Estrogen receptor-negative/progesterone receptor-positive and her-2-negative breast cancer might no longer be classified as hormone receptor-positive breast cancer

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Received: 30 June 2021 / Accepted: 15 March 2022 / Published online: 10 April 2022 © The Author(s) under exclusive licence to Japan Society of Clinical Oncology 2022

Abstract

Background The single progesterone receptor (PR)-positive phenotype (estrogen receptor (ER)-/PR + , sPR positive) is an infrequent and independent biological entity. However, the prognosis of patients with sPR-positive and her-2-negative phenotype is still controversial, and it is not always easy to decide treatment strategies for them.

Methods Patients during 2010–2014 were identified from Surveillance, Epidemiology, and End Results (SEER) database. The Kaplan–Meier method was used to evaluate cancer-specific survival (CSS). The propensity score matching (PSM) method was used to balance differences of characteristics in groups. The Life-Table method was used to calculate 5-year CSS rates and the annual hazard rate of death (HRD).

Results A total of 97,527 patients were included, and only 745 (0.76%) patients were sPR-positive phenotype. The majority of sPR-positive breast cancer were basal-like subtype. Survival analysis showed that the sPR-positive breast cancer had similar prognosis comparing to double hormonal receptor-negative (ER-/PR-, dHoR-negative) breast cancer, and had the highest HRD during the initial 1–2 years of follow-up, then maintained the HRD of almost zero during the late years of follow-up.

Conclusions The patients with sPR-positive and her-2-negative breast cancer, similar to dHoR-negative breast cancer, had a worse survival, and could benefit from chemotherapy significantly. However, the escalating endocrine therapy was not recommended for sPR-positive patients. The patients with sPR positive should be excluded from future clinical trials concerning endocrine therapy.

Keywords Breast cancer · sPR positive · The annual hazard rate of death · Cancer-specific survival

Introduction

Breast cancer is the greatest threat to women’s health and the leading cause of cancer death in young women. In 1973, estrogen receptor (ER) has been recognized as a strong indicator of response to endocrine therapy [1]. Then, ER

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and progesterone receptor (PR) were gradually established as prognostic factors in female breast cancer [2–6]. And steroid hormone receptors (HoRs) were shown to be the strongest predictive markers of response to endocrine therapy in breast cancer [7–10].

There are four hormone-receptor phenotypes, and the single PR-positive phenotype (ER-/PR+, sPR positive) is infrequent, accounting for 0.3–7.1% of all types of malignant breast cancer [11–16]. The existence of the sPR-positive breast cancer used to be controversial. Then, the sPR-positive phenotype was proved by re-evaluating ER and PR status through immunohistochemical staining (IHC) [13, 17] or analyzing PAM50 expression signature and mRNA level of ESR1 [11, 18]. Besides, Borras and his co-authors established the sPR-positive Evsa-T cell line, which also demonstrated the presence of sPR-positive breast cancer [19].

Unlike other types of breast cancer, the sPR-positive breast cancer had unique clinicopathological characteristics and controversial prognosis [17, 20, 21]. Ke-Da et al. showed that the survival of the sPR-positive phenotype was similar to the double HoR-negative (ER-/PR-, dHoR-negative) phenotype [22], while, Ethier et al. indicated that the survival of sPR-positive patients was similar to double HoR-positive (ER+/PR+, dHoR-positive) patients [12]. The prognosis of patients with sPR-positive and her-2-negative breast cancer is still controversial; therefore, we aim to explore the true prognosis of patients with sPR positive through large-sample clinical data analysis.

In the current study, we systemically studied the clinical features, survival outcomes and the annual hazard rate of death (HRD) of patients with sPR-positive and her-2-negative breast cancer to assist physicians in making better treatment decisions for these patients.

