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Magnetic Resonance Imaging as a Predictor of Pathologic Response in Patients Treated With Neoadjuvant Systemic Treatment for Operable Breast Cancer

Neoadjuvant chemotherapy (NCT) is the standard of care treatment used for inoperable cancers. With the awareness of the importance of early diagnosis and the wide availability of screening programs, the diagnosis of inoperable locally advanced breast cancer is reduced but the use of NCT has been greatly increased. It has evolved and become an important treatment modality for immediately operable cancers. Very effective chemotherapy and targeted therapy regimens are available and many patients can achieve pathologic complete response (pCR), which raises a question about the optimal surgery and radiotherapy protocol that can be offered to a patient following NCT. If a patient achieves pCR, she may be treated safely with radiation alone without surgery. However, previous studies in patients who showed a complete clinical remission found a higher locoregional recurrence rate in the no surgery group compared to the surgery group.⁽¹⁾

Compared to mammography, ultrasound and clinical examination, MRI has been proven as the most accurate imaging modality for assessing NCT treatment response. It will be interesting to know the accuracy of MRI in predicting pCR and whether it can help in selecting patients who can be spared of surgery. Particularly, among all diagnostic performance rates, the negative predicting value (NPV) is the most important one. Only when the NPV is approaching 100% (that is, the false negative rate is extremely low) the patient can be confidently treated with

radiation alone without surgery. Many studies have reported that the diagnostic accuracy of MRI is dependent on the molecular subtype,(2-7) but a large sample size is needed to evaluate the accuracy of MRI in predicting pCR in each subtype.

In this article, De Los Santos and colleagues analyzed a large dataset by combining retrospective NCT cases collected at 8 NCI-designated comprehensive cancer centers between Jan 2002 to Feb 2011, with a total of 746 evaluable patients. This multicenter dataset is much larger compared to most studies published in the literature to date, aiming to improve the power to detect significant difference between clinically distinct subsets. However, although a much larger dataset was analyzed, the major findings were similar to previously reported results, including: 1) The pathologic response is strongly dependent on the ER, PR, HER2 status and the combined molecular subtypes based on HR and HER2; 2) The diagnostic accuracy of MRI is also dependent on the combined HR-HER2 molecular subtypes. Specifically, the tumor characteristics that are associated with a better response include smaller size, higher grade, negative HR, and positive HER2 (receiving trastuzumab). The overall NPV is only 47% (85/182), and in each subtype from the best to the worst: 62% (HR-/HER2+), 60%(HR-/HER2-), 42% (HR+/HER2+), 33% (HR+/HER2-). The results suggest that MRI has a high false negative diagnosis, and as such, it will not be suitable for selecting patients to receive radiation alone without surgery.

Although this study successfully collected a large number of NCT patients through a multicenter consortium setting, unfortunately it did not add much knowledge to this research field. One major limitation was that the pathology examination and the MRI reading were done at each

institution, not reviewed by a central lab. For example, a relative high false negative rate (97/182) was found, but it would be very difficult to identify the problems that can be used for further analysis to improve the diagnostic accuracy. It was mentioned that “a complete MRI response was defined as the resolution of all areas of abnormal enhancement, mass, or distortion”. This is a general statement, and it is almost impossible to ensure that all radiologists at 8 different centers over a 10-years period used the same criteria for making diagnosis. The diagnostic performance was analyzed based on the true positive, true negative, false positive and false negative rates. Although these rates are the most commonly reported metrics in the literature, it does not provide sufficient information for determining the true capability of MRI in detecting the extent of post-NCT residual disease. Several recent papers used the size discrepancy between MRI-measured and pathology-measured tumor sizes as the outcome variable for evaluating the diagnostic accuracy of MRI.(3, 4, 7) If a central radiological review can be performed on this very large dataset, many more informative results will be obtained for assessing the true value of MRI in the NCT setting and determining its impact on the choice of subsequent treatment procedures (including surgery, radiation, and the need of additional chemotherapy).

Other than molecular subtypes, it was also reported that different morphological presentation of lesions may show different response patterns, which may affect the diagnostic accuracy of MRI. While mass lesions are more likely to show concentric shrinkage, non-mass-like enhancement lesions may break up into scattered cell clusters within the original tumor bed, and these forms of residual diseases will be very difficult to be detected by MRI. Also, in pathological examination, other than reporting the presence or absence of invasive cancers and DCIS, it is possible to report

the change of cellularity as residual cancer burden (RCB), and it has been reported that patients who can achieve “minimum residual disease” (RCB-1) have the same favorable prognosis as those achieving pCR.(8) As NCT is gradually becoming a widely accepted treatment modality for patients with operable breast cancers, more large datasets will become available soon. Similar to the tailored use of targeted and hormonal therapy based on the molecular biomarker status of each patient, the combined use of surgery, radiation and additional chemo/targeted therapy following NCT can also be tailored depending on tumor characteristics of individual patients and their responses to NCT. MRI is proven to be very useful in evaluating NCT response, but it is far from being used as a tool for selecting patients to receive radiation alone without surgery. In general, MRI has a great potential to contribute in personally tailored treatment strategy following NCT, but more research is needed in this research area to define guiding criteria.

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