**Proton magnetic resonance spectroscopy imaging in the evaluation of patients undergoing gamma knife surgery for Grade IV glioma**

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**Object.** The purpose of this study was to assess the differences in spatial extent and metabolic activity in a comparison of a radiosurgical target defined by conventional strategies that utilize the enhancing lesion and a metabolic lesion defined by proton magnetic resonance spectroscopy (MRS) imaging. The authors evaluated whether these differences manifest themselves in the clinical outcome of patients and assessed the value of incorporating 1H-MRS imaging–derived spatial information into the treatment planning process for gamma knife surgery (GKS).

**Methods.** Twenty-six patients harboring Grade IV gliomas who had previously been treated with external-beam radiation therapy were evaluated by comparing the radiosurgically treated lesion volume with the volume of metabolically active tumor defined on 1H-MRS imaging. The cohort was evenly divided into two groups based on the percentage of overlap between the radiosurgical target and the metabolic lesion volumes. Patients with a percentage of overlap greater than 50% with respect to the metabolic lesion volume were classified as low risk and those with an overlap less than 50% were classified as high risk.

Kaplan–Meier estimators were calculated using time to progression and survival as dependent variables. The metabolite levels within the metabolic lesion were significantly greater than those within the radiosurgical target (p < 0.001). The median survival was 15.7 months for patients in the low-risk group and 10.4 months for those in the high-risk group. This difference was statistically significant (p < 0.01).

**Conclusions.** Analysis of the results of this study indicates that patients undergoing GKS may benefit from the inclusion of 1H-MRS imaging in the treatment planning process.

**Key Words • magnetic resonance spectroscopy • glioma • gamma knife surgery • treatment planning**

**Abbreviations used in this paper:** CNI = Cho/NAA index; EBRT = external-beam radiation therapy; FDG = 18F-fluorodeoxyglucose; GBM = glioblastoma multiforme; GKS = gamma knife surgery; Met = L-[methyl-11C] methionine; MR = magnetic resonance; MRS = MR spectroscopy; PET = positron emission tomography; PRESS = point-resolved spectroscopy; SPECT = single-photon emission computerized tomography; 3D = three-dimensional.
cells usually extend beyond the area of enhancement on T1-weighted images. Both the ill-defined enhancement border and the infiltrative nature of malignant gliomas make them problematic to treat using focal therapy. Thus, radiosurgery would benefit from complementary imaging information.

Proton MRS is a noninvasive in vivo technique that can provide measures of the biochemical and functional statuses of tissues. Four distinct peaks are discernible in spectra from the brain at the clinical field strength of 1.5 teslas: 1) choline compounds (Cho), indicators of cell membrane synthesis and degradation; 2) creatine (Cr), an indicator of energy reserves; 3) N-acetyl-aspartate (NAA), a reputed neuronal marker; and 4) lactate and lipid (LL). Lactate is an end product of anaerobic oxidation, whereas lipid, sometimes colocalized with lactate, reflects cellular breakdown and necrosis. Data from single-voxel MRS studies have demonstrated that metabolic changes can differentiate between various tissue types. For example, normal brain parenchyma typically exhibits Cho and Cr levels that are approximately equal and an NAA peak that is 1.5 to two times larger. Neoplastic tissue exhibits reduced or depleted levels of NAA and, most often, increased Cho levels. Furthermore, minimal metabolic activity occurs in necrotic tissue, which therefore exhibits low levels of Cho, Cr, and NAA together with the possibility of increased LL in Grade IV tumors due to hypoxia or necrosis. Figure 1 depicts characteristic spectra obtained in a patient harboring a recurrent Grade IV glioma. Magnetic resonance spectroscopy improves on MR imaging by providing a 3D array of voxels, enabling one to study the heterogeneity of a larger region with improved spatial resolution.

