Ann Surg Oncol (2019) 26:1173–1175
https://doi.org/10.1245/s10434-019-07240-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – BREAST ONCOLOGY

Routine Use of Oncotype DX Recurrence Score Testing in Node-Positive Hormone Receptor-Positive HER2-Negative Breast Cancer: The Time Has Come

Elizabeth A. Mittendorf, MD, PhD[1], and Tari A. King, MD[1,2]

[1]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; [2]Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA

The recently revised 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer staging system acknowledged the prognostic and predictive significance of underlying tumor biology by incorporating tumor grade, estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor status into a pathologic prognostic stage.[1] In addition, based on the initial report of TAILORx (Trial Assigning Individualized Options for Treatment [Rx]), the committee revising the staging system took the bold step of incorporating genomic assays. Specifically, patients with ER+, HER2−, node-negative breast cancer with an Oncotype DX recurrence score (RS) < 11 enrolled on TAILORx had a 5-year distant recurrence-free survival of 99.3% with adjuvant endocrine therapy alone.[2] Based on this, the AJCC staging system added the modifier that any patient with T1-2N0, ER+, HER2- breast cancer and a RS < 11 would be assigned pathologic prognostic stage IA disease.[1] The committee acknowledged this is a rapidly evolving field and emerging data evaluating other assays and clinical scenarios would need to be evaluated to inform subsequent staging system revisions.

Comment on Wang M, Wu K, Zhang P, et al. "The prognostic significance of the Oncotype DX recurrence score in $T_{1\text{-}2}N_1M_0$ estrogen receptor-positive HER2-negative breast cancer based on the prognostic stage in the updated AJCC 8th edition".

First Received: 31 December 2018;
Published Online: 24 February 2019

E. A. Mittendorf, MD, PhD
e-mail: emittendorf@bwh.harvard.edu

The purpose of the manuscript from Wang et al.[3] was to evaluate the prognostic significance of the RS in patients with ER+, HER2−, node-positive breast cancer. Specifically, they sought to determine if the RS could be used as a modifier when determining the pathologic prognostic stage for patients with node-positive breast cancer as it is for patients with node-negative disease. Using the Surveillance, Epidemiology, and End Results (SEER) database, the authors identified 4059 patients with T1-2N1M0, ER+, HER2- breast cancer diagnosed 2004–2012 with RS results available. RS cutoffs from the TAILORx trial were utilized with RS < 11, 11–25 and > 25 defining low-, intermediate- and high-risk groups respectively. There was a positive correlation between the RS risk groups and the pathologic prognostic stage with the percentage of RS low-risk patients decreasing from 22.2% among patients with pathologic prognostic stage IA disease to 3.4% among those with pathologic prognostic stage IIB disease. Conversely, the percentage of RS high-risk patients increased from 8.3% in stage IA patients to 57.3% in stage IIB. There were higher recurrence scores in patients with more aggressive clinicopathologic characteristics to include grade III disease and negative PR status. However, discordance between clinical risk defined by tumor grade and genomic risk defined by RS has been demonstrated in up to 30% of patients in other datasets of both node-negative and node-positive patients, highlighting the potential for genomic assays to refine prognosis beyond traditional clinicopathologic factors.[4–6]

After a median follow-up of 57 months, there were significant differences among RS risk groups with respect to breast cancer-specific survival (BCSS) and overall survival (OS). Multivariate analysis showed that both RS risk group and the AJCC pathologic prognostic stage were independent prognostic factors for BCSS and OS. When

analyses were limited to patients with low-risk RS, there were no differences in BCSS or OS among the different pathologic prognostic stages. In contrast, for intermediate RS patients, there were significant differences in BCCS and OS when evaluated by pathologic prognostic stage. Conversely, for patients with pathologic prognostic stage IA disease, there were significant differences in BCSS and OS by RS, which appeared driven primarily by the high RS patients having poorer survival.[3] The data presented therefore support consideration be given to using RS to modify the pathologic prognostic stage for patients with ER+, HER2-, node-positive disease similar to the modification for patients with node-negative disease.