**Methods**

**Study population**

The Surveillance, Epidemiology, and End Results (SEER) database was established by the National Cancer Institute with the aim of collecting information about cancer incidence and survival. This national program includes 18 population-based cancer registries among 14 states across the United States, representing about 30% of the population of the United States. We obtained permission to access the research data (reference number, 12,296-Nov2018). The study was approved by the ethics committee of Zhejiang University Jinhua hospital. We used SEER*Stat version 8.3.5 (http://seer.cancer.gov/seerstat) to identify patients diagnosed with breast cancer from January 2010 to December 2014. Patients diagnosed after 2014 were excluded to ensure an adequate duration of follow-up. We retrieved records of year and age at diagnosis, gender, race, insurance, marital status, histological type, differentiated grade, location of tumor, T-classification, N-classification, stage TNM, administration of radiotherapy, administration of chemotherapy, ER, PR, her-2, survival months, and cause of death.

The specific inclusion criteria were as follows: (1) site record ICD-O-3 was limited to breast cancer (C500–506; C508–509); (2) gender was limited to female; (3) histological type ICD-O-3 was limited to infiltrative ductal cancer, infiltrative lobular cancer or mixed with both of them (8500/3, 8520/3, 8521/3, 8522/3, 8524/3, 8541/3); (4) the survival time of patients exceeded 1 months, (5) patients were without distant metastasis; (6) the age at diagnosis was limited from 20 to 80; and (7) patients were not multiple primary tumors. The exclusion criteria were as follows: (1) patients were lacking documentation of race, marital status, insurance status, differentiated grade (included grade IV), location of tumor, ER, PR, her-2, T-classification, N-classification; (2) patients were her-2 positive; (3) patients received neoadjuvant therapy; (4) the cause of death was unknown (For the detailed inclusion and exclusion criteria, see the Supplemental Fig. 1).

**Variable declaration**

Age was regrouped as 20–40 years old, 41–60 years old, 61–70 years old, 71–80 years old, according to our previous study analysis result [23]. Race was divided into white, black...
and other. Marital status was regrouped as married, single and divorced. Insurance status was divided into insured, medic-aid and uninsured. Histological type was grouped as infiltrative ductal cancer (IDC), infiltrative lobar cancer (ILC) and mixture (IDC&ILC). The variable of chemotherapy was only classified as “yes” or “no/unknown”, since SEER treatment information cannot accurately distinguish between “no treat-ment” and “unknown if patients received treatment” [24]. All cases were regrouped according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Based on the immunohistochemical results, if 1% or greater cells stain positive, the test results are classified as ER/PR positive and if less than 1% of cells stain positive, the results are classified as ER/PR negative. The HoR status of the tumor was stratified to dHoR positive, single ER positive (ER+/PR-, sER positive), sPR positive, and dHoR negative.

Statistical analyses

The distribution of clinicopathological characteristic in different HoR status groups was analyzed using Chi-Squared tests. Propensity score matching method (PSM) was used to balance differences of characteristics between chemotherapy and non-chemotherapy groups. The propensity score was calculated by logistic regression including covariates of HoR status, T-Classification and N-Classification. The “Matchit” package in R software was used as the nearest method with ratio 1:1 and caliper = 0.0001. The cancer-specific survival (CSS), the primary endpoint, was calculated from the date of diagnosis to the date of death of breast cancer. Death attributed to other causes was defined as a censored observation. Survival curves were generated using the Kaplan–Meier method, and the log-rank test was carried out to evaluate the survival differences between groups. The 5-year CSS rates were calculated by Life-Table method. The hazard ratio (HR) of the variables for CSS was estimated using Cox proportional hazard regression model. The Life-Table method was used to calculate HRD. The HRD were plotted at each 6-months interval after diagnosis until month 79, with a total of 13 intervals (intervals 0–79). Interpolation was conducted using a locally weighted scatter plot smoothing (LOWESS) function.

R3.5.2 software (http://www.r-project.org/) was used to perform the statistical analyses. When the two-sided P value was less than 0.05, the difference was considered statistically significant.

