special article

Oncotype DX: Where Does It Stand in India?

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Adjuvant chemotherapy has been the standard of care for patients with early breast cancer (EBC) on the basis of early National Surgical Adjuvant Breast and Bowel Project studies. In the 2000s, it was realized that most patients with EBC, especially those with hormone-positive and node-negative disease are being overtreated, and clinical and histologic features may not be sufficient to make decisions regarding adjuvant therapy.

Paik et al[1] proposed a gene recurrence score (RS) called Oncotype DX (Genomic Health, Redwood City, CA) in 2004 in their landmark article based on 21 genes that directly correlate with prognosis. They also showed that patients with a high RS benefited from chemotherapy.[2] Sparano et al[3] published their data on patients with a low RS (1-10) and showed excellent survival with hormone therapy alone. To address the patients with intermediate RS, the report "Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer" was published in the *New England Journal of Medicine* in July 2018.[11] The authors randomly assigned approximately 6,700 patients with early hormone-positive, node-negative breast cancer to hormone therapy alone or hormone therapy in combination with chemotherapy with the objective of demonstrating the noninferiority of hormone therapy to combination therapy. The primary end point was invasive disease-free survival. After a median follow-up of 90 months, hormone therapy was found to be noninferior to chemotherapy in combination with hormone therapy in intention-to-treat population, as well as per-protocol, analysis for all primary and secondary end points. On exploratory analysis, chemotherapy combined with hormone therapy showed an invasive disease-free survival benefit in women younger than 50 years of age with an RS of more than 16. Thus, this trial established new RS cutoffs for offering chemotherapy, which was an RS of more than 26 for women older than 50 years of age and a score of more than 16 for women younger than 50 years of age. We have certain reservations regarding the applicability of these results, especially in the Indian scenario.

First, breast cancer in Indian patients tends to be, on average, a more aggressive disease than in the West. The mean age of patients with breast cancer in the Indian setting is approximately 47 years—a decade younger than in the West.[4,5] Approximately half of Indian patients present with locally advanced or metastatic breast cancer compared with 30% in the West.[6] Various social factors responsible for this include lack of awareness, lack of a definite screening program, and difficult access to quality health care. It has been proposed that biology of breast cancer is different in the Indian population, with a higher number of triple-negative breast cancers (30% compared with 12% to 15% in the West).[7] Although it remains to be explored whether this difference is due to biologic differences with more luminal B disease[8] or demographic reasons alone, it is clear that the number of patients who present with the kind of slow-biology disease who benefit from Oncotype DX is significantly lower in our country.

Second, there is a lack of data regarding the age distribution of RS. It is logical that the middle age group, that is, those between 35 and 50 years of age, will be the ones most likely to benefit from this test. Age is an independent prognostic factor for survival in breast cancer, with patients younger than 35 years of age having an inferior overall survival after adjusting for other prognostic factors, including hormone receptor status.[9,10] These patients also tend to present with more aggressive disease. In the TAILORx trial (ClinicalTrials.gov identifier: NCT00310180), only 5% of patients were younger than 40 years of age, which makes the results difficult to extrapolate to this population.[11] Medical oncologists may feel uncomfortable in avoiding chemotherapy in this young subset regardless of RS until better data are available to this effect. In fact, an age of 40 years in the Indian setting may be the ideal dividing line. Prospective research directed toward the younger breast cancer population may also help identify a subgroup of patients who are currently being overtreated. Thus, specific research on this younger population is an urgent need for breast cancer patients in India.

Third, there is no doubt that the test is extremely expensive in the Indian context. The cost of the test in the United States is approximately $4,000, which is justifiable because of the fact that it helps avoid chemotherapy, which costs approximately $80,000 to $100,000 in the United States.[12] Thus, the cost of the test is approximately 5% of the chemotherapy it avoids. However, the cost of chemotherapy in India is generally 5% to 10% of that in the West, and the cost of the test in India easily exceeds the expected cost of the

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chemotherapy it purports to avoid, thus making no sense from an economic point of view.

To avoid this problem, clinical predictors, such as PREDICT and PREDICT Plus, as well as new Oncotype DX calculators, which aim to calculate the expected benefit of chemotherapy by using cheaper, easily available surrogates, have entered the picture. Many oncologists are using these algorithms in clinics instead of molecular tests. We conducted an online survey of 100 medical oncologists in this regard. Of the available gene expression signatures, although Oncotype DX turned out to be the preferred method with 71% preferring it, 94% felt these tools were too expensive. Fifty-eight percent reported using PREDICT online for adjuvant decision making, and 94% felt that PREDICT online could be used as an alternative to genomic tools in a resource-constrained setting like ours.

Although Oncotype DX has revolutionized the management of patients with EBC, breast cancer oncologists must take into account the biology of the disease in a particular population along with other tumor- and patient-related factors, especially cost, before making treatment decisions because the first-line setting offers the best chance for cure in these patients. In India, prospective validation studies are required for such costly tests, and simultaneously, emphasis on use of clinical predictors must be given.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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