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MRI Measurements of Tumor Size and Pharmacokinetic Parameters as Early Predictor of Response in Breast Cancer Patients Undergoing Neoadjuvant AC-Chemotherapy

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Running Title: MRI as Response Predictor in Breast Cancer

ABSTRACT

Purpose: To investigate the value of using changes in 3 parameters (tumor size, transfer constant (K^{trans}), and rate constant (k_{ep})) obtained after the first treatment-cycle in predicting the final clinical response after 2 to 4 cycles of neoadjuvant AC-chemotherapy.

Materials and Methods: Early changes in the 3 parameters were measured in 29 patients with invasive breast cancer by MRI after 1 cycle of treatment. Changes were then assessed for their predictive value of final clinical response and compared among patients with 4 different response patterns, Group-1: responder(R) after 1 cycle and also R after 4 cycles, Group-2: non-responder(NR) after 1 cycle, but eventual R after 4 cycles, Group-3: NR after 1 cycle and still NR after 4 cycles, and Group-4: NR after 1 cycle and determined as NR after 2 cycles, being switched to the taxane regimen.

Results: Pearson's correlation analysis revealed significant correlation between early changes in tumor size and both pharmacokinetic parameters ($r = 0.49$ and $P < 0.01$ for K^{trans}, $r = 0.66$ and $P < 0.001$ for k_{ep}). The areas under the ROC curve differentiating between R (Groups 1+2) and NR (Groups 3+4) groups using changes in tumor size, K^{trans}, and k_{ep} were 0.88 (SE = 0.06, $P < 0.0001$), 0.63 (SE = 0.11, $P = 0.11$), and 0.77 (SE = 0.09, $P = 0.001$), respectively.

Conclusion: Early tumor size change in MRI after 1 cycle is better response predictor than that of either K^{trans} or k_{ep} in breast cancer undergoing neoadjuvant chemotherapy using AC regimen.

Key Words: DCE- MRI; breast cancer; neoadjuvant chemotherapy; treatment response predictor; pharmacokinetic parameters

INTRODUCTION

Neoadjuvant or preoperative chemotherapy is increasingly becoming an important part of breast cancer treatment and management. Especially in patients with locally advanced cancers, neoadjuvant chemotherapy has become the standard to allow down-staging of cancers to render them operable and/or to facilitate breast conservation surgeries (1–5). Neoadjuvant chemotherapy has also been shown to improve both relapse-free and overall survival in patients with inoperable locally advanced breast cancer (1, 2, 6–9). Patient undergoing neoadjuvant chemotherapy regimen also presents a unique opportunity to observe the change in tumor during treatment to assess treatment efficacy. It also provides an opportunity to intervene during treatment based on response, so that the patient could be spared of the associated morbidity by early termination of an ineffective regimen and benefit from effective regimens sooner.

The most commonly used means for evaluating the chemotherapeutic response in breast cancer is still clinical examination based on a palpable change in tumor size, which is highly subjective and can be inaccurate. Conventional imaging techniques such as mammography and ultrasound can be used to evaluate response; however, partly due to therapy induced fibrosis they may not be very accurate (6, 7, 10-14). Due to its superior spatial resolution, 3-dimensional coverage, and high sensitivity, contrast enhanced MRI is emerging as the best imaging technique for investigating response of breast cancer to neoadjuvant chemotherapy (15–18). Gilles et al (19) first demonstrated the ability of contrast-enhanced MRI in depicting residual breast tumor after neoadjuvant chemotherapy and showed a good agreement (83%) between MRI and pathologic assessment. A similar finding in MRI evaluation of residual tumor size was reported

subsequently by other research groups (20–26). Extensive comparison of contrast-enhanced MRI in evaluation of tumor response to other conventional techniques including physical examination, mammography and ultrasound was reported by Weatherall et al (27) and Balu-Maestro et al (22). Both studies reported more reliable evaluation of residual tumor size by MRI in comparison to histopathological findings than by other techniques.

Analysis of the signal enhancement time-course obtained from DCE-MRI in neoadjuvant chemotherapy response study has been investigated. Qualitative analytic approach without using modeling analysis was reported by Rieber et al (25) and Martincich et al (26). Rieber et al reported a decreased intensity of contrast medium uptake in 88.2% of breast cancer patients with partial response and all patients with complete response. Martinicich et al reported that combining tumor volume and early enhancement ratio after two cycles of primary chemotherapy yielded a 93% diagnostic accuracy in identifying breast tumors achieving a pathological complete response. Hayes et al (28) investigated correlations between qualitative and quantitative analytic methods using Tofts model (29, 30), and reported a reduction in K^{trans} after 1 cycle of treatment more frequently in the eventual responders than in non-responders, which was strongly correlated to changes in the rate of enhancement. Recently several groups investigated the potential of using quantitative early size change and reduction in pharmacokinetic parameters, such as K^{trans} and k_{ep}, as a final response predictor in patients undergoing neoadjuvant chemotherapy (31-34). Different analysis techniques were applied, and different treatment protocols were used, but the general conclusion was that early

changes of tumor size was the best predictor, but the changes of pharmacokinetic parameters could also differentiate between responders and non-responders.

These published studies used various treatment regimens, with regular schedule, one cycle every 3 weeks. In this work we studied whether early changes in tumor size and pharmacokinetic parameters (K^{trans} and k_{ep}) can predict outcome in patients receiving a dose-dense anthracycline-based neoadjuvant chemotherapy. Doxorubicin and Cyclophosphamide was given every 2 weeks instead of 3 weeks. Two MRI studies were performed for each patient, one pre-treatment (or baseline) MRI, and an early follow-up (F/U) MRI after 1 cycle of AC. For those patients who received 4 cycles of AC, another F/U MRI was performed at that time. According to their response patterns, patients were separated into 4 response groups, and also combined as overall responders and non-responders. Based on comparisons between different response groups, we set out to answer 2 questions: 1) whether the early changes observed in tumor size and/or in pharmacokinetic parameters were different between these groups with different response pattern? 2) Can the measured changes in tumor size and/or pharmacokinetic parameters after 1 AC predict the final outcome after completing 4 cycles of AC?

