Metabolic approach for tumor delineation in glioma surgery: 3D MR spectroscopy image–guided resection

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OBJECTIVE The extent of resection is one of the most essential factors that influence the outcomes of glioma resection. However, conventional structural imaging has failed to accurately delineate glioma margins because of tumor cell infiltration. Three-dimensional proton MR spectroscopy (1H-MRS) can provide metabolic information and has been used in preoperative tumor differentiation, grading, and radiotherapy planning. Resection based on glioma metabolism information may provide for a more extensive resection and yield better outcomes for glioma patients. In this study, the authors attempt to integrate 3D 1H-MRS into neuronavigation and assess the feasibility and validity of metabolically based glioma resection.

METHODS Choline (Cho)–N-acetylaspartate (NAA) index (CNI) maps were calculated and integrated into neuronavigation. The CNI thresholds were quantitatively analyzed and compared with structural MRI studies. Glioma resections were performed under 3D 1H-MRS guidance. Volumetric analyses were performed for metabolic and structural images from a low-grade glioma (LGG) group and high-grade glioma (HGG) group. Magnetic resonance imaging and neurological assessments were performed immediately after surgery and 1 year after tumor resection.

RESULTS Fifteen eligible patients with primary cerebral gliomas were included in this study. Three-dimensional 1H-MRS maps were successfully coregistered with structural images and integrated into navigational system. Volumetric analyses showed that the differences between the metabolic volumes with different CNI thresholds were statistically significant (p < 0.05). For the LGG group, the differences between the structural and the metabolic volumes with CNI thresholds of 0.5 and 1.5 were statistically significant (p = 0.0005 and 0.0129, respectively). For the HGG group, the differences between the structural and metabolic volumes with CNI thresholds of 0.5 and 1.0 were statistically significant (p = 0.0027 and 0.0497, respectively). All patients showed no tumor progression at the 1-year follow-up.

CONCLUSIONS This study integrated 3D MRS maps and intraoperative navigation for glioma margin delineation. Optimum CNI thresholds were applied for both LGGs and HGGs to achieve resection. The results indicated that 3D 1H-MRS can be integrated with structural imaging to provide better outcomes for glioma resection.

KEY WORDS magnetic resonance spectroscopy; glioma; neuronavigation; surgical planning; oncology

Gliomas are the most common primary brain tumors, accounting for 80% of malignant central nervous system tumors, and can be categorized into 4 grades according to their biological behavior. Patients with low-grade gliomas (LGGs) typically survive more than 5 years.21 Those with high-grade gliomas (HGGs) have a survival time of approximately 1–3 years. An epidemiology study using primary brain tumor data collected from 1985 to 2005 showed that the 1-year survival rate of patients with malignant glioma is 53.9%, while that of pa-
Patients with glioblastoma is only 30.3%. The prognostic factors for glioma include patient age, Karnofsky Performance Scale score, comorbidities, genetic status, and extent of resection (EOR). Much evidence shows that EOR is one of the most essential factors for progression-free survival (PFS) and overall survival (OS).

It is now well accepted that the principle of glioma surgery is maximal safe resection. Recently, Sanai et al. found that an EOR ≥ 78% impacts patient outcomes and that this trend continues even at the highest levels of resection. Another study showed that more aggressive resections of LGGs lead to a better prognosis with prolonged OS and PFS. Moreover, patients with glioblastoma multiforme have a better prognosis when the EOR > 98%.

Multimodal neuronavigation has become a useful tool in helping surgeons achieve maximal safe resections. According to the Response Assessment in Neuro-Oncology (RANO) standard, volumetric evaluation is based on structural MR images. For LGGs, T2-weighted or FLAIR imaging is used for volumetric assessment by delineating the hyperintense area. For HGGs, complete resection of enhancing lesions on T1-weighted images is considered gross-total resection (GTR). Delineating the hyperintense area.36 For HGGs, complete resection was assessed, as were patient outcomes.

