Refining Treatment Decisions in Older Patients With Breast Cancer
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Chemotherapy decisions have traditionally relied to a large degree on clinical and pathologic features. There has been significant interest in improving tools to better predict benefit to chemotherapy and eliminate treatment in those who do not benefit. The 21-gene recurrence score (RS) is the best-validated prognostic assay and is predictive for determining benefit from adjuvant chemotherapy in patients with estrogen receptor (ER)-positive, node-negative disease. The test has been incorporated into the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines.

In the original validation study of the RS assay in node-negative, early-stage breast cancer, 51% of patients had a low RS, 22% intermediate, and 27% high. This correlated with a 10-year distant recurrence rate of 6.8%, 14.3%, and 30.5% respectively. Subsequent analysis showed that the RS predicted the magnitude of adjuvant chemotherapy benefit in ER-positive, node-negative disease, with a 28% improvement in distant recurrence rates in patients with a high RS treated with chemotherapy. Retrospective studies have also shown prognostic value of the RS in postmenopausal patients with node-positive, ER-positive breast cancer and predicted chemotherapy benefit in this population. Much larger prospective studies evaluating RS in node-positive populations are ongoing, including the RxPONDER trial looking at the benefit to chemotherapy in node-positive patients with low to intermediate RS.

Multiple studies have shown that use of the RS has a significant impact on decision making regarding chemotherapy changing decisions in about one-third of patients, most commonly resulting in avoidance of chemotherapy. In a large meta-analysis of 9 studies analyzing over 1000 patients, the RS led to a change in treatment decision in 35% of patients, with a 51% change in patients who were previously recommended chemotherapy and a 13% change in those previously recommended endocrine therapy alone. Overall, integrating the RS into decision making led to a significant net reduction in chemotherapy. A prospective study analyzed the impact of RS on decision making in node-negative, ER-positive patients, showing that the RS changed the treatment recommendation in 31% of cases. In about two-thirds of these cases, the change was away from chemotherapy, and in 10%, in favor of chemotherapy. Recurrence score also influenced patient treatment preferences and reduced patient anxiety.

Increasing age is a significant risk factor for developing breast cancer, with approximately 40% of breast cancer diagnosed in women older than 65 years. In the report by Dinan et al, utilization of RS was analyzed in a large cohort of Medicare patients. Over the 4-year period between 2005 and 2009, utilization of RS increased from 1% to 10%. The majority of tested patients had small ER-positive, node-negative tumors, in accordance with guidelines. The 26% of patients who did not fall into this cohort appeared to have discordant risk factors (eg, small tumors with other high-risk features such as high grade or involved lymph nodes, where chemotherapy would be considered; or node-positive tumors with otherwise low-risk features, where there was interest in avoiding chemotherapy). As expected, the RS assay was used more frequently in younger patients, in those with fewer comorbid conditions, and in higher-grade disease. These are patients for whom chemotherapy would be more strongly considered if the test suggested benefit. Other risk stratifiers are less clearly understood, including geographic location and marital status. Among patients younger than 70 years with intermediate-risk disease, testing rates increased from 8% to 39%.

Despite the appropriately tested population, the RS score did not result in a significant change in chemotherapy utilization in this older, intermediate-risk group, increasing from 8.2% to 10%, which was not statistically significant. This contrasts with data demonstrating a more significant change in practice patterns. The lack of change in chemotherapy utilization suggests either that the physicians have a bias about treating older patients with chemotherapy that the test did not change regardless of results, or that the test results were concordant with...
their pretest bias. Interestingly, there was a trend toward increasing use of chemotherapy when RS was factored into decision making, while in a previous report,\(^6\) RS more often led to the avoidance of chemotherapy. Patient preferences and biases may have also played a role in the eventual decision about chemotherapy that Dinan et al\(^6\) did not address.

There is a clear need for better prognostic and predictive tools for breast cancer. The desire to optimize treatment and eliminate overtreating patients unlikely to benefit is particularly relevant to the older patient population. This population is likely to have comorbidities potentially worsening adverse effects experienced with chemotherapy. For RS or other genomic tools to be beneficial, an impact on patient outcomes should be demonstrated; otherwise, the cost of testing cannot be justified.

If the use of the RS assay is not altering treatment recommendations in the older patient population, it would be interesting to document whether this is related to tumor characteristics, physician bias, or patient preference. If physicians are biased against treating older patients with chemotherapy, and older patients are biased against receiving such treatment, the RS is unlikely to change practice. In contrast to a younger patient population, the RS is unlikely to result in less chemotherapy in a population already predisposed not to receive it. If anything, the RS would be most useful in changing decision toward chemotherapy.

For the test to have clinical utility in the older population, patients would have to possess an accurate understanding of their risk of recurrence, their life expectancy, and a realistic expectation of the toxic effects related to chemotherapy (which many older patients might tolerate well). Physicians have to be willing to recommend chemotherapy to appropriate older patients who have a high RS, patients for whom they might not ordinarily be as definitive in their treatment recommendations as they would be with a younger patient.

For the most part, older patients with relatively low-risk disease do not want chemotherapy, and physicians do not want to prescribe it. Perhaps the threshold for recommending testing older patients should be adjusted to test only those with higher-risk tumors where there is more inclination toward treatment. If the node-positive data are validated with prospective studies, testing this population of older patients may be more likely to change treatment recommendations. A prospective study of physician and patient decision-making in this patient age group would also be useful in answering some of these questions.

**REFERENCES**