MATERIALS AND METHODS

Patients

The study was a retrospective analysis of a prospective enrollment study. All eligible subjects enrolled into this study had core-biopsy proven primary breast cancer, either inoperable (inflammatory cancer or with skin involvement) or with clinically documented lymph node involvement- i.e. either with biopsy proven positive nodes or

enlarged suspicious node greater than 1 cm visible on mammogram or ultrasound exam. From a total of 67 patients recruited from May 2002 to Oct 2005, we identified a subset population of 29 patients who had one pre-treatment MRI, and another MRI after 1 cycle before 2 cycles AC. The study was approved by the Institutional Review Board and was HIPAA compliant. All participants gave written informed consent. The age of patients at the start of study ranged from 29 to 75 years old (48 ± 11 [SD], median 47 yrs.). The one-dimensional tumor size before treatment ranged from 1.8 to 9.9 cm (median 3.5 cm).

The typical chemo-regimen at our institution consisted of 2–4 cycles of dose-dense AC (Doxorubicin and Cyclophosphamide) followed by Taxane regimen (TCa ± H, Paclitaxel and Carboplatin with Herceptin for Her-2/neu positive patients). After the patient received 2 cycles AC, based on clinical examination and ultrasound findings the oncologist would determine her response and decide whether she should go on to receive additional 2 cycles of AC (if responding well), or be switched to the second regimen (if not). Twenty patients received 4 cycles of AC before switched to Taxane regimen or surgery. The remaining 9 patients only received 2 cycles of AC, and were switched to Taxane regimen earlier due to a poor response. All patients had at least 2 MRI examinations, a baseline MRI prior to initiation of neoadjuvant chemotherapy and a follow-up MRI after 1 cycle of AC regimen (F/U-1). For those 20 patients who received 4 cycles AC, the second F/U MRI (F/U-2) was performed after 4 cycles of AC to determine their final response to AC treatment.

MRI Study Protocol

All MRI study was performed on a 1.5T Philips Eclipse MR scanner using a dedicated bilateral breast coil with the patient in the prone position with an IV access in place. The dynamic contrast enhanced sequence (DCE-MRI) was based on a 3D gradient echo pulse sequence (RF-FAST) with TR/TE = 10/3.6 ms, flip-angle = 20^{o}, 32 bilateral-axial partitions covering both breasts with 4-mm thickness each, FOV = 32–38 cm, and acquisition-matrix = 256x128. Sixteen dynamic frames (repetitions) were prescribed for the DCE-MRI, each of which was acquired in 42 sec. The contrast agent (Omniscan®, 1cc/10 lbs) was injected manually at start of the 5^{th}-frame acquisition, and then followed by 10-cc saline flush. The total amount of time for injecting contrast agent was maintained between 15 and 20 seconds for every patient in order to make the bolus length as consistent as possible. Saline flush was given as a fast bolus. All MR images were transferred from MR-console to a PC for post-processing.

Tumor Size and Therapy Response Evaluation

Two-dimensional tumor size was measured for evaluating therapy response. Measurement of the longest diameter and the longest perpendicular diameter of tumor was carried out based on MIP (Maximum Intensity Projection) of subtraction images (Figure 1). The pre-contrast images acquired at the 3^{rd}-frame in the DCE-MRI sequence was subtracted from post-contrast images acquired at the 6^{th}-frame (about 1 minute post-injection) to obtain subtraction images for each of 32 slices, and the MIP from these subtraction images was generated. One single operator carried out the size measurement for all patients during the same sitting in order to minimize any intra-patient variation in tumor definition. The area (product of the longest diameter and the longest perpendicular

diameter) was then calculated, and the percentage change with respect to that in the baseline MRI was calculated. For those patients with multiple differentiable lesions, the largest lesion was used as the index lesion. The processing of subtraction, MIP, and size measurements were carried out using 'ImageJ' software (NIH, http://rsb.info.nih.gov/ij/ , 1.30v).

The commonly agreed response criterion for solid tumor is 1-D size reduction of 30% or more in RECIST (Response Evaluation Criteria in Solid Tumors) criteria after 4 cycles of AC treatment (i.e. 50% or more in 2-D size reduction, assuming spherical tumor model) (35, 36). Since there is currently no agreed response assessment criterion after 1 cycle of chemotherapy treatment, we used the threshold of 15% 1-D size reduction (i.e. 28% 2-D size reduction) to separate responders from non-responders in the F/U-1 MRI study. According to these criteria after 1 AC and 4 AC, 29 patients included in this study were separated into 4 response groups: Group 1: R–R (responder after 1 AC, and also responder after 4 AC); Group 2: NR–R (non-responder after 1 AC, but responder after 4 AC); Group 3: NR–NR (non-responder after 1 AC, still non-responder after 4 AC); Group 4: NR–T (non-responder after 1 AC, and was switched to Taxane regimen after 2 AC). MIPs of 4 case examples were shown in Figure 1, one from each of the 4 response groups. Patients were also grouped into overall responders and non-responders based on their final clinical response after completing all AC treatment (2 or 4 cycles). This effectively combined Groups 1 and 2 above into responder group, and Groups 3 and 4 into the non-responder group.

