion, which relapsed later, probably because of partial volume effect.

Location of tumor recurrence and radiation dose

The RT planning target volumes PTV 45.0 Gy and 61.2 Gy were overlaid on recurrent tumor contours and MRSI Cho/NAA color maps (Figure 4). The recurrent lesions were located within the region of either PTV 45 Gy or 61.2 Gy in 8 of 9 patients. One patient had a new lesion at a distant location completely away from the irradiated volume. The volume of recurrent lesions that received 100% of the total (61.2 Gy) prescribed dose, V_{100} , was estimated in all 9 patients. For six patients, the V_{100} was 100%. Two patients had recurrent lesions with V_{100} of 70% and 95%. The V_{100} was 58% for one patient with distant recurrence.

DISCUSSION

We compared the status of tumor metabolic activity on MRSI after 3 weeks of RT with pre-RT to evaluate early tumor response to treatment in GBM patients. Spatial tumor metabolic maps were obtained, non-invasively, using volumetric proton MR spectroscopic imaging at 3T. Differences in mean Cho/NAA values between third week RT and pre-RT showed a significant correlation with progression-free survival ($p=0.02$), despite the small patient sample size. In the majority of patients, regions of abnormal tumor metabolic activity, observed at either pre- and/or third week RT, overlapped with the location of tumor recurrence. The prescribed radiation dose of 61.2 Gy, in most cases, completely covered the regions of recurrence. Limitations of this study include the relatively small patient sample size; technical limitations in lesion coverage with the 3D PRESS sequence used that underestimated recurrence in 2 cases, and partial volume effects that may have been responsible for missing CNR increase in a small satellite recurrent lesion.

Although it is well recognized that glioblastoma commonly recurs within the high dose region of radiation therapy, there are now several other therapeutic agents that might be considered at recurrence. It is possible that identification of poor metabolic response could be effectively used as a risk-adaptive approach for utilization of agents like bevacizumab that are effective in recurrent settings (24, 25). Early application might benefit patients prior to having gross radiographic recurrence.

In addition, the metabolic tumor volumes were at times different from tumor volumes defined on structural imaging and inclusion of these volumes in the radiation field could benefit a limited number of patients. While the majority had good coverage of Cho/NAA >2 volumes based on anatomic T_2 and T_1 gadolinium enhanced volumes, a small number (2) did not.

CONCLUSION

Identifying early progression in glioblastoma will increase in importance as more effective alternative therapies are developed. MRSI appears a promising approach and one well suited to a risk adaptive approach during radiation and chemotherapy. Additional data will be needed to explore the full potential impact of these quantitative metabolic approaches.

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Figure 1.

Stable disease show decrease in metabolic status at 3 weeks of RT (tumor Cho/NAA mean $\pm$ std error: 3.79 ± 0.48 to 2.78 ± 0.28) in a 24 year old male with GBM.

Figure 2.

A 52 year old male with GBM and disease progression at last follow up shows an increase in tumor metabolic status at 3 weeks of RT (tumor Cho/NAA mean $\pm$ *std error* 1.33 ± 0.59 to 2.13 ± 0.95).

Figure 3 (a, b).

Comparison of pre-RT vs. third week RT Cho/NAA values of matching MRSI tumor voxels of patients, who were (a) stable and (b) had progression at the time of last follow-up. At third week of RT, the tumor Cho/NAA values for stable group (a) decreased in all patients [mean ($p < 0.01$), median ($p < 0.05$)] and for progression group (b) increased in all but 2 patients [mean ($p < 0.01$), median ($p < 0.01$)] from pre-RT levels.

Figure 4.

MRSI defined tumor metabolic abnormality and the delivered RT dose. Green contours represent the location of tumor recurrence (derived from follow-up T₁ CE MRI scans after fused with RT planning images set). Yellow and red contours indicate RT planning target volume, PTV 45.0 Gy and PTV 61.2 Gy respectively.

Table 1

Patient characteristics and clinical follow-up.

Patient No.	Gender	Age	Pre-RT surgery or biopsy	Total radiation dose received (Gy)	Follow-up (days)	Progression free survival, PFS (days)	Clinical status* at last follow-up
1	F	57	Biopsy	61.2	227	227	Stable
2	M	26	Surgery	61.2	847	847	Stable
3	M	24	Surgery	61.2	896	896	Stable
4	M	58	Biopsy	59.4	195	195	Stable
5	F	70	Surgery	61.2	742	742	Stable
6	M	58	Biopsy	61.2	154	154	Stable
7	M	78	Biopsy	59.4	47	47	Stable
8	M	60	Surgery	59.4	290	290	Stable
9	M	46	Surgery	61.2	153	153	Stable
10	M	47	Biopsy	61.2	218	21	Progression
11	M	56	Biopsy	61.2	517	189	Progression
12	F	38	Surgery	61.2	749	87	Progression
13	M	56	Surgery	61.2	272	170	Progression
14	M	55	Surgery	61.2	244	90	Progression
15	M	52	Surgery	61.2	243	37	Progression
16	F	51	Surgery	61.2	567	313	Progression
17	M	72	Surgery	61.2	352	31	Progression
18	F	66	Biopsy	61.2	176	34	Progression

* Based on Macdonald criteria. See text for details.

Table 2

Cox regression estimates of time-to-progression hazard ratios for one standard deviation (SD) decreases in the MRSI metrics.

Parameter	Standard deviation	Hazard ratio	95% CI	p-value
Abs Diff Cho/NAA ratio * (Mean)	1.0	0.37	0.15-0.91	0.0300
Abs Diff Cho/NAA ratio (Median)	0.7	0.55	0.29-1.05	0.0706
Abs Diff Cho/NAA ratio (75th percentile)	1.3	0.14	0.02-1.13	0.0650
% Diff Cho/NAA ratio † (Mean)	0.6	0.49	0.27-0.89	0.0199
% Diff Cho/NAA ratio (Median)	0.5	0.65	0.35-1.18	0.1530
% Diff Cho/NAA ratio (75th percentile)	0.6	0.57	0.31-1.03	0.0613
Cho/NAA ratio <2 @ 3rd Wk RT ††	0.2	0.55	0.28-1.08	0.0829
Cho/NAA ratio <2 @ 3rd Wk RT Cho/NAA ratio <2 @ Pre-RT	0.2	1.11	0.53-2.33	0.789

Abbreviations

* Absolute different in choline/N-acetylaspartate ratio

† Difference in choline/N-acetylaspartate ratio

†† Radiation Therapy