Optimization of DCE-MRI measurement parameters for predicting response to neoadjuvant chemotherapy by breast cancer subtype

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Purpose:

Breast cancer is a heterogeneous disease comprised of subtypes with different treatment response, relapse risk and overall prognosis. At the molecular level, breast cancer can be classified by hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status: HR+HER2, HER2+, and triple negative (TN)[1]. Previous studies showed that the change in functional tumor volume (FTV) measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is associated with response to neoadjuvant chemotherapy (NACT) for patients with stage II/III breast cancer[2] and this association can be optimized over a set of threshold parameters used to define FTV[3]. The goal of this work was to assess whether optimal thresholds for early FTV change as a predictor of recurrence-free survival (RFS) and pathological complete response (pCR) differed by breast cancer subtype.

Methods:

64 patients with locally advanced breast cancer were imaged by DCE-MRI before treatment (MRI_1), after one cycle of adriamycin-cytoxan (AC) (MRI_2), inter-regimen (MRI_3) and at the completion of chemotherapy prior to surgery (MRI_4). FTV, defined as the volume of tissue exceeding an early percent enhancement (PE=100*(S1-S0)/S0) threshold PE_t and a signal enhancement ratio (SER=(S1-S0)/(S2-S0)) threshold SER_t, was calculated for a range of PE_t (30–200% in steps of 10%) and SER_t (0–2 in steps of 0.2) values. A Cox proportional hazard model was used to estimate the association between early percent change in FTV (ΔFTV_2) and RFS, defined as the time between surgery and disease recurrence. The hazard ratio, 95% confidence interval (CI) and p-value were estimated by the Cox proportional hazard model. Area under the receiver operating characteristic curve (AUC) was used to evaluate the predictive ability of pCR (0 or 1) by ΔFTV_2. Both approaches were used to analyze the full cohort (n=64) as well as each breast cancer subtype (HR+HER2-: n=22; HER2+: n=15; TN: n=11; unknown: n=8).

Results:

Estimated hazard ratios from the Cox analysis showed different behaviors over the range of PE_t/SER_t threshold values for cancer subtypes versus the full cohort, with hazard ratios > 1.2 shown in dark red (Fig. 1). The optimal PE_t/SER_t based on highest hazard ratio in the full cohort and by subtype are shown in Table 1. For the full cohort, no hazard ratios > 1.2 were found for any PE_t/SER_t combination tested. HR+HER2- showed few PE_t/SER_t combinations with hazard ratios > 1.2. HER2+ showed hazard ratios > 1.2 in a higher range of PE_t (160–190%) and lower range of SER_t (0–1). TN showed most PE_t/SER_t combinations with hazard ratios > 1.2 in a high range of PE_t (140–180%) and low range of SER_t (0–1). Different profiles were also seen for the AUC values for prediction of pCR for the full cohort and breast cancer subtypes as well (Fig. 2). For the full cohort, high AUCs (which we define as 0.8–1) occurred at PE_t=140–150% and SER_t=0–0.8. HR+HER2- showed high AUCs at low PE_t range (50–80%) and low SER_t range (0–0.4). Compared to the full cohort and subtype HR+HER2-, both HER2+ and TN showed more PE_t/SER_t combinations with high AUCs at PE_t= 60–170% / SER_t=0–1 for HER2+ and full range of PE_t and low range of SER_t (0-1) for TN.

Table 1

	PE_t/SER_t	n	Hazard Ratio	CI	p-value
Full cohort	150/1.2	64	1.13	1.03–1.24	0.007
HR+HER2-	150/1.2	22	1.33	0.96–1.84	0.08
HER2+	190/0.8	15	1.69	1.09–2.62	0.02
TN	40/2.0	11	1.41	0.95–2.1	0.09

Discussions and Conclusions:

We observed very different RFS risk prediction profiles by ΔFTV_2 over a wide range of thresholds for different cancer subtype groups and versus the entire cohort. The predictive value of threshold dependent MRI parameters such as FTV can be improved with threshold optimization and appears to be different between different cancer subgroups. It is important to note that optimized threshold values are likely to be dependent on imaging parameters such as scan timing and type of contrast agent used. This retrospective study has a few limitations. Findings from this cohort, which included patients undergoing standard AC and taxane-based treatment, may not be applicable to patients who opt for emerging targeted and hormone therapy. Additionally, the sample size was limited when the cohort was subset into subtypes. Future work includes validation with larger cohort and exploration of alternative predictors.

References:

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747–52.
2. Hylton NM, Blume JD, Bernreuter WK, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL. *Radiology*. 2012;263(3):663–72.
3. Jafri NF, Newitt DC, Kornak J, Esserman LJ, Joe BN, Hylton NM. Optimized breast MRI functional tumor volume as a biomarker of recurrence-free survival following neoadjuvant chemotherapy. *J Magn Reson Imaging*. 2014;40(2):476–82.

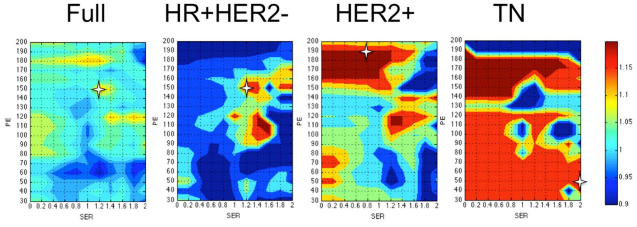

Figure 1 ΔFTV_2 prediction of RFS. Hazard ratios estimated by Cox proportional hazards are shown for the full cohort and by breast cancer subtype over PE_t/SER_t threshold combinations. The star on the heat map shows the optimized PE_t/SER_t threshold combinations.

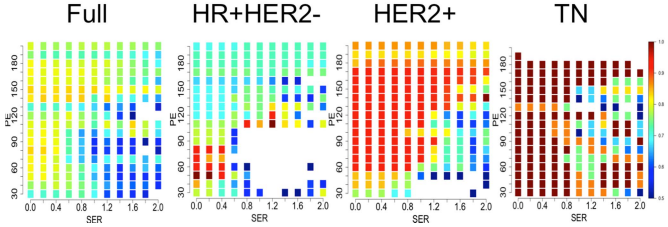

Figure 2 ΔFTV_2 prediction of pCR. AUC maps for the full cohort and by breast cancer subtype. The color bar shows the AUC values ranging from 0.5 to 1.0. The areas with AUC < 0.5 were left as blank.