Pharmacokinetic Analysis of Enhancement Kinetics

The enhancement kinetics was analyzed based on whole-tumor ROI (Region of Interest) averaging approach. The ROI in MRI was first segmented by manually outlining the enhanced lesion on each imaging slice using 1-min. post-injection subtraction image, and the mean signal-intensity time course was calculated by averaging over all tumor pixels. For each patient the same operator performed the manual outlining of tumor ROI in post-treatment F/U MRI at the same time in order to minimize any intra-patient variation in defining lesion boundary. The percent-enhancement time course was calculated by first subtracting the mean of pre-contrast signal intensity (mean of first 4 frames) from each of the subsequent 12 post-contrast signal intensities, and then normalized by the mean pre-contrast signal intensity. The enhancement kinetics was then analyzed based on the 2-compartmental pharmacokinetic model described by Tofts et al (29, 30) to obtain transfer constant and rate constant, K^{trans} and k_{ep}, (representing the uptake rate and wash-out rate, respectively). In our analysis the percent-enhancements were directly fitted without using assumptions to convert them to [Gd] concentration in the tissue; also the true blood [Gd] concentration was not assumed and only decay rate constants were used (34, 37). Therefore, the obtained K^{trans} still carried the % enhancement, in unit of (%/min), and k_{ep} is a rate constant in unit of (1/min), exactly the same as the k_{ep} in Tofts model (29, 30). In order to improve the fitting quality, one additional independent parameter, t_0, was allowed to adjust, where t_0 is the time interval over which the concentration of contrast medium is assumed to follow a linear increase phase in the plasma after injection (37). The fitting process was carried out with software developed in-house using Matlab environment (version 6.0.0.88, The MathWorks, Inc.).

Change in pharmacokinetic parameters observed in the F/U-1 MRI was measured as percentage change with respect to that of baseline MRI.

Statistical Analysis

The changes in tumor size and pharmacokinetic parameters after 1 cycle AC in each group were tested for statistical significance using a paired, two-tailed t-test. The mean baseline (pre-treatment) values of 3 parameters (tumor size, K^{trans}, and k_{ep}) were compared among the 4 response groups using analysis of variance. Analysis of variance was also used to compare their percent changes after 1 cycle AC among the 4 response groups. Analysis using two-tailed t-test with unequal variance was performed to compare the percent changes between the overall responder and non-responder groups. The association between the early changes in pharmacokinetic parameters and tumor size observed in the F/U-1 study after 1 cycle AC was investigated using Pearson's regression analysis. The significance level in all statistical tests was set at $P < 0.05$. Receiver operating characteristic (ROC) analysis based on changes of 3 parameters after 1 AC to separate responders from non-responders was performed.

RESULTS

Four Therapy Response Groups and Their Baseline Parameters

Based on response criteria using the 2-D tumor size change after 1 and 4 cycles of AC as 28% and 50%, patients were separated into 4 response groups. There were 9 patients in Group-1 (R–R), 8 patients in Group-2 (NR–R), 3 patients in Group-3 (NR–

NR), and 9 patients in Group-4 (NR–T). Consequently, there were 17 responders (combining Groups 1+2) and 12 non-responders (combining Groups 3+4). None of the baseline tumor size or pharmacokinetic parameters (Table 1) was statistically different among the 4 response groups or between the responders and non-responders.

Early Changes After 1 cycle AC

The observed changes in the 2-D tumor size, K^{trans}, and k_{ep} after 1 cycle AC were compared among the 4 response groups (Table 2). Only Group-1 (N = 9) showed significant reduction in tumor size and rate constant, k_{ep}. None of the parameters in the other 3 groups showed significant changes. Within the overall responder and non-responder groups, both tumor size and k_{ep} showed significant reduction in responders, and none of the changes were significant in the non-responders. The early changes in 2-D tumor size, K^{trans}, and k_{ep} of all individual patients in each of 4 groups were plotted and compared in Figure 2. A large variation was observed in all groups. Since the group separation was based on 28% tumor area reduction, Group-1 was clearly separated from Groups 2–4 in size change (Fig. 2a). No other pairs among the 3 remaining groups showed differences in the change of tumor size. The changes observed in both K^{trans} and k_{ep} were significantly different between Group-1 and Group-4 (Table 2, $P < 0.001$ for K^{trans} and $P < 0.01$ for k_{ep}). The most interesting comparison was between Group-2 patients (NR–R, N = 8) and Group-3 patients (NR–NR, N = 3), since they were non-responders after 1 AC, but turned out to be final responders (Group-2) and non-responders (Group-3) after 4 AC. However, none of the parameters showed significant

difference between them, i.e. no parameter after 1 AC could be used to predict their final response after 4 AC.

Analysis of Enhancement Kinetic Time Course

The percent signal enhancement time courses from 3 patients, one in each of the Groups 1–3 are shown (Figure 3). These are the same three patients whose MIPs were previously shown (Figure 1). Tumor with a higher vascular volume and vascular permeability will present a faster wash-in and a faster wash-out, leading to a higher K^{trans} and a higher k_{ep} value. In Fig. 3a, from the R-R patient in Fig. 1a, the fitted parameters were K^{trans} = 126 (%/min) and k_{ep} = 0.43 (1/min) in the pre-treatment study and K^{trans} = 103 (%/min) and k_{ep} = 0.32 (1/min) after 1 AC; both parameters decreased (18 % and 26 %, respectively). In Fig. 3b, from the NR-R patient in Fig. 1b, the fitted parameters were K^{trans} = 145 (%/min) and k_{ep} = 0.28 (1/min) in the pre-treatment study. Despite of the unchanged (or even slightly increased) tumor size for this patient, the enhancement kinetics measured after 1 AC showed a slower wash-in, and a change from a plateau pattern to more persistent enhancing pattern during the delayed phase. The fitted parameters after 1 AC were K^{trans} = 118 (%/min), and k_{ep} = 0.24 (1/min), both decreased (reduction of 18 % and 15 %, respectively) as the patient shown in Group-1. In Fig. 3c, from the NR-NR patient in Fig. 1c, compared to pre-treatment kinetics the enhancement kinetics after 1 AC showed a faster wash-in and a more aggressive wash-out pattern. The fitted parameters were K^{trans} = 164 (%/min), and k_{ep} = 0.25 (1/min) in the pre-treatment study and changed to K^{trans} = 169 (%/min), and k_{ep} = 0.31 (1/min) in the F/U-1 study (3% increase in K^{trans}, and 22% increase in k_{ep}, respectively).

