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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Cancers of Special Histologic Subtypes Are Biologically Diverse

Audree B. Tadros, MD, MPH[1], Hannah Y. Wen, MD, PhD[2], and Monica Morrow, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Background/Objective. Cancers classified as "special histologic subtypes" are felt to have a good prognosis. We used the 21-gene Oncotype DX Breast Recurrence Score® multigene assay to examine prognostic variation within special histologic subtypes. We also examined the Recurrence Score® (RS) distribution among the more common ductal (IDC) and lobular (ILC) cancers.

Methods. 610,350 tumor specimens examined in the Genomic Health clinical laboratory from 2/2004 to 8/2017 were included. Specimen histology was classified centrally using a single H&E slide and World Health Organization criteria. RS distribution (low < 18, intermediate 18–30, and high ≥ 31) was compared among histologic subtypes.

Results. Median patient age was 60 years (IQR 51–67); 80% were node negative. Most patients had low RS results (59.2%); only 9.5% had high results. The lowest mean RS was seen in the papillary subtype (11); the highest in the IDC group (18.4). Mean RS for all special subtypes was lower than that of IDC patients. When the high RS threshold was decreased from 31 to 25, as used in the TAILORx and RxPONDER trials, the number of high RS-result patients increased from 9.5% to 16.8%. Patients with ILC had a lower mean RS result than patients with IDC, 16.5 versus 18.4.

Conclusion. There is substantial diversity in predicted prognosis among patients with cancers classified as special histologic subtypes, with 12–25% having intermediate RS results and 0.5–9% having high RS results. Pending further definition of the role of chemotherapy for patients with intermediate RS results by TAILORx and RxPONDER, the RS result may help to inform systemic therapy decisions in these patients.

Over the past decade, the importance of tumor biology in both the staging and treatment of breast cancer patients has become paramount. The majority of breast cancers are classified as infiltrating ductal carcinoma (IDC) not otherwise specified or infiltrating lobular carcinoma (ILC), and it is clinically recognized that wide variations in outcome exist among patients with cancers with these histologic features. The existence of breast cancer histologies with more favorable outcomes than those seen in patients with IDC and ILC is well documented.[1–6] Tubular, mucinous, papillary, and cribriform carcinomas are included in this group, and are termed "special histologic subtypes".

In recent years, molecular assays such as the 21-gene Oncotype DX Breast Recurrence Score® (RS) test (Genomic Health, Redwood City, CA) have been shown to better define prognosis than standard histopathologic features among hormone receptor-positive (HR+)/HER2 negative breast cancer patients, with and without axillary nodal metastases after treatment with endocrine therapy.[7–12] The American Society of Clinical Oncology (ASCO) endorsed RS use for both prognostic and predictive purposes in 2007, and current National Comprehensive Cancer Network (NCCN) guidelines recommend Oncotype DX® assay use for patients with HR+ HER2-negative, lymph node-negative or micrometastatic tumors greater than 5 mm in size, regardless of histologic subtype.[13,14] The increasing use of Oncotype DX testing has resulted in a substantial decline in chemotherapy use in this population.[15,16] However, little is known about the variability of RS results among histologic subtypes of breast cancer, particularly those with a favorable prognosis, to inform its

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M. Morrow, MD
e-mail: morrowm@mskcc.org

use in clinical practice, as the diversity of RS results among these special histologic subtypes has only been studied to a limited extent using institutional databases.[17–22]

Here we determine if RS values differ based upon histologic subtype and whether significant biologic heterogeneity exists within tumors classified as special histologic subtypes.

METHODS

A total of 619,866 invasive breast cancer tumor specimens examined in the Genomic Health clinical laboratory in the U.S. from 02/2004 to 08/2017 were identified. Of these, 9516 specimens were excluded due to missing histologic subtype ($n = 9284$) or recording of > 1 histologic subtype ($n = 232$). Histologic subtype was categorized using World Health Organization criteria after central review of a single hematoxylin–eosin-stained slide from each tumor specimen by board-certified surgical pathologists.[23] Invasive breast cancer tumor specimens classified as ductal, lobular (classic and other variants), mixed ductal/lobular, tubular, papillary, mucinous, and cribriform were included in the study.

