Proton Magnetic Resonance Spectroscopy of the Breast

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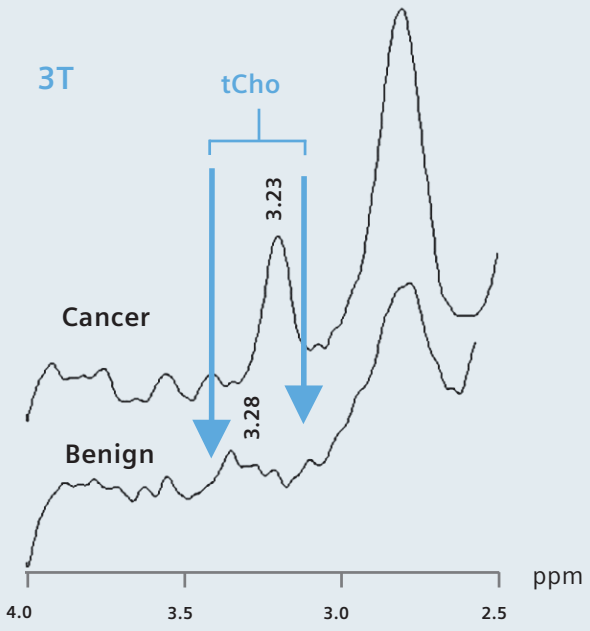
Introduction

Contrast-enhanced magnetic resonance imaging has gained acceptance as an important breast imaging modality [11]. However it does not always provide a definitive pathology. In 2007 Lehman [8] reported that magnetic resonance imaging (MRI) could improve on clinical breast examination and mammography by detecting contralateral breast cancer soon after the initial diagnosis of unilateral breast cancer. The study found that the specificity of MRI in this cohort of patients was 88%. Subsequent guidelines from the American Cancer Society for breast screening, with MRI as an adjunct to mammography, reported that, "MRI 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" [11]. The question now to be addressed is "can the diagnostic accuracy of MRI be improved by adding proton magnetic resonance spectroscopy (MRS)?".

In vivo MRS can be performed along with a conventional MRI study and produces information about the chemical content of the breast, or a distinct breast lesion. Initial studies where in vivo proton MR spectroscopy has been added as an adjunct to dynamic contrast-enhanced MR imaging of the breast have shown promising results and a growing number of research groups are incorporating the technique into their breast MR protocols. The aim of this article is to illustrate the expected examination results and outline some of the pitfalls associated with undertaking a breast MRS examination.
Initially and at 1.5T the diagnosis of breast cancer using MRS, was based on the observation of the choline-containing metabolite (tCho) signal at 3.2 ppm. The resonant frequency of the observed tCho signal has been suggested as having diagnostic potential for discriminating between normal glandular tissue and malignancy [12]. Likewise, quantification of the observed tCho signal has been suggested as means of discriminating between benign and malignant lesions [5] and also for monitoring response to chemotherapy [10].

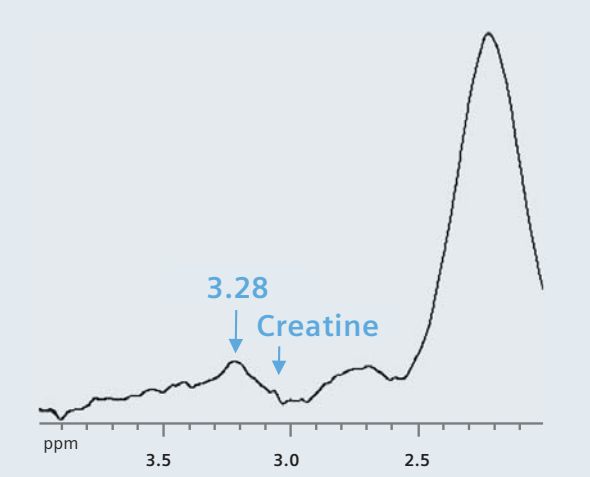
tChol vs the resolved resonances at 3.23 and 3.28 ppm
Historically the tChol signal was measured because it was not possible to achieve the necessary spectral resolution to separate the resonances. However, recognition of the exact resonant frequency of the tCho signal may be helpful to further distinguish malignant from benign with higher accuracy. In addition, it may help to monitor chemotherapy where the biology is such that some of the component resonances alter while others do not [2, 19]. On current hardware it is possible to process the data such that the tChol signal as well as the choline resonant frequency can be inspected and compared (Fig. 1) [12, 13]. In order to undertake such a comparison there are many experimental aspects to be taken into account.

1



1 In vivo breast single voxel spectra (3T, PRESS, TE = 135 ms / TR = 2000 ms, 192 signal averages). Spectra are processed as described [12, 13] were referenced to the methylene resonance of lipid at 1.33 ppm and water at 4.74 ppm. In the spectrum from the cancer bearing patient (top) the resonance is at 3.23 ppm and consistent with phosphocholine. For comparison, a spectrum derived from a fibroadenoma (bottom) is shown. The total choline "tChol" region is shown in blue.

2



2 In vivo breast single voxel spectrum (1.5T; TR = 135 ms; TE = 2000 ms; 256 averages) of a lesion identified intraoperatively as DCIS with no micro-invasion. Data was processed and referenced as shown in figure 1.

DCIS without micro-invasion

In our experience, there are a small number of cases where the pathology was DCIS with no micro-invasion where the resonance present in this region was at 3.28 ppm.

