A high spatial resolution *in vivo* 1H magnetic resonance spectroscopic imaging technique for the human breast at 3 T

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Purpose: The technical challenges that have prevented routine proton magnetic resonance spectroscopic imaging (1H MRSI) examinations of the breast include insufficient spatial resolution, increased difficulties in shimming compared to the brain, and strong lipid contamination at short echo time (TE) at 1.5 T. The authors investigated the feasibility of high spatial resolution 1H MRSI of human breast cancer in a clinical setting at 3 T.

Methods: Ten patient studies (eight cancers and two benign lesions) were performed in a 3 T whole-body clinical imager using a pulse sequence consisting of optional outer volume presaturation, optional CHESS pulse for lipid suppression, CHESS pulse for water suppression, and standard 2D/3D PRESS pulse sequence with an elliptical weighted *k*-space sampling scheme.

Results: All ten studies were technically successful. The spectral quality was acceptable for all cases even the one with a 65 Hz width of water peak at half height. Choline (Cho) signals were clearly visible in malignant lesion areas, while there was no detectable Cho in normal appearing breast or in benign lesions. It was also observed that the distribution of Cho signal can be nonuniform across MRI demonstrated lesions.

Conclusions: To the author's knowledge, this is the first 2D/3D MRSI study of human breast cancer with short TE (less than 135 ms) at 3 T and the highest spatial resolution (up to 0.25 cm³) to date. In conclusion, the authors have presented a robust technique for high spatial resolution *in vivo* 1H MRSI of human breast cancer that uses the combined advantages of high field, short TE, multivoxel, and high spatial resolution itself to overcome the major technical challenges and illustrated its potential for routine clinical examination as well as advantages over single-voxel techniques in studying metabolite heterogeneity. © 2009 American Association of Physicists in Medicine. [DOI: 10.1118/1.3213087]

Key words: breast cancer, high spatial resolution 1H MRSI, choline, creatine, taurine

I. INTRODUCTION

Magnetic resonance imaging (MRI) offers high sensitivity in detecting breast cancer, superior to mammography, clinical examination, and ultrasonography.¹⁻⁴ It is currently used for (1) screening of high risk patients, especially those with dense breasts, (2) staging of known cancers prior to management decisions, (3) assessing residual disease in patients after lumpectomy with positive margins, (4) assessing the effect of chemotherapy, and (5) differentiating scar from recurrence.^{3,5-7} Although the most sensitive modality for noninvasively detecting human breast cancer is breast MRI, it does not always offer a definitive diagnosis. The American Cancer Society guideline in 2007 has the following state-

ments: "MR imaging scans are more sensitive than mammograms, but they are also more likely to show spots in the breast that may or may not be cancer. Often there is no way of knowing whether or not these spots are cancerous short of a follow-up biopsy or some other invasive procedure." Benign lesion biopsies cause anxiety, risk, and are costly. The unsatisfactory specificity of clinical breast MRI has prompted exploration of breast proton magnetic resonance spectroscopy (1H MRS) for more accurate diagnosis of breast cancer.

In vivo 1H MRS can provide completely independent biochemical information to complement MRI findings and can be easily integrated into a clinical MRI protocol without

changing any hardware or the patient's position. It is well documented that metabolism in cancer cells is dramatically different from that of normal or noncancerous tissues. The MRS detectable choline (Cho)-containing compound signal is a classic *in vivo* biomarker for cellular proliferation and consists of free, phospho-, glycerophospho-, and phospholipid choline. Virtually all tumors cause Cho elevation. More specifically, a large increase in the cellular concentration of phosphocholine is one of the earliest responses of tumor cells to growth factor proteins. Breast cancer cells contain at least ten times more phosphocholine than do normal mammary epithelial cells.⁸ *In vitro* MRS of breast cell lines confirms that Cho levels increase with progression from normal to immortalized to oncogene-transformed to tumor-derived cells.⁹ Breast cancers have been distinguished from benign lesions and from normal breast tissues by the dramatic increase (from undetectable to clearly visible at 1.5 T) in Cho at 3.2 ppm.^{10–25} Analysis of early pooled clinical experience with *in vivo* 1H MRS yielded a sensitivity and specificity for the detection of breast cancer of 83% and 85%, respectively, with near 100% for both in a subgroup of young women.¹⁵ A reduction in or disappearance of the Cho signal has been associated with response to neoadjuvant chemotherapy of locally advanced breast cancer.^{20,26,27,24}