Methods

Patients

Patients who had a diagnosis of cerebral glioma were eligible to participate in this study. Patients were excluded when histology indicated a tumor other than glioma. Patients with contraindications to MRI were also excluded. This study was undertaken at the Huashan Hospital in Shanghai, China, with approval from the Huashan Institutional Review Board.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed 1 day before surgery using a 3.0-T iMRI suite (iMRIS) with a Siemens 8-channel head coil. The imaging protocols consisted of a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR 1.900 msec, TE 2.93 msec, flip angle 9°, matrix size 256 × 215, slice thickness 1 mm, FOV 250 × 219 mm, acquisition averages 1) or a T2-FLAIR sequence (TR 9.000 msec, TE 96 msec, TI 2.500 msec, flip angle 150°, slice thickness 2 mm, matrix size 256 × 160). Diffusion tensor imaging (DTI) sequences (TR 7.600 msec, TE 91 msec; slice thickness 3 mm, slice space 0 mm, matrix size 128 × 128, voxel size 1.8 × 1.8 × 3 mm³, directions 30) were acquired for fiber tracking. Functional MRI (fMRI) data were acquired using a single-shot echo-planar imaging (EPI) sequence (TR 3.000 msec, TE 30 msec, FOV 240 × 240 mm, matrix size 96 × 96, slice thickness 3 mm) for language areas or motor areas when necessary. The raw data were exported into the digital imaging and communications in medicine (DICOM) format and processed using iPlan Cranial Version 3.0 (BrainLab).

Three-Dimensional ¹H-MRS

Three-dimensional MRS was performed using a point-resolved spectroscopy sequence (PRESS; TR 1.700 msec, TE 135 msec; slice thickness 15 mm, phase encoding 16 × 16 × 16, FOV 120 × 120 mm, flip angle 90°, scan resolution 10 × 10 × 10 mm). Chemical shift imaging sequences were applied to achieve water suppression. The volume of interest (VOI) was positioned to avoid areas such as bone, subcutaneous lipids, and other areas of magnetic susceptibility to ensure that the quality of the MRS would not be affected. After 3D MRS acquisition, the raw data were transferred to a postprocessing workstation (Syngo Multimodality Workplace, Siemens AG).

Data Processing

The raw spectroscopy data were imported into a Siemens Syngo workstation (Fig. 1). The regional metabolite distributions of Cho and NAA and their ratios were computed inside the VOI with a resolution of 10 mm³. The CNIs were interpolated for each voxel inside the VOI to generate different CNI thresholds for metabolic delineation. Then a 3D chemical shift imaging (CSI) map was generated and transformed into a gray value map, which contained spatial and normalized metabolite Cho/NAA information. An anatomical T2-FLAIR or 3D MPRAGE sequence was scanned for fusion. Bold fMRI and DTI
data were prepared for merging. All of the raw data were saved in the DICOM format and transferred to iPlan Cranial 3.0 (BrainLab). In the iPlan software, the image data were fused using a frame of reference that was based on the anatomical images because all of the image data were acquired during the same session. The data processing procedure is demonstrated in a flowchart (Fig. 1). The accuracy of the fusion was verified using the SpyGlass and Edges functions for visual inspection. All of the data sets were fused and superimposed on anatomical images. For MRS, 3 different thresholds for CNIs (0.5, 1, and 1.5) were applied to contour the MRS margins. The gray scale maps were reconstructed using the rainbow color function and confirmed with previous pseudocolor maps that were generated in the Syngo system. Three different 3D MRS objects were created accordingly. For fiber tracking, the diffusion tensor image was overlaid on anatomical images. Then the region of interest (ROI) was defined (for example, the brainstem and the motor area were selected as the ROI for the lineate pyramidal tract [PT]). The fractional anisotropy threshold was set to 2.0–2.5 to achieve the best tracking results. The results were merged and saved for surgical planning and navigation.

**Volumetric Analyses**

Three-dimensional MPRAGE images were used for the structural volumetric analyses. A GTR was defined as no tumor residuals identified on postoperative MRI, which consisted of T1-weighted contrast-enhanced images for HGGs and FLAIR images for LGGs, according to the RANO standard. A subtotal resection (STR) was defined as residual tumor < 10 cm³. Metabolic volumes were obtained according to the different CNIs and were outlined based on CSI maps. Manual segmentations were performed by a technician using iPlan software and were verified by a neurosurgeon. Additionally, the structural volumes were calculated within the MRS scanning bounding box using volumetric analysis for a better comparison. The data were further divided into 2 groups according to WHO grade: an LGG group including Grade II gliomas and an HGG group including Grades III and IV gliomas. The mixed-effects model for repeated measures was applied in the statistical analyses of tumor volumes, which were performed using SAS 9.2 (SAS Institute Inc.). A p value ≤ 0.05 was considered statistically significant.

