INTRODUCTION

Breast cancer shows distinctly diverse clinicopathological characteristics, different therapeutic responsiveness, and variable outcomes in different subtypes based on gene expression signature.\(^1\)\(^-\)\(^3\) However, gene profiling is still limited in current practice. Therefore, immunohistochemical surrogate markers have been developed including estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). Among them, ER and HER2 have secured their positions as prognostic factors, however, there is still lack of agreement on the role of PgR in breast cancer.\(^4\)\(^,\)\(^5\)

PgR belongs to a large superfamily of ligand-activated nuclear receptors. The binding of progesterone to PgR induces conformational changes that lead to the formation of homo- or heterodimers, increased receptor phosphorylation, interaction with target gene promoters by binding to progesterone response elements, and to specific coactivators and general transcription factors.\(^6\)\(^,\)\(^7\)

Further researches also showed that PgR is a protein in which synthesis is positively regulated by ER. The presence of a functional ER is required for PgR synthesis in the cell. Therefore, the presence of PgR may indicate a more functionally intact ER pathway.\(^8\)\(^,\)\(^9\) A recent published paper\(^10\) demonstrated that in IHC-defined luminal A tumors, more than 20% of PR-positive tumor cells predicted significantly better survival. This was then adopted by St Gallen guideline to use PgR cut off of 20% to distinguish Luminal A-like with Luminal B-like breast cancer. However, the implication of PgR in ER negative breast cancers is nonnegligible phenomenon. Little is known about the characteristics and the role of single PgR positive in this phenotype. Therefore, we explore the significance of single PgR positivity by comparing ER/PgR+/HER2− breast cancers with triple negative breast cancers (TNBCs).

Three hundred nine hundred sixty-six cases of primary invasive breast carcinoma operated consecutively from January 2005 to May 2008 in Cancer Hospital, Chinese Academy of Medical Sciences were examined. Two hundred forty (6%) cases were identified as ER−/PgR+/HER2− breast cancers and 348 (8.8%) cases as TNBCs. Clinicopathological characteristics and survivals were analyzed respectively and then compared between 2 subtypes.

Compared with patients with TNBCs, ER−/PgR+/HER2− tumor tended to have lower tumor grade (Grade 3: 45.7% vs. 37.5%, \(P = 0.051\)) and smaller tumor size (\(P = 0.036\)). However, no differences were found between ER−/PgR+/HER2− and TNBC patients in relapse-free survival (RFS) and OS. The 5-year RFS rates were 80.7% and 77.4%, respectively (\(P = 0.330\)) and the 5-year OS rates were 88.0% and 85.2%, respectively (\(P = 0.290\)). ER−/PgR+/HER2− patients receiving adjuvant endocrine treatment had better RFS (\(P = 0.016\)) and overall survival (OS) (\(P < 0.0001\)) than patients receiving no endocrine therapy.

This exclusive analysis of patients with ER−/PgR+/HER2− breast cancers showed that this subtype exhibited an aggressive behavior as TNBC, suggesting that it should also be regarded as biologically distinctive group and single PgR positive itself is not a good prognostic factor. However, adjuvant endocrine therapy could still benefit this group of patients. Further investigations should be done to elucidate the underlying mechanism.

Abstract: Single progesterone receptor positive (PgR+), especially in form of ER−/PgR+/HER2−, is a nonnegligible phenomenon. Little is known about the characteristics and the role of single PgR positive in this phenotype. Therefore, we explore the significance of single PgR positivity by comparing ER−/PgR+/HER2− breast cancers with triple negative breast cancers (TNBCs).

PROGNOSTIC SIGNIFICANCE OF SINGLE PROGESTERONE RECEPTOR POSITIVITY

A Comparison Study of Estrogen Receptor Negative/Progesterone Receptor Positive/HER2 Negative Primary Breast Cancer With Triple Negative Breast Cancer

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Abbreviations: AJCC/UICC = American Joint Committee on Cancer/International Union Against Cancer, ASCO/CAP = American Society of Clinical Oncology/Coleage of American Pathologists, BCS = breast conserving surgery, BMI = bone mass index, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, MRM = modified radical mastectomy, NA = not applicable, OS = overall survival, PgR = progesterone receptor, RFS = relapse-free survival, SD = standard deviation, TNBCs = triple negative breast cancers.