Results

Clinicopathological characteristics of patients with her-2-negative breast cancer

We identified 97,527 eligible patients with her-2-negative breast cancer from SEER. The endpoint date of the follow-up was November 2014, with a median follow-up of 48 months (range: 1–83 months). There were 0.86% women diagnosed with sPR positive in HoR-positive resectable breast cancer, and 0.76% in all resectable breast cancer.

Compared with the sER positive, patients with sPR positive were younger at time of diagnosis (median age 55 versus 62 years, \( P < 0.001 \)), less likely had infiltrative lobar carcinoma (1.61% versus 13.38%, \( P < 0.001 \)), had more poor-differentiated (80.27% versus 36.71%, \( P < 0.001 \)) as well as late-stage breast cancer. More patients with sPR positive received chemotherapy (73.56% vs. 45.27%, \( P < 0.001 \)). However, patients with dHoR-negative and sPR-positive tumors had similar clinicopathological characteristics. The detail information is indicated in Table 1.

Univariate and multivariate analysis of CSS

In total, 3,454 (3.07%) patients died of breast cancer. The 5-year CSS rates of patients with sPR-positive breast cancer and dHoR-negative breast cancer were 89.03% and 87.69%, respectively. The survival of patients with sER positive and dHoR positive was much better, with 5-year CSS rates of 93.57% and 97.81% \( (P < 0.001, \) Fig. 1). Univariate analysis revealed that showed that ER positive and PR positive were independent prognostic factors for favorable survivals and ER positive had a more important position. However, after combination ER and PR status, patients with sPR-positive phenotype had similar prognosis to dHoR-negative phenotype \( (HR = 0.97, 95\% CI, 0.77–1.23; \ P = 0.827, \) Table 2). Subsequently, we conducted a further univariate analysis of patients with ER-negative and her-2-negative breast cancer and found that PR status was no longer an independent prognostic factor \( (HR = 1.02, 95\% CI, 0.80–1.29; \ P = 0.892) \). The detail results were indicated in Table 3. Other possible prognostic factors including age at diagnosis, race, marital status, insurance, histological type, differentiated grade, T/N classification, stage, chemotherapy and radiotherapy were analyzed according to different ER and PR status, which were respectively indicated in Supplemental Tables 2–5.

The hazard rate of death (HRD) in different phenotypes of breast cancer

The dHoR-positive phenotype continued to have a low level of the HRD during the disease progression. The HRD of sPR-positive phenotype was higher than the other three phenotypes during the initial 1–2 years of follow-up, and then descended rapidly and successively crossed with the other three phenotypes during the 3–5 years of follow-up. However, the HRD of sPR-positive phenotype decreased nearly to zero during the later years of follow-up time (Fig. 2).
Table 1 The characteristics of patients with her-2-negative breast cancer in different hormone receptor status