Consideration for incorporating RS testing into staging for ER+, HER2-, node-positive breast cancer is further supported by work presented by Hortobagyi and colleagues at the 2018 San Antonio Breast Cancer Symposium (SABCS).[7] That study utilized the SEER database to establish BCSS in patients with ER+, HER2−, N0, N1mic, and N1 disease in whom RS data were available. They identified 80,605 patients treated from 2004 to 2014, including 70,087 who were N0, 4335 N1mic, and 6182 N1. The median follow-up was 49 months and more than 20,150 patients were followed for longer than 76 months. Perhaps the most interesting finding in their analysis was that for patients with a RS < 18, the 9-year BCSS was $>$ 97% regardless of nodal status. Because a cutoff of 18 was used, these data differ from the TAILORx data that informed the decision to stage all ER+, HER2−, node-negative breast cancer patients with a RS < 11 as pathologic prognostic stage IA. However, the observed BCSS rate $> 97\%$ regardless of nodal status provides further evidence of the importance of tumor biology over anatomic extent of disease, particularly for patients with early-stage disease, thereby supporting further investigation into modifying the pathologic prognostic stage using the RS in node-positive patients.

Additional findings from the study presented by Hortobagyi and colleagues included the demonstration of a trend for chemotherapy benefit with increasing RS in patients with N0 disease with a cutoff point of 26, supporting the TAILORx data for patients with node-negative disease.[8] For patients with node-positive disease, there were too few events to determine the magnitude of chemotherapy benefit as a function of RS; however, the observed differences in BCSS with chemotherapy for node-positive patients with RS < 25 was $< 1\%$ at both 5 and 9 years, supporting the use of endocrine therapy alone in patients with 1–3+ nodes.[7]

There are caveats to both studies, including possible selection bias. These data include patients in whom the treating physician elected to send the RS from 2004 to 2014. This predates the recommendation for considering a genomic assay for node-positive patients, which was only included in National Comprehensive Cancer Network guidelines as of 2018.[9] In addition, only 36.9% of patients in the study from Wang et al.[3] received chemotherapy, including 19% with low RS, 33.8% with intermediate RS, and 74.7% with high RS. This is notable, as during this time period, chemotherapy was recommended by clinical guidelines for patients with node-positive disease. This low rate of chemotherapy may be attributable to the fact that 45.7% of patients had only micrometastases. Our group has previously reported that among patients with T1 breast cancer, individuals with axillary micrometastases and those with negative nodes have similar survival outcomes.[10] Regardless, the impact of heterogeneous receipt of chemotherapy on the results of the current study is unknown. In addition, it is known that chemotherapy use is underreported in the SEER database. Finally, patients included were not randomized to treatment. However, there are several strengths as well, including the large number of patients identified in a population-based database. SEER includes many patients who would be underrepresented on clinical trials; therefore, these studies present "real world" data. These "real world" data are consistent with other reports showing utility of using RS in patients with node-positive breast cancer, including the SWOG 8814, which showed that the RS was prognostic in tamoxifen-treated patients, and the TransATAC, which showed the RS was predictive of distant recurrence in postmenopausal patients with node-positive disease treated with endocrine therapy.[11–13] In addition, a study of 709 node-positive patients from the Clalit Health Services showed low distant recurrence rates in node-positive patients with a RS < 18 treated with endocrine therapy alone. The prospective phase 3 WSG Plan B trial showed 5-year, disease-free survival rates of 94% for patients with a RS ≤ 11 treated with endocrine therapy alone, regardless of nodal status.[6,13]

As the authors of the current manuscript conclude, further research with longer follow-up is required to determine fully the impact of the RS in patients with node-positive breast cancer. The RxPONDER trial, which enrolled patients with 1–3 positive nodes and randomized those with a RS ≤ 25 to either chemotherapy plus endocrine therapy or endocrine therapy alone is a prospective effort that will provide additional data to answer this question.[14] The trial completed accrual in 2015, and results are highly anticipated. However, there is concern that this cohort may be biased toward a lower number of positive nodes, and we will remain uncertain as to the validity of the RS in patients with higher disease burdens. In the meantime, many oncologists are beginning to incorporate RS testing for node-positive patients into their practice. A recently published study of node-positive patients identified in the National Cancer Database between 2010 and

2012 found that the RS had been ordered for 16.5%.[15] In our program at the Dana-Farber/Brigham and Women's Cancer Center, we routinely order RS for patients with T1–2N1 disease of any grade as part of our reflex testing program whereby the surgical specimen from patients in whom the RS results would inform adjuvant therapy treatment recommendations is sent for RS testing by the surgical team as soon as the pathology report becomes available.[16] Decisions regarding recommendations for chemotherapy are then made based largely on the RS versus being driven by the patient's nodal status.

