Molecular subtyping reveals uniqueness of prognosis in breast ductal carcinoma in situ patients with lumpectomy

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Abstract

Background: We aimed to analyse the discrepancy in clinical features and prognosis between molecular subtypes in primary ductal carcinoma in situ (DCIS) patients with lumpectomy.

Methods: Primary DCIS patients were identified from the Surveillance, Epidemiology, and End Results registries database from 2010 to 2017. Based on immunohistochemistry markers of hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2), enrolled DCIS cases were divided into four molecular subtypes, HR-HER2-, HR-HER2+, HR + HER2-, and HR + HER2+. Clinical features and prognosis were compared between molecular subtypes. Radiotherapy (RT) effects on prognosis were also analysed in each molecular subtype.

Results: A total of 5,628 DCIS cases were retrospectively enrolled in this study. HR-HER2-, HR-HER2+, HR + HER2-, and HR + HER2+ cases have smaller tumor size (72.6%, P < 0.001) and lower grade (23.5%, P < 0.001). In univariate analyses, HR-HER2+ cases have significantly higher ipsilateral breast event (IBE) recurrence than HR-HER2- cases (P = 0.010). HR-HER2- cases show higher disease-specific mortality than HR + HER2+ cases (P = 0.021). In high-risk DCIS cases, RT reduces the absolute 5-year IBE incidence by 1.3%, 0.7%, 1.9%, and 2.6%, respectively in HR-HER2-, HR-HER2+, HR + HER2-, and HR + HER2+ cases, respectively.

Conclusion: In this population-based study, DCIS cases have diverse clinical and prognostic features for different molecular subtypes. Adjusting treatment strategies according to DCIS molecular subtypes is worth advancing.

Keywords: Ductal Carcinoma in situ, Molecular subtype, Lumpectomy, Recurrence

1. Introduction

The gene expression profiling of invasive breast cancers (IBCs) reveals the heterogeneity of this disease [1–3]. There are four main intrinsic subtypes, luminal A, luminal B, human epidermal growth factor receptor-2 (HER2)-enriched, and basal-like, which are clinically classified by molecular profiling [4]. These intrinsic subtypes categorized by gene expression profiling have unique clinical and prognostic features [1,5,6]. Three immunohistochemistry (IHC) markers, estrogen receptor (ER), progesterone receptor (PR), and HER2, are commonly used as reliable surrogates for expression profiling-based subtyping. IHC-based subtyping has relatively high consistency with gene expression profiling-based subtyping in IBC and is recommended by the St Gallen guidelines for clinical diagnosis [7]. The treatment strategy, clinical features, and prognosis are diverse between the four subtypes classified by IHC-based subtyping [8,9].

Ductal carcinoma in situ (DCIS) is a preinvasive disease [10]. The prevalence of molecular subtypes is different between DCIS and IBC [11], and the clinical features and prognosis of distinct molecular subtypes of DCIS are unique from those of IBC. For example, the basal-like subtype has the poorest prognosis among the four subtypes in IBC [12]. However, it has less aggressive behaviors than the other subtypes in DCIS [13]. The molecular subtype of subsequent ipsilateral IBC is frequently inconsistent with primary DCIS [14]. Subclone evolution may cause this inconsistency [15,16]. All of these indicate that the molecular subtypes reflect the intrinsic features of DCIS implying its heterogeneity at molecular level.

Although the breast disease-related mortality for DCIS after surgery is extremely low [17], the possibility of ipsilateral breast event (IBE) incidence increases with time after lumpectomy [18]. In consideration
of molecular subtypes in DCIS, specialized treatment options are applied in clinical trials to reduce IBE incidence. Hormone receptor-positive DCIS patients can be slightly benefit from endocrine therapy to reduce IBE incidence [19]. For HER2-positive DCIS patients, HER2-targeted therapy is an alternative option to reduce IBE incidence after lumpectomy [20]. Apart from the above treatments, the radiotherapy (RT) is a primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy. The effect of RT on reducing IBE incidence is clear in DCIS with lumpectomy after primary treatment for all DCIS patients after lumpectomy.

