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PRECLINICAL STUDY

Relationship of histologic grade and histologic subtype with oncotype Dx recurrence score; retrospective review of 863 breast cancer oncotype Dx results

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Abstract

Purpose Oncotype Dx (ODx) is a multigene assay that is prognostic and predictive in estrogen receptor (ER) positive early breast cancer. ODx recurrence score (RS) is reported to be histologic grade dependent. Relationship of RS with breast cancer histologic subtypes is unknown. This study was designed to assess the relationship of histologic subtype with RS. Histologic grade dependence of RS was also investigated.

Methods Results of consecutive ODx tests (1/2007–7/2016) from two institutions were reviewed. Histologic subtypes (in: Lakhani et al., WHO classification, IARC Press, Lyon, 2012), combined Nottingham histologic grade, age and tumor size were recorded from pathology reports. Univariate and multivariate analysis was performed to investigate the relationship between RS and ODx risk categories and histologic subtypes, grade, age and tumor size.

Results RS was grade dependent. RS of grade 1 and grade 2 tumors were significantly lower than grade 3 tumors. There was no high-risk grade 1 tumor. In favorable histologic subtypes there was no high-risk tumor. Mean RS of grade 1 lobular tumors was significantly higher than grade 1 ductal tumors. Using newer ODx cut-offs, 5 grade 1 tumors were reclassified as high risk (RS > 25) and grade 3 lobular tumors showed significantly higher rate of reclassification as high-risk than grade 3 ductal tumors. In a multivariate analysis, only grade showed a significant positive correlation with RS. Adding dichotomous histologic subtyping (favorable vs. non-favorable) to grade further improved correlation with RS.

Conclusions The Oncotype Dx result is impacted by histologic grade and histologic subtype. Tumors with favorable histologic subtypes and histologic grade 1 tumors do not have high-risk RS. High RS in a grade 1 tumor or in a tumor with favorable histology is unusual that warrants further investigation. Invasive lobular carcinomas rarely show high-risk RS. Histologic grade and histologic subtype should be considered while ordering ODx testing.

Keywords Breast cancer · Prognosis · Survival · Genetics · Chemotherapy · Recurrence score · Ductal carcinoma · Lobular carcinoma

Introduction

Adjuvant chemotherapy reduces breast cancer recurrence risk, even in early stage estrogen receptor positive disease, which has inherently low risk of recurrence [1–3]. Last few decades have seen an intense and continuous effort to identify the clinical, histological and molecular variables providing estimates of breast cancer recurrence. Traditional clinical and pathologic features like anatomic stage (tumor size, extent of lymph node involvement), histologic grade and estrogen (ER), progesterone receptor (PR) and HER2 status determine survival in all breast cancers [4]. Retrospective tissue analysis of NSABP (B-14 and B-20) cohorts showed that Oncotype Dx (ODx) assay (Genomic Health, Redwood

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City, California) provides estimate of risk of distant recurrence and overall survival in ER+ early breast cancer [5]. Recurrence score (RS) is reported to outperform traditional clinical and pathologic factors (age and tumor size) in predicting the recurrence risk [5, 6]. However, findings from TAILORx study confirm strong relationship of RS with tumor grade [7] and histologic grade is one of the anatomic stage modifiers in 8th AJCC breast cancer staging [4]. The strongly weighted components (ER, HER2 and proliferation) included in the mathematical equation used to compute RS are routinely assessed during histological evaluation of the breast cancers [5]. Not surprisingly, many algorithms (like Magee equations) perform at par with ODx when separating low and high recurrence risk groups [8–15].

Histological subtype is one of the many tumor-related parameters that are reported in a standard breast cancer pathology report [16]. Little is known about the relationship of RS with histologic subtypes of breast cancer. Lobular cancers rarely show high recurrence score [17–21]. The so-called good histologic subtypes of breast cancer do not have high RS [22–24]. Distribution of RS in aggressive histologic subtypes is unknown [24]. We were interested in studying the relationship of histologic subtype and histologic grade with RS. We hypothesized that a combination of grade and subtype may improve correlation with the RS.

Materials and methods

Case selection

This is a retrospective study. All consecutive ODx reports between 1/2007 and 7/2016 from two Hospitals (WIHRI and RIH) were reviewed. RS and risk groups were obtained. Cases were stratified into low-risk (RS = 0–17), intermediate risk (RS = 18–30), and high-risk (RS > 30) categories, using originally proposed RS cut-offs. New risk categories were also assigned using updated RS cut-offs: low-risk (RS = 0–10), intermediate risk (RS = 11–25), and high-risk (RS > 25) categories. Histologic subtype (WHO classification), tumor grade (Nottingham histologic grade), tumor size, age and follow-up (if available) were obtained from original pathology reports and cancer registry. Institution review boards approved the study. Univariate and multivariate analysis was performed using SPSS version 24. Differences were considered significant with P value < 0.05.