Despite substantial achievements in the past decade, routine 1H MRS examinations of the breast have not been realized because of technical challenges: Insufficient spatial resolution, increased difficulties in shimming compared to the brain, and strong lipid contamination for short echo time (TE) multivoxel MRS (MRSI) at 1.5 T. A short TE is necessary to improve signal-to-noise ratio (SNR) and, thereby, spatial resolution. Most clinical breast 1H MRS studies to date focus on lesions larger than 1 cm³ with a typical volume of 2 cm³.²⁸ This spatial resolution, however, is inadequate for assessing the majority of suspicious or indeterminate lesions (typically <1 cm in the largest diameter). It is crucial to have high spatial resolution spectra for clinical examinations, particularly since small lesions are the most likely to be ambiguous by MRI and, if malignant, have the best chance for cure. Moreover, spectra acquired with poor spatial resolution can mix patterns of tumor, necrosis, edema, and normal tissues, thus reducing their clinical usefulness. Further, it is not uncommon to have more than one suspicious lesion in one breast. In addition to the capability of examining multiple lesions, multivoxel spectroscopy (MRSI) offers other advantages over single-voxel techniques. Though single-voxel techniques provide a spectrum in a single chosen volume of interest (VOI) with relative ease of shimming, suppression of undesired signals, acquisition, and processing, they have poor sampling efficiency and difficulty accommodating irregularly shaped lesions, which is the typical case for suspected breast lesions. More importantly, the acquisition of high spatial resolution by a single-voxel technique requires very exact localization. However, the higher the spatial resolution, the more severe the motion effects. MRSI reduces these limitations by using a large VOI and then subpartitioning this VOI into smaller, adjacent “individual” voxels.^{29,30} An important property unique to MRSI is the

ability to arbitrarily move the localization grid during post-processing. This capability not only makes precise and time-consuming placement of a VOI in a breast during the examination unnecessary but also permits extraction of the signal from a desired region after the data are acquired. Despite the many advantages of MRSI for clinical studies, most reported breast 1H MRS spectra have been performed using single-voxel techniques. To our knowledge, all published breast 1H MRSI papers use a long TE (270 or 135 ms) at 1.5 T,^{17,18,31–34} with only one exception (a TE of 60 ms).^{31,35} A long TE means a low SNR or a poor spatial resolution. The only published breast 1H MRSI with a short TE (60 ms) used an inversion-recovery pulse to suppress undesired lipid signal, thus resulting in SNR loss of all metabolites.^{31,35} The goal of this study, therefore, is to investigate the feasibility of using the combined advantages of high magnetic field (3 T), multivoxel (MRSI), short TE (30–80 ms), and high spatial resolution (<0.5 cm³) itself to overcome all the major technical difficulties in routine 1H MRS examination of the breast using the most commonly available PRESS sequence.