The Oncotype DX Breast Recurrence Score assay was used to calculate the RS for each tumor specimen. The Oncotype DX test algorithm is based upon quantitative expression of 16 cancer-related genes and 5 reference genes, which has been previously described.[24] The expression of these genes is measured in triplicate using reverse transcription polymerase chain reaction (RT-PCR) from formalin-fixed, paraffin-embedded tumor tissue. Possible RS results range from 0 to 100, where a higher score indicates a greater risk of recurrence. Clinical data, including patient age, nodal status, and tumor grade (as determined by local laboratories), were routinely submitted to Genomic Health. Quantitative estrogen receptor (ER) and progesterone receptor (PR) gene scores based on RT-PCR were calculated for each tumor specimen.[25] A tumor was considered ER negative if gene score < 6.5, ER positive ≥ 6.5, PR negative < 5.5, and PR positive ≥ 5.5. Patients were considered to be HR+ if either ER or PR were positive.

Statistical Analysis

Descriptive statistics were calculated for the RS result based on originally reported cutoffs (Low < 18, Intermediate 18–30, High ≥ 31), as well as the cutoff points used for the TAILORx (Low < 11, Intermediate 11–25, and High > 25) and RxPONDER (Low ≤ 25 and High > 25) clinical trials.[10,26] RS distribution was analyzed by age, histologic subtype, and nodal status. Continuous variables are reported as the mean, median, and interquartile range (IQR). All analyses are descriptive, and because of the large study sample size, even small differences between groups were expected to be statistically significant, but potentially not clinically meaningful. All analyses were performed on de-identified data.

RESULTS

Patient/Tumor Characteristics

A total of 610,350 specimens were examined. Median patient age was 60 years (IQR 51–67), and the majority of patients (77%) were age > 50 years. Only 2.9% ($n = 17,666$) of patients were age < 40 years. There were 504,362 patients with ductal carcinoma, not otherwise specified, accounting for 82.6% of the entire cohort. Classic-type lobular carcinoma was present in 49,819 patients (8.2%), and mixed ductal and lobular carcinoma in 4.1% (25,329/610,350). There were 25,771 (4.2%) tumors of special histologic subtype. Of these, mucinous carcinoma was the most frequent ($n = 16,116$), followed by papillary ($n = 4159$), tubular ($n = 3599$), and cribriform ($n = 1897$) carcinomas, respectively. The highest median age, 64 years, was seen in the papillary subtype; the youngest, 52 years, in the classic lobular subtype. Overall, the majority of patients were HR+ (597,022, 97.8%). Among patients with special histologic subtypes, 99.2% (25,564/25,771) were HR+. The median ER gene score was 10.4; the median PR gene score was 7.6.

The majority of patients in the cohort were node negative (493,924, 80.9%). Only 9.2% (56,100/610,350) of patients were node positive (without further characterization), and the remainder had micrometastatic nodal disease or unknown/indeterminable nodal status. The incidence of nodal positivity varied from 3.5% to 11.5% across histologic subtypes.

The mean RS result for patients with special histologic subtypes was lower than the mean RS result for patients with more common subtypes (Table 1). The mean RS results for mucinous, papillary, tubular, and cribriform carcinomas were 14.9, 11.0, 14.5, and 12.6, respectively, compared to a mean RS of 18.4 for patients with IDC. Patients with special histologic subtypes were more likely to have a low RS (70.4–79.2%) compared to patients with the more common ductal and lobular subtypes (54.0–64.0%). Among the special histologic subtypes, the percentage of patients with a high RS ranged from 0.5% (19/3599) for patients with tubular carcinoma to 8.8% (366/4159) for patients with papillary carcinoma. Patients with IDC were the group most likely to have a high RS result (10.7%, 53,956/504,362). Among all subtypes, the

