Evaluation of choline concentrations in malignant breast lesions in predicting response to neoadjuvant chemotherapy

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Introduction

The presence of choline at 3.2ppm in *in vivo* [1]H MR spectra of breast lesions can be used as a marker of malignancy.[1] However, the value of using changes in choline levels to predict lesion response to neoadjuvant chemotherapy early during treatment has been investigated by very few. Meisamy *et al.*[2] found that changes in choline concentrations within 24h of the 1st dose were highly predictive of eventual response, but their patient sample was small. There have also been several attempts at determining [choline] in malignant breast lesions,[3;4] but various assumptions were made regarding the relaxation parameters of the *in vivo* compounds concerned while correcting for relaxation. As relaxation parameters are specific to the compound and its environment, these assumptions would inevitably lead to inaccuracies in the concentrations obtained. Therefore we report here a measurement of the *in vivo* T_1 and T_2 relaxation times of water and choline in malignant breast lesions, as well as a study using these values to obtain [choline] in these lesions and follow their changes throughout chemotherapy, to see if [choline] is indeed a good predictor of treatment response.

Methods

Examinations were performed on 18 patients with invasive ductal carcinoma enrolled in a study monitoring lesion response to 4 or 6 cycles of neoadjuvant chemotherapy, using a 1.5T scanner (GE Signa Infinity) and a bilateral breast coil (Machnet). Patients were scanned before treatment, 1-8 days after their 1st cycle, and 2-3 weeks after their 2nd and last cycles. Single voxel ^{1}H MR spectra were acquired from the lesion of each patient (voxel size 0.5-11.6cm^3) after a clinical examination that included contrast administration. Two TE-averaging sequences were used, *A*: TR 1.5s, initial TE 35ms, 64 steps of 2.5ms, and 4 water-suppressed acquisitions per TE (15 patients), and *B*: TR 2s, initial TE 145ms, 4 steps of 5ms, and 32 water-suppressed acquisitions per TE[5] (12 patients). Choline concentrations were obtained using LCModel (SW Provencher). To correct for relaxation *in vivo*, lesion water and choline T_1 and T_2 were measured. Water T_1: Inversion recovery-prepared spectra were acquired from the lesions of 10 patients (TR/TE/TI = 2000/144/114,300,600,900ms, 16 averages). A Marquardt fit was performed on the unsuppressed water signal in each spectrum, and the T_1 obtained by non-linear least squares fitting of the peak areas to the inversion recovery equation $A=A_0[1-2\exp(-TI/T_1)+\exp(-TR/T_1)]$. Choline T_1: Sequence *B* spectra were acquired from the lesion of 1 patient (TR = 1.3, 2, 4s). A Marquardt fit was performed on the choline signal in each spectrum, and the T_1 obtained by non-linear least squares fitting of the peak areas to the saturation recovery equation $A=A_0[1-\exp(-TR/T_1)]$. Water and choline T_2: Sequence *A* spectra were acquired from the lesions of 27 patients for water and 6 patients for choline. The unsuppressed water and choline signal amplitudes were measured for each TE and fitted to the T_2 decay equation $A=A_0\exp(-TE/T_2)$ to obtain the T_2. For choline quantification, the average values of each relaxation parameter were used, except for water T_2, where each patient's own individual value was used. Spectral processing where required included 2.5Hz Gaussian line broadening, zero-filling to 4K points, Fourier transformation, phasing and baseline correction.

Results and Discussion

The *in vivo* relaxation parameters obtained are shown in Table 1. A measurement of lesion choline T_1 has not been reported before. For pre-treatment spectra acquired with *A* and *B*, 11 and 9 patients respectively had a quantifiable choline peak. Of these, 8 and 6 respectively were responders based on a reduction in lesion volume at the end of treatment of at least 65%. The average±SD pre-treatment [choline] obtained were 7.69±1.93 mM and 7.76±2.76 mM respectively, while the median pre-treatment [choline] (and range) were 7.66 (5.13-10.63) mM and 7.69 (2.90-11.91) mM respectively. Figure 1 shows the variation in [choline] normalised to pre-treatment levels with treatment cycle obtained from both sequences. It is clear that there is no apparent difference in behaviour of [choline] between responders and non-responders. An independent sample t-test showed no significant difference in pre-treatment or 1st cycle [choline] between the 2 groups (all p>0.1). The only noticeable difference appears to be at the 2nd cycle time point, where those lesions that still had a measurable choline signal were ultimately classed as non-responsive. This could be because, being non-responsive tumours, they were still relatively large at the 2nd cycle time point, so choline could still be easily detected. More data is needed before anymore conclusions can be drawn on this point, even so, waiting until the end of the 2nd cycle to evaluate treatment efficacy may not be quick enough to make a meaningful difference to patient or resources. All this is in contrast to the findings of Meisamy *et al.*,[2] and shows that the variation of [choline] throughout treatment could be due more to a biological response of the tumour cells to the cytotoxic drugs, when demand for cell growth and division is reduced, rather than any macroscopic indication of lesion shrinkage.

Compound	T_1/ms	T_2/ms
Water	440 ± 69 (10)	75 ± 20 (106)
Choline	1210 ± 2 (1)	181 ± 46 (12)

Table 1: Average ±SD relaxation parameters for lesion water and choline (±SE of fit for choline T_1), with number of measurements in brackets.
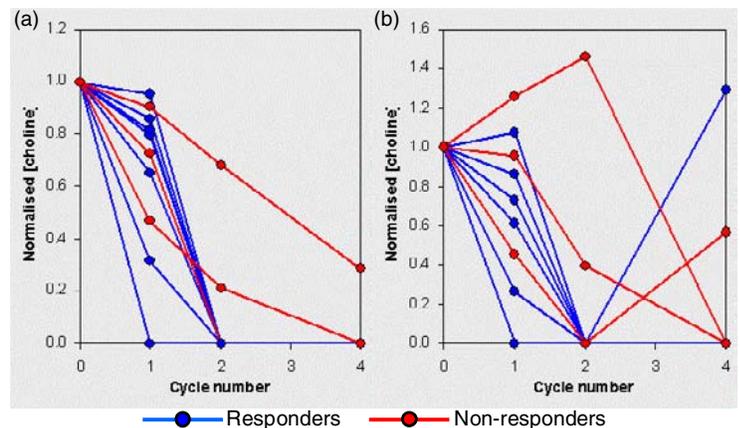

Figure 1: Variation of normalised choline concentrations with treatment cycle. Choline concentrations were obtained from spectra acquired using (a) Sequence *A* and (b) Sequence *B*.

Conclusion

Monitoring [choline] of malignant breast lesions does not appear to be a robust way of predicting their response to chemotherapy.

References

[1]Katz-Brull *et al* (2002) J. Natl. Cancer Inst. **94** 1197-1203. [2]Meisamy *et al* (2004) Radiology **233** 424-431. [3]Bolan *et al* (2003) Magn. Reson. Med. **50** 1134-1143. [4]Klomp *et al* (2005) Proc. ISMRM **13** 1854. [5]Tan *et al* (2005) Proc. ISMRM **13** 1855.