II. MATERIAL AND METHODS

II.A. Pulse sequence

The pulse sequence consists of three parts: outer volume presaturation (OVP), two independent CHESS pulses for water and lipid suppression, respectively, and a standard PRESS pulse sequence with an elliptical weighted *k*-space sampling scheme.^{36–38} Both the OVP and the CHESS pulse for lipid suppression are optional: Can be turned on or off, depending on the situation. OVP is determined by applying slice-excitation pulses to select the area outside the VOI and is typically used when the area of interest is near the surface. Each OVP excitation consists of a 2.56 ms sinc pulse with a bandwidth of 3400 Hz and a 2 mT/m gradient pulse in the presaturation direction, corresponding to a thickness of 40 mm. CHESS for lipid suppression is a simple Gaussian pulse with a bandwidth of 100 Hz, followed by spoiling gradients. The frequency of the Gaussian pulse is set at 1.35 ppm. This optional CHESS pulse can be used to prevent sideband artifacts and digitizer overflow when necessary.²⁸ To reduce the relatively long acquisition time associated with conventional MRSI, an elliptical weighted *k*-space sampling scheme is used to acquire the MRSI data set.^{36–38} The weighted *k*-space samples only the points located on or within the *k*-space ellipse. When the number of averages (NA) is greater than 1, the central points of *k*-space are measured NA times and points on the boundary of the ellipse at least once. For intermediate points, the sampling frequency is determined by their radial distance from the center of *k* space. This incorporates a Hamming filter during measurement, which can result in an improved SNR per measurement of approximately 20% on a phantom test.^{36–38}

II.B. Patient studies

The study was approved by the institutional Human Investigation Committee and consent was obtained from each

patient. Ten patients participated in the study. Eight had histologically proven carcinoma (two invasive lobular carcinoma and six invasive ductal carcinomas), six out of eight had untreated breast cancer, while the other two of the eight were receiving chemotherapy when MRS was performed. The remaining two out of ten had benign lesions (one with MRI BI-RAD 2—benign finding, and one with histologically proven benign and MRI BI-RAD 3—probably benign).

II.C. Experimental procedure

All patient studies were performed in a 3.0 T whole-body clinical imager (Siemens Syngo, Erlangen, Germany). A four-channel breast coil (two for each breast) was used both for MRI and 1H MRSI. Raw data were combined automatically by accompanying Siemens software. Patients lay prone with their breasts in the coil; when possible, gentle breast compression was applied to minimize motion. After global shimming, clinical DCE-MRI was performed which defined the VOI for 1H MRSI. DCE MRI was performed using 20 cc of Magnevist® and a 3D fat-suppressed imaging sequence with TR of 4.90 ms, TE of 1.46 ms, temporal resolution of 58 s, and spatial resolution of $0.9 \times 0.7 \times 1.8 \text{ mm}^3$. One pre-gadolinium and seven postgadolinium sets of images were obtained over 8.5 min. 1H MRSI spectra were then acquired. Typical measurement parameters were field of view (FOV) = $120 \times 120 \text{ mm}^2$, a TR of 1500 ms, a TE of 30 or 80 ms, a slice thickness from 10 to 20 mm, a 24×24 elliptical weighted k -space sampling, and 2 averages for total data acquisition time of 11.9 min. The data were processed with the Siemens spectral processing package. Data processing consisted of line broadening (Gaussian function with 256 ms), standard fast Fourier transformations, and phasing. No baseline correction was applied. The metabolite images were formed from spectral fitting and zero filled to 256×256 points using the Siemens spectroscopy software package.

III. RESULTS

All ten studies were technically successful. Cho was detected in all six patients with untreated breast cancer. No Cho was seen in the two benign cases. For the two patients undergoing chemotherapy, a small but significant Cho was seen in one but not in the other case. The width of water peak at half height (WWHH) from the VOI after shimming ranged from 20 to 65 Hz with an average of about 35 Hz. Spectral quality was acceptable for all cases even the one with the worst shimming. Illustrative examples are described below.

Figure 1 shows representative spectra and their corresponding location in MRI images from a patient with proven invasive lobular carcinoma. The spectra were acquired with FOV = $120 \times 120 \text{ mm}^2$, a TR of 1500 ms, a TE of 80 ms, a slice thickness of 14 mm, and a 24×24 elliptical weighted k -space sampling with 2 averages for total data acquisition time of 11.9 min. Figures 1(a) and 1(b) are spectra from the same voxel shown in the MRI image of Fig. 1(c), but displayed in different scale and spectral range. Figures 1(d)–1(f) are spectra from three different MRI lesion areas of the same

