Proton Magnetic Resonance Spectroscopy and Intraoperative MRI Navigation for Frameless Biopsy

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Summary

Objective: To assess the clinical efficacy of the combined application of Proton Magnetic Resonance Spectroscopy (1H-MRS) and intraoperative Magnetic Resonance Imaging (iMRI) navigation in frameless biopsy of intracranial lesions.

Method: 1H-MRS was used to analyze the metabolism of the lesions and to locate appropriate biopsy point. We selected target points with the highest Cho/NAA ratio as shown by 1H-MRS for frameless biopsies. Thirty-one cerebral biopsy procedures were performed to identify the pathological diagnosis with the help of a 1.5T iMRI and a navigation system. After the biopsy, we routinely injected 0.5-1.0ml of air to the target zone through the biopsy needle. It can either serve as a marker and confirm that the targeted tissue has already been acquired, or form an air plug for local hemostasis.

Results: Frameless biopsies were successfully performed in all 31 cases, and pathological diagnosis were made in 30 patients, with a success rate of 96.8% (30/31). None of the patients suffered from significant complications, such as intracranial bleeding or new neurological deficit.

Conclusion: 1H-MRS assists in finding the best biopsy lesion point and iMRI can guide biopsy accurately. The combined application of 1H-MRS and iMRI navigation is technically feasible and safe for frameless biopsy of intracerebral lesions.

Key words: Proton magnetic resonance spectroscopy, Intraoperative magnetic resonance imaging (iMRI), neuronavigation, Biopsy, needle

Çerçevesiz Biyopsi için İntraoperatif MRG ve Proton Manyetik Rezonans Spektroskopi

Özet

Proton manyetik rezonans spektroskopi (1H-MRS) patolojik doku ile ilgili metabolik değişiklikleri ya da biyokimyasal bilgileri sağlayan hızlı, invaziv olmayan bir yöntemdir. Dahası, heterojen yapıya sahip gliomlarda en iyi biyopsi sahasını göstermesi açısından kullanılabilir. Bu makalenin amacı kafa içi lezyonlarının çerçevesiz biyopsisinde intraoperatif Manyetik Rezonans Görüntüleme (iMRG) ve Proton Manyetik Rezonans Spektroskopi (1H-MRS)'nin birlikte uygulanmasıyla klinik etkinliğinin değerlendirilmesidir. Operasyonlar sırasında 1H-MRS, lezyonun metabolizmasını analiz ve en uygun biyopsi noktasını tesbit etmek için kullanıldı. Çerçevesiz biyopsiler için hedef noktasını 1H-MRS'nin gösterdiği en yüksek kolin/NAA oran fostörü seçerek gerçekleştirilmiştir. Navigasyon sistemi ve 1,5T iMRG yardımı ile ki bize “beyn sapması” olayına bir çözüm olacak tarzda patolojik tani elde amacı ile otuzbir beyin biyopsi işlemi gerçekleştirildi. Tüm hastalarda (n=31) çerçevesiz olarak alınan biyopsilerden 30 hasta patolojik tani kondu ve başarı oranı %96,8 (30/31) oldu. Biyopsi sonrası hiçbir hastada yeni nörolojik defisit ya da intraserebral kanama gibi ciddi
komplikasyon gelişmedi. Böylece yazarlar 1h-MRS'nin en uygun biyopsi noktasını saptamada ve iMRG navigasyon yardımı ile biyopsinin hatası almabileceğini kanısına vardılar. İntraserebral lezyonların çerçevesiz biyopsisi için 1H-MRS ve iMRG navigasyon kombinasyon uygulaması teknik olarak kolay ve güvenilir bir yöntemdir.

Anahtar Kelimeler: Proton manyetik rezonans spektroskopisi, Intraoperatif manyetik rezonans görüntüleme (iMRG), nöronavigasyon, Biyopsi, iğne

INTRODUCTION

The optimal treatment of patients with intracerebral lesions requires assessment of the pathological diagnosis. The traditional needle biopsy of intracranial lesions (Frame-based/Frameless stereotactic) has a positive diagnostic rate of 85%-96.8%\(^2,4,7,11,13\). However, ambiguous or misleading results do occur, and there were also cases of diagnosis failure even biopsy point was accurate\(^2,3,11\). This is because MRI only provides structural data but not the metabolic/biochemical changes of the pathological tissue. In conventional MRI, it is often difficult to delineate the heterogeneous structure of glioma. Proton magnetic resonance spectroscopy (\(^1\)H-MRS) is a fast, non-invasive method which can provide metabolic changes, or biochemical information of pathological tissue. Hence, it can be used to locate the best spot for biopsy\(^1,13\). We introduced a 1.5T intraoperative MRI system in February 2009, which can also be used to perform brain MRS scanning (Fig 1). Frameless biopsies were performed with \(^1\)H-MRS and iMRI guided navigation. Our experience of 31 cases was retrospectively analyzed and reported in this study.