Previous work from our laboratory has indicated that 1H-MRS imaging may play a role in the GKS treatment planning process by improving discrimination between normal tissue and glioma. Graves, et al., showed that patients with metabolic abnormalities extending outside the radiosurgical target experienced a shorter time to additional treatment and a shorter survival compared with patients harboring metabolic abnormalities primarily within the GKS target volume. In that earlier study, the abnormality’s relation to the GKS target was assessed on a visual basis by a spectroscopist who subjectively classified voxels as abnormal if Cho was elevated and NAA was depressed compared with typical normal brain spectra.

To use 1H-MRS imaging routinely in a clinical environment, the definition of abnormality should be more quantitative to reduce the subjectivity of interpretation and the need to interact with the spectroscopist. In the current study, we examined the differences between the radiosurgical target defined by conventional strategies that use the enhancing lesion and the metabolic lesion defined by 1H-MRS imaging results. We propose an objective criterion for defining the spatial extent of metabolic lesions and study the value of incorporating 1H-MRS imaging-derived spatial information into the GKS treatment planning process.

Clinical Material and Methods

Patient Population and Treatment

The patient cohort studied by Graves, et al., and the patient cohort of this study are mutually exclusive. Our population consisted of 26 patients harboring histologically confirmed Grade IV glioma, according to the World Health Organization II criteria. All patients signed consent forms approved by the Committee on Human Research at our institution. The patient population included 13 men and 13 women, with ages ranging from 26 to 83 years and a median age of 52 years. One patient had a gliosarcoma, whereas all others had GBM. All patients had been previously treated with EBRT. Eight patients underwent GKS (Elekta Instruments, Inc., Atlanta, GA) as a boost to EBRT, whereas the remaining 18 were treated at the time of glioma recurrence. The patients underwent GKS between December 1998 and August 2001. The head of each patient was fixed in a stereotactic frame prior to imaging. Standard MR images were obtained immediately prior to GKS. The radiosurgical target was delineated as the contrast-enhancing region plus a peripheral margin of approximately 1 to 2 mm. The physicians outlining the target did not know the extent of the metabolic lesion as defined on MRS imaging. Dose maps in the same reference frame as the treatment planning images were created. Patients were treated with a median dose of 1600 cGy (range 1000–2665 cGy) to the 50% isodose line.

Magnetic Resonance Imaging and MRS Imaging Acquisition

All MR and MRS imaging examinations were performed prior to treatment either on the day of or within 1 week before treatment began. Studies were performed on a 1.5-tesla clinical imager (Signa Echospeed; General Electric Medical Systems, Milwaukee, WI) equipped with a standard head coil. The imaging sequence included the acquisition of an axial post-Gd T1-weighted 3D spoiled-gradient echo image with the following parameters: TR 32 msec, TE 8 msec, number of excitations 1, number of slices 124, slice thickness 1.5 mm, and flip angle 45°. The spoiled-gradient echo image was used as the reference image to which all other
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Postprocessing of MRS Imaging

All data were sent to a computer workstation (SUN Ultra 10; Sun Microsystems, Inc., Mountain View, CA) for postprocessing by using programs developed in our laboratory. The acquired free-induction decay curves were apodized with a 2-Hz lorentzian filter and then Fourier transformed spatially in three dimensions and temporally in one dimension. The spectra were then baseline, frequency, and phase corrected. Peak heights were estimated using a priori knowledge about the relative positions of the major peaks. The relative metabolite levels were expressed as the peak heights normalized to the standard deviation of the spectral noise from the right side of the spectrum where no peaks were present.

For each voxel in the 3D array, the CNI was calculated using an automated regression technique. The CNI is equal to the number of standard deviations that the Cho/NAA ratio of a voxel is away from the Cho/NAA ratio of the regression line through the population of control voxels. In essence, the CNI is a quantitative measure of the probability of metabolic abnormality. The resultant 3D CNI map was then resampled to match the resolution of the reference image and contoured using a CNI value of 2, which has been shown to be a sensitive differentiator between tumor and nontumor. Care was taken not to include the resection cavity within the contour. The metabolic lesion was defined as the volume within this contour in which tissue exhibited elevated Cho and/or reduced NAA levels and thus had a high probability of being metabolically abnormal. The metabolic lesion was superimposed onto the reference image to visualize its relationship to the radiosurgical target and anatomical landmarks. An example of the previous steps and the contoured reference image is featured in Fig. 2.