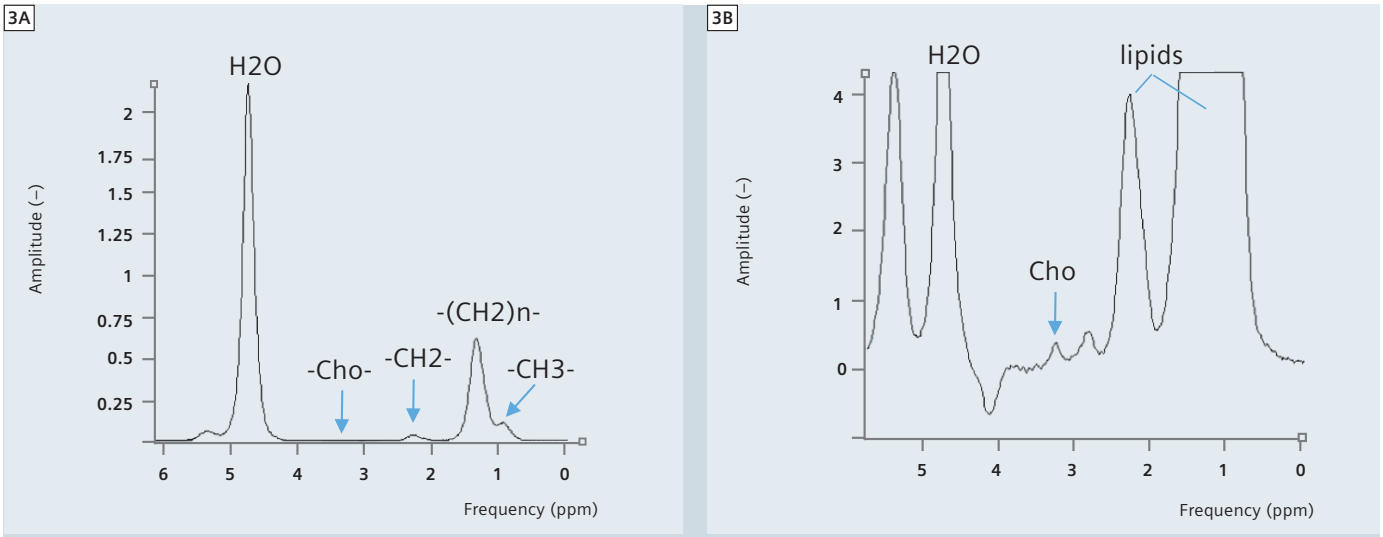
Size of detectable lesion

With the new MR technologies and coils we are in a better position to interrogate lesion sizes 8 mm and above that need pathological discrimination. Thus an understanding of the significance of the choline resonance detected in vivo is even greater, especially seeing that any detected resonances in this spectral region may have arisen from surrounding "normal" or preinvasive breast tissue and maybe involve processes other than a malignant process (e.g. hormonal).
We and others have demonstrated that 1D MRS can be successfully applied to the breast in vivo, preoperatively and non invasively, giving a diagnosis of breast pathology that distinguishes the categories of malignant, benign, and healthy with a high level of accuracy but these reports were on tumors 1 cm or larger.

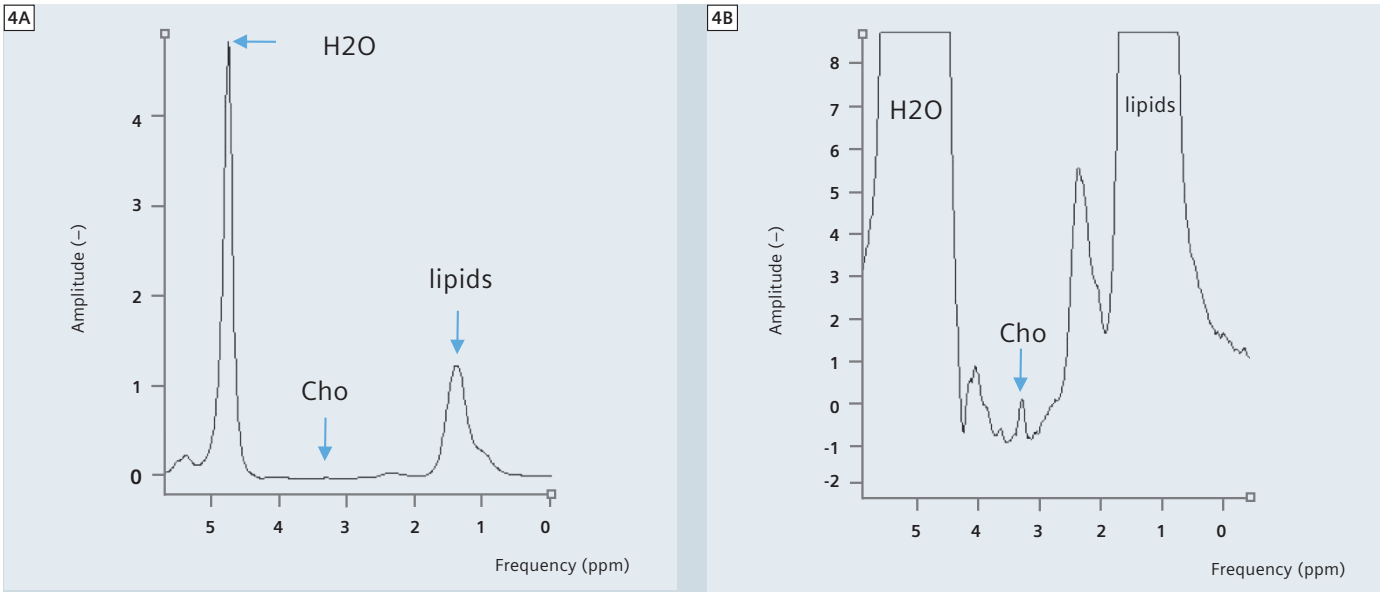
Experimental concerns

This technology is routinely operational at the sites of the authors. However it should be recognized that the operators of the scanners at both sites are highly trained. Many technical difficulties can and do occur and this requires expertise at the scanner. Below we summarize some of the issues that can be faced in order to produce high quality spectral data.

What you might expect with standard software on the scanner



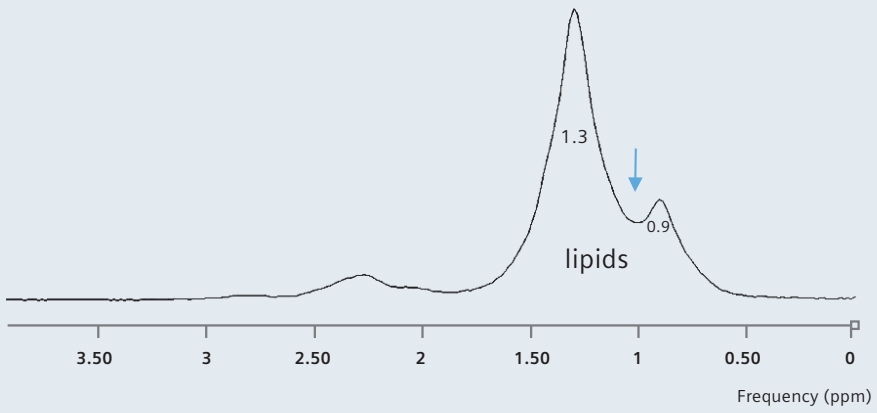
3 Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135 ms) from glandular tissue in a breast volunteer. **A)** Non-water suppressed spectrum shows strong water and lipid signals and a barely visible choline resonance (arrow). **B)** The vertical display is increased with the choline signal becoming more apparent.