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cancer is still unknown. Previously, single PgR positivity was believed to be a rare phenomenon and may be false positive in IHC examination. There once was a debate on whether it is time to stop PgR testing in breast cancer management. However, more and more researches supported that it was not insignificant, accounting for 3.4% to 7% of total cases. In addition, some even found that PgR status was a strong prognostic factor for survivals. Although previous literatures suggested that ER−/PgR+ tumors might have biologic characteristics somewhere in between ER+/PgR+ and ER+/PgR−, HER2 was not taken into consideration at that time. Thus, up until now, very little was known about the clinical—pathological characteristics and outcomes of ER−/PgR+/HER2− phenotype.

Triple negative breast cancer (TNBC) is a distinct subtype of breast cancer, which is characterized as ER negative, PR negative, and HER2 negative, featuring rapid progression and poor prognosis. To illustrate the true significance of single PgR positivity, we compared a group of ER−/PgR+/HER2− patients with TNBC patients. To our knowledge, this is the first study to investigate the differences and similarities between ER−/PgR+/HER2− and TNBC patients. Also this is the largest series of ER−/PgR+/HER2 tumors ever explored to evaluate the efficacy of adjuvant endocrine therapy exclusively in this group of patients.

METHODS

Patient Selection and Data Collection

A consecutive cohort of 3966 breast cancer patients operated from January 1, 2005 to May 31, 2008 at Cancer Hospital and Institute, Chinese Academy of Medical Sciences which is the National Cancer Center of China were retrospectively collected. All the immunohistochemistry slides for ER/PgR/HER2 were reviewed again by 2 independent pathologists. Immunohistochemistry staining of 4 μm sections of formalin-fixed paraffin-embedded tissue was performed with anti-ER (clone SP1, Ventana), anti-PR (clone 1E2, Ventana), anti-HER2 (clone 4B5, Ventana) primary monoclonal antibodies. Universal secondary antibody (Dako) was applied for 15 minutes. Diaminobenzidine was used as chromogens and slides were counterstained with hematoxylin before mounting. Tumors with ≥1% nuclear-stained cells were considered ER and/or PgR positive according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. The magnitude of PgR positivity were classified into +/+/++ by percentage of PgR staining. + was defined as PgR positive if finding of 1% to 25% of tumor cell nuclei were immunoreactive. ++ was defined as PgR positive if 25% to 50% of tumor cell nuclei were immunoreactive. +++ was defined as PgR positive if more than 50% of tumor cell nuclei were immunoreactive. HER2 staining was evaluated from 0 to 3 + according to the ASCO/CAP guidelines and 3 + was considered positive while 0 and 1+ was considered negative. Samples with HER2 2+ were either confirmed by FISH or excluded. Totally, 273 patients were identified as ER−/PgR+/HER2− cases and 398 patients were diagnosed with TNBC cases. Eighty-three patients were excluded from the final analysis (see Fig. 1).

Staging of primary tumors was based on the TNM system of the Seventh American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) manual.

Ethics Statement

The retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.
Sciences (No. 12-123/657). Detailed demographic, clinical, pathologic, and treatment information and follow-ups were obtained from clinic records or pathologic reports. Patient records/information was anonymized and deidentified before analysis. Therefore, the informed consent was remitted by the Ethics Committee.

Endpoints and Statistical Analysis
Relapse-free survival (RFS) was measured from the date of diagnosis to the date of first documented local or distant recurrence. Patients who were still relapse free or died before recurrence were censored at their dates of last follow-up or dates of death. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or last follow-up.

