Supplementary Results. Narrative review of non-meta-analyzed features and meta-analysis of DWI results.

Narrative review of imaging features assessed for their relation with HER2 overexpression in individual studies but with insufficient data for meta-analysis.

**Mammography**

Seo et al. and Wen et al. respectively reported that mass density,\(^1\) and nipple retraction were not significantly related to HER2 status in their studies.\(^2\)

**Breast ultrasound**

Au-Young et al. reported on multifocality, duct extension and presence of a cystic component, all decreasing the chance of HER2 overexpression in their data, but numbers were small and results did not reach statistical significance.\(^3\) Wan et al. studied several contrast-enhanced ultrasound features in relation to prognostic factors, of which a perfusion defect and centripetal enhancement both significantly increased the chance of HER2 overexpression (OR 4.64, \(P=0.008\) and OR 3.43, \(P=0.017\) respectively).\(^4\)

A further four studies showed data on tumor vascularity. Chen et al. reported a significantly higher vascularization index (mean tumor vascularity) and vascularization flow index (overall perfusion) in HER2 positive breast cancer, whereas the flow index was not related to HER2 status.\(^5\) Two other studies reported higher measures of vascularity in HER2 positive breast cancer without reaching statistical significance,\(^6,7\) and one study reported no association between HER2 status and resistive index.\(^8\)

**Magnetic resonance imaging**

Four studies reported choline concentration data as assessed by MRS in relation to HER2 status, but this could not be meta-analyzed due to marked differences in assessment and reporting.\(^9,12\) The earliest publication on this topic reported that HER2 positive breast cancer more often had a detectable choline peak than HER2 negative disease (91% versus 76%, \(P=0.26\)), but that the mean total choline levels were somewhat lower in HER2 positive breast cancer (1.50 versus 2.03 mmol/kg, \(P>0.05\)).\(^9\) The other three studies showed similar results: mean total choline
concentration of 3.8 versus 4.4 mmol/kg ($P>0.05$),\textsuperscript{10} median normalized total choline-containing compound of 0.25 versus 0.72 arbitrary units/mL ($P=0.19$),\textsuperscript{11} and mean normalized choline signal of 0.82 versus 1.10 ($P>0.05$),\textsuperscript{12} for HER2 positive versus negative breast cancer respectively.

Two studies reported on high-temporal resolution DCE-MRI to study perfusion parameters. Koo et al. assessed the relation between perfusion parameters and prognostic factors using 42 post-contrast images at 11 second intervals.\textsuperscript{13} They did not find a significant relation between HER2 status and vascular permeability (median $K_{\text{trans}}$: 0.442 versus 0.415, $P=0.60$), the rate constant (median $k_{\text{ep}}$: 1.075 versus 0.851, $P=0.99$) nor the extracellular extravascular space (median $v_e$: 0.400 versus 0.534, $P=0.11$). Makkat et al. studied tumor blood flow in relation to HER2 status with 22 post-contrast images at 10 second intervals,\textsuperscript{14} and reported non-significant higher tumor blood flow in HER2 positive breast cancer. Reanalysis of their data defining HER2 overexpression as IHC 3+ or IHC 2+ and FISH+ found median tumor blood flow 83 versus 58 in favor of HER2 positive breast cancer ($P=0.21$).

Three studies reported data on non-mass like enhancement in relation to HER2 status, but numbers were too small for meaningful discussion.\textsuperscript{15-17} Furthermore, Constantini et al. reported data on the presence of necrosis, fibrosis, infiltration, multicentricity, and perilesional edema, none of which was significantly related to HER2 status in that study, except for multicentricity that increased the chance of HER2 overexpression (OR 2.17, 95%CI: 1.05-4.47, $P=0.034$).\textsuperscript{18}

**Meta-analysis of diffusion weighted imaging in relation to HER2 overexpression.**

Six studies reported data on DWI in relation to HER2 status (DWI imaging protocols shown in Supplementary Table S5).\textsuperscript{17-22} Three reported lower ADC values for HER2 positive breast cancer,\textsuperscript{17,21,22} one of which was significant.\textsuperscript{17} The other three reported higher ADC values for HER2 positive breast cancer,\textsuperscript{18-20} one of which reached statistical significance.\textsuperscript{19} After mean and standard deviation approximation for two studies,\textsuperscript{19,21} we were able to meta-analyze five studies totaling 840 breast cancers with 229 HER2 positives.\textsuperscript{17,19,21,22} The fixed effect estimate showed that ADC values were on average $0.061\times 10^{-3}$ mm$^2$/s lower in HER2 positive than HER2 negative breast cancer (95%CI: -0.100 to -0.021; $P=0.003$). However, heterogeneity was high ($I^2 0.82, P(Q)<0.001$), and the random effect estimate was not significant (random effect pooled mean difference: $-0.004\times 10^{-3}$ mm$^2$/s; 95%CI: -0.116 to 0.108; $P=0.94$). The
study that could not be included in the meta-analysis showed that breast cancers with a HER2 IHC score of 3+ had somewhat higher median ADC values than breast cancers with an IHC scores of 0, 1+, and 2+, although the difference was not significant (P=0.41). 20

Excluding studies for which mean and standard deviation were approximated, or limiting studies to only invasive cancers, 3 or 1.5 Tesla systems, did all not substantially influence the results (data not shown).

References