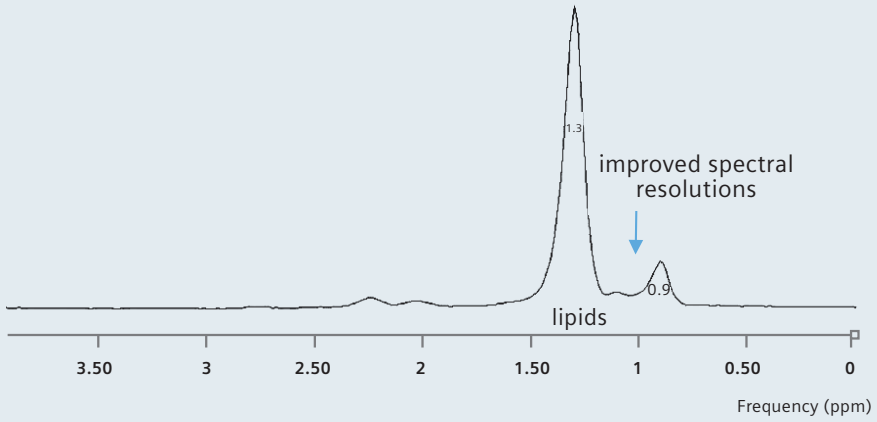
4 Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135 ms) from a biopsy-proven breast cancer. **A)** Non-water suppressed spectrum shows strong water and lipid signals and a barely visible choline resonance (arrow). **B)** The vertical display is increased with the choline signal becoming more apparent.

Shimming

5A



5B

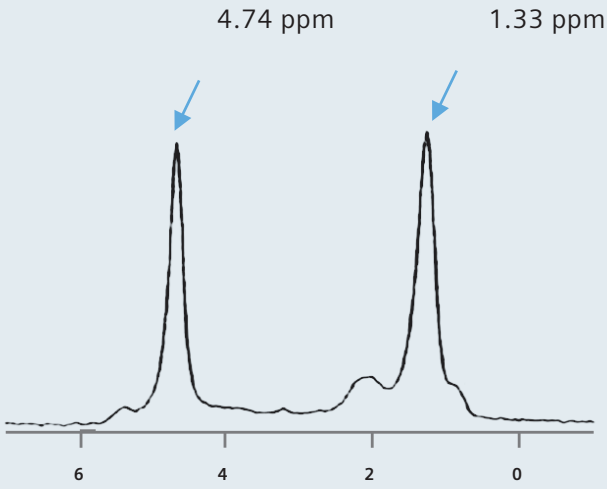


5 Voxel shimming. Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135 ms) in a breast volunteer.
A) Spectrum was acquired using the automatic shimming program only. Prominent signals are visible from lipids at 0.9 and 1.3 ppm.

B) Spectrum was acquired with the addition of manual shimming. Prominent signals from lipids are again noted (0.9 & 1.3 ppm) but with enhanced spectral resolution with these two peaks now resolved to their baselines.