**Results**

From May to July 2013, 18 patients with brain gliomas were identified for 3D 1H-MRS scanning. Three cases were excluded from evaluation because the pathological diagnosis was metastasis. Therefore, 15 patients with primary cerebral gliomas were eligible for further analyses (Table 1).

Different CNI thresholds were applied to delineate the metabolic volumes. The volumetric assessments based on both structural and metabolic imaging are summarized in Tables 2 and 3. The differences between the metabolic volumes with different CNI thresholds were statistically significant (p < 0.05). For the LGG group, the differences between the structural and the metabolic volumes with CNI thresholds of 0.5 and 1.5 were statistically significant (p = 0.0005 and p = 0.0129, respectively). For the HGG group, the differences between the structural and metabolic volumes with CNI thresholds of 0.5 and 1.0 were statistically significant (p = 0.0027 and p = 0.0497, respectively). For all of the patients, tumor resections were performed under...
the guidance of the 3D MRS and DTI results. The selection of the metabolic margin was based on the principle of achieving a maximal safe resection in individual patients. Postoperative MRI confirmed GTRs in 13 patients (Table 4). The average resected volume according to the metabolic margin was 59.48% greater than the structural volume. Only 1 patient suffered from a transient postoperative language deficit. No long-term motor deficits were found in any of the patients. At the 1-year follow-up, no tumor recurrence was found in the LGG group (Table 1). One patient from the HGG group was found to have a tumor recurrence at the 9-month follow-up.

Illustrative Cases

Case 10

This 50-year-old male was referred to our hospital and presented with a 1-year history of headache and weakness of the left limbs. He suffered from left facial paralysis 1 week before admission. The neurological examination revealed classic left central paralysis, and the muscle strength of the left limbs was Grade 4 (manual muscle testing). In addition, he had hyperactive deep tendon reflexes of the left lower extremities. A head MRI study showed a right frontal lesion with irregular contrast enhancement (Fig. 2A and C). The preoperative diagnosis was HGG. Diffusion tensor imaging was performed to trace the pyramidal tract (PT; Fig. 2C–F). Three-dimensional 1H-MRS revealed different metabolic margins that were generated for CNIs of 0.5, 1.0, and 1.5. Dice’s coefficient between CNI 1.0 and structural volume showed a strong association in this case. Data were uploaded into iPlan 3.0 Cranial software for presurgical planning. Because a CNI of 1.0 was adjacent to the PT, while 0.5 overlapped with the PT, to achieve maximal safe resection, the EOR was carried as close as possible to the metabolic margin generated with a CNI of 1.0. A safe margin of 0.8 mm was set to avoid further neurological deficits even though this margin was near the PT (Fig. 2E and F). Ultimately, an STR was achieved (Fig. 2B). The patient suffered no neurological deficits postoperatively.

Case 4

This 33-year-old female came to our hospital with a 10-month history of repeated seizure attacks. She suffered no neurological deficits on admission. Magnetic resonance imaging showed a lesion located in the right parietal lobe. The lesion was not contrast-enhanced by gadolinium. Diffusion tensor imaging and 3D 1H-MRS were scheduled 1 day before her operation. The metabolic margins were delineated and superimposed on structural images (Fig. 3A). Fiber tracking revealed the relationship between the