Radiosurgical Target Compared With the Metabolic Lesion

We wanted to assess the volume and metabolic differences between the two volumes of interest, that is, the radiosurgical target defined by conventional strategies that
use the enhancing lesion as the primary high-dose target and the metabolic lesion defined by MRS imaging. In each patient, the radiosurgical target and the metabolic lesion volumes were calculated. In addition, the metabolite and CNI maps were resampled, and the mean relative levels of Cho, Cr, NAA, and LL; the mean CNI; the maximal CNI within the limited radiosurgical target and the metabolic lesion volumes were calculated. For each metabolic parameter, the median and quartile values for the cohort were then noted. Differences in the volumes and metabolic parameters in a comparison of the radiosurgical target and the metabolic lesion in each individual were assessed using the Wilcoxon signed-rank test, which is the nonparametric analog of the paired t-test. Commercially available software was used (SPSS; SPSS, Inc., Chicago, IL) for this and subsequent statistical analyses, with significance being defined at a probability value less than 0.05 for two-tailed tests.

Clinical Outcomes

The cohort was evenly divided into two groups based on the percentage of overlap between the radiosurgical target and the metabolic lesion volumes. Those with an overlap greater than 50% with respect to the metabolic lesion volume were classified as low-risk patients and those with an overlap less than 50% were classified as high-risk patients. The risk groups were defined at the end of data accrual.

Clinical outcome was measured using two parameters: time to progression, in which progression was defined as the time point at which the contrast-enhancing volume increased by 25% (generally confirmed on follow-up MRS images) as determined by the neuroradiologist; and survival. The typical frequency of follow-up MR/MRS imaging was every 1 to 3 months. Both time to progression and survival were measured from the time of GKŠ. Statistical analysis consisted of Kaplan–Meier estimators, with time to progression or survival function as the dependent variables. Time to progression was censored if the patient was progression free at the time of analysis. Survival was censored if the patient was alive at the time of analysis. The null hypothesis (H₀: Slow-risk(t) = Shigh-risk(t), where S represents the time to progression or survival function and t represents time) was first assumed and then tested against the alternative hypothesis (H₁: S_{low-risk}(t) > S_{high-risk}(t)). The estimated median time was the value of t at S_{risk group}(t) = 0.5. A log-rank test was used to test whether there was a significant difference between the low- and high-risk patient groups. The patient cohort was reanalyzed by dividing the population into two equally sized groups based on the cohort median value of the radiosurgical target volume and by using survival as the dependent variable.
Proton MRS imaging of patients with glioma treated using GKS

Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex, Tumor Type</th>
<th>TFD (mos)</th>
<th>TTP (mos)</th>
<th>Survival (mos)</th>
<th>Boost to EBRT</th>
<th>50% Radiosurgical Target Dose (cGy)</th>
<th>Metabolic Lesion Vol (cm³)</th>
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low-risk median 52 6.95 5.0 15.4 1600 14.7 3.40 high-risk median 51.5 6.23 5.5 11.3 1682 7.2 4.20 cohort median 52 6.63 5.0 16.9 1600 10.1 4.00

Results

Table 1 lists relevant clinical data for each patient. The time from diagnosis equals the time from the patient’s first diagnosis of glioma to the time of GKS. The median time from diagnosis was 6.63 months, with a range of 0.77 to 49.13 months. The median time to progression was 5 months, with a range of 1 to 16 months. The median survival was 16.9 months, with a range of 3.47 to 33.4 months.

The Mann-Whitney (Wilcoxon rank-sum) test was used to test for differences between the low- and high-risk groups. Age, time from diagnosis, radiosurgical target dose, metabolic lesion volume, and all the metabolite levels (including mean and maximal CNI) were not significantly different between the two groups. All the patients had a Karnofsky Performance Scale score greater than or equal to 70. The eight patients who received GKS as a boost to EBRT were evenly distributed between the low- and high-risk groups.