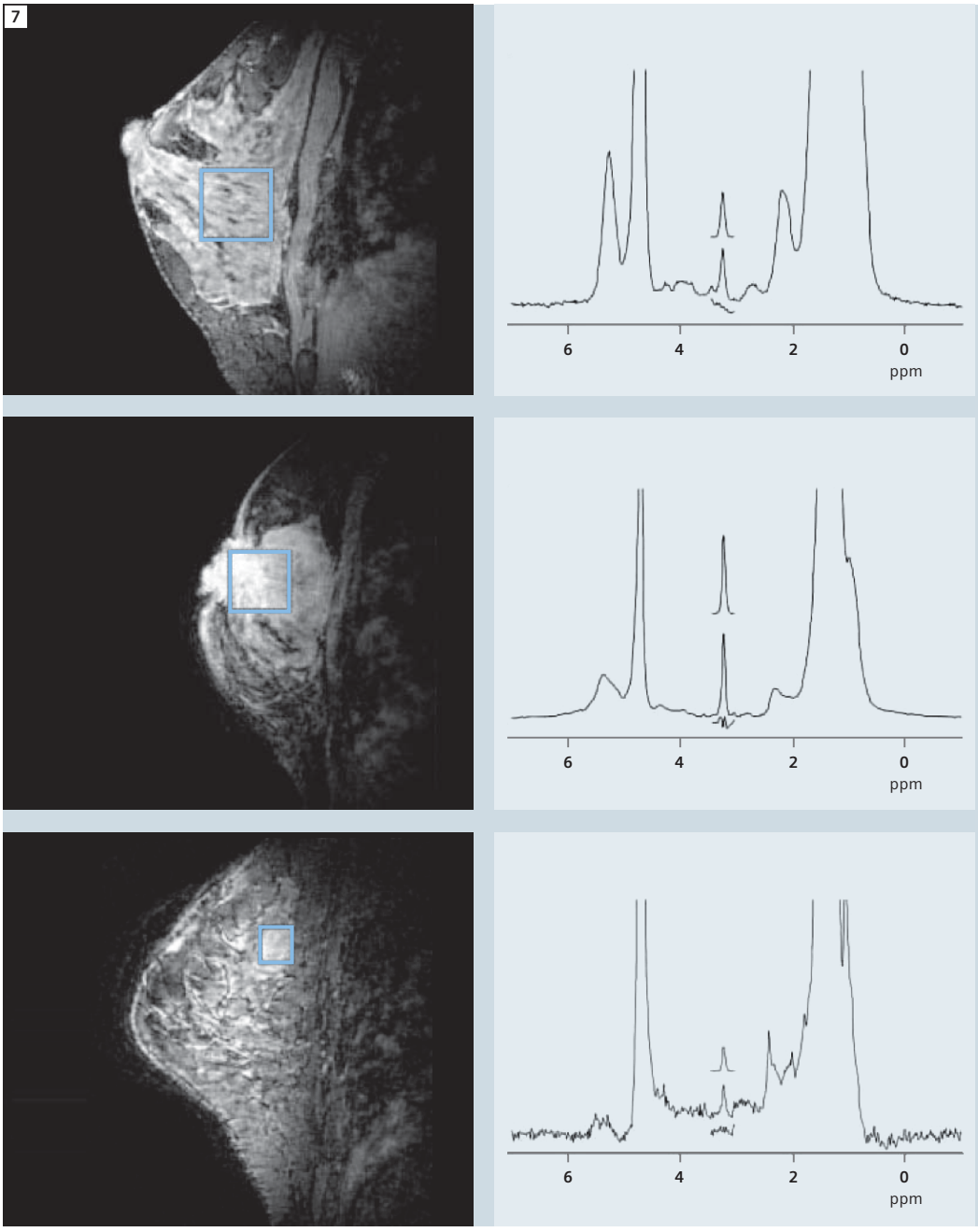
Referencing

6



6 Correct referencing is undertaken on the non suppressed water spectrum and provides necessary accuracy which is required to distinguish the 3.23 ppm from 3.28 ppm resonances seen in figures 1 and 2.

Quantification

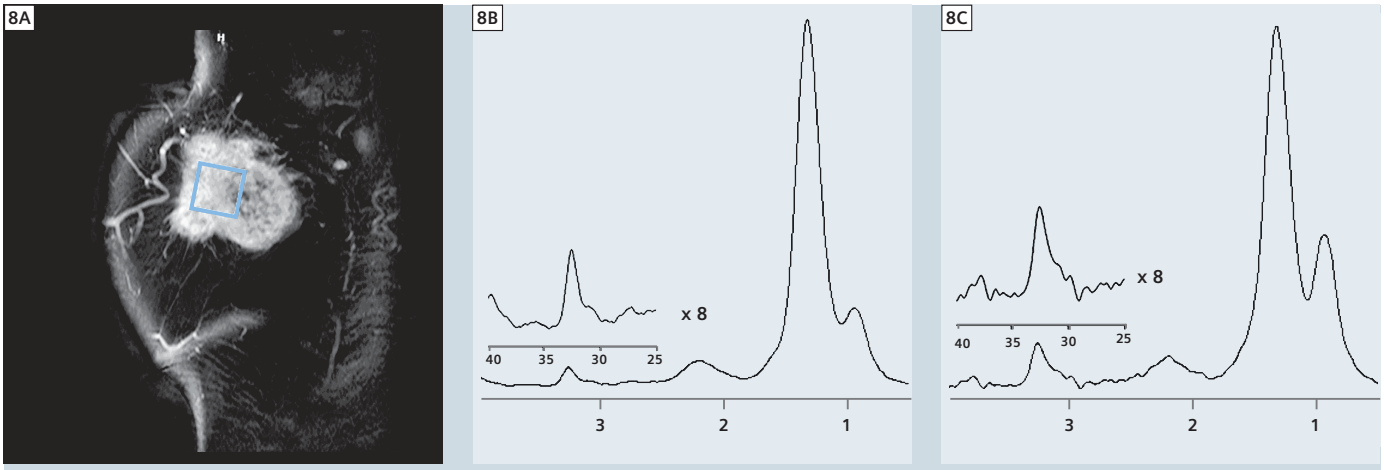


7 Quantification of t-choline-containing compounds. For each row the voxel location is shown on a contrast-enhanced localiser image on the left, while a water-suppressed spectrum is shown on the right, with the tCho fit shown above and the residual underneath.

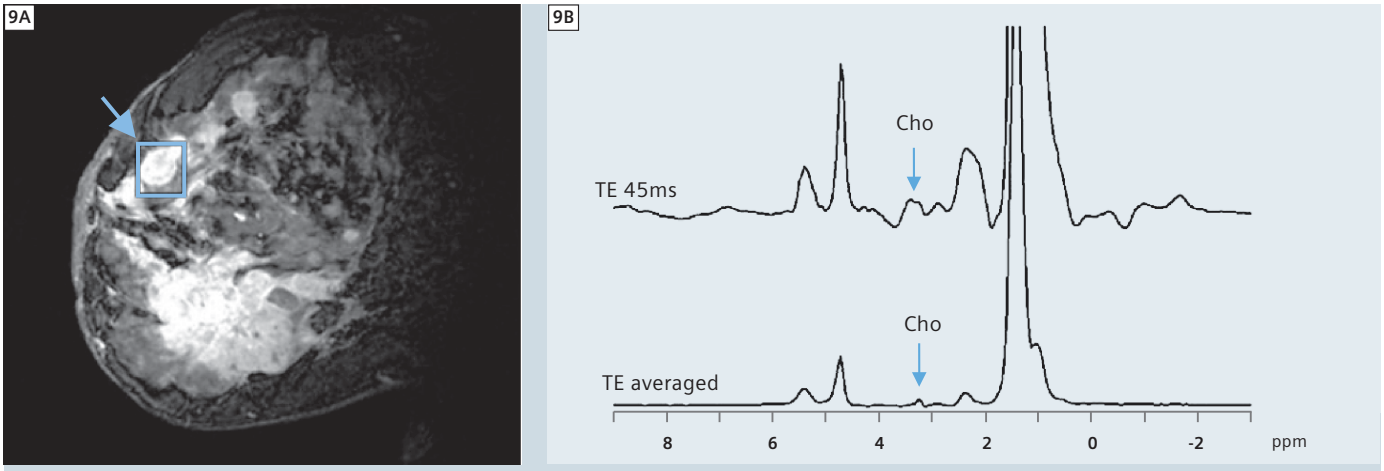
Top row, normal gland, volume = 13.0 ml, [tCho] = 0.66 ± 0.06 mmol/kg, lipid fraction = 3%.

Middle row, malignant tumor of invasive ductal carcinoma, volume = 6.8 ml, [tCho] = 6.1 ± 0.08 mmol/kg, lipid fraction = 8%.

