Amide chemical exchange saturation transfer at 7 T: a possible biomarker for detecting early response to neoadjuvant chemotherapy in breast cancer patients

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Abstract

Background: The purpose of this work was to investigate noninvasive early detection of treatment response of breast cancer patients to neoadjuvant chemotherapy (NAC) using chemical exchange saturation transfer (CEST) measurements sensitive to amide proton transfer (APT) at 7 T.

Methods: CEST images were acquired in 10 tumors of nine breast cancer patients treated with NAC. APT signals in the tumor, before and after the first cycle of NAC, were quantified using a three-pool Lorentzian fit of the z-spectra in the region of interest. The changes in APT were subsequently related to pathological response after surgery defined by the Miller-Payne system.

Results: Significant differences (P < 0.05, unpaired Mann-Whitney test) were found in the APT signal before and after the first cycle of NAC in six out of 10 lesions, of which two showed a pathological complete response. Of the remaining four lesions, one showed a pathological complete response. No significant difference in changes of APT signal were found between the different pathological responses to NAC treatment (P > 0.05, Kruskal-Wallis test).

Conclusions: This preliminary study shows the feasibility of using APT CEST magnetic resonance imaging as a noninvasive biomarker to assess the effect of NAC in an early stage of NAC treatment of breast cancer patients.

Trial registration: Registration number, NL49333.041.14/NTR4980. Registered on 16 October 2014.

Keywords: 7 T MRI, APT CEST, NAC treatment, Breast cancer, Response prediction

Background

Neoadjuvant chemotherapy (NAC) is a systemic therapy that downstages cancer, enabling breast-conserving surgery and reducing axillary treatment [1–4]. Unfortunately, patients undergoing NAC may experience severe side effects and, in approximately 20% of patients, treatment does not result in tumor size reduction [5, 6]. To spare patients from ineffective treatment, it would be beneficial to predict the pathological response early in the course of treatment, allowing adjustments for patient-specific therapy.

Currently, the effect of NAC is generally evaluated based on change in the size of the tumor. Since underlying tumor changes in response to treatment usually precede a relatively slow process of change in tumor size [7–9], we set out to investigate metabolic properties of breast cancers that are expected to reveal changes early in the course of treatment.

Image contrast in standard clinical magnetic resonance imaging (MRI) is based on the concentration of water protons, and T2- and T1-weighted imaging reveal anatomical information of different tissues. A recently developed MRI method, chemical exchange saturation transfer (CEST), allows detection of interactions between metabolites and water in the body [10, 11].
Amide proton transfer (APT) CEST MRI detects the transfer of magnetization of labeled amide protons (resonating at 3.5 ppm downfield from the water) \[12\] and is sensitive to cellular mobile protein content as well as tissue pH. NAC treatment may cause an effect on these properties; therefore, we expect to observe changes in APT early in the course of treatment which can be predictive of the pathological response. Dula et al. also assessed the reproducibility of APT imaging in breast cancer patients at 3 T and showed group changes in APT during NAC, suggesting it may predict treatment response \[13\]. Going to higher field strength (7 T) will improve the signal to noise ratio (SNR) and contrast to noise ratio (CNR), improving the sensitivity of APT and increasing field strength, resulting in an increase in CEST signals \[15–18\].

A few studies have shown reproducible methods which maximize the SNR for APT CEST MRI in the breast at 7 T. They measured the APT effect with a standard deviation of 1% in healthy glandular tissue \[14, 19\]. Assuming approximately the same standard deviation in tumor tissue, in this preliminary study we set out to investigate the possibility of using personalized APT MRI at 7 T to evaluate the effect of NAC treatment in a cohort of nine breast cancer patients.

**Methods**

**Subjects**

This MRI study was performed in accordance with the guidelines of the UMC Utrecht ethics committee and was part of a larger study. Nine breast cancer patients with a total of 10 lesions gave informed consent to participate in this study. Patients being treated with NAC were selected, and they were examined with APT CEST MRI before (pre-) and after (post-) the first cycle of NAC. The procedure for selecting the ROI in the tumor (the green circle in Fig. 1b) was different in the two facilities. Third-order image-based shimming was performed for all the slices containing the tumor. The mean APT signal in the whole tumor, this procedure was performed for all the slices containing the tumor. The mean APT signal in the ROI, as a function of the frequency (\(\nu\)-spectra), was fitted with a three-pool Lorentzian model (water, APT, and magnetization transfer
(MT)) using the Levenberg-Marquardt algorithm (see Table 2 for fit parameters [16, 25]):

\[
\frac{M_z(\Delta\omega)}{M_0^0(\Delta\omega)} = Z(\Delta\omega) = Z_{base} - \sum_i L_i(\Delta\omega) \tag{1}
\]

with

\[
L_i(\Delta\omega) = A_i \frac{\Gamma_i^2}{4} \frac{1}{\Gamma_i^2/4 + (\Delta\omega - \delta_i)^2} \tag{2}
\]