Clinicopathological characteristics were compared between 2 phenotypes by the Chi-square test or Fisher exact test. RFS and OS were computed and compared by Kaplan–Meier method using log-rank test. Cox proportional hazard regression model was used to identify variables that were independently associated with survival. P values less than 0.05 were considered statistically significant; all tests were 2 sided. All the statistical analyses were carried out using SPSS17.0 (SPSS, Inc., Chicago, IL).

RESULTS
Characteristics of Patient cohort
Characteristics of 240 (6%) ER-/PgR+/HER2− cases and 348 (8.7%) TNBC cases are listed in Table 1. For PgR positivity, 164 (68.3%) tumors were PgR+, 55 (22.9%) were PgR++, and 21 (8.8%) were PgR+++ . Compared with patients with ER-/PgR+/HER2− tumor, TNBC patients tended to have higher tumor grade (Grade 3: 45.7% vs. 37.5%, \( P = 0.051 \)) and larger tumor size (\( P = 0.036 \)). Other baseline characteristics were comparable between the 2 groups (Table 1).

In terms of systemic treatment, undoubtedly, more ER-/PgR+/HER2− patients (76.3%) received adjuvant endocrine therapy than TNBC patients (4.6%). On the contrary, more TNBC patients received taxane-based chemotherapy than ER-/PgR+/HER2− patients (54.0% vs. 45.4%, \( P = 0.031 \)). Forty-eight cases in ER-/PgR+/HER2− group and 80 cases in TNBC group presented with BC-specific recurrence including regional relapse and distant metastasis. The metastatic pattern was similar between the 2 groups (\( P > 0.05 \)), that is, recurrent cases in both groups tended to have visceral metastasis with lung as the most common metastatic site, and less likely to develop bone metastasis (Table 1).

Survivals
Median follow-up of the entire cohort was 66 months (range, 22 months to 96 months). The 5-year RFS rate and OS rate for the entire cohort were 79.1% and 86.4%, respectively. In the recurrent cases, the median RFS time of ER-/PgR+/HER2− and TNBC was 20.0 and 18.3 months, respectively, and no significant difference was demonstrated (\( P = 0.984 \)).

There were also no significant differences in RFS and OS between ER-/PgR+/HER2− patients and TNBC patients. The 5-year RFS rates were 80.7% and 77.4%, respectively (\( P = 0.330 \)) and the 5-year OS rates were 88.0% and 85.2%, respectively (\( P = 0.290 \)) (Fig. 2A and B).

In ER-/PgR+/HER2− group, cases with adjuvant endocrine therapy had significantly better RFS (5-year RFS rate, 84.0% vs. 70.1%, \( P = 0.016 \)) and also significantly longer OS (5-year OS rate, 93.0% vs. 71.9%, \( P < 0.0001 \)) than cases receiving no adjuvant endocrine therapy (Fig. 3A). The magnitude of PgR positivity, whether it is +, ++, or +++ was associated neither with PFS (\( P = 0.656 \)) nor OS (\( P = 0.608 \)). When compared with TNBC, ER-/PgR+/HER2− patients who were not given endocrine drugs had a worse prognosis (5-year OS rate, 71.9% vs. 85.2%, \( P = 0.005 \)) while those treated with endocrine therapy had a better prognosis (5-year OS rate, 93.0% vs. 85.2%, \( P = 0.006 \)) (Fig. 3B).