Association between Early Changes in Tumor Size and Pharmacokinetic Parameters

Association between the measured changes in size and pharmacokinetic parameters after 1 cycle AC was investigated by pooling all patients together and using regression analysis (Figure 4). The changes in both K^{trans} and k_{ep} were significantly correlated with tumor size changes: $r = 0.49$, $P < 0.01$ for K^{trans} (Fig. 4a) and $r = 0.66$, $P < 0.001$ for k_{ep} (Fig. 4b). The results might suggest that changes in tumor size and pharmacokinetic parameters were both associated with therapy treatment. Between the two pharmacokinetic parameters, rate constant (k_{ep}) appeared to be more sensitive to treatment effects than transfer constant (K^{trans}). The changes in k_{ep} were more strongly associated with the changes in tumor size with a higher linear correlation coefficient. The changes in k_{ep} were also significantly different between the Responder and the Non-responder groups, whereas the changes in K^{trans} were not (Table 2).

Predictive Value of Early Changes in Tumor Size and Pharmacokinetic Parameters

ROC analysis was performed based on the early changes observed in tumor size, K^{trans}, and k_{ep} to differentiate between overall responders and non-responder groups, i.e. to predict the final outcome. ROC curves generated by all 3 parameters are plotted (Figure 5). The areas under the ROC curve were 0.88 (SE = 0.06, $P < 0.0001$) for tumor size, 0.63 (SE = 0.11, $P = 0.11$) for K^{trans}, and 0.77 (SE = 0.09, $P = 0.001$) for k_{ep}.

DISCUSSION

For patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy, early response prediction may facilitate a more effective treatment management. We investigated if early changes in the 3 MRI parameters (tumor size, K^{trans} and k_{ep}) measured after 1 cycle of AC treatment could be used to predict the final outcome after completing 2 or 4 cycles of AC. Our results showed that the early change in tumor size based on bi-dimensional product (WHO) (35) was highly predictive of the final response. The area under the ROC curve in differentiating between responders and non-responders was 0.88. It also had a stronger predictive value compared to that of K^{trans} and k_{ep} (with area of 0.63 and 0.77, respectively). Early change of tumor size in MRI has been shown to be a good response predictor in a number of previous publications (23, 24, 26, 33, 34). Cheung et al (23) reported relative early size reduction after 1 cycle of treatment based on RECIST criterion (36) predicted final response after 3 cycles of epirubicin and taxol regimen in 33 patients. Partridge et al (24) also reported that an early change in MRI tumor volume after 1 cycle of AC was significantly correlated with final change after 4 cycles of AC in 62 patients. Martincich et al (26) reported a similar finding in 33 patients undergoing anthracycline and taxane based primary chemotherapy, which showed that the tumor volume reduction after 2 cycles of treatment was associated ($P < 0.01$) with a major histopathological response after 4 cycles of treatment. Pickles et al and Manton et al (32, 33) reported a similar finding showing a positive correlation between early change and final change in tumor volume after 2 and 6 treatment cycles. In a recent study by Padhani et al (34), change in the product of the bi-dimensional diameter of tumor size after 1 cycle of treatment ($N = 25$) and after 2 cycles of treatment ($N = 15$) was

used in predicting clinicopathologic response after completing all chemotherapy. It was reported that based on size change the area under ROC curve was 0.90 (after 1 cycle) and 0.93 (after 2 cycles), thus concluded that decrease in tumor size is an early predictor of final response.

The choice of two-dimensional tumor size over the 3-D volume analysis approach was based on easy clinical use and reproducibility. We hoped to employ a clinically relevant approach in size evaluation that is easy to implement. The 2-D tumor size evaluated on MIPs (as shown in Figure 1) is well-accepted by clinicians. The MIP was projection image along the superior-inferior direction, and the product of the longest and the perpendicular dimension yields 2-D area (in unit of cm^2). Although volumetric evaluation can be potentially more accurate in estimating the true tumor size, it is based on manual ROI drawing slice by slice, thus can be highly operator-dependent and less reproducible.

The predictive value of early changes in pharmacokinetic parameters, K^{trans} and k_{ep}, was also investigated in our study. For change in K^{trans}, no statistically significant difference could be established between the final responders and non-responders (area under the ROC curve of 0.63). Change in k_{ep} presented a better predictive value than K^{trans} (with the area under ROC curve of 0.77), but still not as strong as the tumor size. Previously published studies using pharmacokinetic parameters as early response predictor reported varying results. Hayes et al (28) reported a reduction in K^{trans} after 1 cycle of treatment more frequently in the eventual responders than in non-responders, but not early change in v_e ($v_e = K^{trans}/k_{ep}$) (30). The reduction in K^{trans} was consistent with decelerated rate of enhancement in response to chemotherapy, as previously observed by

Knopp et al (38). Reduction in k_{ep} as an early treatment-related change was reported by Wasser et al (31). k_{ep} was reduced after the first cycle of epirubicin and paclitaxel based chemotherapy in patients showing post-treatment tumor regression after the third cycle. In a more recent study by El Khoury et al (39), a significant decrease of tumor pixels with washout (related to k_{ep}) after two courses of chemotherapy was reported. They applied a heuristic modeling analysis on a pixel-by-pixel basis during chemotherapy consisting of 5-fluorouracil, cyclophosphamide, and epirubicin in 19 patients. Pickles et al and Manton et al (32, 33) reported that none of the early changes in pharmacokinetic parameters (K^{trans}, v_e, and k_{ep}) derived from ROI-averaged analysis after 2 treatment cycles was correlated with the final tumor volume response after typical 6 treatment cycles; however, the results analyzed from the hot spot did (32). Padhani et al (34) also reported that none of the early changes in median values of K^{trans}, v_e or k_{ep} from pixel-by-pixel analysis after 1 cycle of treatment predicted tumor response. However, changes in K^{trans} after 2 cycles of treatment were equally accurate for predicting the absence of pathologic response as the change in tumor size.