<table>
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<th>Variable</th>
<th>Value</th>
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<tr>
<td>Age in yrs</td>
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</tr>
<tr>
<td>Range</td>
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<tr>
<td>No. of males (%)</td>
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</tr>
<tr>
<td>Clinical onset (no. [%])</td>
<td>Seizure 7 (46.67)</td>
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<tr>
<td>Headache</td>
<td>5 (33.33)</td>
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<tr>
<td>Language deficit</td>
<td>1 (6.67)</td>
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<tr>
<td>Accidentally found</td>
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<tr>
<td>Tumor location (no. [%])</td>
<td>Frontal lobe 7 (46.67)</td>
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<tr>
<td>Parietal lobe</td>
<td>4 (26.67)</td>
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<td>Temporal lobe</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Insular</td>
<td>1 (6.67)</td>
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<tr>
<td>Histological type, WHO tumor grade (no. [%])</td>
<td>Diffuse astrocytoma, II 4 (26.67)</td>
</tr>
<tr>
<td>Oligodendroglioma, II</td>
<td>4 (26.67)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma, III</td>
<td>1 (6.67)</td>
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<tr>
<td>Anaplastic oligodendroma, III</td>
<td>2 (13.33)</td>
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<tr>
<td>Glioblastoma multiforme, IV</td>
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<td>GTR (no./total no. [%])</td>
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<tr>
<td>Low grade (I or II)</td>
<td>7/8 (87.50)</td>
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<tr>
<td>High grade (III or IV)</td>
<td>6/7 (85.71)</td>
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<td>Postop deficit (no./total no. [%])</td>
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<td>1-year PFS (no./total no. [%])</td>
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Table 2. Summary of volumetric assessment results based on structural and metabolic imaging*
metabolic margins and the PT (Fig. 3C–F). The margin with a CNI of 0.5 overlapped the PT (Fig. 3D and E). A resection based on a margin of 0.5 would most likely have caused postoperative motor deficits (Fig. 3F). For areas adjacent to the PT, a CNI margin of 1.0 was applied for tumor resection (Fig. 3C and D). Dice’s coefficient of the volumes in this case indicated a strong correlation between the CNI 1.0 margin and the structural margin. For noneloquent areas, a CNI margin of 0.5 was applied for resection (Fig. 3B). An STR was achieved based on the intraoperative MRI studies. There were no neurological deficits in this patient.

Discussion

In the present study we aimed to perform metabolically based tumor resection by integrating neuronavigation data with 3D 1H-MRS, which can detect metabolic abnormalities confirmed by biopsy diagnosis of gliomas. Three different thresholds of CNIs were established to delineate the metabolic margins for either HGG or LGG resection. Taking eloquent areas into consideration, one can apply the most suitable CNI-based tumor boundary to achieve a maximal safe resection as well as avoid potential neurological deficits. By adopting this method, we found no tumor recurrence in our LGG group and only 1 patient from the HGG group who had a tumor recurrence after the 1-year follow-up. Our results indicate that tumor resection with 3D 1H-MRS–aided navigation is safe and feasible for maximal safe resection.

Metabolic Index for Tumor Margin Delineation and Presurgical Planning

Conventionally, glioma resections are based on tumor margins delineated using structural T1 and T2-FLAIR MR images. However, the benefits gained from navigational resections are limited, with a poor prognosis even in the GTR patients. It is now clear that glioma cells far exceed the margins revealed on traditional structural images. Proton (1H) MRS has shown its ability to detect metabolic abnormalities where conventional MRI cannot make such distinctions. Previous studies have found that

<table>
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<th>Case No./Sex/Age at Admission (yrs)</th>
<th>Presenting Symptom</th>
<th>Tumor Location</th>
<th>WHO Glioma Grade</th>
<th>Structural Vol (cm³)</th>
<th>Metabolic Vol (cm³)</th>
<th>Postop Cavity (cm³)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>1.0</td>
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<td>1/M/33</td>
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<td>III</td>
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<td>60.00</td>
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<td>IV</td>
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<td>56.64</td>
<td>3.84</td>
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<td>II</td>
<td>27.84</td>
<td>29.76</td>
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<td>19.46</td>
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<td>7/M/47</td>
<td>Headache</td>
<td>Rt insular</td>
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<td>102.72</td>
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<td>26.88</td>
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<td>23.04</td>
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<td>II</td>
<td>65.28</td>
<td>37.44</td>
<td>56.64</td>
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* Gross-total resection could not be achieved in Cases 4 and 10 because of the invasion of PTs.
gliomas tend to have decreased NAA and creatine and elevated Cho levels compared with levels in normal brain tissue. Yang et al. also found that there were statistically significant differences in CNIs between the HGGs and LGGs. In their study, the mean CNI was 5.9 ± 2.62 for HGGs and 1.65 ± 1.37 for LGGs. In a previous study, we performed needle biopsies to extract different tissue samples in a patient series according to different CNI indexes. Immunohistochemical staining was performed to identify the tumor cell infiltration, and the corresponding threshold ratios of CNIs were calculated. Our results indicated that CNI thresholds of 0.5, 1.0, and 1.5 can predict tumor infiltration with probabilities of 38%, 60%, and 79% in HGGs and 16%, 39%, and 67% in LGGs, respectively. According to these analyses, we applied different CNI thresholds to delineate the metabolite-based glioma margins for tumor resection in the present study. We showed that different CNI margins can be used for HGGs and LGGs to achieve an individualized tumor resection strategy. Further volumetric analyses revealed that the metabolic volumes are larger than the structural volumes under a CNI of 0.5, and this difference is statistically significant. For HGGs, CNI thresholds of 1.0 and 0.5 both exceeded the structural margins defined by contrast-enhancing boundaries (p < 0.05). Therefore, a CNI of 1.0 can be used for navigation to achieve the same effect as structural margins in LGGs. The margin with a CNI of 0.5 can be used for further resection. Accordingly, our 2 cases with glioma invading eloquent areas demonstrated that metabolic imaging can provide various choices of metabolic margins based on their spatial relationship with eloquent areas. Previous DTI studies have indicated that a safe margin of 8 mm should be maintained between the resection margin and the PTs. Our results also indicated that a well-planned individualized surgical strategy can be implemented by the integration of MRS data and functional mapping and structural margins. Surgeons sometimes have to adjust the surgical plan based on functional mapping, either from direct electrical stimulation (DES) or neuroimaging. For tumors invading eloquent cortex, preoperative task-related fMRI and DTI can be performed. Intraoperative language and/or motor cortical stimulations can also be performed to identify eloquent sites. A 10-mm margin from a DES-positive site was preserved during tumor resection to avoid permanent