Univariate and Multivariate Analysis of ER-/PgR+/HER2− Disease and TNBC
Prognostic factors which were significantly correlated with PFS and OS in univariate analysis are highlighted in Table 2. Multivariate analysis suggested that axillary lymph node metastasis status was an independent adverse prognostic factor for both RFS and OS in ER-/PgR+/HER2− disease (HR 1.728, 95% CI: 1.251–2.387, \( P = 0.001 \); HR 2.778, 95% CI: 1.639–4.078, \( P < 0.0001 \)). Adjuvant endocrine therapy is also an independent prognostic factor, significantly decrease the risk of recurrence (HR 0.4454, \( P = 0.008 \)) and death (HR 0.218, \( P < 0.0001 \)). In TNBC, Unlike ER-/PgR+/HER2− disease, tumor size >2 cm was identified as a poor prognostic factor for RFS (HR 2.028, 95% CI: 1.167–3.524, \( P = 0.012 \)). Similar to ER-/PgR+/HER2− disease, multivariate Cox regression models showed that positive lymph node was an independent adverse prognostic factor for both RFS (HR 2.157, 95% CI: 1.624–2.865, \( P < 0.0001 \)) and OS (HR 2.623, 95% CI: 1.883–3.653, \( P < 0.0001 \)) in TNBC tumors (Table 3).

DISCUSSION
Determination of ER and PgR expression by IHC analysis is fundamental for daily clinical practice and is routinely used to predict the prognosis and to identify patients who are most likely to benefit from endocrine therapy. Although the clinical significance of ER positivity has been firmly established, the implication of PgR positivity, especially single PgR positivity has long been questioned. Olivoto et al11 reported that among 192 patients with ER− disease on IHC testing, 191 (99.5%) were also PgR−; they recommended it was time to stop PgR testing in breast cancer management. However, this was opposed by Rakha et al14 and Colomer et al12 that in their studies, ER−/PgR+ patients is not insignificant (3.4% and 7%). Similar results was found in our study that 6% of patients presented with ER−/PgR+/HER2− phenotype, therefore, single PgR entity is definitely not a negligible phenomenon and needs to be further investigated.

Although the presence of single PgR have been more and more widely accepted, studies evaluating its role as an independent prognostic factor yielded conflicting results.9-9 Banerjee et al23 applied a tree-based model for breast cancer prognostication and found PgR positive is a good prognostic factor. More recently, Rakha et al13 also examined a large series of 1944 breast cancer cases, focusing on single hormone-receptor positive phenotype. They found that when compared with the double-negative phenotype, ER+/PgR− showed better outcome but no such survival advantage was detected in ER−/PgR+ tumors. The latter exhibited more aggressive behavioral characteristics. This result was echoed in another study reported by Keshgegian and Cnaan,24 but slightly different from Bernoux et al’s25 study which showed ER−/PgR+ patients had a small but significant better OS compared with ER−/PgR− patients. However,
TABLE 1. Patient Characteristics