Results

The histologic subtypes (HSu) of 863 cases sent for ODx testing (during the study period) are provided in Table 1. The two most common HSu are invasive ductal carcinoma of no special type (IDC, NST; $n = 633$, 73.3%) with an average RS of 17.1 ± 9.0, followed by invasive lobular carcinoma (ILC, $N = 121$, 14.0%) with an average RS of 16.9 ± 6.9. Other subtypes included mixed ductal and lobular carcinoma (ICDL), invasive ductal carcinoma with micropapillary features (ICMP), mucinous carcinoma (MC), mixed ductal and mucinous carcinoma (IDMC), and tubular/cribriform carcinoma (TC). The RS in 1 case of carcinoma with medullary features was 63 (high risk).

We next investigated the RS in the so-called favorable HSu. In favorable HSu (MC and TC; $n = 18$), there were 12 (67%) low-risk, 5 (27%) intermediate-risk and 1 (6%) high-risk RS tumor (RS = 35). The high-risk RS tumor was a histologic grade 2 mucinous carcinoma with extensive in situ component. Review of original pathology, to clarify the HSu-RS discordance, revealed that the mucinous tumor showed morphological features of a micropapillary variant of mucinous carcinoma. Therefore, this tumor would not be included in favorable histologic subtype. The tumor cells were arranged in micropapillae that displayed reverse polarization. In unfavorable HSu (ICMP, $n = 21$) there were 13 (61.9%) low-risk, 6 (28.6%) intermediate risk and 2 (9.5%) high-risk tumors. The mean RS in aforementioned favorable and unfavorable HSu were similar.

Out of 208 histologic grade 1 tumors (24.1%), 140 (67.3%) were classified as low risk and 68 (32.7%) were predicted as intermediate risk for recurrence. No grade 1 high-risk tumor was identified (Table 2). Out of 115 grade 3 tumors, 30 (26.1%) were low risk (RS < 18) and 33 (28.7%) were high risk (RS > 30). The RS was dependent on histologic grade. Mean RS of grade 3 tumor (24.99; 22.83–27.16) was significantly higher from grade 1 (14.76; 14.02–15.5) and grade 2 (16.14; 15.44–16.83) tumors (Table 3). RS difference between grade 1 and grade 2 tumors did not achieve statistical significance ($P = 0.121$).

The mean RS for lobular (16.93 ± 6.9; $n = 121$) and ductal tumors was (16.99 ± 9.0; $n = 742$) similar. When RS was compared in grade-matched ductal and lobular tumors, histologic grade 1 lobular tumors showed significantly higher mean RS than ductal tumors (17.56 ± 3.5 vs. 14.49 ± 5.5; $P = 0.003$). Mean RSs between grade 2 and 3 ductal and lobular tumors were similar. Lobular carcinoma had significantly higher proportion of grade 2 tumors (77% vs. 60.1%).

In multinomial regression analysis, using older or new RS cut-offs, the odds ratios for grade 1 and 2 tumors to be low or intermediate risk were significantly higher than grade 3 tumors. The odds of a lobular tumor to be in intermediate risk were significantly higher than ductal tumors. In a multivariate analysis, histologic grade showed a significant positive correlation with RS. Tumor phenotype, age and size were not significant predictors of the RS.

Table 1 Cases in recurrence risk categories based on histologic subtypes and grade