Each Lorentzian function \(L_i\) of effect \(i\) is defined for the offset frequency \(\Delta\omega\) by amplitude \(A_i\), full width at half maximum \(\Gamma_i\), and displacement from the frequency of free water protons \(\delta_i\). The parameter \(Z_{base}\) corrects for constant signal reduction. The calculated APT map was obtained using the amplitude of the fit of the APT signal. To facilitate the comparison of different lesions in terms of APT signal change following the first NAC cycle, the mean APT signal pre-NAC was normalized to 1. The whole tumor analysis was compared to a single-slice approach containing the largest diameter of the tumor.

**Pathology**

The pathological responses to NAC are defined according to the Miller-Payne system [26]; complete response is classified as grade 5 and nonresponse as grade 1. Pathological

**Table 1** Patient demographics and tumor characteristics

| Patient | Age (years) | Treatment regimes | ER | PR | HER2 neu | Diameter (mm)* | TNM stage |
|---------|-------------|-------------------|----|----|----------|----------------|-----------|
| 1       | 61          | 4xAC–12xplicitaxel | +  | -  | +        | 24             | T2N1M0    |
| 2       | 50          | 3xFEC–3xdocetaxel  | +  | +  | -        | 30             | T4N1M0    |
| 3R      | 57          | 3xFEC–3xdocetaxel  | +  | +  | -        | 35             | T2N0M0    |
| 3L      | 57          | 3xFEC–3xdocetaxel  | +  | +  | -        | 15             | T1N0M0    |
| 4       | 43          | 3xFEC–3xdocetaxel  | +  | -  | -        | 24             | T2N0M0    |
| 5       | 59          | 3xFEC–3xdocetaxel  | +  | +  | -        | 32             | T2N1M0    |
| 6       | 39          | 3xFEC–3xdocetaxel  | +  | -  | -        | 110            | T3N2M0    |
| 7       | 55          | 6xTaxotere–AC      | -  | -  | -        | 32             | T2N0Mx    |
| 8       | 63          | 6xTaxotere–AC      | +  | +  | -        | 15             | T2N1Mx    |
| 9       | 35          | 6xTaxotere–AC      | -  | -  | -        | 30             | T2N0M0    |

*Measurement performed on 3 T magnetic resonance imaging acquired for standard clinical practice.

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**Fig. 1** MR imaging dataset from patient 1 (see Table 1). a The last image of the DCE series was used to aid in drawing the ROI in the tumor. b S0 image (acquired at 33.6 ppm) was used to draw the tumor ROI (green circle) before applying this on the APT map. c Calculated APT map on top of the DCE image from the dataset before the patient started with neoadjuvant chemotherapy (NAC) treatment. d Calculated APT map after the first cycle of NAC treatment. The blue circles indicate the insert of the tumor region for better viewing of the underlying APT map. Color bar = percentage of APT effect.
nonresponse indicates no change or some alteration to individual malignant cells, but no reduction in overall cellularity compared to pretherapy core biopsy. We grouped grades 1 and 2 together as nonresponders, grades 3 and 4 as partial responders, and grade 5 as complete responders.

### Statistical analysis

Statistical analysis was performed using an unpaired Mann-Whitney test (GraphPad Prism, GraphPad Software, San Diego, CA, USA), with a two-tailed distribution to show statistical difference ($\alpha = 0.05$) between the APT signal pre-NAC and after the first cycle of NAC.

A Kruskal-Wallis test with a post-hoc Dunn’s multiple comparison test was used to assess statistical difference in APT signal between the groups with different pathological responses (nonresponders, partial responders, and complete responders).

### Results

#### Data analysis

Figure 1c and d present calculated color APT maps manually overlaid on the image of the DCE series before (Fig. 1c) and after (Fig. 1d) the first cycle of NAC treatment. Within this tumor, a reduced amide signal of 21% in the APT map was observed after the first cycle of NAC.