It is believed that a reduction in pharmacokinetic parameters in response to chemotherapy, such as amplitude, K^{trans} and k_{ep}, observed here and elsewhere, is associated with antivascular/antiangiogenesis effect of therapeutic agents to some extent, and as such, they may provide a different perspective other than cell death measured by tumor shrinkage. However, since all reported chemotherapy regimen mainly contain cytotoxic agents, such as anthracyclines (e.g., doxorubicin, epirubicin), taxanes (e.g., paclitaxel, docetaxel), and cyclophosphamide, the early change in tumor size still plays a major role in predicting response (23, 24, 26, 32-34). Targeted, non-cytotoxic agents,

particularly anti-angiogenic drugs, however, are not anticipated to produce immediate tumor shrinkage, and pharmacokinetic parameters based on DCE-MRI may more likely play a significant role.

The reported results from different investigators could not be directly compared. There was a great effort trying to bring all different models to converge to a unified one (29, 30). In order to apply Tofts' model to obtain K^{trans} in (1/min), the tissue [Gd] concentration and the blood [Gd] concentration had to be calculated based on a great deal of assumptions. Padhani et al. had clearly described all necessary steps (34). While these assumptions might be reasonable, its accuracy could be debated. In our approach we did not force to use assumptions to convert the measured enhancement percentage to Gd concentration, nor to use a fixed blood Gd concentration. Therefore, the % enhancement was not normalized out. On the other hand, since the same analysis approach was applied in pre- vs. post-treatment studies, the % change calculated in K^{trans} could be compared to that of Padhani et al. We reported the % change in K^{trans} after 1 cycle AC as (- 42 to 30 % mean – 4.5 %) in responder, and (- 22 to 44 %, mean 8.1%) in non-responders, while that (change in median) in Padhani et al. as (- 75 to 357 %, mean -22%) in responders and (- 44 to 71%, mean - 6.5%) in non-responders. Our individual changes had smaller deviation, possibly due to the whole-tumor ROI averaging analysis approach, well within the reported ranges of Padhani et al. The pixel-by-pixel based analysis, such as reported by El Khoury et al (39) and Padhani et al (34), could take tumor heterogeneity into account. Pickles et al also demonstrated that the analysis based on the hot spot analysis might yield different results compared to that using the whole tumor-averaged ROI (32).

Furthermore, caution has to be taken in interpreting findings reported by different groups, as different treatment regimens would have different mechanisms of action. The dose, the interval of each cycle, and how many days after the treatment was the follow-up MRI study performed, may further contribute to varying findings. Rieber et al (25) used a minimal time interval of 6 weeks after initiation of chemotherapy. The minimum time to show response is influenced by treatment regimens and individual patients, and may vary from days to weeks. In our series we found some patients showed substantial tumor shrinkage 1 week after the first cycle was given (Group-1), and some did not (Group-2), however, they were eventual responders after 4 cycles of treatment. The analysis of DCE-MRI may further contribute to varying findings.

In this study the first F/U MRI for all patients were performed at a mean of 13 days after the first cycle of AC (± 4.6 [SD], median 13 days). Some patients might be followed too early before changes could occur. The F/U time was comparable between overall responder group (13 ± 5.3 [SD], median 13) and non-responder group (14 ± 3.6 [SD], median 14). The most interesting aspect in this study is to differentiate between Group-2 (NR–R) and Group-3 (NR–NR). They were non-responders in the F/U-1 study, but 8 turned out to be responders and 3 remained as non-responders. We compared the follow-up time between Group-2 (11 ± 3.7 [SD], median 10) and Group-3 (16 ± 3.2 [SD], median 15). They were not statistically different, and therefore the argument of too early F/U could not explain their different responses. None of the changes in tumor size, K^{trans} or k_{ep} showed significant differences between them either. Therefore, if a patient was a non-responder after 1 cycle AC treatment, we could not reliably predict whether she would be a final responder or non-responder. All patients went on to receive the second

cycles of AC treatment, and before the third treatment was due, the patient would receive a clinical and an ultrasound examination. If she were determined as a non-responder, instead of receiving the third cycle of AC, the patient would receive the first cycle of taxane regimen. This protocol resulted that the majority of our patients classified into the non-responder group (9/12) did not actually complete 4 cycles of AC. Consequently, there were only 3 patients who completed 4 cycles of AC were confirmed non-responders. Partly due to the small subject number in this group, it was difficult to find changes significantly different between Group-2 and Group-3.

In summary, to address the 2 questions: 1) whether the early changes observed in tumor size and/or in pharmacokinetic parameters were different between these groups with different response pattern? We found that changes in tumor size and k_{ep} were significantly different between the overall responders (Groups 1+2) and non-responders (Groups 3+4), but not K^{trans}. Changes in K^{trans} and k_{ep} were significantly different between Group-1 (R – R) and Group-4 (NR – T). Thus, our results were generally in agreement with published results in the literature. 2) Can the measured changes in tumor size and/or pharmacokinetic parameters after 1 AC predict the final outcome after completing 4 cycles of AC? Separation between Group 2 (NR – R) and Group-3 (NR – NR) can have a great clinical impact to decide whether the patient should continue this treatment or not. However, none of these three parameters (tumor size, K^{trans}, or k_{ep}) could differentiate between them, thus not have a predictive value, within the limited number of subjects investigated in this study.