Fig 1: Intraoperative magnetic resonance imaging system (Siemens Espree, Erlangen, Germany)

MATERIAL AND METHODS

1. Clinical data

From August 2009 to July 2011, 31 cases (M:F 18:13), aged 10-67 yrs (mean 35.2 yrs) were enrolled into this study. Indications for biopsy included, atypical clinical/radiological diagnosis, tumors involving important functional areas or diffuse pathology not amenable to complete excision. All patients had routine MRI scanning and \(^1\)H-MRS to analyze
intralesional metabolism before biopsy. The local ethical committee approved the protocol of this study, and consent forms were attained from the patient or proper representatives.

2. Imaging protocol

All frameless biopsies were performed with a standards neuronavigation system (VectorVision Sky, BrainLAB, Feldkirchen, Germany), with real-time tracking system (Fig 2a).

For $^1$H-MRS analysis, a 3D T1 axial sequence ($\text{TR/TE} = 2020/4.38\text{ms}$; thickness $1\text{mm}$; sequence time $5\text{min}\,30\text{sec}$) was acquired first, followed by a T2 axial ($\text{TR/TE} = 4000/97\text{ms}$, thickness $3\text{mm}$; sequence time $2\text{min}$) and a $^1$H-MRS multi-pixel sequence ($\text{TR}=1500\text{ms}$, $\text{TE}=135\text{ms}$, sequence time $7\text{min}\,12\text{sec}$, thickness $15\text{mm}$; VOI=$60\text{mm}\times60\text{mm}$) (Fig 2b and 2c). After acquisition of axial T2 and post contrast T1-weighted axial and coronal MR tomograms, a multi-voxel $^1$H-MRS was conducted. After selection of the VOIs, one or two water-suppressed metabolite spectra were acquired using a double spin-echo localization technique (PRESS) and frequency selective water suppression (CHESS). The voxel-positioning, in relation to solid tumor components was controlled in order to exclude considerable partial volume effects, and to avoid close contact with intra-parenchymal calcification, adjacent bone tissue, necrosis or hemorrhage, tissue heterogeneity and so on.

3. Spectroscopy analysis

Spectroscopic raw data were analyzed with the Syngo B15 software (Siemens Medical Solution, Erlangen, Germany). The choice for detection of substances generally includes N-acetylaspartate (NAA), total creatine (tCr), Choline (Cho), lipids (Lip) and lactate (Lac). The area with the highest Cho/NAA ratio was chosen as the target of biopsy point. In study, the computer automatically calculates the Cho/NAA values. The colors red, orange, yellow, green, and blue were used to represent different values in descending order. Red represents the highest value and colorless represents a value close to zero (Fig 2d). Therefore, we generally choose the red dot area with the following 3 exceptions: a) If the tumor center becomes necrotic, Cho and NAA will both be reduced, such point should be excluded even if it has the highest Cho/NAA ratio; b) Since the drop in NAA peak reflects the degree of damage of neurons by tumor cells, when neurons were severely damaged, the small NAA value will lead to a large Cho/NAA ratio. Under such circumstances, we should consider the spot with the highest Cho value rather than spot with the highest Cho/NAA ratio, which is important in non-neuroepithelial tumors; c) When the point with the highest Cho/NAA ratio is located in areas of eloquent function, the point with the second highest Cho/NAA ratio shall be chosen instead.

4. Intraoperative navigation

All data is transmitted to the navigation station via network and converted with PatXfer 5.2 software. Navigation registration was performed with surface matching method. After the placement of the burr hole and the installation of the starlink biopsy device (BrainLAB, Feldkirchen, Germany), the biopsy needle was inserted with the guidance of the neuronavigation. Spatial orientation of the needle was automatically displayed on the image signal with the help of neuronavigation. The yellow line presents the biopsy needle and the extension cord of biopsy needle is shown as a dotted line. The angle of the needle was then adjusted with the help of real-time monitor (Fig 4). When reaching the intended target, which was determined preoperatively by the MRS analysis result, multiple biopsy tissues could be obtained. After the biopsy, 0.5-1.0ml of air was injected into the
biopsy needle to serve as a marker when conducting the following iMRI scan, in order to confirm that the biopsy point is indeed the planned biopsy point (Fig 2f). The air pressure also might serve as a plug for hemostasis. After biopsy, iMRI scans were conducted to confirm the location of biopsy, and to exclude hemorrhage and other complications. All tumor specimens were histologically assessed according to the WHO classification of tumors of the nervous system. The pathological results were verified by 2 senior pathologists independently. In cases when conflicting opinions existed, the pathological results were submitted to three or more senior pathologist for further discussion and confirmation.

