Kinetic and Morphologic Parameters on MRI Predict Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

D. J. Margolis[1], B. L. Daniel[1], G. Glover[2], R. J. Herfkens[1], S. Pal[1], S. Plevritis[1], B. Sigal[1], D. Ikeda[1]

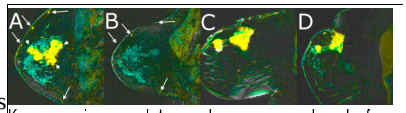
[1]Radiology, Stanford University, Stanford, CA, United States, [2]Director, Radiological Science Lab, Stanford University, Stanford, CA, United States

Introduction: When followed by local treatment with surgery and radiation, preoperative neoadjuvant chemotherapy results in local response of large breast tumors in up to 70%-90% of patients (1). Women with locally advanced disease show improved survival comparable to non-locally advanced disease, although it is difficult to predict which breast cancers will respond to a specific chemotherapy regime. Specific tumor morphologies on high-spatial resolution contrast-enhanced MRI and the shape of enhancement curves over time during dynamic contrast enhancement differentiate cancer from benign tumors (2). Some experts have suggested that a combined analysis of both morphology and enhancement rate curves provides the most accurate diagnosis of malignancy (3). Breast cancers change their morphology and enhancement rates during chemotherapy (4). In this study, K_{21}, an estimate of the exchange rate of contrast concentrations between the intra- and extracellular fractions, and tumor was evaluated on breast cancers in women undergoing neoadjuvant chemotherapy, with morphology and K_{21} values and pathologic classification for each tumor evaluated by three radiologists independently. The goal is to identify discriminators for which patients will and will not respond to chemotherapy.

Medthods: In total, 24 patients were identified who met the inclusion criteria of large T2 breast tumors and breast MRI scheduled before and after neoadjuvant chemotherapy. Using a four-channel phased-array breast RF coil (MRI Devices) on a conventional 1.5 T GE Signa scanner, a high resolution 3-dimensional spectral-spatial magnetization transfer pulse sequence (3DSSMT: TR/TE 33-40/7 ms, 512x192 matrix, 60 slices, scan time of 1.0-2.0 min., using centric phase encoding, water-selective excitation and on-resonance magnetization transfer pulse) provided high resolution morphologic data to localize the lesion and a rapid 3D GRE sequence (20-interleave spirals, 20 cm FOV, TR/TE 38/11.9 ms, 50° flip angle, 4.5 to 6 mm thick slices, 188x188 matrix, 20 slices volume, scan time of 10.86s, gadolinium contrast at 1 mmol/kg, given as a bolus during the initial spiral sequences and flushed immediately with 20 cc of sterile saline) produced 3.5 minutes of kinetic data of breast lesion enhancement. MRI findings were classified for morphology using the American College of Radiology BI-RADS MRI Lexicon, using mass/non-masslike enhancement, borders, shape and internal enhancement characteristics (homogeneous, heterogeneous, or rim), and number of lesion categories; largest dimension, enhancement curve shape, K_{21}, and parametric maps as described elsewhere (5). Region of interest contrast kinetic parameters were recorded for the entire lesion, periphery, and area with the highest value. Electronic charts were reviewed for each patient to document the duration of chemotherapy and date of surgery as well as excised tumor size, tumor histology, surface receptors (estrogen, progesterone, and Her2-neu) and for the presence of DCIS and LCIS. Response to chemotherapy was assessed on the MRI scans and classified as complete (no residual tumor), partial response (at least 50% reduction in tumor size), or no response (greater than 50% residual tumor) with respect to the surgical specimen and with follow-up MRI.

Results: There were 6 complete, 5 partial, and 12 non-responders at surgery and one complete responder by MRI who had no surgery. Chemotherapy was predominantly 4-6 cycles of Cytoxan, adriamycin, and 5-fluorouracil (5FU), with 4 patients also receiving Taxotere (3 of whom did not receive 5FU and one of whom also received Xeloda) and 2 received additional methotrexate. Average follow-up of 792 days was available for 23 patients.

Worse response to chemotherapy at surgery was significantly correlated with smaller initial size (p=0.015) and positive progesterone receptor status (p=0.02) and was correlated with borders (p=0.065), lobular histology (p=0.10), positive estrogen receptor status (p=0.17) and Her2-neu (p=0.18) although these last findings did not reach significance. Negative estrogen receptor status is significantly associated with development of metastases (p = 0.047). Negative progesterone receptor status, single lesion, and the parameter K_{21} may correlate with the development of metastases (p=0.12, 0.07, 0.10 respectively) but none of these reached statistical significance.



K_{21} maps in complete- and non-responders before (A,C) and after (B,D) chemo-therapy. Vessels (arrows) retain high K_{21} values (yellow shading).

We performed a further analysis of patients regarding K_{21} since we observed that four non-responders had much higher values of K_{21} than the others. Using Fisher's exact test to compare non-responders with the other two categories combined, this relationship had a p-value <0.05 for one tail and <0.1 for both tails, which raises the possibility of determining a cut-off value for K_{21}, above which patients would not be expected to respond to neoadjuvant chemotherapy, although a larger sample size is necessary to perform classification tree analysis to determine such a value. We also found that no CR was found to have metastasis at follow-up, but this did not reach significance (p=0.078).

Discussion: The initial size of a lesion is a significant predictor of response to neoadjuvant chemotherapy, and response appears to correlate inversely with spiculated borders. The high spatial-resolution dynamic data also appears to be predictive of outcomes, both for response to chemotherapy and development of metastasis on follow-up. However, the classification tree analysis to determine this value with adequate certainty was precluded as the sample size was too small, which was in part because some patients initially recruited were excluded when it was found chemotherapy was initiated prior to their first MRI. FDG PET has been shown to be predictive of which patients may be responsive to neoadjuvant chemotherapy in one series, and MRI morphologic data have shown some modest predictive value for response to chemotherapy, but heretofore literature for both PET and MRI of the breast suggest it is necessary to compare scans before and after induction of chemotherapy to predict response (6). This investigation identifies MRI-detected morphologic and kinetic findings prior to induction of chemotherapy that are predictive of response, and may lead to the establishment of parameters to spare expected non-responders chemotherapy before definitive surgical management.

1. Carlson R, Favret A. Multidisciplinary management of locally advanced breast cancer. The Breast Journal 1999;5:303-307.
2. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, Schild HH. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? [see comments]. Radiology 1999;211(1):101-110.
3. Orel SG. Differentiating benign from malignant enhancing lesions identified at MR imaging of the breast: are time-signal intensity curves an accurate predictor? [editorial; comment]. Radiology 1999;211(1):5-7.
4. Tsuboi N, Ogawa Y, Inomata T, Yoshida D, Yoshida S, Moriki T, Kumon M. Changes in the findings of dynamic MRI by preoperative CAF chemotherapy for patients with breast cancer of stage II and III: pathologic correlation. Oncol Rep 1999;6(4):727-732.
5. Agoston AT, Daniel BL, Herfkens RJ, Ikeda DM, Birdwell RL, Heiss SG, Sawyer-Glover AM. Intensity-modulated parametric mapping for simultaneous display of rapid dynamic and high-spatial-resolution breast MR imaging data. Radiographics 2001;21(1):217-226.
6. Martincich L, Montemurro F, De Rosa G, Marra V, Ponzone R, Cirillo S, Gatti M, Biglia N, Sarotto I, Sismondi P, Regge D, Aglietta M. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. Breast Cancer Res Treat 2004;83(1):67-76.