TABLE 1 Mean Recurrence Score and nodal status by histologic subtypes

	Total	Mean RS (SD)	Node negative
Overall	610,350	18 (10.8)	493,924 (80.9)
Ductal carcinoma, NOS	504,362	18.4 (11.2)	401,761 (79.7)
Lobular carcinoma, classic type	49,819	16.3 (6.9)	38,783 (77.9)
Lobular carcinoma, other variants	5069	18.2 (9.4)	3980 (78.5)
Invasive carcinoma, mixed	25,329	16.4 (8.5)	19,407 (76.6)
Mucinous carcinoma	16,116	14.9 (8.9)	13,902 (86.3)
Papillary carcinoma	4159	11 (13.5)	3422 (82.3)
Tubular carcinoma	3599	14.5 (5.7)	3175 (88.2)
Cribriform carcinoma	1897	12.6 (9.6)	1583 (83.5)

RS Recurrence Score, *SD* standard deviation

majority of patients had a low RS result (59.2%, 361,574/610,350) and only 9.5% (58,027/610,350) had a high RS result (Fig. 1). Patients with classic-type ILC had a lower mean RS result than patients with IDC, 16.5 versus 18.4, while the mean RS for ILC variants (18.2) was very similar to the mean RS for IDC (18.4). In addition, patients with classic ILC were much less likely to have a high RS result compared to patients with ILC variants (2.5% vs. 8.4%).

In the ongoing TAILORx and RxPONDER trials, the high-risk RS threshold was defined as > 25 rather than the > 30 cutpoint used in the original validation studies.[7,8,10,26] Using the lower threshold of > 25 to define a high score, the number of patients with a high-risk RS result increased from 9.5% (58,027) to 16.8% (102,348) (Figs. 2, 3). Patients with tubular carcinoma remained the least likely subtype to have a high RS (3.2%), and patients with ILC variants (18.5%) and IDC (18.3%) were the most likely to have a high RS. Using the TAILORx RS cutoffs, the majority of patients with special histologic subtypes had an RS of 11–25 except those with papillary carcinoma, where 62.8% of patients had an RS < 11.

DISCUSSION

Traditionally, tumors of special histologic types including mucinous, papillary, tubular, and cribriform carcinomas have been thought to portend a favorable prognosis compared to the more common subtypes of invasive ductal and lobular carcinoma. A retrospective review of 1090 node-negative patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-06 demonstrated improved survival among those patients with tubular, mucinous, and papillary carcinoma.[5] Patients with favorable subtypes were found to have a significantly improved relative risk for 10-year mortality compared to patients with unfavorable histologic

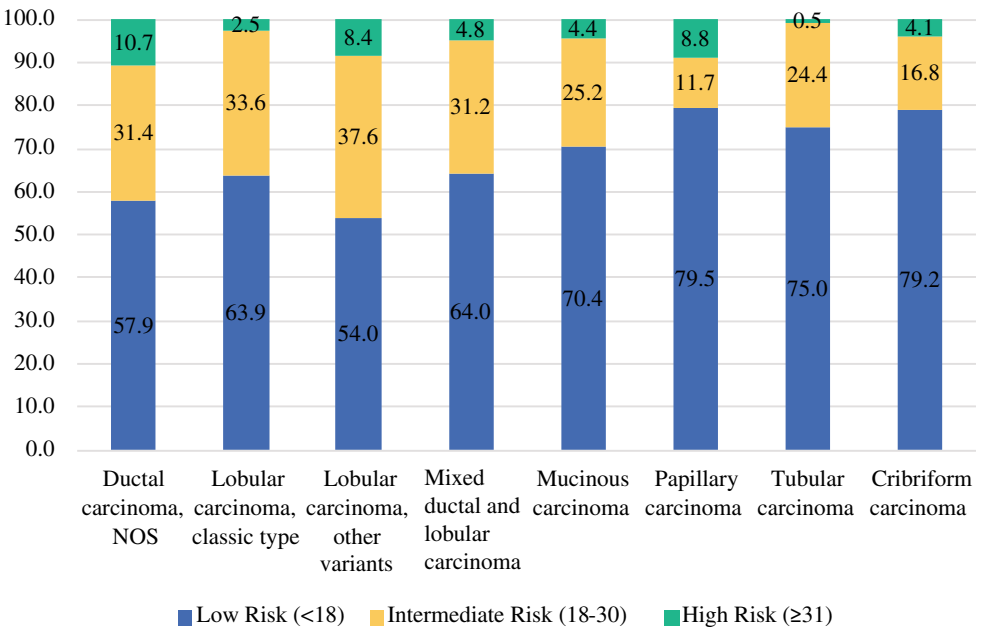

FIG. 1 Distribution of Recurrence Score result by tumor subtype using standard cutoffs