Bottom row, atypical hyperplasia volume = 1.1 ml, [tCho] = 1.4 ± 0.7 mmol/kg, lipid fraction = 14%. Adapted from Bolan, et al. [5].



8 Effect of echo time (TE) in breast spectroscopy. Proton single-voxel spectrum acquired with the PRESS sequence from a biopsy-proven breast cancer. **A)** Indicates the voxel placement within the breast cancer. **B)** Single-voxel spectrum acquired with TR of 2000 ms, TE of 135 ms. **C)** Single-voxel spectrum acquired with TR of 2000 ms, TE of 270 ms. Increasing the TE from 135 to 270 ms reduces the amplitude of lipid (at 0.90 and 1.33 ppm) due to increased T2 relaxation [13].



9 Lipid-induced sidebands. Proton single-voxel spectrum collected in a breast cancer patient. **A)** Contrast-enhanced image demonstrates a 15 x 16 x 15 mm^3 voxel surrounding a biopsy-proven case of inflammatory breast cancer with included surrounding adipose tissue. **B)** Water-suppressed spectra, top spectrum collected with a single echo time (45 ms), bottom spectrum collected with TE-averaged acquisition (TE 45-196 ms). The Cho signal (vertical arrows) is more distinct in the TE-averaged acquisition due to reduction in gradient-induced artifacts compared with the single TE acquisition. (Adapted from Bolan, et al. [3]).

Lipids

The in vivo spectra from the breast are often dominated by lipid resonances. When adipose tissue that is not part of the pathologic process is included in the voxel this inclusion can cause several problems [3, 13]. The impact of lipids can be reduced by increasing the echo time [7] or by employing a TE-averaging acquisition [3].

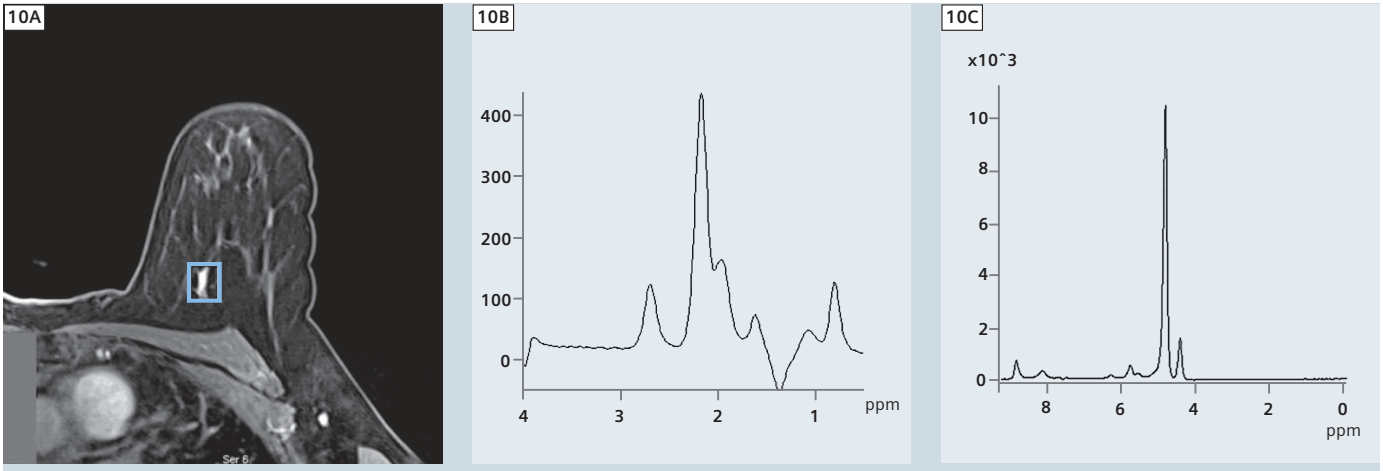
Pre-scan set-up

In MR spectroscopy the line width of a peak is dependent both on the intrinsic T2 relaxation time of that metabolite and the homogeneity of the magnetic field in the region. The line width of a peak due to its intrinsic T2 relaxation time is typically less than 1 Hz, whereas the line width from field inhomogeneity (i.e. poor localized shim) may be from 5 to 10 Hz. In any MRS experiment the MR acquisition parameters are adjusted on a patient-by-patient basis in order to obtain optimum spectral resolution and signal-to-noise ratio (SNR) ratio. Two important parameters in the acquisition of high quality in vivo breast MRS data are pre-scan adjustment and shimming and thus it is crucial to spend the necessary time to achieve a well-shimmed region-of interest (ROI) and to ensure all pre-scan conditions have been successfully completed.

Shimming

Shimming is the process by which the local B0 field is made as homogeneous as possible. Obtaining a good localized shim is critical for the identification and characterization of any observable peaks. The quality of localized shim also directly affects the accuracy of referencing, and hence chemical assignment, of any observed choline signal in breast MRS. Due to inherent adjacent susceptibility differences encountered in breast MRS examinations (e.g. air-filled thorax, respiratory-motion) manual shimming is often required to optimize the final MRS result.