In this study, we aimed to use a population-based database to analyse the discrepancy in clinical features and prognosis between molecular subtypes in primary DCIS patients with lumpectomy.

2. Material and methods

2.1. Data sources and cohort selection

We identified primary DCIS cases from the Surveillance, Epidemiology, and End Results (SEER) registries database (November 2020 submission) [21]. SEER*Stat version 8.3.9 was used to conduct case listings. Since patient-level identifiers are not available to SEER users, this study was exempted from IRB review and approval. As the HER2 record was included for breast disease in the SEER database after 2010, we only included the primary DCIS cases from 2010 to 2017 in this study. Cases with behavior code 2 and the following histology codes were identified as DCIS: 8010, 8050, 8201, 8230, 8500, 8501, 8503, 8504, 8507, 8522, and 8523. Female patients with lumpectomy (surgery codes 20–24) and a follow-up time and/or interval time between primary DCIS and IBE of more than 6 months were included in this study. Patients who received chemotherapy were excluded. In total, 5,628 cases with intact ER, PR, and HER2 records were identified for further study. The flowchart shows the process of case selection in Fig. 1.

2.2. Outcome variables

IBE and disease-specific (DS) mortality are the two main outcomes in this study. The IBE recurrence time is defined as the interval time between the primary disease and the first in situ and/or invasive recurrence. The DS mortality time is defined as the interval time between the primary disease and the death of breast disease. Moreover, the incidence of in situ IBE, invasive IBE, and non-DS mortality was also the secondary outcome in this study. Non-DS mortality is defined as death of other causes other than breast disease.

2.3. Statistical analyses

To address the missing data regarding race (n = 35, 0.6%), grade (n = 584, 10.4%), and size (n = 1,028, 18.3%), we imputed these missing data using the following variables in the model: year of diagnosis, age, race, histology subtype, grade, tumor size, hormone receptor (HR) status, HER2 status and RT. As ER and PR statuses have high consistency, we combined these two variables into HR status for analyses. After imputation ten times, the new data set with no missing data was used for further analyses.

According to HR and HER2 statuses, DCIS cases in this study were classified into four molecular subtypes, HR-HER2-, HR-HER2+, HR+HER2+, and HR+HER2-. The clinical features were compared among these four molecular subtypes by Chi-square test in SPSS software version 26 (IBM Corp., Armonk, NY, US). The modified prognostic score, which is a designed scheme with 6 total points by scoring age (>60 years, 40–60 years, and <40 years), tumor size (<16 mm, 16–40 mm, and >40 mm), and grade (low, intermediate, and high) from 0 to 2 for each factor, was used to stratify local recurrence risk for DCIS patients [18,22]. The cumulative incidence curves of IBE recurrence and mortality were compared between the four molecular subtypes by log-rank test. Multivariate analyses for prognosis between the four molecular subtypes were compared in non-weighted Cox proportional hazards and Fine & Gray competing risks regression models. In competing risk models, IBE recurrence and all-cause mortality, DS mortality and non-DS mortality, as well as invasive and in situ IBE recurrence were regarded as competing events in this study.

To evaluate the RT effects on prognosis in each subtype, in consideration of imbalanced clinical features between the RT and non-RT groups, we balanced variables between the two groups by inverse propensity score weighting (IPSW). The propensity score was calculated in SPSS software by using covariates (year of diagnosis, age, race, histology subtype, grade, and tumor size) through a binary logistic regression model. Cases in the RT and non-RT groups for each molecular subtype were weighted by inverse propensity score calculated as (1/propensity score) or (1/(1-propensity score)), respectively. The cumulative incidence of IBE and mortality for RT and non-RT groups in each molecular subtype were compared by weighted log-rank test. Multivariate analyses, the effects of RT on prognosis were computed in weighted and non-weighted Cox proportional hazards regression models, as well as Fine & Gray competing risks regression models.