Radiosurgical Target Compared With Metabolic Lesion Volumes

The radiosurgical target and metabolic lesion volumes for the patient cohort ranged from 3.2 to 37.4 cm³ (median 10.1 cm³) and 0.02 to 15.1 cm³ (median 4 cm³), respectively (Table 1). In the low-risk group, the radiosurgical target and metabolic lesion volumes ranged from 5.9 to 37.4 cm³ (median 14.7 cm³) and 0.02 to 14.9 cm³ (median 3.4 cm³), respectively. As for the high-risk group, the radiosurgical target and metabolic lesion volumes ranged from 3.2 to 28.8 cm³ (median 7.2 cm³) and 1.1 to 15.1 cm³ (median 4.2 cm³), respectively.

The difference between the two volumes of interest in each individual was statistically significant (p < 0.0001). The metabolic lesion was consistently smaller, by at least 2.5 cm³, than the radiosurgical target in 22 (85%) of 26 patients. Note that the other four patients whose metabolic lesion was larger than the radiosurgical target belonged to the high-risk group.

Table 2 lists the cohort median and quartile values for

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Radiosurgical Target</th>
<th>Metabolic Lesion</th>
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<tr>
<td>Mean Cho</td>
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<td>Mean Cr</td>
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<td>Mean NAA</td>
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<td>Mean LL</td>
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<td>Max CNI</td>
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<td>4.70</td>
</tr>
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</table>

* Med = median.  † Wilcoxon signed-rank test.

Proton MRS imaging of patients with glioma treated using GKS

Table 1

Summary of data in 26 patients harboring Grade IV glioma*
mean metabolite levels, mean CNI, and maximal CNI. A
semiqualitative analysis of the differences in metabolite
levels in a comparison between the volumes of interest shows
that the sample median Cho, Cr, and NAA levels within
the radiosurgical target relative to the metabolic lesion were
respectively smaller by 42, 34, and 23%. This explains the
53% drop in the median CNI within the radiosurgical target
compared with the metabolic lesion. The median LL level
and maximal CNI in a comparison between the target and
metabolic lesion were not substantially different.

Figure 4 illustrates the differences between the volumes
of interest on an individual basis in which the radiosurgi-
cal target was paired with the metabolic lesion in the same
patient. The probability values are summarized in Table 2.
Twenty-four (92%), 23 (88%), and 21 (81%) of 26 patients
had mean Cho, Cr, and NAA levels, respectively, that were
lower in the radiosurgical target compared with those in the
metabolic lesion. The mean Cho, Cr, and NAA levels were
significantly lower in the radiosurgical target compared
with the metabolic lesion (p < 0.0001, p < 0.0001, and p =
0.001, respectively). Twenty patients (77%) had a mean
CNI less than two within the radiosurgical target. The mean
and maximal CNI were also significantly lower in the radio-
surgical target compared with those values in the metabolic
lesion (p < 0.0001 and p = 0.006, respectively).

Clinical Outcomes

There were 14 and 12 patients in the low-risk and high-risk
groups, respectively. Table 3 features the results from the
Kaplan–Meier analysis. The Kaplan–Meier estimators re-
presenting the time to progression functions in the two risk
groups are shown in Fig. 5. The low- and high-risk groups
had median times to progression of 5 and 4 months, respec-
tively. According to results of a log-rank test, this difference
was not a significant finding (p = 0.73).

Kaplan–Meier estimators representing the survival func-
tions for the two risk groups are shown in Fig. 6. The low-
and high-risk groups had median survivals of 15.7 and 10.4
months, respectively, as computed using the Kaplan–Meier
analysis; this difference of 5.3 months was found to be sta-
tistically significant (p = 0.01). The 1-year survival rate was
64% in the low-risk group and 50% in the high-risk group.
The 18-month survival rate was 30% in the low-risk group
and 8% in the high-risk group.