**Fig 2a:** Starlink frameless stereotactic biopsy system. Just tighten it a switch, while the three joints can be fixed.

**Fig 2b:** Postgadolinium contrast enhanced T1-weighted MRI of patient no. 8

**Fig 2c:** T2-weighted MRI of patient no. 8
Fig 2d: Spectroscopic images of patient no. 8 with an astrocytoma (WHO grade II), color-coded and overlaid on T2w MRIs. Metabolic map of Cho (B) and NAA (C). (A) Map of the Cho/NAA ratios. (D) Anatomical reference (T2w) overlaid with the CSI grid and the VOI (PRESS box, blue rectangle). The levels of Cho is increased and the NAA value is reduced in tumor. Followed by red, orange, yellow, green, blue color indicates the values from high to low. The colorless represent its value close to zero. The area of highest Cho / NAA ratio shown in red was chosen as the target of biopsy point.

Fig 2e: Screenshots of the frameless stereotactic system software (patient no. 8). 3D reconstructed biopsy sampling plan and real-time monitoring.

Fig 2f: After biopsy successfully, we pushed into 0.5-1ml of air for it could play a marked role and confirmed the biopsy point is certainly preoperative set for the target when iMRI scan. Air to form a tension has the role of hemostasis.
RESULTS
In 28 of the 31 cases, $^1$H-MRS with good quality was obtained, while in the remaining 3 cases the results were not good enough due to partial volume effects. The increased Cho/NAA ratio in tumor tissue and the Gaussian distribution in normal brain tissue were utilized to develop an algorithm for the differentiation of tumor tissue versus normal brain tissue. All tumors were automatically segmented in the Cho/NAA images based on the assumption of Gaussian distribution of Cho/NAA values and all patients had successful biopsy sampling (31/31). Pathological diagnosis was achieved in 30 cases. These included 14 Gliomas, 8 Inflammation, 4 Lymphomas, 2 Germinoma, 1 Gliosis, 1 Heterotopias and 1 without successful pathological diagnosis. All patients had single attempt of biopsy successfully except one, who had two times(Fig 3a-3c). Only one had craniotomy after needle biopsy, who's final pathological diagnosis was consistent with the pathological diagnosis of biopsy. The other 30 patients didn't have craniotomy after needle biopsies because all tumors were involving important functional areas or diffuse pathology not amenable to complete removal. 20 patients' tumors became smaller in size with radiotherapy and chemotherapy. The response in treatment provides evidence to the diagnoses made. One patient (3.2%) suffered slight hemorrhage after a frontal biopsy while the other patients were free of hemorrhage, as determined by intraoperative imaging performed immediately after the biopsy. All patients were free of postoperative new neurological deficit.

![Fig 3a: Proton Magnetic Resonance Spectroscopy of patient no. 16. The area of Blue box with highest Cho / NAA ratio shown in red was chosen as the target of biopsy point](image)

![Fig 3b: In operation 1st scan, the biopsy point (Thin arrow) was not the planned biopsy lesion point. The pathological diagnosis of this point is astrocytoma WHO II, which is not completely consistent with the final pathological diagnosis after craniotomy.](image)
DISCUSSION

The invention of iMRI gave us a solution to “brain shift”. In iMRI, the image data set which guides the surgery can be continuously updated throughout the course of the procedure at the request of the surgeon. It also helps to improve positive biopsy rate to around 96-100% (3,8,10). iMRI also provides other advantages of immediate assessment and rectification of problems such as inaccurate biopsy site, inadequate size and complication like hemorrhage.

On the other hand, it has been alleged that even though iMRI can effectively confirm an accurate biopsy point, the following problems still exist at the pathological diagnosis stage (2,3,11): (1) the tissue taken was not typical enough. Since iMRI only provides anatomical data, it does not reflect tissue metabolism/biochemical information. Therefore, it is possible that the target is not typical enough, and in some cases, the tissue taken may even be necrotic issue at the center of the tumor, which may result in false-negative results. (2) The tissue taken is not representative enough. Due to the heterogeneity of tumors, some tumors may contain different levels of malignant cells (9), and determining the highest level of malignant tumor is essential to accurate diagnosis. The use of low-level malignant tumor tissue will result in misdiagnosis.

