Evidence-based Rating: B

Personal Rating: 3

**Clinically Meaningful Tumor Reduction Rates Vary by Prechemotherapy MRI Phenotype and Tumor Subtype in the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657)**

Neoadjuvant chemotherapy (NAC) has two main benefits: to allow for in vivo monitoring of each individual patient's response to different drug regimens to improve the likelihood of achieving pathologic complete response (pCR); and for downstaging tumors to facilitate breast conservation surgery and achieve a better cosmetic outcome. With these benefits, NAC has become an important treatment modality for breast cancer patients who will need some form of chemotherapy as part of treatments. An accurate evaluation of post-chemotherapy residual disease by imaging will provide critical information for the choice of optimal surgery (type and timing) as well as subsequent treatments such as radiation and hormonal therapy. Several large series studies have investigated factors influencing the accuracy of post-NAC MRI.(1-6) It was consistently reported that the accuracy of MRI is dependent on molecular biomarkers (HR-hormonal receptor and Her2 receptor) and tumor phenotypes.

In this article Mukhtar and colleagues analyzed 198 patients enrolled into a multi-center trial I-SPY 1 TRIAL (CALGB 150007/150012, ACRIN 6657). One main innovation in this article is the attempt to categorize tumors into 5 MRI phenotypes: 1- well defined, unicentric mass; 2- well defined, multilobulated mass; 3- area enhancement with nodularity; 4- area enhancement without nodularity; 5- septal spreading. These 5 phenotype patterns were first reported in

Esserman et al in 2001,(7) and shown to be associated with response to doxorubicin and cyclophosphamide neoadjuvant chemotherapy. Another new concept proposed in this article was the definition of a “clinically meaningful tumor reduction after NAC” based on a tumor size ≤ 4 cm on surgical pathology. The rationale was that when the residual disease is ≤ 4 cm the patient is considered a suitable candidate for breast conservation treatment (BCT). However, the BCT rate in all 174 patients with pre-treatment tumor size > 4 cm was 35%; whereas in the 141 of 174 patients who achieved the “clinically meaningful tumor reduction” to ≤ 4 cm, the BCT rate was only slightly increased to 37%. Therefore, using this criterion for analysis does not seem meaningful. The authors did analyze and report the post-NAC tumor size discrepancy measured by MRI and pathology, which is a commonly used outcome measure for evaluating the accuracy of MRI.

The main findings reported in this article were: 1) Solid tumors had a higher clinically significant tumor reduction rate and a higher BCT rate compared to diffuse type tumors. 2) The concordance of post-NAC tumor size measured by MRI and pathology varied by molecular subtypes (better in triple negative than HER2+ than Her2-/HR+) and by MRI phenotypes (better in sold tumors than in diffuse types). 3) The difference in pre-treatment tumor size measured by MRI and palpation was related to tumor phenotypes (MRI size was smaller than palpation in sold tumors, and bigger than palpation in diffuse type tumors). These findings were consistent with results reported in the literature. Since the tumor phenotypes and the molecular subtypes were correlated, they were not independent predictors of MRI accuracy. In this I-SPY 1 TRIAL dataset, the triple negative group made up a larger proportion of the well-defined MRI phenotypes (35 %) than the diffuse phenotypes (15 %); and that the HR+ group had a higher proportion in diffuse type (68 %) than

in the well-defined type (52 %). The accuracy of MRI is known to be very high for mass lesions that have a good response showing concentric shrinkage after NAC, and low for non-mass lesions that break apart into scattered cell clusters.(1, 8, 9) Triple negative tumors are more likely to present as mass lesions, and in general they respond well to NAC; therefore both contributing to a high post-NAC MRI diagnostic accuracy. For HR+ tumors, they are more likely to present as diffuse type tumors, and in general not have a great response to NAC, therefore both contributing to a lower MRI accuracy compared to triple negative tumors. The knowledge can be taken into consideration when planning for surgery after NAC.

Despite the effort to determine 5 phenotypes, the main finding was analyzed based on the two combined types: well defined type (or solid tumors, combining phenotypes 1 and 2) and diffuse type (combining phenotypes 3, 4 and 5). These two types were consistent with the mass and non-mass-like enhancements as described in BI-RADS MRI Lexicon, and widely used by other studies in the literature. Since 5 tumor phenotypes were determined in this study, it will be very interesting to further investigate how the MRI accuracy differs between the two solid types (unicentric vs. multilobulated) and among the three diffuse types (area enhancement with and without nodularity and septal spreading). Unfortunately, the sub-group phenotype analysis results were not presented. Although an example was graphically illustrated for each type, how well a tumor can be precisely classified into one particular type was questionable. Since the determination was made by local radiologists at each separate institution (after some training), the intra-rater and inter-rater variability could be substantial. Therefore, unless the classification of these 5 phenotypes can be done precisely with a very high consistency, the results may not have much clinical value.

The authors are currently developing an algorithm based on biologic and MRI features to predict the accuracy of post-NAC MR to help guiding decision-making process. It has been reported that tumor histological type, grade, and the use of chemotherapy regimens may also affect the tumor response and the accuracy of MRI,(1, 2) therefore a very large dataset is needed to consider all variables properly. A multicenter consortium setting such as I-SPY 1 (and the subsequent I-SPY 2) with standardized protocol and central training is critically needed to collect high quality data. With more research effort devoted into this area, it is highly likely that some models considering clinical, biological and imaging information will become available in the near future for guiding personally tailored management for breast cancer patients electing to receive NAC.

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