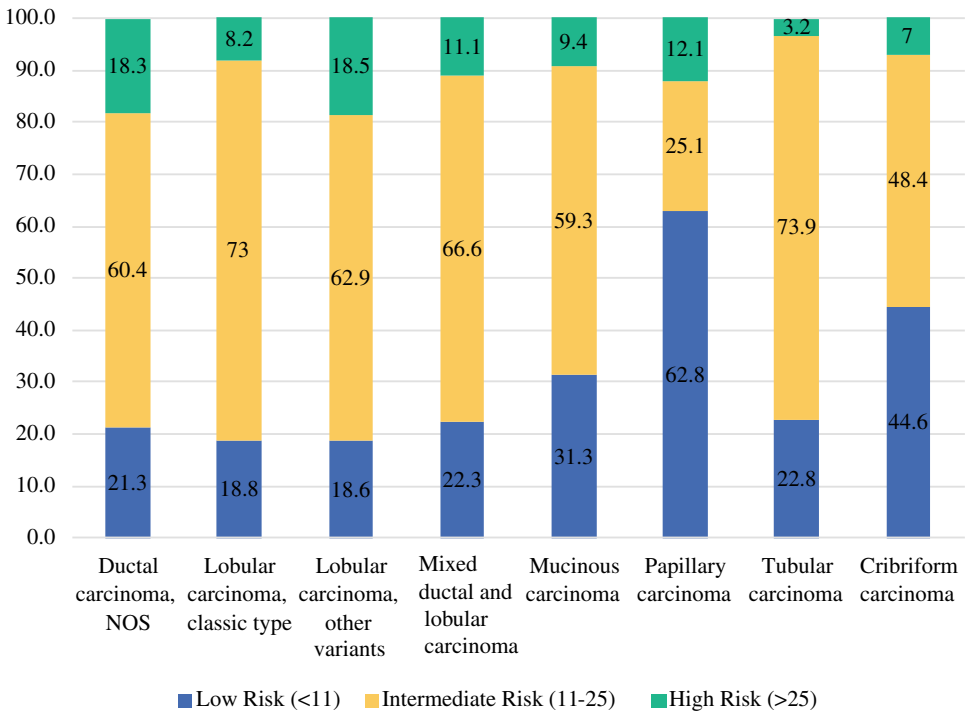

FIG. 2 Distribution of Recurrence Score result by tumor subtype using TAILORx cutoffs