patient. Figure 1(g) is a spectrum from a normal appearing area. Figure 1(h) is a color-coded Cho image overlaid on the corresponding MRI. As illustrated in the representative spectra, Cho signal was significantly elevated in the MRI lesion area [Figs. 1(b) and 1(d)–1(f)], consistent with its malignancy, while there is no detectable Cho in the normal appearing area [Fig. 1(g)]. Interestingly, the distribution of Cho signal was nonuniform across the MRI lesion area, as shown in Fig. 1(h). Moreover, despite the small voxel size, total creatine (Cr) at 3.03 ppm and taurine (Tau) at 3.42 ppm were detected in some voxels, as demonstrated in Figs. 1(d) and 1(e). The peak assignment is based on a previous report.^{28,39} The elevation of Cr and Tau in breast cancer is consistent with the previous *in vitro* 1H MRS studies of breast cancer specimens.^{39–41} Similar to Cho, their distribution was also nonuniform across the MRI lesion area, as demonstrated by comparing Figs. 1(b) and 1(d)–1(f).

Figure 2 shows the spectra from an MRI lesion and nearby normal appearing area of another patient. Needle biopsy indicated that the patient had invasive ductal carcinoma, poorly differentiated, as well as DCIS in intermediate phase. The patient was in the middle of neoadjuvant chemotherapy when the 1H MRS was performed, and the patient did not respond to the chemotherapy well. As shown in the figure, a tiny but distinct Cho signal was detected in the MRI lesion area [Figs. 2(a) and 2(b)] compared to the surrounding normal appearing breast tissues [Figs. 2(c) and 2(d)], which demonstrates an important advantage of multivoxel techniques over single-voxel techniques in helping identify abnormal metabolite areas for patients with tiny Cho signal.

Figures 3(a) and 3(b) are the spectra extracted from a 3D MRSI with a 62 Hz WWHH over the whole volume of interest. Despite the poor shimming result, the spectral quality is acceptable [Fig. 3(b)]. 3D 1H MRSI was performed for the patient because there were two lesions in the breast [Figs. 3(c) and 3(d)].

IV. DISCUSSION

Our results clearly demonstrate the feasibility of routinely acquiring high spatial resolution breast 1H MRSI at 3 T using a conventional PRESS pulse sequence. To the best of our knowledge, this is the first 2D/3D 1H MRSI study of human breast cancer with a short TE (less than 135 ms) at 3 T and has the highest spatial resolution for human breast cancer to date. The improved spatial resolution came from the combination of a short TE and higher magnetic field compared to studies at 1.5 T.

Achieving a homogeneous magnetic field for the breast is a major problem for routine applications of breast 1H MRSI. This is due to the anatomical location of the breast, motion associated with breathing, and the interference of strong lipid signal for a phase-based shimming routine. The situation becomes worse at 3 T compared to 1.5 T. Our experience indicates that good shimming often cannot be obtained even with more than 10 min shimming at 3 T. For our system, we can routinely obtain about 35 Hz of the WWHH over the VOI (typically 25 cm^3) after 1 min quick manual shimming

FIG. 1. Typical quality high spatial resolution ^1H spectra of the breast in a patient with histologically proven invasive lobular carcinoma demonstrating ^1H metabolite heterogeneity. (a) ^1H spectrum from a tumor area (the voxel in (c)). (b) ^1H spectrum from the same area as (a) but displayed in different scale and spectral range. (c) Coronal MRI guiding the MRSI. (d)–(f) are spectra from three different MRI-lesion areas of the same patient. (g) is a spectrum from a normal appearing area. (h) is a color-coded Cho image overlaid on the corresponding MRI.

following the Siemens automatic shimming package. A 35 Hz WWHH for MRSI is not much worse than the typical 25 Hz WWHH that we can obtain for single-voxel MRS. It has been suggested that even at 1.5 T, there is a significant contribution of T_2^* to the linewidth of Cho in breast ^1H

