Radiology: Imaging Cancer

COMMENTARY

One Size Fits All?—Not Anymore: Personalizing Breast Cancer Treatment with Use of a Semiautomated Functional Tumor Volume–based Predictive Model in the Assessment of Neoadjuvant Therapy Response

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Personalized treatment specific to tumor characteristics and biology as well as patient preference is at the forefront of breast cancer care. Neoadjuvant chemotherapy is recommended in certain cases, such as locally advanced and inflammatory breast cancers, and is also increasingly used in early-stage triple-negative and human epidermal growth factor receptor 2 (HER2)–positive molecular subtypes of breast cancers. Pathologic complete response (pCR) to neoadjuvant chemotherapy is confirmed at surgery and is associated with improved survival.

Early prediction of neoadjuvant chemotherapy response is part of the endeavor to tailor treatment for each patient with breast cancer appropriately and is an area of active research. Currently, medical oncologists and breast surgeons use physical examination and imaging to assess treatment response prior to surgery. Breast MRI has shown to be the most accurate imaging modality in evaluating treatment response after neoadjuvant therapy (1).

Although MRI may be the most accurate imaging modality available, subjective assessment of tumor extent at MRI shows variable performance in predicting pCR, and accuracy depends on tumor molecular subtype (2). Functional tumor volume (FTV) estimation has been shown to be a more accurate predictor than longest diameter alone (3). Predictors of response after completion of chemotherapy serve as prognostic indicators, while earlier predictors of response may immediately affect management by informing decisions on treatment escalation or de-escalation. The end goal is to improve patient outcomes, while minimizing therapy toxicity. These factors highlight the need to find a validated objective, automated method of FTV estimation to improve accuracy of MRI in the early prediction of neoadjuvant therapy response.

In this issue of *Radiology: Imaging Cancer*, Onishi and Bareng et al (4) evaluate a predictive model based on semiautomated FTV measurements and their longitudinal variability in volume under- or overestimation as a potential early predictor of neoadjuvant therapy response. In this retrospective analysis, data were obtained from eligible participants in the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2), which included women aged 18 years or older with stage II or III breast cancer without distant metastases. All participants underwent 12 cycles of weekly paclitaxel with or without experimental agents, followed by four cycles of anthracycline-cyclophosphamide. Half of the trial participants meeting certain inclusion criteria and matched for tumor subtype and pCR outcome were randomly sampled for the main analysis, resulting in a sample size of 432 participants. In addition to the main analysis, a multireader subanalysis was also performed by randomly sampling a quarter of the main analysis cohort to test the reproducibility of the modeling approach.

For the main analysis, the authors collected automated FTV measurements calculated on dynamic contrast-enhanced (DCE) MRI scans obtained at different time points during neoadjuvant chemotherapy. The FTV measurements obtained at three time points were as follows: baseline (FTV0), percentage change in FTV at early treatment (FTV1 change) and inter-regimen time points (FTV2 change) relative to baseline. These FTV measurements were then categorized into high-standard or standard groups based on subjective visual assessment of FTV over- or underestimation. The FTV measurements that were visually assessed as highly accurate were categorized as high standard, while the standard group included FTV measurements perceived as overtly underestimated or overestimated.

Predictor logistic regression modeling was performed separately for the high-standard and standard groups using

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See also article by Onishi and Bareng in this issue.

single predictors (FTV or FTV change at each time point) and multiple predictors (all three). The area under the receiver operating characteristic curve (AUC) of the two groups and the difference between the two groups were calculated. In the main analysis, the authors found consistently higher AUC for the high-standard FTV estimation group compared with the standard FTV estimation group in predicting pCR, with a statistically significant difference using the multiple predictor model. The authors conclude that less longitudinal variation in FTV estimation leads to improved performance of early FTV change as a predictor of pCR.

The authors discuss factors leading to FVT over- or underestimation. Background parenchymal enhancement had an impact on variation in FTV estimation as it resulted in increased overestimation, especially at the baseline MRI and in cases of nonmass enhancement. Younger age and premenopausal status were significantly associated with increased longitudinal variation in FTV estimation, likely due to background parenchymal enhancement–related overestimation. Hormone receptor–positive, HER2-negative tumors were associated with FTV underestimation at the later time points. These findings support findings from previous studies also showing milder and more delayed enhancement of luminal-type cancers after treatment (1), making them prone to underestimation of residual disease.

Previous studies investigating FTV change as a predictor of treatment response used DCE MRI and fast DCE MRI and included patients with triple-negative breast cancer (5,6). Fast DCE MRI offers a higher sampling rate to present more detailed information on tumor perfusion kinetics. Musall et al (5) concluded that FTV change obtained after completion of four cycles of chemotherapy and measured at 1 minute after injection at fast DCE MRI can predict treatment response. Onishi and Bareng et al included patients with cancers of all molecular subtypes in their cohort and investigated early FTV change on conventional DCE MR images obtained at multiple time points as a predictor of treatment response. The high-standard FTV estimation group performed better in the prediction of pCR compared with the standard group, regardless of tumor subtype.

There are a growing number of studies evaluating various other imaging markers obtained from MRI as potential early predictors of treatment response. For example, radiomics is an evolving field, incorporating thousands of quantitative image-based features that could potentially be used to characterize tumors and predict treatment response (7). Some other imaging markers previously investigated include changes in tumor heterogeneity (8), diffusion-weighted imaging (9), and necrosis volume (10). Several of these studies investigate findings from MRI performed prior to initiation of chemotherapy. From a practical standpoint, it would be convenient to predict treatment response based on baseline MRI findings. However, pretreatment MRI may be limited by more recent postbiopsy changes such as hematomas and biopsy tract enhancement. One of the strengths of the study by Onishi and Bareng et al is that the authors incorporate findings from MRI performed both before and during therapy, rather than the pretreatment phase alone.

The authors appropriately discuss several study limitations including potential biases secondary to use of representative sections for visual assessment of FTV and random sampling of a partial cohort rather than all eligible participants. Interestingly, the smaller multireader subanalysis performed by Onishi and Bareng et al to test reproducibility of the predictive model showed increased AUC in the high-standard group; however, differences in AUC did not reach statistical significance. Interreader agreement for FTV was variable, revealing the limitation of using a measurement technique that is only semiautomated and still reliant on some manual input. Hence, there remains the need to find a consistent, objective, and preferably fully automated method of calculating FTV measurements, which may result in more accurate therapy response predictions. While the study findings may not directly impact breast cancer management today, it is a step toward improving MRI accuracy in predicting treatment response.

In summary, early changes in FTV may potentially be used in predicting treatment response in conjunction with several other imaging-based features currently being investigated, including the use of radiomics and artificial intelligence. Early predictors of response obtained before or during neoadjuvant therapy rather than after treatment completion are valuable as they offer opportunities to guide modifications in chemotherapy as needed. A comprehensive multiple predictor model incorporating biomarkers derived from advanced imaging and clinical information may be transformative in refining the process of personalized breast cancer care in the future.

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