Developing markers for stratifying patients into good vs. poor prognostic categories using pre-neoadjuvant chemotherapy three time points breast contrast-enhanced MRI and histogram analysis

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INTRODUCTION

Early prediction of failure is essential in treatment planning for breast cancer patients. The aim of this study was to develop pre-neoadjuvant chemotherapy predicators for stratifying patients into good vs. poor prognostic categories using three time-points contrast-enhanced (CE) MRI and histogram analysis.

METHODS

Participants: We studied 31 consecutive women, who had histopathologically verified primary invasive ductal carcinoma and preoperatively underwent four cycles of adriamycin and cytoxan (AC) therapy between April 1995 and September 2002. High spatial resolution three time point CE MRI data were acquired prior to chemotherapy. Based on the most recent follow-up till August 2007, these patients were divided into 'recurrence-free' (n=18) and 'recurrence' (n=13) groups.

MRI Acquisition: A 3D fast gradient-recalled echo imaging sequence was employed on a 1.5-T Signa scanner (General Electric Medical Systems, Milwaukee, WI) with TR/TE = 8/4.2 msec; flip angle = 20°; number of average = 2; acquisition matrix = 256x192x60; slice thickness = 2 mm. The contrast agent, Gd-DTPA (Magnevist; Schering, Berlin, Germany) was administered intravenously at a dose of 0.1 mmol/kg body weight. The signal intensity (SI) for each voxel was denoted as S0 for the pre-contrast acquisition, and S1 and S2 for the two post-contrast acquisitions acquired in two consecutive 5-minute intervals. The central phase encoding lines of each data set were acquired halfway through the scan, yielding effective post-contrast sample times of 2.5 and 7.5 minutes.

Data Analysis: For each tumor voxel, relative SI for the wash-in and wash-out phases were calculated as rSI_{in} = (S1-S0)/S0, and rSI_{out} = (S2-S0)/S0. The signal enhancement ratio (SER) was calculated as (S1-S0)/(S2-S0). Only voxels with substantial enhancement (rSI_{in} > 70% and rSI_{out} > 40%) were included for analysis. SER and rSI_{out} histograms were produced for each tumor with the size of the bin = 0.1. The density (number of voxels in each bin) function for each tumor was saved in database. The minimum (or maximum) densities for each bins in each group were plotted against the bin subscripts, and were used to explore the characteristic regions of SER (or rSI_{out}) which presented greatest difference between the recurrence and recurrence-free groups. The number of voxels within these characteristic regions were then used as the markers for predicting recurrence after surgery.

A Theory for Prediction: Stratifying patients into good vs. poor prognostic categories was based on the following theory: If a parameter, k, for a population has a range of $[k_{min}, k_{max}]$, an individual is unlikely to belong to this population if his/her k value was either < k_{min}, or > k_{max},.

RESULTS

Minimum (Fig. 1a and 1c) and maximum (Fig. 1b and 1d) density in each bin for both groups are plotted on the same graph for comparison. Predictors were chosen as the numbers of voxels within characteristic ranges (paired red lines on fig. 1 a-d) and tabulated in Table 1. Accounting for overlap, a total of 5 out of 13 (38%) patients with recurrence and 15 out of 18 (83%) recurrence-free patients were identified (Table 1). None of the recurrence-free patients was misidentified as likely to recur, and none of the recur-patients was misidentified as unlikely to recur.

DISCUSSION AND CONCLUSION

This study evaluated pre-chemotherapeutic three time points CE MRI in predicting disease recurrence after surgery. Markers developed based on histogram analysis have shown high specificity in predicting recurrence. The most interesting funding was that rSI_{out} was complementary to SER in predicting tumor recurrence. In conclusion, the combined use of these two parameters, SER and rSI_{out}, which were orthogonal to each other, leads to more robust prediction of disease recurrence.

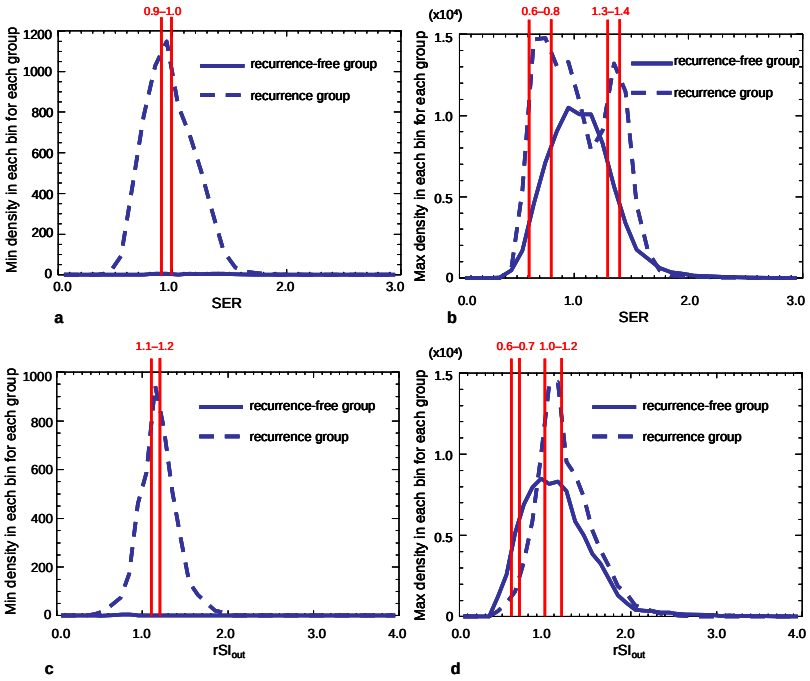

Fig. 1. Plots of minimum and maximum density in each bin vs. SER or rSI_{out} for the recurrence and recurrence-free groups.

Table 1. Predictors and patients identified

Predictors -- number of voxels in regions:	min or max # of voxels in this region for recurrence group	min or max # of voxels in this region for recurrence-free group	# patients in the recurrence group, who were identified as "recurrence"	# patients in the recurrence–free group, who were identified as "recurrence-free"
SER 0.9 – 1.0	Min: 1149	Min: 6	n/a	10/18, criterion: < 1149
SER 0.6 -0.8	Max: 26202	Max: 11671	3/13, criterion: > 11671	n/a
SER 1.3 – 1.4	Max: 13210	Max: 5634	1/13[a], criterion: > 5634	n/a
rSI_{out} 1.1 – 1.2	Min: 945	Min: 0	n/a	7/18[b], criterion: < 945
rSI_{out} 0.6 – 0.7	Max: 1555	Max: 5165	n/a	5/18, criterion: > 1555
rSI_{out} 1.0 – 1.2	Max: 28752	Max: 16507	2/13, criterion: > 16507	n/a
Totally identified			5/13 (38%)	15/18 (83%)

[a] This was overlapped with the subjects identified with (# voxels)$_{rSIout\ 1.0-1.2}$ > 16507.
[b] This was overlapped with the subjects identified with (# voxels)$_{SER0.9-1.2}$ < 1149.