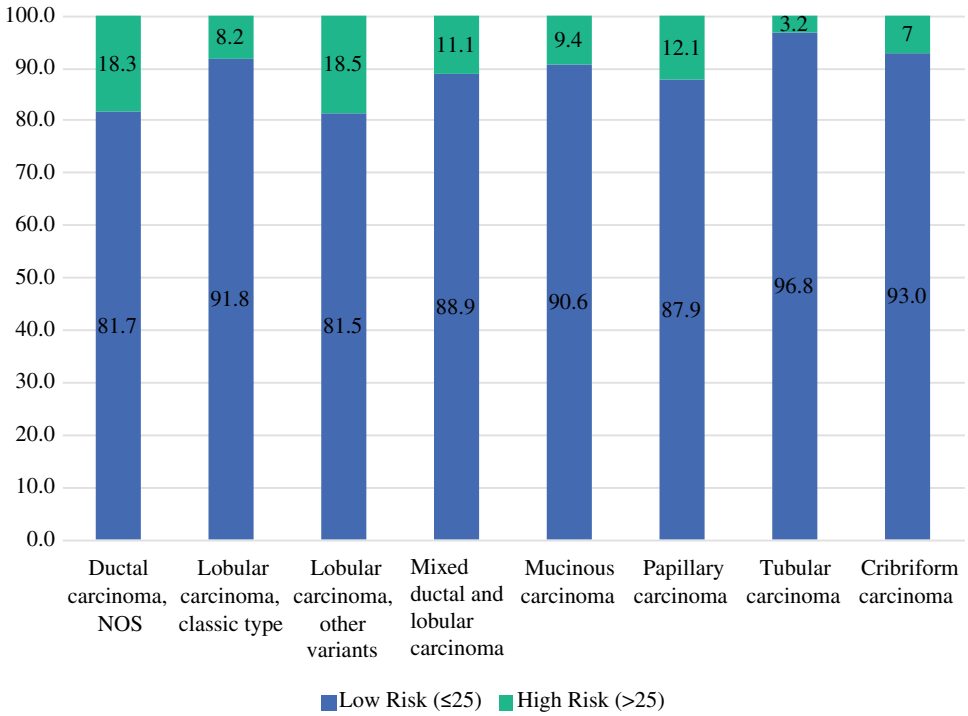

FIG. 3 Distribution of Recurrence Score result by tumor subtype using RxPONDER cutoffs

subtypes which included ductal carcinoma NOS and atypical medullary carcinoma (0.25 vs. 1.00, $p < 0.0001$). A consecutive series of 1621 women with primary, non-metastatic breast cancer diagnosed between 1973 and 1987 demonstrated improved survival among patients with tubular, mucinous, and cribriform carcinomas compared to patients with IDC.[6] In their series, the 10-year survival for patients with IDC was 47% compared to 90%, 91%, and 80% for tubular, cribriform, and mucinous carcinoma, respectively.

In this study utilizing a large, prospectively collected database of a nationwide sample of breast cancer patients with centralized pathology review and standardized assessment of RS result, we found significant diversity

among RS results for patients with tumors classified as special histologic subtypes. The mean RS results for patients with special histologic subtypes were lower than was seen for patients with IDC and ILC variants, and the majority of patients within all special histologic subtypes had a low- or intermediate-risk RS. High RS results were seen in only 0.5% of patients with tubular cancers, but among other special histologic subtypes, the rate of high RS results ranged from 4.1% to 8.8%, indicating considerable variability between subtypes, and this variability increased considerably when the cutoff for a high risk score of > 25 was used.

Our results are similar to those reported in 3 small single-institution studies retrospectively examining the diversity of RS results among special histologic subtypes.[18–20] Memorial Sloan Kettering Cancer Center reported their experience of 57 patients with special histologic subtypes of breast cancer with favorable prognosis treated from 09/2006 to 01/2015.[20] Thirty-three patients had mucinous carcinoma, 10 patients had tubular carcinoma, and 14 patients had papillary carcinoma. All patients had a low- or intermediate-risk RS, and all patients had a tumor grade of 1 or 2. Median recurrence scores for mucinous carcinoma, tubular carcinoma, solid papillary carcinoma, and encapsulated papillary carcinoma were 13, 14, 7, and 3, respectively. These median recurrence scores are similar to the mean RS results reported in our study for mucinous, tubular, and papillary carcinoma (14.9, 14.5, and 11.0, respectively). Similarly, Hanna et al.[19] found in their institutional experience of 62 patients with tubular carcinoma that all patients had a low- or intermediate-risk RS. Bomeisl et al.[18] reported on a small experience of 4 patients with invasive mucinous carcinoma and 1 patient with tubular carcinoma. The mean RS result for patients with invasive mucinous carcinoma was 17.2, and the RS result for the patient with tubular carcinoma was 10. In contrast, our study found that there is a subset of patients among each of these special histologic subtypes that falls into the high RS group. We hypothesize that the lack of high RS results seen in these prior studies was likely due to their small sample sizes.