MRS studies, and reducing the contribution of static field inhomogeneity could gain a significant increase in SNR.⁴² Although the field homogeneity over a whole VOI is typically not excellent, the magnetic field homogeneity over the area of each small voxel is generally acceptable, assuming

FIG. 2. Advantage of ^1H MRSI in localizing small abnormal metabolite areas in a patient undergoing neoadjuvant chemotherapy for histologically proven invasive ductal carcinoma. (a) and (b) are spectra from two different MRI lesion areas. (c) and (d) are spectra from two nearby normal appearing areas of the same patient. The patient did not respond well to the chemotherapy.

there is no rapid change in susceptibility over the VOI, which is typically the case unless it is too close to the surface or a magnetized material without using the optional OVP. In this study, we demonstrate that the combination of MRSI and high spatial resolution, which can only be achieved with a high magnetic field and a short TE, can overcome the shimming difficulty through reducing the SNR loss due to T_2^* . In other words, the higher the spatial resolution, the smaller the B_0 variation over each tiny voxel. This is the reason why Cr and Tau can still be detected sometimes even in such a high spatial resolution (see Fig. 1). For the same reason, spectral quality was still acceptable even for bad shimming cases (Fig. 3). Thus, the combination of MRSI and high spatial resolution makes the technique robust in terms of the requirement for shimming.

Lipid contamination used to be another major hurdle for a short TE ^1H MRSI of human breast cancer because most studies have been performed at 1.5 T. Lipid is a term for a group of specific organic compounds, including triacylglycerides, phospholipid, cholesterol esters, saturated fatty acid, unsaturated fatty acid, etc. *In vivo* MRS-visible breast lipid signals include $\text{CH}=\text{CH}$ around 5.5 ppm, $\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}$ around 2.8 ppm, $\text{CH}_2\text{CH}=\text{CH}$ around 2.3 ppm, $\text{CH}_2\text{CH}_2\text{CH}_2$ around 1.3 ppm, and CH_3CH_2 around 0.9 ppm.⁴³ Among these lipid signals, $\text{CH}_2\text{CH}_2\text{CH}_2$ around 1.3 ppm has the highest intensity, while $\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}$ around 2.8 ppm typically gives the lowest amplitude. Although efficient suppression of the lipid signal at 1.3 ppm is extremely helpful for obtaining high quality spectra, it is the peak around

2.8 ppm (labeled as fat3 in all figures) that causes the difficulty for short TE ^1H MRSI of breast cancer at 1.5 T. Despite the smallest intensity among the lipid signals, the 2.8 ppm lipid signal can easily be more than ten times stronger than the desired Cho signal at 3.2 ppm [see Figs. 1(f) and 2] and cause severe contamination to the Cho for a short TE MRSI at low magnetic field such as 1.5 T. This is probably the reason why almost all *in vivo* breast ^1H MRSI studies use a long TE at 1.5 T, where the lipid signal around 2.8 ppm is reduced to a negligible level. The only report of a ^1H MRSI study of human breast cancer with a TE less than 135 ms added an inversion-recovery technique to suppress just this signal.³⁵

We demonstrate here that the combination of high spatial resolution MRSI and high magnetic field can solve the major technical challenges for its routine breast applications. High spatial resolution MRSI ensures an acceptable shape of the Cho peak for each tiny voxel even with a nonoptimal shimming result for the whole VOI (which is often the case at 3 T), and the higher magnetic field further reduces the potential overlap between the desired Cho and the lipid signal. It is well known that the separation between the Cho and the lipid peaks increases linearly with the magnetic field. Even for a TE as short as 30 ms, we can still obtain an acceptable quality of spectra without severe overlapping between the desired metabolite and the lipid signals under a typical shimming condition. We recommend a TE of 80 ms rather than 30 ms simply because the preliminary results suggest that the former offers a flatter baseline than the latter, thus easier for postprocessing. With the elliptical k -space sampling scheme,

FIG. 3. Spectra extracted from a 3D MRSI with a 62 Hz WWHH over the whole volume of interest in a patient with two disparate lesions in the same breast. (a) Spectrum from the control region. (b) Spectrum from one tumor region. (c) A color-coded Cho image overlaid on the corresponding MRI slice covering the tumor lesion for spectrum 3b. (d) A color-coded Cho image overlaid on the corresponding MRI covering the another lesion in the same breast. Other parameters are as follows: TE=30 ms, TR=2000 ms, average=2, matrix= $12 \times 12 \times 8$, and acquisition time=11:43 min.

the total acquisition time can be managed to around 12 min, which is an acceptable time for routine clinical use.