The analyses in this study were conducted in RStudio software version 1.4.1103 (RStudio, Inc., Boston, MA, USA). The imputation process was conducted by mice package. The survival analyses were conducted by survival package. A two-tailed P value < 0.050 was considered statistically significant.

3. Results

3.1. Molecular subtypes have unique clinical characteristics

We identified 5,628 female patients who received lumpectomy from 2010 to 2017. By IHC-based molecular subtyping, 299 (5.3%) cases are HR-HER2-, 498 (8.9%) cases are HR-HER2+, 1,086 (19.3%) cases are HR+HER2+, and 3,745 (66.5%) cases are HR+HER2-. The diversity of clinical features among the four molecular subtypes is shown in Table 1. HR-HER2- cases have smaller tumor size (P < 0.001) and lower grade (P < 0.001). Comedo necrosis is more frequent in HR-HER2- (24.4%, P < 0.001) and HR-HER2+ cases (24.3%, P < 0.001). We then applied
3. Prognostic score [18] classification to each molecular subtype. Cases scored 0–2 were classified into low-risk group, and cases scored of 3–6 were classified into high-risk group. HR-HER2+ cases have the highest proportion of the high-risk group (65.7%, P < 0.001), whereas HR+HER2- cases have the lowest proportion of the high-risk group (27.9%, P < 0.001).

3.2. Molecular subtypes have unique prognoses

During the follow-up period (from 7 to 107 months), 121 cases of IBE recurrence, 37 cases of DS mortality, and 249 cases of mortality with other causes were recorded. In HR-HER2-, HR-HER2+, HR+HER2-, and HR+HER2-cases, the 5-year IBE incidence for each group is 1.9%, 3.7%, 2.3%, and 1.4%, respectively. The 5-year DS mortality for each group is 1.1%, 0.2%, 0.2%, and 0.5%, respectively; and the 5-year non-DS mortality is 2.7%, 4.9%, 3.0%, and 3.3%, respectively. For DCIS cases with invasive IBE records, 4 of 6 (66.7%) HR-HER2-, 8 of 11 (72.7%) HR-HER2+, 7 of 20 (35.0%) HR+HER2-, and 42 of 49 (85.7%) HR+HER2- DCIS cases share the same molecular subtype with invasive IBE (Supplementary Table 1).

In univariate analyses, we compared prognosis between four molecular subtypes. HR-HER2+ cases have significantly higher IBE recurrence than HR+HER2-cases (P = 0.010, Fig. 2A). HR-HER2-cases show higher DS mortality than HR+HER2+ cases (P = 0.021, Fig. 2B). For non-DS mortality, there is no difference between the four molecular subtypes (P > 0.05).

In multivariate analyses (Table 2), HR-HER2+ cases also show a higher risk of IBE recurrence in both Cox proportional hazards (P = 0.027) and Fine & Gray competing risks (P = 0.032) regression models comparing with HR+HER2-cases. For DS mortality, HR-HER2-cases do not show a significantly higher risk compared to HR+HER2-cases.

Table 1: Clinical characteristics by molecular subtypes.