An exemplary three-pool Lorentzian fit is depicted in Fig. 2a. The acquired data points from the tumor ROI (green circle in Fig. 1c) are shown as blue dots representing the Z-spectrum magnitude at the 32 frequency offsets, the water fit as a yellow line, the MT fit as a green line, the APT fit as a purple line, and the full fit consisting of the three fits in orange. Figure 2b shows the corresponding Z-spectrum within the tumor before (blue line) and after the first cycle of NAC treatment (red line) based on the 32 frequency offsets from the same case as in Fig. 1. Figure 2c is the insert of the dashed box in Fig. 2b, presenting the Lorentzian fit for the APT signal before (blue) and after (red) NAC treatment. The 21% decrease in APT signal after the first cycle of NAC treatment can be observed.

The mean and standard deviation of the APT signal inside the tumor before and after the first cycle of NAC for all the ten lesions, together with the pathological response, are shown in Table 3. The asterisks in Table 3 indicate a significant difference comparing the APT signal before and after the first cycle of NAC treatment of each patient. Table 3 is further visualized in Fig. 3 where the nonresponders are shown in red, the partial responders in blue, and the complete responders in green. The dashed lines in Fig. 3 indicate the absence of a change in the APT signal before and after the first cycle of NAC treatment.

Normalized changes in APT signal after the first cycle of chemotherapy with pre-NAC APT signal normalized to 1 for all the tumors can be observed in Fig. 4. The one-slice approach (slice with largest tumor diameter; Fig. 4a) was compared with the change in the APT signal in the whole tumor (Fig. 4b). A distinction between the mean of the nonresponders (bright red line), the mean of the partial responders (bright blue line), and the mean of the complete responders (bright green line) is visible. Each blurred line in the backgrounds represents a different patient and the standard deviation in each group is shown as error bars. Note that the distinction between the partial responders and complete responders in the single-slice approach is clearer than in the change of APT signal in the whole tumor.

### Statistical analysis

Based on the 3D whole-tumor analysis, six out of the ten lesions showed a significant change in the APT signal in the tumor, where two out of three complete responders (patients 1 and 4) showed a significant difference ($P < 0.0001$ for both patients; Table 3). The third complete responder, patient 7, showed no significant difference ($P = 0.5259$). Of the partial responders, three lesions (patients 2 and 3R and 3L) also showed a significant difference in APT signal ($P = 0.0458$, $P = 0.0004$, and $P = 0.0003$, respectively), whereas the other partial responders (patients 6 and 8) showed no significant differences ($P = 0.4135$ and $P = 0.4170$, respectively). One nonresponder showed a significant difference (patient 9, $P < 0.0001$) while the other nonresponder showed no statistical difference between the APT signal before and after the first cycle of NAC (patient 5, $P = 0.5749$). However, note that both nonresponders showed an increase in APT signal while the other responders (patient 8 as an exception) showed a decrease in the APT signal, suggesting that the nonresponders can be differentiated quite well from the responders based on the direction of the change in the APT signal.

### Table 2 Starting points and boundaries of all fit parameters of the three-pool Lorentzian fit.

|        | Start | Lower | Upper |
|--------|-------|-------|-------|
| $\delta_{\text{base}}$ | 0.5   | 0.5   | 1     |
| $\delta_{\text{water}}$ | 0.8   | 0     | 1     |
| $\Gamma_{\text{water}}$ | 1     | 0.1   | 2.5   |
| $\delta_{\text{water}}$ | 0     | -1    | 1     |
| $\delta_{\text{APT}}$ | 0.1   | 0     | 1     |
| $\Gamma_{\text{APT}}$ | 5     | 3     | 100   |
| $\delta_{\text{amide}}$ | 0     | -0.5  | 0.5   |
| $\Gamma_{\text{amide}}$ | 1     | 1     | 1.5   |
| $\delta_{\text{amide}}$ | 3.5   | 3.3   | 3.7   |

The chemical shift $\delta$ and FWHM $\Gamma$ are given in ppm. $\Gamma$ FWHM, $\delta$ chemical shift, MT magnetization transfer.


The Kruskal-Wallis test with the post-hoc Dunn's multiple comparison test revealed no significant difference in the change of APT signal after the first cycle of NAC ($P = 0.1057$) between the three different pathological responses.

**Discussion**

In this preliminary study, the potential for using CEST at 7 T to monitor treatment effects in breast cancer was evaluated. We demonstrated that amide CEST signals can be measured in breast cancer before and after the first cycle of NAC. Significant differences in the APT CEST MRI signal were observed ($P < 0.05$) in six out of ten breast tumors. For the direction of the change in APT signal, the nonresponders (patients 5 and 9) showed an increase in APT signal whereas the other patients (except patient 8) showed a decrease in the APT signal. A larger patient population is required for a more comprehensive analysis of change in APT signal in relation to pathological response.