Prescan frequency adjustment

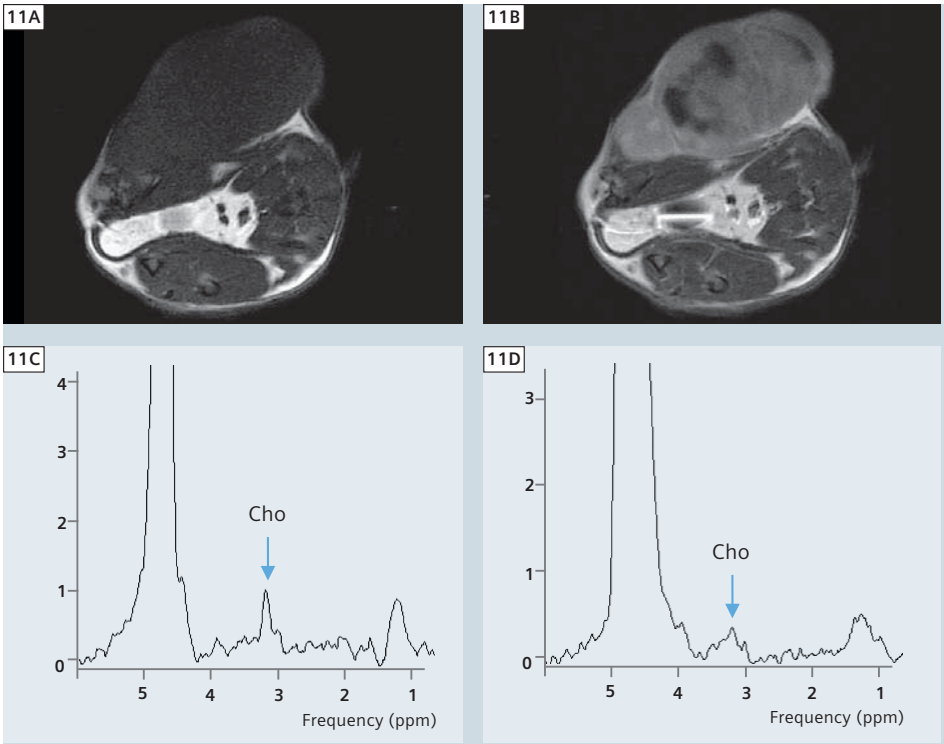


10 Prescan frequency adjustment. Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135ms) in a breast cancer patient. **A)** Contrast-enhanced image demonstrates a 15 x 12 x 14 mm^3 voxel surrounding a small ductal cancer with included surrounding adipose tissue. **B)** Water suppressed spectrum with unusual appearance of resonances. **C)** Non-water suppressed reference spectrum demonstrates lipid-water ratio of approximately 11 which resulted in the prescan adjustment wrongly assigning the lipid resonance at 1.3 ppm (the highest amplitude peak) as the water and thus applying water suppression at the wrong frequency. The result was the abnormal appearing spectrum in B).

Frequency confirmation:
During the pre-scan set-up it is routine for the MR system to assign the highest peak in the pre-acquisition phase as the water resonance. This is not always the case in breast MRS. If this situation is not recognized, and corrected, before the acquisition it is possible that the erroneous application of water suppression can lead to spectral artifacts in the final spectrum. This can be avoided by selecting the "frequency confirmation" box that allows the user to confirm that the MR system has selected the correct peak for water suppression.

Contrast agents

Some gadolinium-based MR contrast agents have been shown to affect the spectra from breast tumors [6]. Other agents have been suggested as acceptable for MRS studies [9].

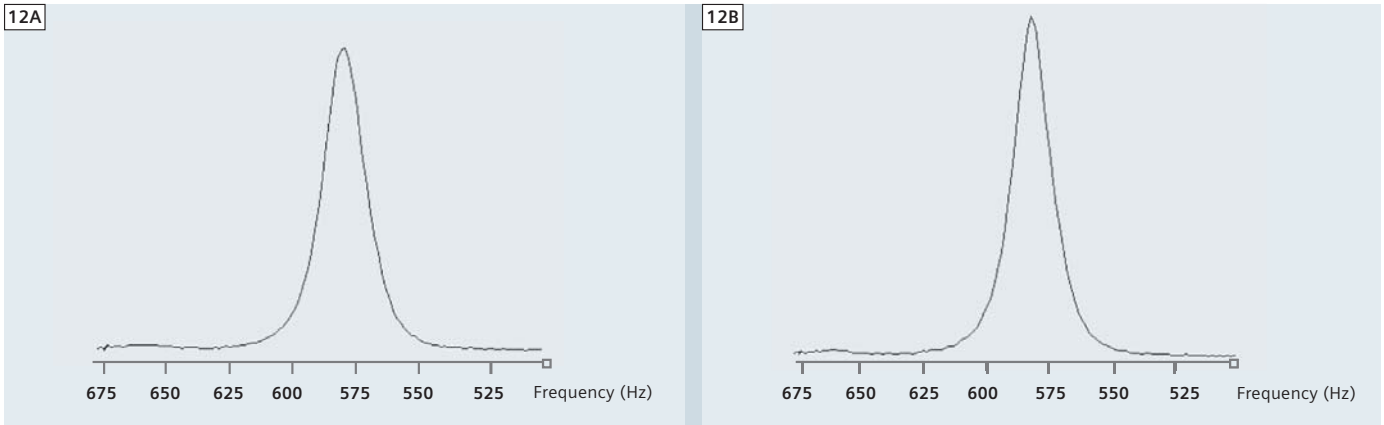


11 Contrast agents. Proton single-voxel spectrum (repetition time (TR) 2000 ms, echo time (TE) 144 ms) collected from mammary adenocarcinoma implanted in female Fischer rat.

A) Pre-contrast image demonstrates tumor on rat hind limb.
B) Contrast-enhanced image demonstrates uptake of contrast agent.
C) Localized spectrum collected prior to injection of contrast media.
D) Localized spectrum collected 15 minutes after the injection of contrast media. There is a significant reduction in Cho signal following the administration of this particular contrast agent. (Adapted from Lenkinski, et al. [9]).