To test whether survival was correlated with the treat-
ment volume, the Kaplan–Meier analysis was applied using
the radiosurgical target volume as the independent variable.
The cohort was divided into two equally sized groups based
on the cohort median volume of the radiosurgical target (10
cm³). The Kaplan–Meier estimators were calculated for
each group (Fig. 7), resulting in median values of 14.2 and
15.1 months for the small- and large-target groups, respec-
tively. This difference was not significant (p = 0.67).

Discussion

Radiosurgical Target Compared With Metabolic Lesion

The median and range of volumes for the radiosurgical
target was typical for the treatment of glioma. Overall,
the metabolic lesion volumes were smaller than the radiosurgical target volumes, implying that the metabolic lesions could have been easily treated with GKS without violating the target size limitation of less than 3 to 4 cm in any one direction. Nonetheless, PRESS box placement was somewhat restricted, resulting in the report of smaller metabolic lesions compared with the true values.

We believe that the difference in radiosurgical target volumes in a comparison between the low- and high-risk groups arises because the risk classification was dependent on the overlap between the radiosurgical target and metabolic lesion. A larger radiosurgical target would be more likely to encompass a smaller metabolic lesion, thus classifying the patient as a member of the low-risk group. Assuming the extreme case when the smaller metabolic lesion is fully within the radiosurgical target, the larger radiosurgical target volume indicates that GKS is targeting more than the tumor, most likely necrosis, gliosis, or edematous tissue. This led us to investigate the overall metabolic characteristics of the radiosurgical target and compare it with the metabolic lesion.

The individual mean and cohort median Cho, Cr, and NAA levels were consistently and significantly smaller in the radiosurgical target compared with the values in the metabolic lesion. Given that low levels of Cho, Cr, and NAA specify necrosis and that Grade IV gliomas usually exhibit necrotic cores at the center of enhancement, the significantly reduced metabolite levels in the radiosurgical target indicate that tissues treated with GKS are likely to include substantial necrosis.

The individual mean and maximal CNI were consistently and significantly smaller in the radiosurgical target compared with the metabolic lesion. Again, this result indicates that the high-dose region is not focused on the most metabolically active part of the tumor and that some of this lesion outside of the enhancement is left untreated.

Although conventional GKS dose plans may include treatment of necrosis, resulting in an increase in complications (edema and decadron dependence) and a decrease in the therapeutic ratio, it is not necessarily appropriate to change the dose plan drastically to exclude necrosis. Although a voxel may exhibit a characteristic necrotic spectrum, because of partial voluming effects the tissue encompassed within the voxel may include a combination of a large fraction of necrosis and a small fraction of tumor. An alternative strategy is to modify the dose plan to encompass regions with high CNI. This strategy led us to analyze whether inclusion of most of the metabolic lesion into the radiosurgical target resulted in an observable clinical outcome.

Clinical Outcome

The initial hypothesis, which had been based on data from our previous study, was that patients whose metabolic lesion was mostly within the radiosurgical target would experience, first, longer freedom from progression and, second, longer survival. The difference is expected given that in low-risk patients, most of the active tumor is irradiated using a high dose, which should presumably result in better clinical outcomes.

In the current cohort of patients, the time to progression was not significantly different between the two risk groups. We attribute this result to the change in the clinicians’ referral pattern for GKS since publication of the previous findings by Graves, et al.3 We believe that, although the radio-
surgical target may have been defined from the anatomical images, fewer patients with large metabolic lesions were referred for GKS. Patients who were entered into this study had less extensive metabolic abnormalities outside of the target compared with the patients from the previous study. With the objective definition of the metabolic lesion, we validated the survival results of the previous study. The difference in median survivals between the high- and low-risk groups in the current study was 5.3 months, which is promising, especially in the context of the short survival in patients with Grade IV glioma. The correlation between survival and the fraction of metabolic lesion treated makes it reasonable to modify the radiosurgical target to include the metabolic lesion.

Although the size of the target volume has been previously reported to be a risk and a prognostic factor, the new data were used to adapt the GKS target.