There is controversy in the literature regarding the prognosis of patients with ILC compared to IDC, with studies reporting worse, similar, or better outcomes for ILC when comparing these 2 subtypes.[27,28] ILC is a distinct histologic entity from IDC, which is associated with larger tumor size at diagnosis, better tumor differentiation, higher rates of hormone receptor positivity, and a poorer response to neoadjuvant chemotherapy.[27,29,30] Patients with ILC can be separated into 2 groups: classic versus other variants (pleomorphic, solid, alveolar, signet ring, apocrine, and histiocytoid).[31,32] Patients with other variants of lobular carcinoma have been described in the literature as having a greater degree of cellular atypia and pleomorphism, which is often associated with a poor clinical outcome compared to classic-type ILC and IDC.[28] When comparing classical-type lobular carcinoma to other variants of lobular carcinoma, a more favorable outcome has been shown for patients with classical-type lobular carcinoma.[33–35] Given the poor overall response of patients with lobular carcinoma to chemotherapy, the use of the RS result as a predictive tool to identify those likely to benefit from chemotherapy is of great interest.

Three studies have previously looked at the variation in RS result among patients with ILC.[17,18,21] In a retrospective review of 131 cases of IDC, 30 cases of ILC, and 15 cases of mixed ductal/lobular carcinoma, mean RS results were 19.4, 15.7, and 14.1, respectively, and 13.7% of patients with IDC had a high RS compared to 0% of patients with ILC. Among the ILC group, all patients had a tumor grade of 1 or 2. Felts et al.[21] examined the variation in RS results for 36 patients with ILC (all subtypes except pleomorphic) and 6 patients with pleomorphic ILC treated from 2001 to 2011. Only 1 of 36 patients with ILC and non-pleomorphic variants was found to have a high RS result. In our study, the mean RS result for patients with classic ILC (16.3) was lower than was seen for variants of ILC (18.2). In addition, a higher proportion of patients with variants of ILC had a high-risk RS result compared to patients with classic ILC (8.4% vs. 2.5%). Patients with variants of ILC and IDC had a similar mean RS result and distribution of recurrence scores, while patients with ILC of classic type had a lower mean RS and a lower percentage of patients with a high recurrence score compared to patients with IDC.

At this time, the clinical impact of the use of the RS result in patients with tumors of special histologic subtypes is highly dependent upon the definition used for a high score and the outcome of the TAILORx trial examining the benefit of chemotherapy in patients with intermediate-risk recurrence scores.[26] When the TAILORx RS cutoffs (Low RS < 11, Intermediate 11–25, and High ≥ 25). were applied to our cohort, high risk scores were seen in more than 5% of patients with all special histologic subtypes except those with tubular cancer, suggesting that these patients are candidates for chemotherapy. The majority of patients across all special histologic subtypes except papillary carcinoma had an intermediate risk score. Should the TAILORx trial show a benefit for chemotherapy in the intermediate RS group, this would provide compelling evidence for the use of the Oncotype DX Breast Recurrence Score test in patients with tumors of special histologic subtypes.

Strengths of our study include the very large sample size which allowed us to analyze more than 25,000 tumors of uncommon histology and the central confirmation of the

pathologic diagnoses. However, there were weaknesses. It is possible that patients with tumors of special histologic subtype felt to be at higher risk for recurrence based on standard clinic-pathologic features were selected for Oncotype DX testing, and that our results overestimate the proportion of high RS results in this group, although the likelihood of this is minimized by the large number of samples studied. Additionally, the number of patients with tumors of special histologic subtypes included in the development and validation of the RS is unknown, and likely to be small, so outcome data specific to these subtypes is lacking.

CONCLUSIONS

There is substantial diversity in predicted prognosis among patients with breast cancers classified as special histologic subtypes, with 12–25% having intermediate RS results and 0.5–9% having high RS results. Patients with classic-type ILC are less likely to have a high RS result when compared to patients with other variants of ILC and IDC. Pending further definition of the role of chemotherapy for patients with intermediate RS results by the TAILORx trial as well as the role for Oncotype DX Breast Recurrence Score testing for patients with nodal metastasis in the RxPONDER trial, the RS result may help to inform systemic therapy decisions in these patients.

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