| Characteristics         | HR-HER2-(N (%)) | HR-HER2+(N (%)) | HR+HER2-(N (%)) | HR+HER2+(N (%)) | Chi square | P     |
|-------------------------|----------------|----------------|----------------|----------------|------------|-------|
| Year of diagnosis       |                |                |                |                |            |       |
| 2010-2013               | 3,517 (62.5)   | 214 (71.6)     | 296 (59.4)     | 687 (63.3)     | 13,242     | 0.004 |
| 2014-2017               | 2,111 (37.5)   | 85 (28.4)      | 202 (40.6)     | 399 (36.7)     | 37,427     | <0.001|
| Age, years              |                |                |                |                |            |       |
| ≤60                     | 2,805 (49.8)   | 124 (41.5)     | 254 (51.0)     | 623 (57.4)     | 1,425 (38.1)|       |
| >60                     | 2,823 (50.2)   | 175 (58.5)     | 244 (49.0)     | 463 (42.6)     | 1,261 (41.9)|       |
| Race                    |                |                |                |                |            |       |
| African American        | 789 (14.0)     | 56 (18.7)      | 41 (8.2)       | 135 (12.4)     | 557 (14.9) |       |
| Caucasian               | 4,404 (78.3)   | 220 (73.6)     | 420 (84.3)     | 876 (80.7)     | 2,888 (77.1)|       |
| Other                   | 435 (7.7)      | 23 (7.7)       | 37 (7.4)       | 75 (6.9)       | 300 (8.0) |       |
| Tumor size, mm          |                |                |                |                |            |       |
| <16                     | 3,918 (69.6)   | 185 (61.9)     | 281 (56.4)     | 732 (67.4)     | 2,720 (72.6)|       |
| 16-40                   | 1,377 (24.5)   | 98 (32.8)      | 172 (34.5)     | 284 (26.2)     | 823 (22.0) |       |
| >41                     | 333 (5.9)      | 16 (5.4)       | 45 (9.0)       | 70 (6.4)       | 202 (5.4) |       |
| Grade                   |                |                |                |                |            |       |
| Low                     | 964 (17.1)     | 11 (3.7)       | 6 (1.2)        | 67 (6.2)       | 880 (23.5) |       |
| Intermediate            | 2,304 (40.9)   | 63 (21.1)      | 54 (10.8)      | 356 (32.8)     | 1,831 (48.9)|       |
| High                    | 2,360 (41.9)   | 225 (75.3)     | 438 (88.0)     | 663 (61.0)     | 1,034 (27.6)|       |
| Histology Subtype       |                |                |                |                |            |       |
| Intraductal, solid      | 2,240 (39.8)   | 128 (42.8)     | 221 (44.4)     | 484 (44.6)     | 1,407 (37.6)|       |
| Comedo necrosis         | 599 (10.6)     | 73 (24.4)      | 121 (24.3)     | 142 (13.1)     | 263 (7.0) |       |
| Cribriform              | 525 (9.3)      | 9 (3.0)        | 16 (3.2)       | 58 (5.3)       | 442 (11.8) |       |
| Other                   | 2,264 (40.2)   | 89 (29.8)      | 140 (28.1)     | 402 (37.0)     | 1,633 (43.6)|       |
| Radiotherapy            |                |                |                |                |            |       |
| Yes                     | 4,040 (71.8)   | 243 (81.3)     | 390 (78.3)     | 824 (75.9)     | 2,589 (69.0)|       |
| No                      | 1,588 (28.2)   | 56 (18.7)      | 108 (21.7)     | 262 (24.1)     | 1,162 (31.0)|       |
| Prognostic Score*       |                |                |                |                |            |       |
| Low risk                | 3,549 (63.1)   | 142 (47.5)     | 171 (34.3)     | 536 (49.4)     | 2,700 (72.1)|       |
| High risk               | 2,079 (36.9)   | 157 (52.5)     | 327 (65.7)     | 550 (50.6)     | 1,045 (27.9)|       |

Abbreviations: N, numbers; HR, hormone receptor; HER2, human epidermal growth factor receptor-2.
Note: * Prognostic score is a scoring method by age, tumor size, and grade to stratify DCIS patients into low-risk and high-risk group.

Fig. 2. Ipsilateral breast event (IBE) and disease-specific (DS) mortality in each molecular subtype. A. IBE; B. DS mortality. (Abbreviations: IBE, ipsilateral breast event; DS, disease specific; HR, hormone receptor; HER2, human epidermal growth factor receptor-2. Note: P value was calculated by log-rank test.)
not show a higher risk than HR+HER2+ cases in the two regression models (P > 0.050).