Histologic subtype	Low (0–17), *n* (%)	Intermediate (18–30), *n* (%)	High (31–100), *n* (%)	Total
Invasive ductal carcinoma				
Grade 1	113 (69.8)	49 (30.2)	0	162
Grade 2	239 (63.1)	119 (31.4)	21 (5.5)	379
Grade 3	23 (25.0)	41 (44.6)	28 (30.4)	92
Subtotal	375 (59.2)	209 (33.0)	49 (7.7)	633
Invasive lobular carcinoma				
Grade 1	9 (50.0)	9 (50.0)	0	18
Grade 2	53 (56.4)	39 (41.5)	2 (2.1)	94
Grade 3	3 (33.3)	5 (55.6)	1 (11.1)	9
Subtotal	65 (53.7)	53 (43.8)	3 (2.5)	121
Invasive carcinoma with ductal and lobular features				
Grade 1	10 (71.4)	4 (28.6)	0	14
Grade 2	32 (78.0)	9 (22.0)	0	41
Grade 3	3 (37.5)	4 (50.0)	1 (12.5)	8
Subtotal	45 (71.4)	17 (27.0)	1 (1.6)	63
Mucinous carcinoma				
Grade 1	6 (75.0)	2 (25.0)	0	8
Grade 2	2 (50.0)	1 (25.0)	1 (25.0)	4
Subtotal	8 (66.7)	3 (25.0)	1 (8.3)	12
Mixed ductal and mucinous carcinoma				
Grade 1	0	2 (100)	0	2
Grade 2	2 (50.0)	2 (50.0)	0	4
Subtotal	2 (33.3)	4 (66.7)	0	6
Tubular/cribriform carcinoma				
Grade 1	2 (50.0)	2 (50.0)	0	4
Grade2	2 (100)	0	0	2
Subtotal	4 (66.7)	2 (33.3)	0	6
Carcinoma with medullary features				
Grade 3	0 (0)	0 (0)	1 (100)	1
Carcinoma with invasive micropapillary component				
Grade 2	12 (75.0)	4 (25.0)	0 (0)	16
Grade 3	1 (20.0)	2 (40.0)	2 (40.0)	5
Subtotal	13 (61.9)	6 (28.6)	2 (9.5)	21
Total	512 (59.3)	294 (34.1)	57 (6.6)	863

Table 2 Cases in recurrence risk categories with respect to grade and prognostic group

	Low (0–17), no. (%)	Intermediate (18–30), no. (%)	High (31–100), no. (%)	*P* value[a]
Histologic grade				
Grade 1	140 (67.3)	68 (32.7)	0	< 0.001
Grade 2	342 (63.3)	174 (32.2)	24 (4.5)	
Grade 3	30 (26.1)	52 (45.2)	33 (28.7)	
Prognostic group (Grade + HSu)				
Good	145 (68.1)	68 (31.9)	0	< 0.001
Poor	42 (32.3)	56 (43.1)	32 (24.6)	

[a]Likelihood ratio

Table 3 Recurrence score in different grades, histologic subtypes and prognostic groups of tumors

	Recurrence score, mean	Upper bound	Lower bound	*P*-value
Grade				
1	14.8	14	15.5	< 0.0001
2	16.1	15.4	16.8	
3	25	22.8	27.2	
Histology				
Ductal	17	16.3	17.7	0.94
Lobular	16.9	15.7	18.1	
Prognostic group				
Favorable	14.8	14.1	15.5	< 0.0001
Unfavorable	23.3	21.3	25.3	

Combining histologic grade and HSu, tumors were further classified into "favorable" ($n = 130$) and "unfavorable" ($n = 213$) prognostic groups. "Favorable" group: grade 1 tumors and or TC and MC; and "unfavorable" group: ICMP and grade 3 tumors. No tumor in the favorable prognostic group was classified as high risk. The RS of favorable prognostic group was significantly lower than the unfavorable prognostic group (14.8 ± 5.3 vs. 23.3 ± 11.4; $P < 0.001$). In unfavorable prognostic group, there were 42/130 (32.3%) cases with low RS, compared to 145/213 (68.1%) cases with low RS in favorable prognostic group (Table 3). Regression analysis confirmed a slightly better correlation of the prognostic group scheme with the RS ($r^2 = 0.24$ vs. 0.25) than just histologic grade.

Using older RS cut-offs, there were 512 (59.3%) low risk, 294 (34%) intermediate risk and 57 (6.7%) high-risk tumors. With updated RS cut-off, 344 (67.2%) originally low-risk tumors were reclassified as intermediate risk and 51 (17.3%) intermediate-risk tumors were reclassified as high risk. Using new cut-off of > 25 for high risk, 5/208 (2.4%) grade 1 tumors were reclassified as high-risk. Using updated cut-offs 695 (80.5%) tumors were eligible for neoadjuvant chemotherapy (RS > 10). The shift in the risk category was seen in all the histologic grades, however, it was phenotype dependent. With updated cut-off, amongst grade 3 tumors, lobular phenotype had a significantly higher chance of shift to high-risk category than the ductal phenotype ($P = 0.0004$).

Follow-up data was available for 318 patients. None of the tumors with RS < 11 recurred. There was one distant recurrence in a tumor with RS < 18 and two distant recurrences in tumors with RS > 17. All three recurrences were seen with ductal carcinomas.