FIG. 2. Case 10. The process of converting and merging 3D 1H-MRS images with structural images. A: 3D 1H-MRS revealed different metabolic margins generated for CNIs of 0.5, 1.0, and 1.5, which were transferred into iPlan 3.0 Cranial. The pseudocolor maps were then generated. B: Postoperative MR image. C: Functional MRI and DTI located the hand motor areas and PTs. D and E: The contour line for a CNI of 1.0 was adjacent to the PTs. Red: 1.5; yellow: 1.0; and blue: 0.5. To achieve a maximal safe resection, the EOR was carried as close as possible to the metabolic margin generated for a CNI of 1.0. F: Sagittal view revealing the relationship of the PTs and metabolic margins. A safe margin of 0.8 mm was set to avoid further neurological deficits even though this margin was near the PTs. An STR was achieved in this patient. Figure is available in color online only.

FIG. 3. Case 4. Metabolic maps for LGG. A: Different MRS contour lines were generated for an LGG resection; the metabolic margins were delineated and superimposed on structural images. B: For noneloquent area, a CNI margin of 0.5 was applied for tumor resection, and a margin of 1.0 was applied when near the PT to preserve motor functions. An STR was achieved based on intraoperative MRI. C: A safer resection could be achieved with a CNI contour line of 1.0. D: Fiber tracking revealed the relationship between the metabolic margins and the PT, which revealed the relationship among different CNI contour lines and the PT. E and F: A CNI contour line of 0.5 better delineated the tumor region; however, the margin overlapped the PT in this case. A resection based on a margin of 0.5 would most likely have caused postoperative motor deficits. Figure is available in color online only.
functional deficits. However, preoperative task-related BOLD fMRI showed a variety of sensitivities and specificities because of numerous factors such as patient status and the selection of the functional stimulus.4,10 Awake surgery, which is deemed a gold standard for functional mapping, may also be subject to the limited selection of intraoperative tasks. Plenty of studies have shown that the short-term functional deficit rates after awake surgery are higher than those with general anesthesia, although the patients showed better recovery in the long-term.6,8,27

Metabolic Versus Structural Resection for Gliomas

Previous studies have applied proton MRS for image-guided biopsies and postoperative radiotherapies.25,29,33 However, no postoperative outcomes for proton MRS–guided tumor resections have been reported. In this study, GTRs or even supratotal resections were performed in 13 of 15 patients. After surgery, all patients received standard radioc- and chemotherapies according to their WHO glioma grades. At the 1-year follow-up, no tumor progression was found in the LGG and HGG groups. From the Surveillance, Epidemiology, and End Results (SEER) program, Porter et al. have found that the 1-year survival rate for malignant glioma, LGG, and HGG patients is 50.4%–57.3%, 68.2%–93.4%, and 30.3%–77.8%, respectively.24 Keles et al. also found that the mean glioma progression time is 13.3 months in GTR patients and 11.5 months in STR patients.13 In our study, no progression was found at the 12-month follow-up. This may result from the metabolic resections beyond the margin of GTR in our patients. A systematic review on glioma EOR and survival revealed that more extensive resections may be linked to a more favorable life expectancy for both LGG and HGG patients.26 Despite the better survival rate presented in our study, a well-designed clinical trial with large case numbers is needed to draw further conclusions.

