

The Impact of Gd-DTPA on Breast ¹H MRS

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Introduction: *In vivo* magnetic resonance spectroscopy (MRS) in the human breast can be used for improving diagnostic accuracy and monitoring response to chemotherapy by detecting or quantifying the levels of choline-containing metabolites. Most commonly, MRS measurements are performed after a dynamic contrast enhanced MRI examination, which includes the intravenous administration of a Gadolinium-based contrast agent (GBCA).

There is some evidence that GBCAs may affect the choline resonance and bias the breast MRS examination. In Joe et al. (1) the authors performed MRS measurements both pre- and post-contrast in 22 examinations of 15 subjects using the contrast agent Gd-DTPA-BMA (Omniscan, GE Healthcare), a neutral GBCA with a linear structure. This study found that Gd-DTPA-BMA produced an increase in linewidth (~17%) and a decrease in the choline peak area (~15%). More recently, Lenkinski et al. described MRS measurements comparing the impact of several different GBCAs both *in vitro* and in a murine subcutaneous xenoplant model of breast cancer (2). They found that negatively-charged GBCAs produced an increase of the choline linewidth *in vitro*, attributable to the reduction of T₂, while the neutral contrast agents had no effect. *In vivo* they found that while none of the contrast agents produced a statistically significant broadening of the choline resonance, the negatively-charged GBCAs reduced the choline peak area substantially (43%), whereas the neutral GBCAs had only a small reduction of peak area (5%). This is an important topic as there are a number of ongoing studies using MRS in breast cancer along with contrast-enhanced MRI, and any bias of the MRS measurements caused by the GBCAs needs to be understood and minimized. Additionally, several of these studies use water as an internal reference for quantifying the choline peak, and the effect of the GBCA on the water resonance may also alter the quantitative measurements. In this work we describe our study performing MRS before and after administration of Gd-DTPA (Magnevist, Berlex), a negatively-charged linear GBCA, at 4 Tesla in human breast cancers, and report the effects on choline, water, and lipid peaks, as well as on the water T₂.

Methods: All studies were performed with IRB approval. The scans were performed on a 4 T MR system (Varian console, Siemens gradients, Oxford magnet) with custom-built unilateral breast coils. Single-voxel MR spectroscopy measurements were performed using LASER localization (3), 6 kHz spectral bandwidth, TR = 3 s, and TE Averaging from 45-196 ms in either 128 or 256 increments (4). For choline measurements, water suppression with the VAPOR technique was used. Water T₂ measurements were performed using no water suppression, TR = 6s, and TE = 45-401ms in 10 steps. Spectroscopy was performed before and after a dynamic contrast-enhanced protocol, consisting of 3D fat-suppressed GRE imaging before and after manual injection of 0.1 mmol/kg Gd-DTPA.

All spectral analysis was done with in-house software written in Matlab. Peak intensity, integral, and full-width at half maximum (FWHM) were measured in absorption mode after phasing and using linear baseline correction. Water T₂ was calculated by measuring water peak amplitudes in magnitude mode and fitting to an exponential decay model with Matlab. The "predominant" lipid peak was measured in the water reference spectra using either the 1.3ppm lipid resonance, or the combined 1.3ppm + 0.9ppm resonances if they were not resolvable. Pre- and post-GBCA measurements were compared using paired t-tests, and two outliers (marked in red in Fig. 2) were removed before statistical analysis.

Results: We had 6 comparisons with measurable choline, 10 comparisons of water reference scans (5 of which had measurable lipid resonances), and 5 water T₂ comparisons both pre- and post-GBCA. The time between the pre- and post-contrast scans ranged from 13 to 33 minutes, with a median value of 19 minutes. The effect on the choline linewidth and integral are shown in Fig 1. There was a trend that the choline linewidth increased (mean 13.8% +/- 23.0%) and the integral decreased (mean -13.5% +/- 15.3%) after contrast, but the effect was not significant (p=0.22 and p=0.15). The choline peak intensity did show a significant decrease (mean -19.2% +/- 16.5%, p=0.03) after contrast. The water peak showed increased linewidth (mean 10.9% +/- 12.4%, p=0.02), decreased intensity (mean -10.5% +/- 13.7%, p=0.06), and decreased area (-3.4% +/- 9.2%, p=0.15). Water T₂ decreased slightly (mean -3.0% +/- 6.2%), but the change was not significant (p=0.15). There was no significant effect on the lipid peak's linewidth, integral, or intensity. Several of these effect sizes are shown in Fig 2.

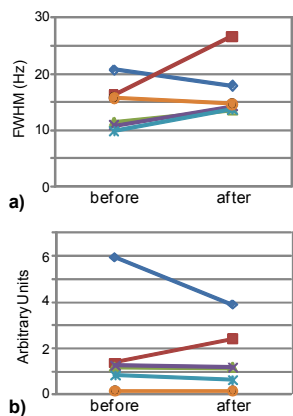


Fig 1. a) Linewidth and b) integral of the choline resonance before and after GBCA injection.

Discussion: Our finding that there is a relatively small, negative effect of Gd-DTPA on the choline linewidth, intensity, and area is consistent with the report of Joe et al. (1), who used Gd-DTPA-BMA. We did not observe the large effect of the negatively-charged Gd-DTPA described in the mouse study by Lenkinski et al., perhaps in part because this was a human study. The observed effects can be largely described by changes in the magnetic susceptibility of the extracellular space due to the influx of the GBCA.

In this study, it was not possible to separate the effect of the GBCA from the potential impact of subject motion over the >10 minute period between the pre- and post-contrast MRS measurements. It is clear that by the time of post-contrast MRS the GBCA concentration within the voxel is not sufficient to produce a measurable reduction in the water T₂. Note also that the *in vivo* linewidths are dominated by magnetic susceptibility effects and not the intrinsic T₂, as the transverse relaxation rate constants attributed to measured linewidths (FWHM = 10-30 Hz corresponds to T₂* = 32-10 ms) are substantially smaller than the measured T₂ rate constants (57-102 ms). This further supports the hypothesis that these effects are due to susceptibility gradients rather than direct choline-Gd interaction.

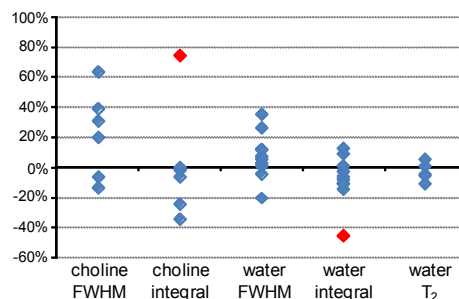


Fig 2. Change of MRS parameters when repeated after GBCA injection. Red markers were excluded from statistical analyses as outliers.

Conclusion: Gd-DTPA has a measurable effect in MRS of the human breast, reducing the choline peak intensity and increasing the water linewidth. This can impact the quantification of choline levels, with an effect size of 10-15%.

References: 1. Joe BN, et al., Invest Radiol. 2005; 2. Lenkinski RE, et al., Magn Reson Med. 2009; 3. Garwood M, DelaBarre L. J Magn Reson. 2001; 4. Bolan PJ, et al., Magn Reson Med. 2002

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