| Characteristics                  | ER−/PgR+/HER2− (n = 240) (N, %) | TNBC (n = 348) (N, %) | P-Value |
|----------------------------------|---------------------------------|-----------------------|---------|
| Age, years                       |                                 |                       |         |
| Median (range)                   | 49.0 (26–79)                    | 49.0 (22–91)          | 0.922   |
| ≤50                              | 135 (56.2%)                     | 198 (56.9%)           | 0.933   |
| >50                              | 104 (43.8%)                     | 150 (43.1%)           |         |
| Menopausal status                |                                 |                       | 0.549   |
| Premenopausal                    | 149 (62.1%)                     | 207 (59.5%)           |         |
| Postmenopausal                   | 91 (37.9%)                      | 141 (40.5%)           |         |
| BMI (kg/m²)                      |                                 |                       | 0.214   |
| Mean ± SD                        | 25.4 ± 3.8                      | 25.0 ± 3.6            | 0.205   |
| <25.0                            | 121 (50.4%)                     | 179 (51.4%)           | 0.867   |
| ≥25.0                            | 119 (49.6%)                     | 169 (48.6%)           |         |
| Histology                        |                                 |                       | 0.051   |
| IDC                              | 214 (89.2%)                     | 297 (85.3%)           |         |
| Other                            | 26 (10.8%)                      | 51 (14.7%)            |         |
| Grade                            |                                 |                       | 0.051   |
| 1 or 2                           | 150 (62.5%)                     | 189 (54.3%)           |         |
| 3                                | 90 (37.5%)                      | 159 (45.7%)           |         |
| Lymphovascular invasion          |                                 |                       | 0.789   |
| No                               | 215 (89.6%)                     | 308 (88.5%)           |         |
| Yes                              | 25 (10.4%)                      | 40 (11.5%)            |         |
| Tumor size                       |                                 |                       | 0.036   |
| T1                               | 126 (52.5%)                     | 145 (41.7%)           |         |
| T2                               | 98 (40.8%)                      | 174 (50.0%)           |         |
| T3                               | 14 (5.8%)                       | 20 (5.7%)             |         |
| T4                               | 2 (0.9%)                        | 9 (2.6%)              |         |
| Lymph nodes                      |                                 |                       | 0.587   |
| N0                               | 133 (55.4%)                     | 200 (57.5%)           |         |
| N1                               | 59 (24.6%)                      | 86 (24.7%)            |         |
| N2                               | 31 (12.9%)                      | 33 (9.5%)             |         |
| N3                               | 17 (7.1%)                       | 29 (8.3%)             |         |
| Adjuvant endocrine therapy       |                                 |                       | <0.0001 |
| Yes                              | 183 (76.2%)                     | 15 (4.3%)             |         |
| No                               | 57 (23.8%)                      | 333 (95.7%)           |         |
| (Neo)adjuvant chemotherapy       |                                 |                       | 1.000   |
| Anthracycline based              | 213 (88.8%)                     | 308 (88.5%)           |         |
| Taxane based                     | 208 (86.7%)                     | 297 (85.3%)           | 1.0     |
| Anthracycline/taxane based       | 109 (45.4%)                     | 188 (54.0%)           |         |
| Nonanthracycline/taxane based    | 108 (45.0%)                     | 183 (52.6%)           |         |
| Surgical approach                |                                 |                       | 0.722   |
| BCS                              | 33 (13.8%)                      | 52 (14.9%)            |         |
| MRM                              | 207 (86.2%)                     | 296 (85.1%)           |         |
| Adjuvant radiation               |                                 |                       | 0.797   |
| Yes                              | 95 (39.6%)                      | 134 (38.5%)           |         |
| No                               | 145 (60.4%)                     | 214 (61.5%)           |         |
| Recurrence                       |                                 |                       |         |
| Visceral/other                   | 26 (54.2%)                      | 48 (60.0%)            | 0.581   |
| Lung                             | 22 (45.8%)                      | 45 (56.3%)            | 0.277   |
| Liver                            | 18 (37.5%)                      | 23 (28.8%)            | 0.332   |
| Brain                            | 7 (14.6%)                       | 18 (22.5%)            | 0.359   |
| Bone                             | 16 (33.3%)                      | 27 (33.8%)            | 1.0     |
| Local–regional relapse           | 20 (41.7%)                      | 27 (33.8%)            | 0.449   |
| No. of metastasis                |                                 |                       | 0.481   |
| 1                                | 17 (35.4%)                      | 24 (30.0%)            |         |
| 2                                | 18 (37.5%)                      | 26 (32.5%)            |         |
| 3+                               | 13 (27.1%)                      | 30 (37.5%)            |         |

BCS = breast conserving surgery, BMI = bone mass index, ER = estrogen receptor, HER2 = human epidermal receptor2, IDC = invasive ductal carcinoma, MRM = modified radical mastectomy; PgR = progesterone receptor, SD = standard deviation, TNBC = triple-negative breast cancer.
significant difference was also not found in disease-free interval and the metastasis-free survival. These studies all presented with 2 issues: first, the prognostic value of PgR was evaluated by analyzing mixed population including both ER− and ER+ patients. When ER is negative, whether PgR is prognostic is an interesting issue that has not been addressed yet; more importantly, the status of HER2 was not taken into consideration, however, we know now ER pathway has crosstalk with HER2 pathway. There might also be inconsistency of antibodies for IHC testing, but it is doubtful whether this will bring dramatic changes within 2 years of diagnosis and had lungs as the most common site of visceral metastases. All these implied that ER−/PgR+/HER2− tumor should also be regarded as biologically and clinically distinctive subgroup of breast cancer and PgR still cannot be established as a prognostic marker.