| Risk factors                  | N (%) | ER+/PR+, N (%) | ER+/PR-, N (%) | ER-/PR+, N (%) | ER-/PR-, N (%) | P*     |
|-------------------------------|-------|----------------|----------------|----------------|----------------|--------|
| Total                         | 97,527| 76,521 (78.46) | 9162 (9.39)    | 745 (0.76)     | 11,099 (11.38) | <0.001 |
| Age at diagnosis              |       |                |                |                |                |        |
| 20–40                         | 5057  | 3521 (4.6)     | 412 (4.5)      | 62 (8.32)      | 1062 (9.57)    |        |
| 41–60                         | 46,071| 36,267 (47.39) | 3815 (41.64)   | 424 (56.91)    | 5565 (50.14)   |        |
| 61–70                         | 29,363| 23,178 (30.29) | 3119 (34.04)   | 171 (22.95)    | 2895 (26.08)   |        |
| 71–80                         | 17,036| 13,555 (17.71) | 1816 (19.82)   | 88 (11.81)     | 1577 (14.21)   |        |
| Race                          |       |                |                |                |                | <0.001 |
| White                         | 78,800| 63,117 (82.48) | 7059 (77.05)   | 544 (73.02)    | 8080 (72.8)    |        |
| Black                         | 9475  | 6001 (7.84)    | 1173 (12.8)    | 147 (19.73)    | 2154 (19.41)   |        |
| Others                        | 9252  | 7403 (9.67)    | 930 (10.15)    | 54 (7.25)      | 865 (7.79)     |        |
| Marital status                |       |                |                |                |                | <0.001 |
| Married                       | 61,275| 48,398 (63.25) | 5586 (60.97)   | 472 (63.36)    | 6819 (61.44)   |        |
| Single                        | 14,181| 10,962 (14.33) | 1309 (14.29)   | 115 (15.44)    | 1795 (16.17)   |        |
| Divorced                      | 22,071| 17,161 (22.43) | 2267 (24.74)   | 158 (21.21)    | 2485 (22.39)   |        |
| Insurance                     |       |                |                |                |                | <0.001 |
| Insured                       | 86,233| 68,046 (88.92) | 8047 (87.83)   | 631 (84.7)     | 9509 (85.67)   |        |
| Medicaid                      | 9970  | 7469 (9.76)    | 1006 (10.98)   | 102 (13.69)    | 1393 (12.55)   |        |
| Uninsured                     | 1324  | 1006 (1.31)    | 109 (1.19)     | 12 (1.61)      | 197 (1.77)     |        |
| Histological type             |       |                |                |                |                | <0.001 |
| IDC                           | 81,531| 62,512 (81.69) | 7434 (81.14)   | 721 (96.78)    | 10,864 (97.88) |        |
| ILC                           | 9907  | 8560 (11.19)   | 1226 (13.38)   | 12 (1.61)      | 109 (0.98)     |        |
| IDC&ILC                       | 6089  | 5449 (7.12)    | 502 (5.48)     | 12 (1.61)      | 126 (1.14)     |        |
| Differentiated grade          |       |                |                |                |                | <0.001 |
| Well                          | 26,503| 24,286 (31.74) | 2026 (22.11)   | 14 (1.88)      | 177 (1.59)     |        |
| Moderate                      | 45,260| 39,568 (51.71) | 3773 (41.18)   | 133 (17.85)    | 1786 (16.09)   |        |
| Poor                          | 25,764| 12,667 (16.55) | 3363(36.71)    | 598 (80.27)    | 9136 (83.21)   |        |
| T-Classificationb             |       |                |                |                |                | <0.001 |
| T1                            | 66,942| 54,691 (71.47) | 5857 (63.93)   | 393 (52.75)    | 6001 (54.07)   |        |
| T2                            | 26,832| 19,158 (25.04) | 2838 (30.98)   | 314 (42.15)    | 4522 (40.74)   |        |
| T3                            | 3289  | 2384 (3.12)    | 405 (4.42)     | 27 (3.62)      | 473(4.26)      |        |
| T4                            | 464   | 288(0.38)      | 62.0.68)      | 11(1.48)       | 103 (0.93)     |        |
| N-Classificationb             |       |                |                |                |                | <0.001 |
| N0                            | 71,234| 55,835 (72.97) | 6666 (72.98)   | 533 (71.54)    | 8180 (73.7)    |        |
| N1                            | 20,418| 16,319 (21.33) | 1820 (19.86)   | 173 (23.22)    | 2106 (18.97)   |        |
| N2                            | 4021  | 3072 (4.01)    | 399 (4.35)     | 23 (3.09)      | 527 (4.75)     |        |
| N3                            | 1854  | 1295 (1.69)    | 257 (2.81)     | 16 (2.15)      | 286 (2.58)     |        |
| Stage                         |       |                |                |                |                | <0.001 |
| Stage I                       | 58,453| 47,727 (62.37) | 5147 (56.18)   | 332 (44.56)    | 5247 (47.27)   |        |
| Stage II                      | 31,773| 23,390 (30.57) | 3206 (34.99)   | 355 (47.65)    | 4822 (43.45)   |        |
| Stage III                     | 7301  | 5404 (7.06)    | 809 (8.83)     | 58 (7.79)      | 1030 (9.28)    |        |
| Chemotherapy                  |       |                |                |                |                | <0.001 |
| No/Unknown                    | 62,979| 55,210 (72.15) | 5014 (54.73)   | 197 (26.44)    | 2558 (23.05)   |        |
| Yes                           | 34,548| 21,311 (27.85) | 4148 (45.27)   | 548 (73.56)    | 8541 (76.95)   |        |
| Radiotherapy                  |       |                |                |                |                | <0.001 |
| No                            | 37,847| 28,643 (37.43) | 3676 (40.12)   | 327 (43.89)    | 5201 (46.86)   |        |
| Yes                           | 59,680| 47,878 (62.57) | 5486 (59.88)   | 418 (56.11)    | 5898 (53.14)   |        |