Although the CHESS pulse for suppressing the strong lipid around 1.3 ppm is optional in this study, it is recommended.²⁸ On the other hand, the lipid information has been demonstrated to be useful for monitoring therapy response,^{23,44} and most digitizers today can handle a large range of signals. For the optional OVP, our preliminary experience indicates that it is very helpful in cases where lesions are near the surface. OVP can reduce the potential con-

tamination from outside the VOI or minimize the potential rapid change in susceptibility induced by air-tissue interferences. The combination of high magnetic field, multivoxel technique, short TE, and high spatial resolution itself is the key for the success of this approach. It will not work well if any one of these key components is missing.

Breast cancer is heterogeneous in nature. Although metabolite heterogeneity of brain tumors has been well studied by *in vivo* 1H MRS, it is a virtually unexplored area for breast cancer due, in part, to the technical difficulties dis-

cussed above. Our preliminary results clearly demonstrate the feasibility of high spatial resolution 1H MRSI for studying 1H metabolite heterogeneity of human breast cancer, as demonstrated in Fig. 1. Information on Cho heterogeneity could be helpful for the selection of the optimal biopsy site. Previous *in vivo* and *in vitro* 1H MRS studies have demonstrated that high Cho is associated with malignancy.^{10–25} It is intriguing to further investigate the implication of Cr and Tau characteristics for clinical and basic study of breast cancer. Metabolite patterns in tumors have been suggested as tools in cancer characterization and possibly as prognostic factors.³⁹ *In vitro* MRS studies suggest that increased taurine and phosphocholine correlate with tumor grade and that there may be a central role of taurine and glycine in the potential discrimination between lymph node positive and negative patients.^{40,41,45}

Another advantage of multivoxel over single-voxel technique is its usefulness in helping to localize abnormal metabolite areas in the breast, as illustrated in Fig. 2. Although Cho is typically not detectable in normal breast tissue at 1.5 T, this may not be the case at a high field, particularly for a large volume of interest.²⁸ Moreover, Cho signal can be clearly visible in healthy lactating breast tissue even at 1.5 T.^{14,46,47} On the other hand, it has been well documented that choline-containing phospholipid levels increase with progression from normal to immortalized to oncogene-transformed to tumor-derived cells, and Cho level increases significantly in breast cancerous specimens compared to non-involved specimens.^{9,41} Thus, the capability of comparing spectra from a suspicious abnormal MRI area with the spectra acquired simultaneously from normal MRI breast tissues should be very helpful in identifying abnormal metabolite areas. Interestingly, we often observed the lipid peak at 2.8 ppm shifted to 3.2 or even 3.4 ppm due to inhomogeneous magnetic field across the whole VOI. Without nearby spectra for comparison, this smallest lipid peak could be mistaken for a Cho peak. There are other potential benefits with high spatial resolution multivoxel capability. In addition to studying small lesions and metabolite heterogeneity, high spatial resolution 1H MRSI also permits the detection and characterization of tumors beyond MRI-defined lesion areas and simultaneous examination of multiple breast lesions. One of the potential applications for 1H metabolite heterogeneity is to help determine the optimal biopsy site.

In summary, we have presented a robust technique for high spatial resolution *in vivo* 1H MRSI of human breast cancer that uses the combined advantages of high magnetic field, short TE, multivoxel, and high spatial resolution itself to overcome the major technical challenges, all with an acquisition time of less than 12 min, and demonstrated its potential for routine clinical examination.

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