Animal studies [27, 12] demonstrated increased APT effects in tumors compared with healthy tissue, and Salhotra et al. attributed this effect to increased cellular proliferation and subsequent accumulation of defective proteins [27, 28]. In breast tumors, Dula et al. [13] observed changes in the APT signal and attributed this to changes in the concentration of proteins and peptides or in the amide proton exchange rates, influenced by a change in pH, and perhaps $T_1$ [12, 29–33] due to therapy effects. Remarkably, the nonresponders in this...
preliminary study showed an increase in APT signal after the first cycle of NAC, which possibly hints at a continuing increase in the concentrations of proteins and peptides since the tumor was not affected by the NAC treatment. However, the increase in APT signal in the tumor is likely related to a combination of all the above-mentioned effects. Assuming these processes occur at the core of the tumor, the largest expected change in the APT signal would be at that location. This could explain the larger APT increase observed in the single-slice (with largest tumor diameter) analysis compared to the 3D whole-tumor volume analysis. (Fig. 4). As for the single-slice approach, the core contributes relatively more to the APT signal resulting in a larger mean change in APT signal compared with the mean change in APT signal of the whole tumor. It also seems that in the single-slice approach the distinction between the partial responders and the complete responders becomes clearer, hinting at a more linear distribution of change in APT signal for the three response groups. Further research needs to be performed to examine if the single-slice approach results in a better distinction between the different response groups. Although a single-slice approach could save scan time or allow for more frequency offsets in the same scan time, caution is needed as it may be prone to unwanted interinstitutional variations due to differences in slice selection.

Although patient 7 was a complete responder, the tumor APT signal change (Fig. 3) was located in the middle of the partial responders (blue), suggesting the same change in APT signal as the partial responders. Interestingly, this was the only triple negative tumor from the three complete responders. Triple negative tumors feature a unique microenvironment distinct from that of other subtypes [34, 35], possibly explaining the different APT signal in this type of tumor; however, this observation remains to be confirmed.

Due to the small sample size ($n = 10$) we did not correct for age or menstrual cycle effects, which are known

| Patient | Pathological response | Mean (± SD) APT signal before NAC | Mean (± SD) APT signal after the first cycle of NAC | Delta mean APT signal | $P$ value$^a$ |
|---------|-----------------------|----------------------------------|-----------------------------------------------|----------------------|--------------|
| 1       | 5                     | 0.0494 (± 0.0062)                | 0.0388 (± 0.0046)                             | −0.0106              | < 0.0001*    |
| 2       | 3                     | 0.0319 (± 0.0046)                | 0.0311 (± 0.0056)                             | −0.0008              | 0.0458*      |
| 3R      | 4                     | 0.0289 (± 0.0055)                | 0.0231 (± 0.0046)                             | −0.0058              | 0.0004*      |
| 3L      | 4                     | 0.0189 (± 0.0020)                | 0.0149 (± 0.0034)                             | −0.0040              | 0.0003*      |
| 4       | 5                     | 0.0420 (± 0.0098)                | 0.0275 (± 0.0043)                             | −0.0145              | < 0.0001*    |
| 5       | 2                     | 0.0132 (± 0.0037)                | 0.0140 (± 0.0040)                             | +0.0008              | 0.5749       |
| 6       | 4                     | 0.0272 (± 0.0049)                | 0.0229 (± 0.0053)                             | −0.0043              | 0.4135       |
| 7       | 5                     | 0.0254 (± 0.0056)                | 0.0252 (± 0.0043)                             | −0.0002              | 0.5259       |
| 8       | 3                     | 0.0319 (± 0.0068)                | 0.0326 (± 0.0054)                             | +0.0007              | 0.4170       |
| 9       | 2                     | 0.0381 (± 0.0045)                | 0.0465 (± 0.0072)                             | +0.0084              | 0.0001*      |

$^a$Unpaired Mann-Whitney test with two-tailed distribution

$^{*}$Significant difference

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**Fig. 3** Mean APT signal and standard deviation within the ROI (tumor) for all ten lesions. **a** The mean APT signal after the first cycle of NAC is plotted versus the mean APT signal before the start of NAC for the nonresponders (red), partial responders (blue), and complete responders (green). **b** The mean change in APT signal is plotted versus the mean APT signal before NAC. The dashed lines in both **a** and **b** indicate the absence of a change in APT signal before and after the first cycle of NAC treatment.
to affect the breast density. The water content of the breast parenchyma particularly changes during the menstrual cycle [36], possibly influencing the CEST effect [16, 17]. Additionally, all patients in this study received NAC treatment which is known to influence the menstrual cycle.