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Table 1 – Pre-treatment mean values of tumor size and pharmacokinetic parameters for different response groups

Parameter	Final Response		Early and Final Response			
	Responder	Non-responder	Group-1 (R – R)	Group-2 (NR – R)	Group-3 (NR – NR)	Group-4 (NR – T)
N	17	12	9	8	3	9
Size (cm^2)	19.9 ± 4.4	24.2 ± 7.8	23.4 ± 7.4	15.9 ± 4.5	40.9 ± 28.7	18.7 ± 5.4
K^{trans} (%/min)	136.2 ± 8.5	137.5 ± 8.6	134.5 ± 13.6	138.2 ± 10.7	144.8 ± 10.5	135.0 ± 11.2
k_{ep} (1/min)	0.361 ± 0.019	0.331 ± 0.019	0.376 ± 0.024	0.344 ± 0.029	0.310 ± 0.028	0.338 ± 0.025

None of the mean values (± SE) were significantly different based on analysis of variance with the significance level of 0.05: Responder (Group-1 & 2) vs. Non-responder (Group-3 & 4) and Group-1 vs. Group-2 vs. Group-3 vs. Group-4.

Table 2 – Changes (%) in tumor size and pharmacokinetic parameters after 1 cycle of AC with respect to pre-treatment

Parameter	Final Response		Early and Final Response			
	Responder	Non-responder	Group-1 (R – R)	Group-2 (NR – R)	Group-3 (NR – NR)	Group-4 (NR – T)
N	17	12	9	8	3	9
ΔSize (%)	-37.0 ± 6.7 (*P* < 0.005)	-1.3 ± 5.1 (*P* > 0.2)	-57.1 ± 6.8 (*P* < 0.005)	-14.5 ± 4.6 (*P* > 0.05)	-1.8 ± 7.2 (*P* > 0.4)	-1.2 ± 6.6 (*P* > 0.5)
ΔK^{trans} (%)	-4.5 ± 5.2 (*P* > 0.5)	8.1 ± 6.2 (*P* > 0.3)	-14.2 ± 7.0 (*P* < 0.1)	6.4 ± 6.0 (*P* > 0.1)	-3.2 ± 3.3 (*P* > 0.1)	11.9 ± 7.9 (*P* > 0.1)
Δk_{ep} (%)	-14.4 ± 5.2 (*P* < 0.05)	6.5 ± 3.9 (*P* > 0.1)	-21.2 ± 7.5 (*P* < 0.05)	-6.8 ± 6.4 (*P* > 0.1)	9.1 ± 7.3 (*P* > 0.1)	5.7 ± 4.7 (*P* > 0.1)

P-value for change (± SE) in each group and for contrast between Responder (Group-1 & 2) and Non-responder (Group-3 & 4) is calculated from 2-tailed t-test.

FIGURE LEGENDS

Figure 1. The MIPs from 4 case examples, one from each of 4 response group: (**a**) Group-1: R–R (responder after 1 AC, and also responder after 4 AC); (**b**) Group-2: NR–R (non-responder after 1 AC, but responder after 4 AC); (**c**) Group-3: NR–NR (non-responder after 1 AC, still non-responder after 4 AC); and (**d**) Group-4: NR–T (non-responder after 1 AC, and was switched to Taxane regimen after 2 AC). The MIPs of pre-treatment (baseline), after 1 cycle of AC and after 4 cycles of AC (or taxane) are shown in each case. The patient in Group-4 did not complete 4 cycles of AC and the MIP after 2 cycles of Taxane treatment was shown instead in (**d**).

Figure 2. Percentage changes in tumor size and pharmacokinetic parameters for individual patients after 1 cycle of AC represented compared to their own pre-treatment values. Each symbol represents a single patient within each group. (**a**) Changes in 2-D tumor size; (**b**) Changes in K^{trans}; (**c**) Changes in k_{ep}. Group-1, -2, -3 and -4 represent the 4 response groups: R–R, NR–R, NR–NR and NR–T, respectively.

Figure 3. The percent signal enhancement time course measured from 3 sample cases with fitted line using the 2-compartmental model. (**a**) Group-1 (R–R) case with the fitted K^{trans} and k_{ep} as 126 (%/min) and 0.43 (1/min) for pre-treatment, and 103 (%/min) and 0.32 (1/min) for 1 AC-post. (**b**) Group-2 (NR–R) case with the fitted K^{trans} and k_{ep} as 145 (%/min) and 0.28 (1/min) for pre-treatment, and 118 (%/min) and 0.24 (1/min) for 1 AC-

post. (**c**) Group-3 (NR–NR) case with the fitted K^{trans} and k_{ep} as 164 (%/min) and 0.25 (1/min) for pre-treatment and 169 (%/min) and 0.31 (1/min) for 1 AC-post.

Figure 4. The scatter plot of the percent changes in tumor size and pharmacokinetic parameters after 1 cycle of AC. Patients in Groups 1-4 are indicated by different symbols: Group-1 (○), Group-2 (●), Group-3 (Δ) and Group-4 (▲). The changes in tumor area are significantly correlated with (**a**) K^{trans} (r = 0.49, P < 0.01); and (**b**) k_{ep} (r = 0.66, P < 0.001).

Figure 5. ROC analysis based on the early changes (after 1 cycle of AC) in tumor size, K^{trans} and k_{ep} in differentiating between overall responders (Groups 1+2) and non-responders (Groups 3+4). The areas under the ROC curve were 0.88 (SE = 0.06, P < 0.0001) for tumor size, 0.63 (SE = 0.11, P = 0.11) for K^{trans} and 0.77 (SE = 0.09, P = 0.001) for k_{ep}.

FIGURES

Figure 1.