Another issue that needs to be born in mind is that PgR exists in 2 isoforms, PR-A and PR-B.26 It was reported that high PR-A:PR-B ratio predicted shorter disease-free survival, indicating resistance to tamoxifen either intrinsically or a more tumors had similar clinicopathological features with TNBC patients except that ER−/PgR+/HER2− tumors tend to present with lower tumor grade (P = 0.051) and smaller tumor size (P = 0.036). These data suggested that ER−/PgR+/HER2− might have a less aggressive biologic feature than TNBC. However, no significant differences were found in RFS or OS between ER−/PgR+/HER2− and TNBC cases. This is just as expected since lymph node status, as the strongest prognostic indicator, showed no difference. They both tended to relapse within 2 years of diagnosis and had lungs as the most common site of visceral metastases. All these implied that ER−/PgR+/HER2− tumor should also be regarded as biologically and clinically distinctive subgroup of breast cancer and PgR still cannot be established as a prognostic marker.

As the matter of fact, results of our study revealed that Chinese breast cancer patients with ER−/PgR+/HER2−...
TABLE 2. Univariate Analyses of RFS and OS in ER−/PgR+/HER2− Patients and TNBC Patients

|                | ER−/PgR+/HER2− | TNBC |
|----------------|----------------|------|
|                | RFS            | OS   | RFS            | OS   |
| BMI (<25.0 kg/m² vs. ≥25.0 kg/m²) | 0.340 | 0.803 | 0.404 | 0.903 |
| Surgical approach(MRM vs. BCS)   | 0.784 | 0.937 | 0.292 | 0.242 |
| Primary tumor size (<2 cm vs. >2 cm) | 0.097 | 0.365 | <0.0001 | 0.001 |
| Axillary lymph node metastasis [0,1] | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| LVI (yes vs. no)                   | 0.163 | 0.078 | 0.465 | 0.964 |
| Radiation (yes vs. no)             | 0.221 | 0.040 | 0.001 | 0.0001 |
| Anthracycline-based chemo (yes vs. no) | 0.137 | 0.052 | <0.0001 | <0.0001 |
| Taxane-based chemo (yes vs. no)    | 0.990 | 0.649 | 0.271 | 0.567 |
| Endocrine therapy (yes vs. no)     | 0.013 | 0.013 | 0.428 | 0.284 |

TNBC = triple-negative breast cancer. Bold: statistically significant.

TABLE 3. Multivariate Analyses of RFS and OS in ER−/PgR+/HER2− Patients and TNBC Patients

|                | ER−/PgR+/HER2− | TNBC |
|----------------|----------------|------|
|                | RFS            | OS   | RFS            | OS   |
| Primary tumor size (<2 cm vs. >2 cm) | 1.555 | 0.826 – 2.928 | 0.172 | 0.238 | 0.056 – 2.051 | 0.238 | 2.028 | 1.167 – 3.524 | 0.012 | 1.886 | 0.925 – 3.848 | 0.081 |
| Axillary lymph node metastasis (negative vs. positive) | 1.728 | 1.251 – 2.387 | 0.001 | 2.778 | 1.639 – 4.708 | <0.0001 | 2.157 | 1.624 – 2.865 | <0.0001 | 2.623 | 1.883 – 3.653 | <0.0001 |
| Endocrine therapy (yes vs. no) | 0.445 | 0.244 – 0.812 | 0.008 | 0.218 | 0.101 – 0.470 | <0.0001 | NA | NA | NA | NA | NA | NA |

ER = estrogen receptor, HER2 = human epidermal receptor2, NA = not applicable, OS = overall survival, PgR = progesterone receptor, RFS = relapse-free survival, TNBC = triple-negative breast cancer.
used in this subset. Further studies are warranted to find possible methods to improve the poor outcome of this special subtype.

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