$^1$H-MRS has been used extensively for the evaluation of brain tumors. As early as 1992, Fulham et al. showed that images for Cho and NAA are most suitable for tumor spectroscopy (5). Many studies have reported increased levels of Cho and a reduction in signal intensity of NAA in brain tumors (1). In order to minimize the effect from the former two reasons which lead to wrong pathological diagnosis, we combined the metabolic data shown by $^1$H-MRS when performing biopsies, in order to find the best biopsy lesion point. Cho is composed of choline, phosphocholine and glycerophosphocholine. The signal of these metabolites is often elevated in the presence of tumorous tissue, which is caused by increased membrane synthesis in rapidly dividing tumor cells. NAA is only found in neurons and synapses and its amount reflects the density of the neuron. The drop in NAA peak reflects the degree

![Fig 3c: In operation 2nd scan, the biopsy point (Thick arrow) was exact the planed biopsy lesion point. The pathological diagnosis of this point is anaplastic astrocytoma WHO III.](image-url)

of damage of neurons by tumor cells. Almost all lesions would lead to the reduction of NAA\(^{13}\).

We selected target points with the highest Cho/NAA ratio as shown by \(^1\)H-MRS for frameless biopsies. In this group the diagnostic yield was 100\%(31/31), and the success rate of pathological diagnosis was 96.8\%(30/31), which are higher than those biopsies with conventional framed, frameless image guidance biopsies without \(^1\)H-MRS\(^{1,4,6,9,10,12}\) information, and are consistent with those biopsies with \(^1\)H-MRS\(^{15}\). In this study, only one of the patients had craniotomy conducted due to the following reasons: the other tumor involves important functional areas, diffuse pathology, or the tumor was not amenable to complete excision.

No severe complication occurred postoperatively, which is consistent with the reported literature on iMRI\(^{3,8,10}\). According to some reports, the complication rate for biopsy under iMRI navigation is lower than other methods. The possible explanations can be: (1) renewal of images can be done when brain shift appears, thus minimizing damage of normal brain tissue and blood vessels. (2) Sawin et al\(^6\) suggests that complication rate increases with the point and volume of biopsy. As iMRI navigated biopsy allow very accurate biopsy of representative tissue, the point and volume of biopsy can be minimized, lowering the chances of complication. (3) Before the closure, iMRI scan can be conducted to detect and exclude procedure-related complications, thus reducing morbidity and mortality.

After the biopsy, we routinely injected 0.5-1.0ml of air to the target zone through the biopsy needle. It can either serve as a marker and confirm that the targeted tissue has already been acquired, or form an air plug for local hemostasis. The method was effective in 30 of the 31 cases, and no severe hematoma occurred. However, this method is only a preliminary experience with limited testing, and its reliability needs to be further tested.

Although \(^1\)H-MRS represents a promising technological advance, its effectiveness is subjected to the following limitations\(^{14}\): intraparenchymal calcification, adjacent bone tissue, necrosis or hemorrhage, tissue heterogeneity, and partial volume effects altering \(^1\)H-MRS imaging. In addition, the common intracranial occurrence of cerebral edema may cause poor quality spectrum. In our study, there were 3 cases of poor quality spectrum: in one case the lesion was too close to the ventricle; and in the other 2 cases there was serious edema. In both cases the spectrum of poor quality did not affect the choice of biopsy target and did not affect the final pathologic results.

Our study is limited by the small sample size, and the outcome only reflects our preliminary clinical experience on the application of \(^1\)H-MRS. We will continue to expand the sample size and develop prospective randomized controlled study to compare this method with frame/frameless based biopsy under traditional navigation and iMRI (without analysis of tissue metabolism). The positive diagnostic rate and the complication rate will be compared.

Despite the above limitations, \(^1\)H-MRS is an appealing noninvasive technology for tissue biochemistry and metabolism imaging. With \(^1\)H-MRS, the best biopsy point can be located based on metabolism process instead of surgeon's experience. With the help of \(^1\)H-MRS, we can obtain an accurate biopsy of the most representative tissue and therefore improve the positive biopsy rate. There will be enormous prospect for the application of this state of the art technology.

Acknowledgments
We thank members of the department of neurosurgery, PLA general hospital(Yuanzheng Hou MD; Bing-xiang Xiao MD; Guang-hong Yu MD; Yan Zhao MD; Fei
Wang MD; Yu-bo Wang MD; Xi Zhao MD) for their collaborative support.

Disclosures

This work was supported by the National Natural Science Foundation of China (No. 30800349). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Received by: 10 April 2012
Revised by: 07 July 2012
Accepted: 10 July 2012

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