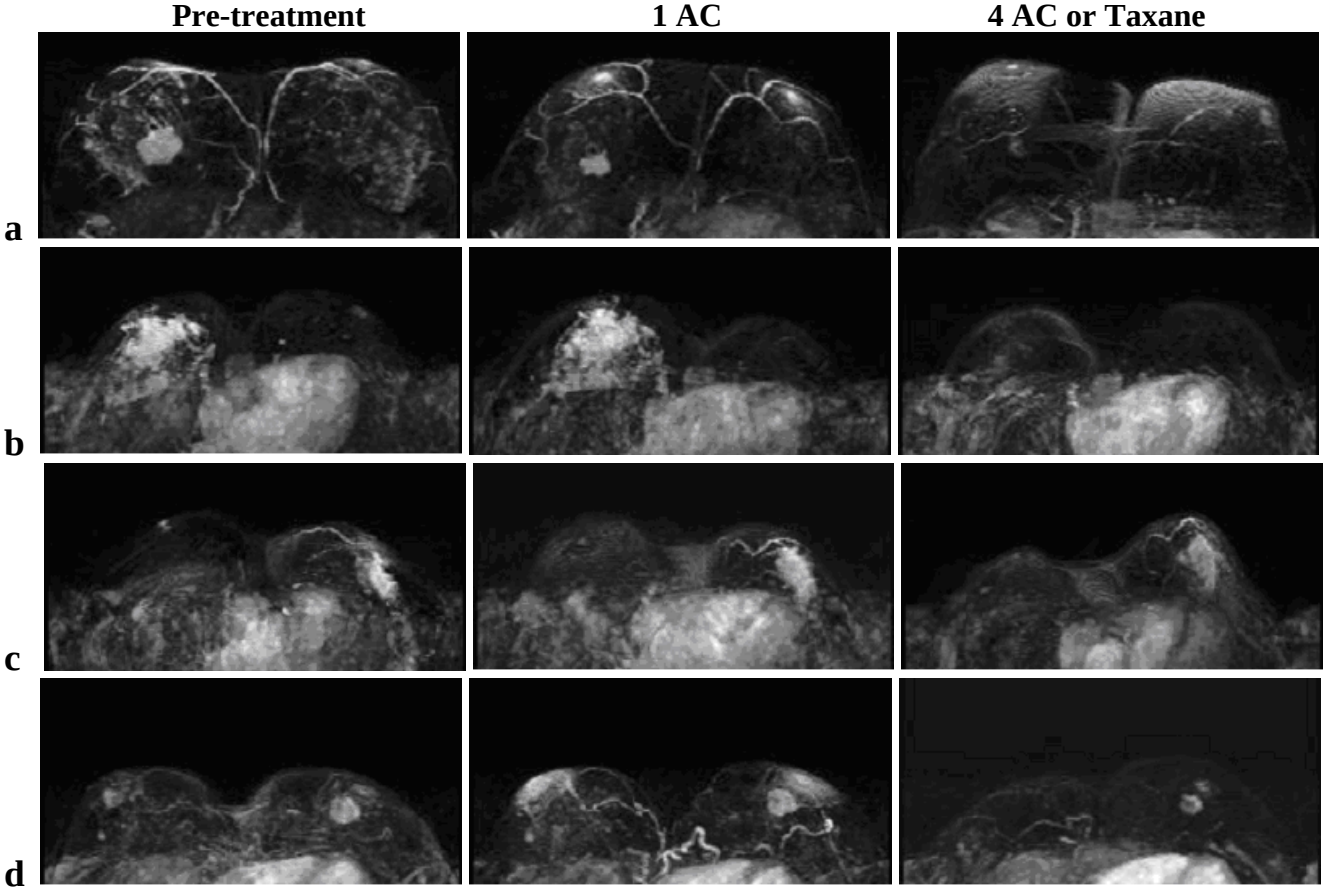


Figure 2. **a** **b** **c**

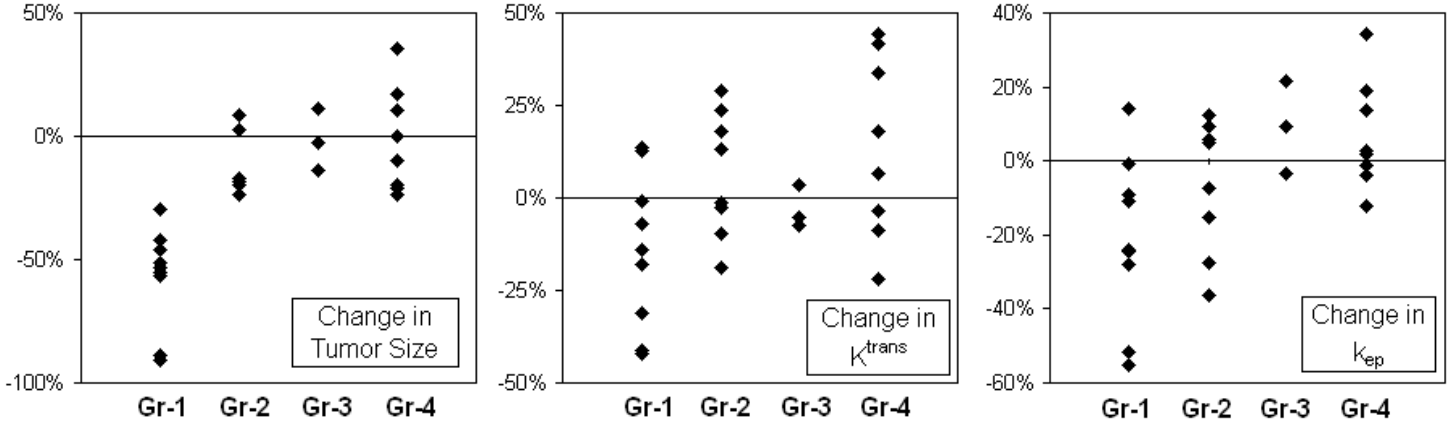

50%
0%
-50%
-100%
Change in Tumor Size
Gr-1
Gr-2
Gr-3
Gr-4
50%
25%
0%
-25%
-50%
Change in K trans
Gr-1
Gr-2
Gr-3
Gr-4
40%
20%
0%
-20%
-40%
-60%
Change in k ep
Gr-1
Gr-2
Gr-3
Gr-4