CONCLUSIONS

Level 1 evidence may be required before the AJCC breast cancer staging system will be further revised to incorporate genomic assays into staging node-positive patients. The RxPONDER trial will provide that data. In the meantime, the preponderance of evidence supports routine testing of patients with 1–3 positive nodes and considering endocrine therapy alone for those with a RS < 18. As we await the prospective trial results, perhaps we should consider other questions that can be addressed using genomic assays to differentiate the impact of biology versus the anatomic extent of disease to include determining the utility of these assays in patients with even greater nodal burden and in informing local regional therapy.

DISCLOSURES EAM has no relevant disclosures but does report having received compensation for participating in scientific advisory boards for Amgen, Astra-Zeneca, Genentech/Roche, Merck, Peregrine, SELLAS, and Tapimmune. TAK has received honoraria as a speaker and for participating in scientific advisory boards for Genomic Health.

REFERENCES

1. Hortobagyi GN, Connolly JL, Edge SB, et al. (2016) Breast. In: Amin MB, editors. AJCC Cancer Staging Manual. New York, Springer.
2. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med.* 2015;373(21):2005–14.
3. Wang M, Wu K, Zhang P, et al. The prognostic significance of the Oncotype DX recurrence score in $T_{1\text{-}2}N_1M_0$ estrogen receptor-positive HER2-negative breast cancer based on the prognostic stage in the updated AJCC 8th edition. *Ann Surg Oncol.* 2018. https://doi.org/10.1245/s10434-018-7068-3.
4. Petkov VI, Miller DP, Howlader N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer*. 2016;2:1607. https://doi.org/10.1038/npjbcancer.2016.17. eCollection 2016.
5. Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat*. 2017;163(2):303–10.
6. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2− node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. *NPJ Breast Cancer*. 2017;3:32. https://doi.org/10.1038/s41523-017-0033-7eCollection2017.
7. Hortobagyi GN, Shak S, Sledge Jr. GW, et al. Breast cancer-specific mortality (BCSM) in patients (pts) with node-negative (N0) and node-positive breast cancer (BC) guided by the 21-gene assay: A SEER-genomic population-based study. In: [P3-11-02] San Antonio Breast Cancer Symposium 2018.
8. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111–21.
9. National Comprehensive Cancer Network. Breast Cancer (Version 3.2018)
10. Mittendorf EA, Ballman KV, McCall LM, et al. Evaluation of the stage IB designation of the American Joint Committee on Cancer staging system in breast cancer. *J Clin Oncol*. 2015;33(10):1119–27.
11. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomized trial. *Lancet Oncol*. 2010;11(1):55–65.
12. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol*. 2010;28(11):1829–34.
13. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomized phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017;165(3):573–83.
14. Tamoxifen Citrate, Letrozole, Anaastrozole, or Exemestane with or without chemotherapy in treating patients with invasive breast cancer (RxPONDER). https://clinicaltrials.gov/ct2/show/NCT01272037. Accessed 29 Dec 2018.
15. Jasem J, Fisher CM, Amini A, et al. The 21-gene recurrence score assay for node-positive, early-stage breast cancer and impact of RxPONDER trial on chemotherapy decision-making: have clinicians already decided? *J Natl Compr Canc Netw*. 2017;15(4):494–503.
16. Natsuhara KH, Losk K, King TA, et al. Impact of genomic assay testing and clinical factors on chemotherapy use after implementation of standardized testing criteria. *Oncologist*. 2018 Aug 3 [Epub ahead of print]. https://doi.org/10.1634/theoncologist.2018-0154