Discussion

ODx is frequently used to guide adjuvant treatment of early stage ER+ breast cancer [4]. Recently, updated AJCC cancer staging incorporated use of ODx in modifying the anatomic stage [4]. However, exact predictive and prognostic implications of RS value are still under investigation. One of the significant predictor of RS is tumor histologic grade [7, 25], which is not surprising since histologic grade is computed using histological findings (mitosis, nuclear atypia and tubule formation) that are indirectly related to individual genes (ER, HER2 and proliferation) products contributing to ODx [15, 25].

We did not find any grade 1 tumor with high RS supporting strong relationship of grade and RS. Unusually high RS has been reported in a low-grade tumor [26]. High RS in this setting is attributed to the presence of reactive stromal cells or mitotically active inflammatory cells that are present intermixed with the tumor. Finding of an elevated RS (intermediate or high-risk) in a low-grade tumor should also raise a question of validity of the results [24]. Pathologists should be careful in selecting the correct tissue block for ODx assay and the tissue block containing previous biopsy site changes or excessive inflammatory cells or reactive stroma should be avoided for ODx testing.

Another interesting finding in our study is the relationship of ODx with the histologic subtype. Pure tubular, cribriform, and mucinous carcinomas are considered favorable histologic subtypes with good prognosis [27]. Conversely invasive micropapillary carcinoma is an aggressive histologic subtype that presents with higher T stage and frequent lymph node metastasis at presentation [28]. Only one of the 18 favorable histologic subtype tumor in our study showed high RS, which was a mucinous carcinoma. On rereview of the histology of this case, the tumor was reclassified as micropapillary mucinous carcinoma.

Micropapillary variant of mucinous carcinoma is a recently identified aggressive histologic subtype that shares morphological finding with a mucinous and a micropapillary carcinoma [29]. Our finding adds weight to the relationship of ODx and tumor histologic subtypes. Accurate histologic classification of the tumor is imperative since histologic subtype may explain unusual ODx results. On the contrary, unusually higher RS has been reported in Tubular carcinoma which is attributed to cellular desmoplastic stroma that is a histologic hallmark of this favorable histologic tumor type [26]. As previously discussed, falsely elevated RS may also be secondary to core needle biopsy related reparative changes.

ODx results in lobular carcinoma are frequently reported to be either low or intermediate risk [17–21]. In

our cohort, there were significantly higher intermediate risk tumors in lobular phenotype than ductal carcinomas. Most of the lobular carcinomas were grade 2 (77%). In a study by Kelly et al. all lobular tumors ($n = 40$) had low/intermediate risk RS [17]. In a larger cohort of ILC ($n = 135$), with 27 non-classical ILC, only 2 (1.5%) tumors had high-risk RS, both of which were pleomorphic-type ILC [18]. Similar findings were reported in a different study of 158 lobular carcinomas. Like ductal carcinoma, in ILC, authors reported association of RS with PR and KI-67 [19]. In a recent study of 102 lobular carcinomas RS was reported to be significantly different between lobular and ductal carcinoma and between classical and pleomorphic-type ILC [20]. In our cohort, there were 3/121 ILC with high-risk RS, 2 of these were grade 2 and 1 was grade 3. Like previous studies, we report low incidence of high-risk RS in lobular carcinoma as compared to ductal carcinoma (15.5% vs. 2.5%). This association was not significant in multivariate analysis and it is likely grade-dependent. We also noted a significantly higher average RS in grade 1 ILC than grade 1 ductal carcinomas, which has not been noted in the earlier studies.

The cut-offs for the ODx risk groups have been revised recently [7]. In our cohort, using new cut-offs, the risk categories changed in 45.7% tumors, with 67% originally low risk and 17% of intermediate risk tumors moving to intermediate and high-risk categories, respectively. Interestingly, five grade 1 tumors were classified as high-risk. Grade 3 lobular tumors more frequently shifted to high-risk category than ductal tumors. Kizy et al. recently reported that with new cut-offs up to 8% of ILC were categorized as high risk [21].

In summary, we report, in detail, relationship of histologic grade and histologic subtypes with ODx recurrence score. Knowledge of grade–histotype–RS relationship is imperative while ordering and interpreting RS. Most importantly, RS should be interpreted in the context of histological findings like grade, especially the mitosis, and histologic subtype. RS results that appear to be discordant (high RS in grade 1 tumors) should be addressed and reconciled in a multi-disciplinary setting.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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