Figure 3. **a** **b** **c**

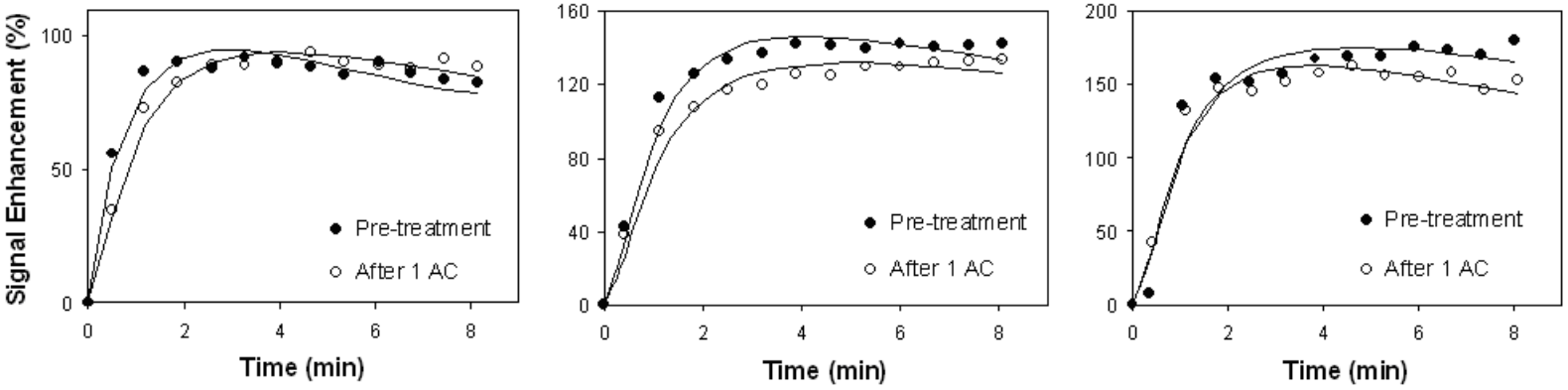

Signal Enhancement (%)
Time (min)
Pre-treatment
After 1 AC
Time (min)
Pre-treatment
After 1 AC
Time (min)
Pre-treatment
After 1 AC

Figure 4.

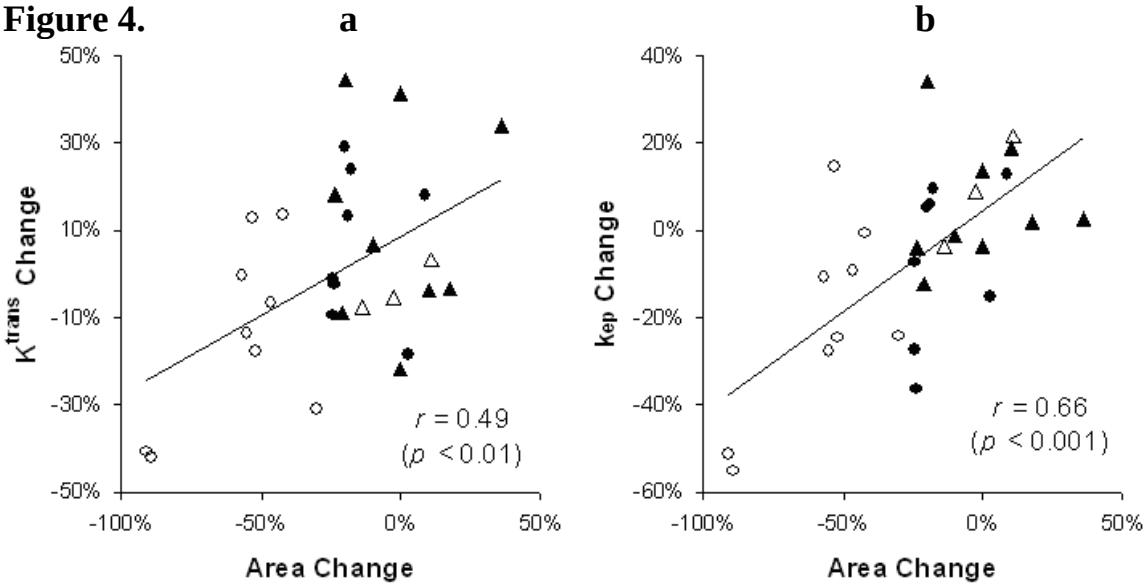
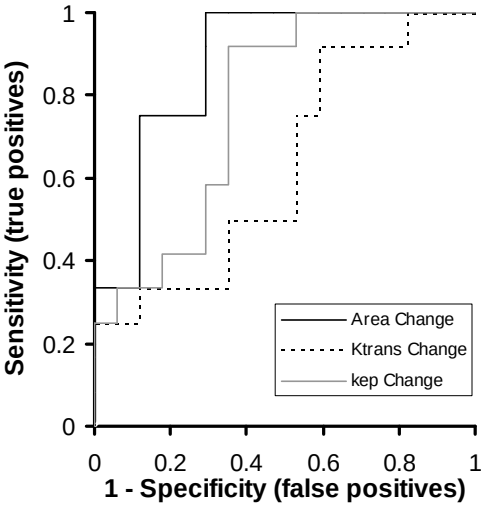

a
50%
30%
10%
-10%
-30%
-50%
-100%
-50%
0%
50%
K^{trans} Change
Area Change
r = 0.49
(p < 0.01)
b
40%
20%
0%
-20%
-40%
-60%
-100%
-50%
0%
50%
kep Change
Area Change
r = 0.66
(p < 0.001)

Figure 5.


Sensitivity (true positives)
1 - Specificity (false positives)
0
0.2
0.4
0.6
0.8
1
Area Change
Ktrans Change
kep Change