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To interview Francesco Ravera, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of Ravera, click here. Visit our newsroom.

Liquid Biopsy Augments MRI for Predicting Response to Neoadjuvant Treatment in Patients With Breast Cancer

PHILADELPHIA – A liquid biopsy test to assess plasma cell-free DNA (cfDNA) integrity could improve the accuracy of magnetic resonance imaging (MRI) for predicting the achievement of complete response among patients with locally advanced breast cancer who had received neoadjuvant chemotherapy, according to results presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

“Breast cancer is the most commonly diagnosed cancer worldwide, with roughly 2 million cases diagnosed in 2020,” said Francesco Ravera, MD, PhD, fellow in the Department of Internal Medicine at the University of Genoa in Italy. “Identifying the best ways to evaluate treatment response can help to better guide further management of this common malignancy,” he said.

Treatment for locally advanced breast cancer often begins with neoadjuvant chemotherapy to shrink or eliminate the tumor. About 20 percent of patients will experience a complete response following this treatment, Ravera said, and will likely then undergo a sentinel lymph node biopsy to confirm that the cancer has not spread to the axillary nodes. Patients who do not experience an axillary-node complete response undergo axillary lymph node dissection, in which all of the lymph nodes in the armpit are removed. This procedure is significantly more extensive than sentinel lymph node biopsy and can have permanent side effects. It is, therefore, important to accurately assess response to neoadjuvant chemotherapy to guide surgical management, Ravera explained.

The current presurgical assessment of clinical response among patients with breast cancer is based on MRI, yet this imaging method has suboptimal accuracy, noted Ravera. “Finding a more accurate method for the assessment of complete response in axillary lymph nodes to neoadjuvant chemotherapy in patients affected by breast cancer may allow the omission of sentinel lymph node biopsy in complete responders, which could be replaced by longitudinal radiological monitoring. This would represent substantial progress in the pursuit of an effective, minimally invasive treatment of patients affected by breast cancer,” he said.

Previous research has demonstrated that the integrity of cfDNA can be potentially utilized as a useful biomarker for predictive purposes among patients with breast cancer, noted Ravera. Low cfDNA integrity, which corresponds to high cfDNA fragmentation, is a typical feature of neoplastic patients. When healthy cells die, they typically release similarly sized DNA fragments into the bloodstream. However, when cancer cells die, they release DNA fragments of varying sizes. By measuring the quantity of different fragment sizes, clinicians can estimate the integrity of patients’ cfDNA, Ravera explained.

To better understand if cfDNA integrity could predict response to neoadjuvant chemotherapy among patients with locally advanced breast cancer, Ravera and colleagues evaluated plasma taken from 38 patients who had completed an anthracycline/taxane-based treatment prior to surgery. The researchers assessed the concentration of differently sized cfDNA fragments in plasma samples collected before surgery and determined which fragment sizes were the most indicative of response to neoadjuvant

treatment upon the result of post-surgical histopathological examination. These parameters were then used to calculate a normalized measure of cfDNA integrity, namely cfDNA integrity index, which was used

to build an explorative classifier of response to systemic treatment. Results of such a classifier were then compared to those achieved by MRI in predicting if patients had a complete response to their neoadjuvant chemotherapy.

Among the 38 patients evaluated, 11 experienced a pathologic complete response following neoadjuvant chemotherapy, while 27 patients experienced an incomplete response, with residual disease either in the breast or axillary nodes following treatment. MRI had an accuracy of 77.1 percent, while the cfDNA integrity index had an accuracy of 81.6 percent in predicting the achievement of a complete response at histopathological examination.

Ravera and colleagues also evaluated whether the cfDNA integrity index could be combined with MRI to improve prediction. The two techniques were concordant in their prediction of a complete response in roughly 70 percent of patients. When both MRI and the cfDNA integrity index were concordant, their combined prediction of a complete response achieved an accuracy of 92.6 percent, with a positive predictive value (accuracy in predicting a positive result) and a negative predictive value (accuracy in predicting a negative result) of 87.5 percent and 94.7 percent, respectively.

“Our work identifies a new parameter that is easily combinable with MRI for a more accurate prediction of response following neoadjuvant treatment, with possible implications for current protocols for the evaluation of nodal residual disease among patients with breast cancer undergoing neoadjuvant chemotherapy,” Ravera said.

Limitations of this study include its small sample size. “Future work is needed to validate this new parameter to verify its utility for clinical practice, besides investigating the biological bases underlying cfDNA integrity alterations in patients with breast cancer, which was outside the scope of the present study,” Ravera said.

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Ravera declares no conflict of interest.

Abstract

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Abstract Body:

Background: Locally advanced breast cancer (BC) is currently treated with neoadjuvant chemotherapy (NACT) followed by surgery. NACT is able to achieve about a 20% rate of pathological complete response (pCR), defined as the absence of invasive cancer in breast and in axillary nodes. To date the pre-surgical assessment of clinical complete response (cCR) is mostly based, even though with suboptimal accuracy, on magnetic resonance imaging (MRI). Knowledge of cCR is useful to guide the surgical management of post-NACT BC. The study of plasma cell-free DNA integrity (DI) has shown serious potential for providing useful information in neoplastic patients in regard to early diagnosis, recurrence, and response to therapy. The aim of the present study is to estimate the accuracy of an electrophoresis-based method for DI assessment in the evaluation of the response to the systemic treatment in BC patients undergoing NACT. **Methods**: 62 BC patients undergoing anthracycline/taxane based NACT followed by surgery were recruited. Plasma samples were collected from each patient at diagnosis (T0), after anthracycline administration (T1), and after NACT completion before surgery (T2). After cfDNA extraction, cfDNA fragmentation profiling (DFP) was performed for each sample by automated electrophoresis on an Agilent Tapestation 2200 device. The concentration of differently sized cfDNA fragments, respectively of 90-150 base pairs (bp), 150-220 bp, 221-320 bp, 100-300 bp, and 321-1000 bp was assessed. cfDNA fragments size ranges evaluated as the most informative of the response to NACT were finally selected to calculate a normalized measure of DI, namely cfDNA integrity index (DII), expressed as the ratio of 321-1000 bp sized fragments concentration to 150-220 bp sized fragments one. DII was finally used to build an explorative classifier for BC response to NACT, directly comparing its performance with MRI, via bootstrapped logistic regression. **Results**: After preliminary essays to identify the most promising time point, DFP was performed on 38 plasma samples collected from as many patients at T2, with a 70/30 ratio between pCR and non pCR patients. DII showed an overall accuracy in correctly predicting the achievement of pCR of 81.6, with a cutoff above 2.71 having sensitivity = 81.8 and specificity = 81.5. MRI overall accuracy in the same cohort amounted to 77.1, with a sensitivity and a specificity of 72.7 and 81.5 respectively. The performance of the two techniques combined, in case of concordance, achieved an overall accuracy of 92.6 with a predictive value of complete response of 87.5 and a predictive value of absence of complete response of 94.7. **Conclusions**: DII measured before surgery after NACT completion shows great potential to correctly predict the achievement of pCR in BC patients. The evaluation of its use in combination with MRI is warranted in prospective studies.

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