3.3. Treatment effects on prognosis diverse in molecular subtypes

As RT is universally applied in the treatment of DCIS, we then analysed the RT effects on IBE recurrence and mortality in different molecular subtypes. In each subtype, the clinical features are different between RT and non-RT groups. To balance the clinical features between RT and non-RT groups, we conducted IPSW in each molecular subtype to balance the differences between the two groups.

The 5-year IBE incidence is 0.9% in the RT group in HR-HER2- cases, which is significantly lower than that in the non-RT group (2.6%) for this subtype in univariate (P < 0.001, Fig. 3D) and multivariate analyses (P < 0.001, Table 3). Compared with cases without RT, the absolute 5-year IBE incidence is 0.5% lower in HR-HER2+ cases and 1.5% lower in HR+HER2+ cases with RT, whereas the differences are not statistically significant in neither univariate (P > 0.050, Fig. 3B and C) nor multivariate analyses (P > 0.050, Table 3). For DS mortality, there is no significant difference between the RT and non-RT groups for each subtype in neither univariate analyses (P > 0.050) nor multivariate analyses (P > 0.050).

After prognostic score stratification in each subtype, high-risk cases have a higher 5-year IBE incidence than low-risk cases in both RT and non-RT groups. In high-risk cases, RT reduces the absolute 5-year IBE incidence by 1.3%, 0.7%, 1.9%, and 2.6% in HR-HER2-, HR-HER2+, HR+HER2+, and HR+HER2- cases, respectively. In multivariate regression models, the IBE incidence reduction by RT is statistically significant in low-risk and high-risk HR+HER2- cases (P < 0.050).

4. Discussion

In this study, we analysed the differences in clinical outcomes between four molecular subtypes in primary DCIS. Each DCIS molecular subtype has unique clinical features. There are more high-risk cases in the HR-HER2+ subtype, but fewer in the HR+HER2- subtype. HR-HER2+ cases also have a significantly higher probability of IBE recurrence than HR+HER2- cases.

The different gene expression profiles between DCIS and IBC reflect the need to classify DCIS by its own features [23, 24]. However, attempts on classify DCIS by genomic signatures still need more studies for verification [25]. Although IHC-based subtyping of DCIS is derived from

### Table 2

Comparing risk of ipsilateral breast event (IBE) and disease-specific (DS) mortality among four molecular subtypes in multivariate analyses.

| Molecular Subtype     | Estimated 5-year incidence | Cox proportional hazards | Fine & Gray competing risks |
|-----------------------|----------------------------|--------------------------|-----------------------------|
|                       | IBE                        | DS mortality             |
|                       | HR-HER2-                   | HR-HER2+                 | HR+HER2-                    | HR+HER2+                 |
|                       | 1.9%                       | 3.7%                     | 2.3%                        | 1.4%                     |
|                       | 1.326 (0.608–2.890)        | 1.345 (1.079–3.506)      | 1.140 (0.701–1.852)         | 1 (referent)             |
|                       | 0.479                      | 0.027                    | 0.598                       | –                        |
|                       | 1.319 (0.604–2.877)        | 1.940 (1.057–3.430)      | 1.140 (0.702–1.852)         | 1 (referent)             |
|                       | 0.490                      | 0.032                    | 0.670                       | –                        |
|                       | 1.1%                       | 0.2%                     | 0.2%                        | 0.5%                     |
|                       | 3.410 (0.946–11.300)       | 1.750 (0.374–8.192)      | 1.440 (0.441–4.698)         | 1.440 (0.443–4.710)      |
|                       | 0.061                      | 0.477                    | 0.546                       | 0.540                    |
|                       | 3.470 (0.967–12.500)       | 1.770 (0.376–8.280)      | 1.440 (0.443–4.710)         | 0.540                    |

Abbreviations: *HR, hazard ratio; CI, confidence interval; IBE, ipsilateral breast event; DS, disease specific; HR, hormone receptor; HER2, human epidermal growth factor receptor-2.