Respiratory motion

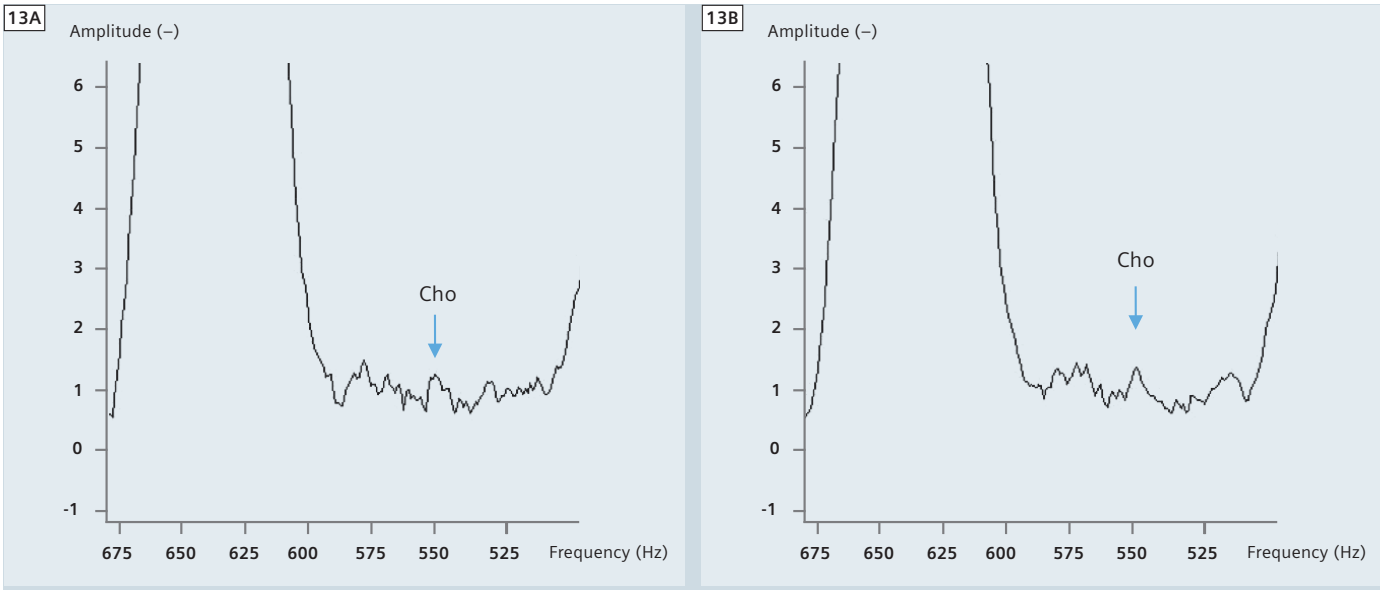
Respiratory motion during the acquisition of breast MRS produces B_0 magnetic field distortions resulting in shot-to-shot frequency shifts [4]. These variations can be corrected by frequency shifting each individual measurement prior to summing the total number of averages resulting in an improvement in spectral resolution.



12 Compensation for respiratory induced artifact. Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135 ms) in a breast cancer patient. **A)** Non-water suppressed spectrum with FWHM of the water peak = 20 Hz without correction of frequency shifts due to respiration. **B)** Non-water suppressed spectrum with FWHM of the water peak = 16 Hz following correction of frequency shifts.

Signal-to-noise ratio (SNR)

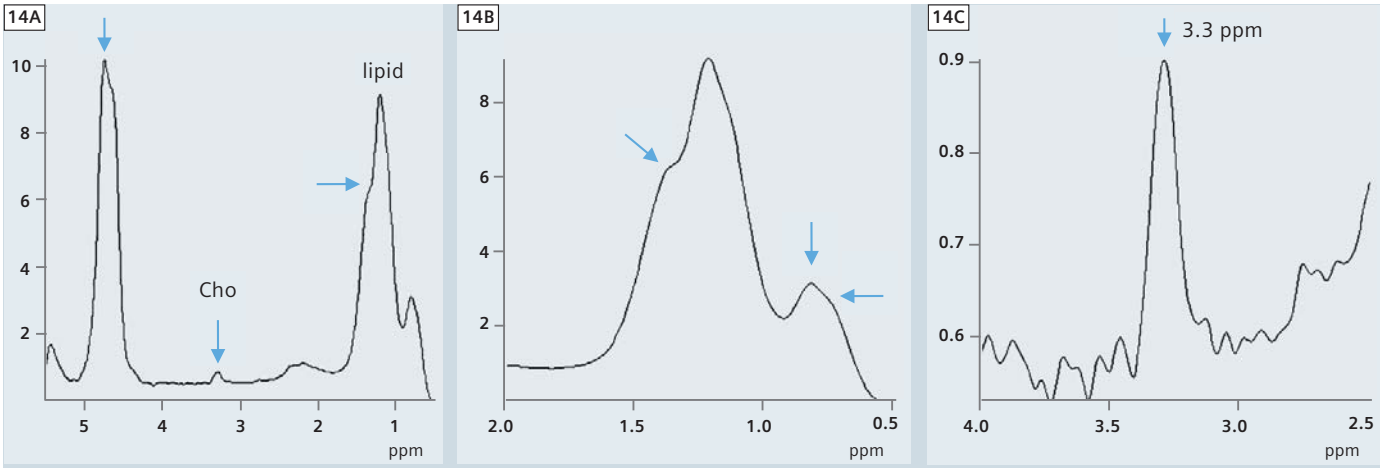
In MRS, adequate SNR is needed to detect and characterize any detected MRS signal. In breast MRS the signal from choline-containing metabolites is often small necessitating the collection of spectra with high SNR to allow for the accurate depiction of the choline signal, and determination of its MRS characteristics (e.g. chemical shift, signal integral).



13 Signal-to-noise ratio, effect of acquisition time. Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 msec, echo time (TE) 135msec) in a breast cancer patient. **A)** Spectrum acquired from a 7 x 15 x 10 mm^3 voxel with 128 signal averages. A choline resonance is visible but barely above the background noise level. **B)** Spectrum acquired from the same location with the same voxel dimensions but with 256 signal averages. Choline signal is now clearly discernible above the background noise level.

Gross patient movement

As in all MR techniques patient movement can degrade the diagnostic utility of an examination. In MRS gross motion artifact can be identified by distortion of the resonant peaks, often with a double appearance of each peak.



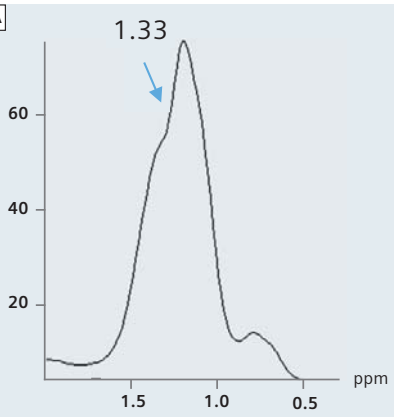
14 Proton single-voxel spectrum acquired with the PRESS sequence (repetition time (TR) 2000 ms, echo time (TE) 135 ms) in a breast cancer patient. **A)** Non-water suppressed spectrum demonstrating distortion (double peaks) of water and lipid resonances consistent with gross patient movement. **B)** Same spectrum as in A), displayed from 0.5 to 2.0 ppm demonstrating distortion of the lipid resonances at 0.9 and 1.3 ppm. **C)** Same spectrum as in A) & B), displayed from 2.5 to 4.0 ppm demonstrating distortion and frequency shifting of the choline resonance at 3.2 ppm.