Techniques for Navigational Integration of 3D 1H-MRS

The 3D 1H-MRS data were scanned under a 3.0-T iMRI operating suite. Compared with single-voxel MRS and multivoxel 2D 1H-MRS, 3D 1H-MRS can provide more spatial coverage of multiple tumor regions. A previous study has shown that the sensitivity, specificity, and diagnostic accuracy of 3D 1H-MRS were 94.1%, 100%, and 96.2%, respectively.44 Stadlbauer et al. have attempted to integrate 2D 1H-MRS into a neuronavigation system. They replaced the raw data of the anatomical slices with processed MRI/MRS hybrid data sets and successfully performed biopsies in all patients.22 A recent study by Ken et al. proposed a method of integrating 3D MRS into a treatment planning system for radiation therapy.14 The red-green-blue snapshots of anatomical-metabolic images were processed for coregistration. In our study, several attempts were made to integrate CNI with the navigational system. One approach was to use third-party free software (Sivic, Tarquin, and so forth) to perform MRS analysis before integration. However, these software packages did not support the Siemens 3D MRS data sets. Finally, we tried to integrate 3D 1H-MRS into a neuronavigation system by generating gray scale maps with DICOM information (Fig. 1). Our method of integration may have several advantages: 1) postprocessing of MRS data is more convenient because the coregistration of metabolic and structural images can be performed automatically; 2) data obtained using the other modalities such as DTI and fMRI can be easily coregistered as the original structural images remain intact; and 3) multiple metabolic margins can be presented at the same time for tumor resection guidance.

Limitations and Perspectives

Given the nature of metabolic imaging, the spatial resolution of MRS images is lower than that of structural images. Higher magnetic intensity may provide better signal quality and imaging resolution. Magnetic resonance spectroscopy signal is poor when tumors are located near convex or ventricular systems, which could result in false-positive high CNIs in normal brain tissue and in tissue near the cranial bone. This problem can be partially overcome by using water suppression in specific regions and carefully selecting margins based on MRS. Another issue is that this technique can only be applied on the BrainLab navigational system at this time. As far as we know, the 3D MRS data sets do not work well on other navigation modalities such as Medtronic or with third-party software, partly because of the different scanning parameters between anatomical slices and spectroscopy slices. A more generalized and user-friendly module for 3D MRS integration is needed for future study. Meanwhile, other metabolites, such as myoinositol,31 citrate,2 phosphorylcholine, and lactate may also be applied for tumor margin delineation.44 In addition, newly developed technologies, such as phosphorus MRS (P-MRS)28,37 and whole-brain proton MRS,31 may also contribute to the delineation of tumor margins in future surgery.

In current practice, although there is no Class I evidence that the EOR improves OS in glioma patients, maximum resection as far as is feasible is still recommended for both LGGs30 and HGGs.38 The current standard for total glioma resection is solely based on structural images. For LGGs, because of the gradual growth of the tumor, the brain may adapt and reorganize function as the tumor infiltrates.41 In this study, we demonstrated the feasibility of integrating 3D MRS and neuronavigation and proved that metabolic resection is feasible and may provide a better prognosis than structural tumor resection alone. We have applied various CNIs to delineate the glioma metabolic margins and found that these margins exceeded the structural margins with a CNI less than 1.0 in LGGs and 1.5 in HGGs. Since CNI is highly correlated with glioma cell infiltration, the metabolic margin may be valuable information for the EOR.

Conclusions

In this study, glioma margin delineation using 3D 1H-MRS was presented and integrated with neuronavigation for metabolic glioma resection. The results showed that optimal CNI thresholds can be applied for LGG and HGG resection. The 1-year follow-up indicated that glioma resection based on 3D 1H-MRS may contribute to a better prognosis. Taking eloquent areas into consideration, we determined that the most suitable CNI-based tumor
boundary can be applied to avoid potential neurological deficits. Combining 3D $^1$H-MRS, fMRI, and DTI, the maximal safe resection for gliomas can be defined as follows: for noneloquent areas, the minimal CNI threshold of 0.5 could be used for maximal tumor resection; for tumors near eloquent areas, a safe margin of 8 mm should be used to reduce postoperative deficits. Further high-quality randomized control studies are suggested to confirm the outcomes of metabolic glioma resection.

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Disclosures
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