In 93% of the patients, the target definition for radiotherapy by comparing the contrast enhancement, T2 hyperintensity, and MRS imaging abnormality in patients undergoing radiotherapy. Grosu et al., studied 18 patients with glioma who were undergoing linear accelerator radiotherapy and found that the FDG-PET abnormality closely correlated with enhancement and in most cases fully covered the enhancement. They concluded that FDG-PET scans did not provide additional information for treatment planning. Levivier et al., studied 34 patients with recurrent brain tumor by using a second radiotracer, Met, to define the tumor volume better. In 93% of the patients, FDG- or Met-PET scans contributed new data, and in 74% the new data were used to adapt the GKS target.

The potential incorporation of MRS imaging into the treatment planning process for conventional fractionated radiotherapy has also been studied previously. Pirzkall et al., assessed the impact that MRS imaging would have on the target definition for radiotherapy by comparing the contrast enhancement, T2 hyperintensity, and MRS imaging abnormality in 34 presurgical patients with high-grade glioma. The MRS imaging abnormality, defined as the volume with a CNI greater than two, was typically larger and resided mostly beyond the region of contrast enhancement. Eleven of 12 patients with Grade IV glioma had MRS imaging abnormalities that extended up to 18 mm beyond the contrast enhancement in the ipsilateral direction and 23 mm in the contralateral direction. In addition, the hot spots within the MRS imaging abnormality, which are presumed to be the most metabolically active, typically laid outside the enhancement.

The MRS imaging data nicely complement the MR images that are used in treatment planning. The SPECT and PET scans would have to be registered to such MR images, requiring additional processing time. Also, SPECT and PET data require additional scans on a different machine, making either procedure more cumbersome or uncomfortable for the patient wearing the stereotactic head frame. Other shortcomings of PET include the need to inject a radiotracer into the patient and the need for a local cyclotron because of the short half-life of the radiotracers. Because of the simpler registration between anatomical MR and MRS images, the relative ease of obtaining an MRS image at the end of MR imaging, the shorter imaging time involved with MRS, and its noninvasive nature, MRS imaging proves to be an efficient choice in terms of time and cost.

Limitations and Further Work

One limitation of the MRS images acquired in the current study relates to the coverage provided. A major factor that influences the spatial coverage of the data is the duration of the spectroscopy examination. For example, merely increasing the number of phase encodes from \( 12 \times 12 \times 8 \) to \( 16 \times 16 \times 8 \) (a 33% increase in two dimensions) while keeping all other parameters constant results in an increase in spectroscopy imaging time from 19 to 34 minutes. The rectangular shape of the PRESS box also makes it difficult to position within brain parenchyma while avoiding subcutaneous lipid and tissue–air interfaces. It is also important to be wary of lipid suppression and to include a sufficient amount of contralateral normal brain tissue while extending the coverage of the PRESS box to calculate the CNI reliably. Another restriction on the current data was its 1-cm\(^3\) nominal spatial resolution. Although the objective method of linear interpolation helps to visualize the extent of the metabolic lesion, the boundaries do not exactly correspond to the edges of the tumor. Different interpolation methods also produce different contours. Further work would include histopathological validation of the CNI contour boundaries. Recent developments with higher-field magnets will also help to improve the spatial coverage and resolution of MRS imaging.

Conclusions

The results of this study demonstrate the potential impact of the integration of MRS imaging with MR imaging to tailor GKS dose distribution plans. Our findings indicate that radiosurgical targets and metabolic lesions are characteristically different and that current GKS treatment plans may involve the overtreatment of parts of the contrast enhancement deemed not metabolically active (for example, necrotic tissue) while missing metabolically active tumor that resides beyond the contrast enhancement. In addition, survival appears to be better in those patients whose metabolic lesion was treated mostly with a high dose of radiation. This indicates that integration of MRS imaging into the GKS treatment planning process may improve local tumor control, patient clinical outcome, and patient quality of life.

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Proton MRS imaging of patients with glioma treated using GKS

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