The overall calculated APT contrast can also be influenced by the degree of fat suppression. We used RF and gradient spoiling to reduce lipid artefacts. However, insufficient fat suppression in the tumor may have resulted in an underestimation of the CEST amplitude [37], possibly affecting the change in APT signal.

CEST MRI is sensitive to the B1 + field, since different exchanging groups are affected by the B1 + . Variation in B1 + may cause more contrast from slower (or faster) exchanging species. We were interested in the APT CEST MRI signal generated by the slow exchanging amide protons, and the optimal B1 + for detecting this exchange is approximately 1 µT [38]. The peak B1 amplitude in this study was set to 2 µT to account for B1 loss due to the hardware setup. The unilateral setup consisted of a quadrature RF coil placed in front of the breast, while the bilateral setup was an exact copy of this coil, only for both breasts. This setup led to a decrease in B1, varying from 60% in the front of the breast to 50% towards the pectoralis major. The sequence was optimized to achieve an acquired B1 of approximately 1 µT throughout the breast. Therefore, the location of the tumor can possibly influence the measured change in the APT CEST signal. In this study, we assumed that the location of the tumor was the same between the two measurements receiving the same amount of B1 and therefore not influencing the measured change in the APT CEST signal. Several B1 + inhomogeneity correction methods have been proposed [25, 39, 40] to improve the CEST images. These methods, however, require an accurate B1 map or acquisition at multiple B1 amplitudes. Due to limited scan time this was unfortunately not possible in this study. Another solution to deal with B1 inhomogeneity would be a new design for the coil setup at 7 T where a homogeneous B1 field can be achieved. For example, the use of dipole antennas has been shown to achieve this in body imaging [41]. These methods for improving the B1 field could be good options for future studies to further improve the quality of the APT maps of the breast.

It would be interesting to translate these findings to the clinical field strength of 3 T. Klomp et al. [14], however, compared APT CEST MRI at 3 T with 7 T and found that the variance of noise in measurements at 3 T was large (i.e., approximately 5% of CEST effects when compared with the water signal, larger than the alterations in CEST effects we have observed in our study), thereby limiting the ability to discern subtle changes during, for example, first-line therapy. At 7 T, however, the increased SNR and increased spectral resolution enabled a fourfold reduction in the noise of the observed APT CEST compared with 3 T. Due to the inherently small CEST signal, at the moment changes within these CEST effects seem challenging to detect at 3 T. Fortunately, 7 T has been Food and Drug Administration (FDA) approved and thereby will likely become available to more hospitals.

Predictive biomarkers are critical for the evaluation of neoadjuvant therapies, as well as the effect of novel targeted agents intended to be incorporated into neoadjuvant therapy [42]. The potential for high-field-strength CEST MRI of the breast as a biomarker for the evaluation of NAC response is promising, as is the capability to noninvasively detect changes in protein and peptide levels. These may play a key role in understanding breast tumor progression and response to treatment [19].

Conclusions
In a small group of breast cancer patients, this preliminary study shows the feasibility of using APT CEST MRI at 7 T as a noninvasive biomarker to predict the effect of neoadjuvant chemotherapy in an early stage of treatment. This can be useful in personalized breast cancer treatment planning.
Abbreviations

AFT: Amide proton transfer; CEST: Chemical exchange saturation transfer; CNR: Contrast to noise ratio; DCE: Dynamic contrast-enhanced; MRI: Magnetic resonance imaging; MT: Magnetization transfer; NAC: Neoadjuvant chemotherapy; NOE: Nuclear Overhauser effect; RF: Radiofrequency; ROI: Region of interest; SNR: Signal to noise ratio; T: Tesla

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and legal reasons, but are available from the corresponding author on reasonable request.

Authors’ contributions

The design of the study was made by JPW, DWJK, HWMvL, and PRL. EK, JPW, and the NWO (VENI grant: J.P.Wijnen 016.148.002) for financial support. The Medical Research Ethics Committee (METC) of the University Medical Center Utrecht confirms that it has reviewed the amendment to the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch an European regulations. Based on the requirements of the WMO, the METC of the University Medical Center Utrecht hereby issues an approval of the amendment to the above mentioned study.

Consent for publication

Consent for publication was obtained from all participants in the study.

Competing interests

The authors declare that they have no competing interests.

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