Undertaking MRS after:

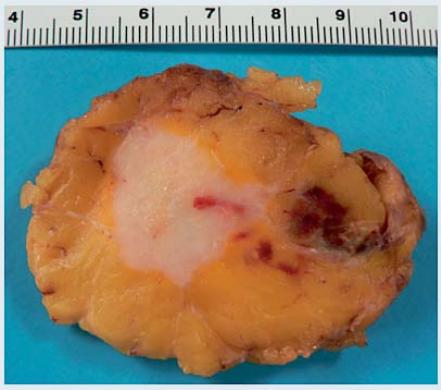
A. Core biopsy
Core biopsies cause tissue damage and bleeding. The effect of this on the tumor is seen below. The effect on the MR spectrum is a broad series of resonances at 1.2 ppm from blood and bruising. This makes referencing of the spectrum difficult to impossible.

B. Placement of magnetic clip
Undertaking MRS in vivo on a breast lesion marked by a magnetic clip, for the surgeon to locate the tumor, results in a broad spectrum. The presence of a clip makes shimming very difficult to impossible. There are now non-magnetic clips available.

15A



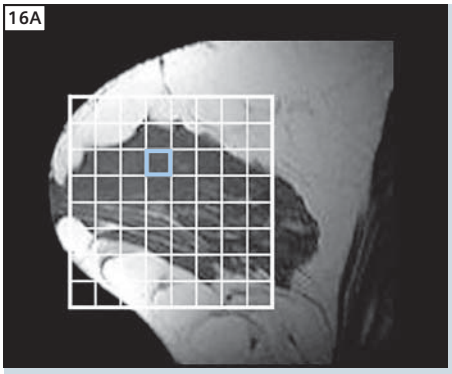
15B



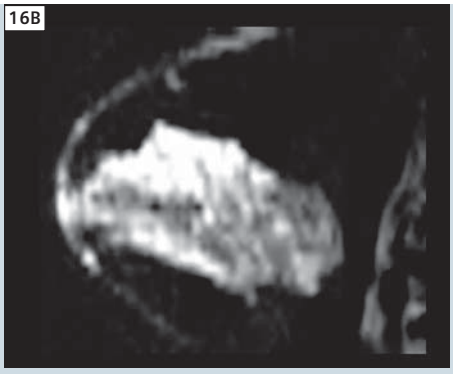
15 **Left:** Methylene region of the spectrum from a breast lesion following a core biopsy.
Right: The excised tumor obtained intraoperatively with bleeding and bruising.

Monitoring therapy

16A



16B



16C

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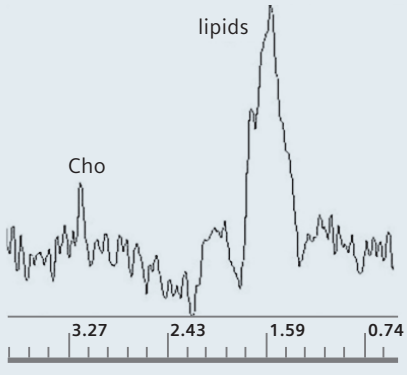
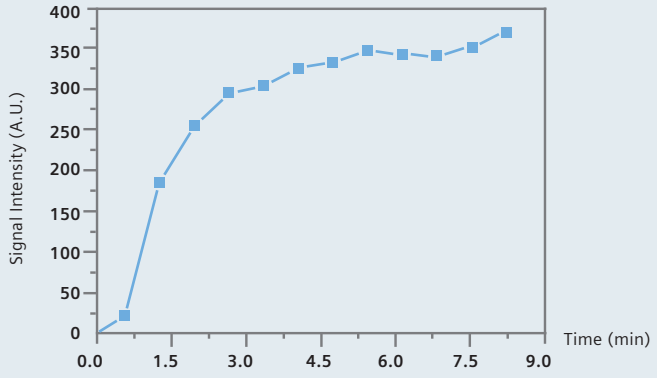


16E



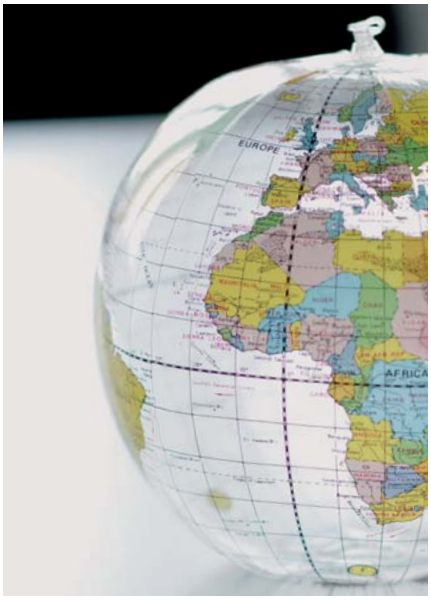
16 Taken from Baek et al. [1] where they monitor predicting pathologic response to neoadjuvant chemotherapy in breast cancer by using MR imaging and quantitative proton MR spectroscopy. Here they use the MRS method effectively to show that the choline signal is increasing in intensity with tumor recurrence. **A)** Showing selected voxel. **B)** Post-contrast images demonstrating contrast-media enhancement. **C)** Choline map. **D)** MRS with increased tCho. **E)** Corresponding signal-intensity time curve derived from dynamic MR exam.

Summary

First MRS reports on breast interrogated large tumors of 1.5 x 1.5 x 1.5 cm^3 or above. However, very often lesions detected by MRI are smaller (3–15 mm in size) and the following issues need to be addressed in order to make in vivo MRS robust and diagnostically useful. If successful this should increase the accuracy afforded by dynamic T1w MRI combined with breast MRS.

The issues to be considered include:

- The MRS exam needs to be undertaken prior to the placement of a clip and prior to a core biopsy being taken.
- Tumor size needs to be 8 mm or above for robust measurement of the chemical species responsible for appearance of diagnostic signals.
- Shimming is integral to a successful exam.
- Relative quantities of the diagnostic resonances can be measured as well as tCho using either 4, 7 or 16-channel coils.
- When using the method for definitive diagnosis or monitoring therapy the spectra need to be accurately referenced.
- Some tumors will have a mixture of pathology.



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