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Brief Commentary

Breast cancer prognostic tools: A promising Indian option

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Gene expression assays are primarily intended to help prognosticate selected patients of early stage breast cancers, i.e., mainly Stages I and II, who further need to be hormone receptor positive, HER2-neu negative, and lymph node negative.[1] Some of the assays include lymph node-positive tumors as well, especially if the nodal burden is low (1–3 nodes). The gene expression assays provide prognostic information beyond that obtained from the classical clinicopathologic factors such as age, tumor size nodal status, grade, hormone receptor status, and the HER2 neu status.[2] These assays have also been used to identify breast cancer patients who are more likely to benefit from the addition of chemotherapy to adjuvant endocrine therapy.

The commercially available assays include Oncotype DX, MammaPrint, Prosigna, EndoPredict, and Breast Cancer Index. These assays are typically performed following surgery (from formalin-fixed paraffin-embedded tissue). The analytical methods used to predict the genomic risk include reverse transcription-polymerase chain reaction, microarray, and multimode analysis systems. The clinical use of the above-mentioned gene expression assays has been endorsed by various breast cancer management guidelines and is being followed by oncologists globally.[3,4] The National Comprehensive Cancer Network (NCCN) guidelines have endorsed Oncotype DX andMammaPrint with a Level I recommendation, with the former being given a preferred recommendation. Further, health technology assessment studies from affluent nations have found the gene expression assays to be likely cost effective; however, the grades of recommendations in the studies were ranging from low to moderate.[1]

However, the penetration of the above-mentioned gene expression assays in routine clinical practice in the Indian subcontinent is low and this has largely been attributed to its higher costs and the increased turnaround times. Another major drawback remains the fact that these tests have been validated only in the Caucasian patients and not in the Indian patients who are known to be ethnically different. Further, insurance companies in many of the low- to middle-income countries often tend not to reimburse the above-mentioned high-cost gene expression assays, and hence, these assays are performed only for the few patients who themselves pay for the tests. The issue of costs was further brought about in a survey of 100 medical oncologists across India. Although nearly 71% of the respondents seemed to prefer the gene expression assay, Oncotype DX, the vast majority (94%) felt that the assay was way too expensive for the average Indian patient.[5]

There was, hence, a need for exploring more affordable prognostic tools in the management of breast cancers, especially tests that have been validated in patients from the Indian subcontinent. Many oncologists have explored the use of the more affordable prognostic tools such as PREDICT,

PREDICT Plus, and the new Oncotype DX calculators. Some other risk prediction models include Adjuvant! Online, (Now not in clinical use) St Galen's, Nottingham Prognostic Index, and new Magee equations; however, each of them has some distinct shortcomings.

Meanwhile, efforts were on to determine whether the routinely available histopathological and immunohistochemical markers could help predict recurrences in addition to the traditional clinical factors. Cuzick *et al*.[6] suggested that combined the standard clinical and pathological parameters (IHC 4) could possibly be better than the Oncotype DX assay for prognostication. Such studies seem very appealing given their simplicity and the potential for cost savings. A promising new kid in the block is the CanAssist-Breast test (CAB).[7]

The CAB is an immunohistochemistry-based prognostic test, which uses a support vector machine trained algorithm based on the expression of five biomarkers (CD44, ABCC4, ABCC11, N-Cadherin, and Pan-Cadherin) and three clinical parameters (tumor size, grade, and node status). The test generates a risk score which stratifies patients into two actionable risk groups, high and low risk, with no intermediate-risk group. The risk scores of CAB are valid for up to 7 years following the diagnosis of breast cancer. It is in fact the only prognostic test to be developed and extensively validated in the Indian patients.[7] Interestingly, the CAB test stratified a higher number of patients into low risk (who could avoid chemotherapy) as compared to Oncotype DX and MammaPrint. This test is applicable for breast cancer patients of all age groups and irrespective of the nodal status. This is an important consideration as the recurrence score of Oncotype DX seems to have different implications in breast cancer patients <50 years.[8] This was further brought out in a survey conducted by Indian Cooperative Oncology Network on 57 oncologists across India, a majority of whom responded that they would prefer CAB while prognosticating breast cancer patients <50 years. The risk stratification score by CAB was reported to be more accurate as compared to the Ki-67 and IHC4 score. The use of CAB has in fact prevented under treatment in a majority of the low Ki67 (luminal-A) patients and has also prevented overtreatment in patients with a high Ki67 (luminal-B) subtype, while it accurately identified the risk for patients in the intermediate-risk category of IHC4.

Given the fact that, CAB has the largest cohort of Indian patients in any study of prognosis/prediction in early breast cancers added with the added advantage of having a much better affordability, personalized medicine practicing oncologists from India should endorse CAB with a preferred recommendation.

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