Note: Multivariate analyses in Cox proportional hazards regression model and Fine & Gray competing risks regression model were adjusted by year of diagnosis, age, race, tumor size, grade, histology subtype, and radiotherapy.

Fig. 3. Effects of radiotherapy on ipsilateral breast event (IBE) in each molecular subtype. IBE in HR-HER2- (A), HR-HER2+ (B), HR+HER2+ (C), and HR+HER2- (D). (Abbreviations: IBE, ipsilateral breast event; HR, hormone receptor; HER2, human epidermal growth factor receptor-2. Note: P value was calculated by log-rank test.)
In this study, the majority (66.5%) of DCIS cases are HR-HER2+. This molecular subtype is also the major subtype in IBC [11]. The HR + HER2- DCIS cases have a smaller tumor size, lower grade, less comedo necrosis, and lower LT acceptance than the other three subtypes (Table 1). When stratifying HR + HER2- DCIS cases by prognostic score, only 27.9% of HR + HER2- cases are high risk, which is the lowest among the four subtypes. These less aggressive features lead to indolent biological behaviors of HR + HER2- DCIS cases. The cumulative incidence curves also show relatively low IBE recurrence in the HR + HER2- subtype (Fig. 2A). During the follow-up period, 56 HR + HER2- DCIS cases are recorded to have invasive IBE recurrence. 49 invasive IBEs have records of HR and HER2 statuses, 42 of which (85.7%) have the same subtype as primary HR + HER2- DCIS cases (Supplementary Table 1).

In our previous study, we stratified primary DCIS cases by prognostic score and found that RT could reduce IBE incidence [18]. In general, the high-risk group has a significantly higher IBE incidence than the low-risk group [18]. Regarding the distinction of each DCIS molecular subtype, we analysed the RT effects on IBE recurrence and DS mortality in each molecular subtype. In HR + HER2- cases, RT significantly lower the probability of IBE recurrence (P < 0.001, Fig. 3D and Table 3). Both invasive (P = 0.061) and in situ (P < 0.001) IBE incidence is reduced after RT in HR + HER2- cases. In HR + HER2- and HR + HER2+ cases, the absolute 5-year IBE incidence is reduced in the RT group without statistical significance. By prognostic score stratification, the RT group also shows a lower 5-year IBE incidence in high-risk cases for each subtype. This result suggested that RT still has roles in risk reduction in each molecular subtype, especially in high-risk DCIS cases.

As molecular subtypes identify relevant biology, some studies have explored new treatment strategies for different DCIS molecular subtypes. Combining adjuvant tamoxifen therapy with RT can significantly reduce the risk of IBE recurrence for DCIS cases in NSABP B-24 [36]. NSABP B-35 shows superior disease-free survival provided by anastrozole compared with tamoxifen therapy in HR + DCIS cases, especially in patients younger than 60 years old [37]. The B-35 study also finds that endocrine therapy does not reduce the IBE incidence. However, endocrine therapy significantly reduces the risks of contralateral breast events (CBEs) [37]. Because of the extremely low probability of CBE over a long follow-up period and the potential adverse effects of endocrine therapy, few HR + DCIS cases received endocrine therapy, even under recommendation [38]. For HER2+ DCIS cases with aggressive features, HER2 targeted therapy significantly reduced mortality in HR + HER2+ DCIS cases [39]. However, in NSABP B-43, trastuzumab plus RT treatment only achieves a statistically insignificant IBE reduction of 19% [20]. The controversies about HER2 targeted therapy in DCIS cases still exist. More trials aiming to improve disease-free survival and quality of life for DCIS cases are ongoing to reach an ideal treatment milestone.
In summary, we found that DCIS cases have diverse clinical and prognostic features for different molecular subtypes. More treatment strategies aimed at unique DCIS molecular subtypes may help to reach a more satisfactory outcome.

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Declaration of competing interest

The authors declare that they have disclosed no potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.03.019.

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