Abbreviations N Number, IDC Infiltrating duct carcinoma, ILC Infiltrating lobular carcinoma, ER: Estrogen receptor, PR Progesterone receptor

*P values obtained from the χ² test. All statistical tests were two sided

bThe T-classification was subclassified as T1, T2, T3, or T4 and the N-classification was subclassified as N0, N1, N2, or N3 according to the 8th edition of the American Joint Committee on Cancer TNM staging system
Analyzing treatment benefits according to HoR status in the PSM cohort

In the initial data, the sample size of patients in the chemotherapy group was fewer than the non-chemotherapy group. Also, there were different baseline characteristics between these two groups (Table 1). Therefore, the PSM method was used to balance differences of baseline characteristics. A total of 21,208 patients with chemotherapy were matched with 21,208 patients without chemotherapy (Supplemental Fig. 2). All covariates included were well balanced between chemotherapy and non-chemotherapy groups in the PSM cohort (Supplemental Table 1).

In the PSM cohort, patients with sPR-positive and dHoR-negative phenotypes benefited significantly from chemotherapy both with $P < 0.001$, while patients with sER positive could not benefit from chemotherapy with $P = 0.052$ (Fig. 3). Furthermore, we performed an interaction analysis using Cox model between the chemotherapy and HoR status in the PSM cohort (Fig. 4). The results showed that the sPR-positive phenotype benefited more from chemotherapy than dHoR-negative phenotype ($P$ for interaction = 0.001). Besides, in the non-chemotherapy group, patients with sPR-positive phenotype had worse survival than dHoR-negative phenotype with $P = 0.034$. In the patients with chemotherapy, patients with sPR positive had similar prognosis to dHoR negative with $P = 0.614$ (Supplemental Fig. 3).

Systematic review of the intrinsic subtypes with sPR-positive phenotype

Intrinsic molecular subtypes of breast cancer have been thoroughly studied and can indicate the existence of sPR-positive phenotype [11, 12, 22]. In total, the sPR-positive phenotype had a higher likelihood of being the basal-like subtype (46.15%). Normal-like and her-2-positive subtypes comprised a small proportion, accounting for 4.41%, 9.89%, respectively (Table 4).

Discussion

Breast cancer with sPR positive is a rare and a biologically distinct subgroup, which accounts for just 0.3–7.1% of breast cancer [14]. There was a variation in the frequency...
of sPR-positive phenotype. The reasons for the different proportions were as follows: 1. The patients mentioned in the literature above (total 205 cases were sPR positive) were recruited from 9 different medical institutions with different immunohistochemical processes, ER or PR antibody, which all have an impact on the results. 2. Different cut-off value for ER/PR positivity. Three of the nine medical institutions used < 10% nuclear immunostaining rate to define the negative categories, and the other six medical institutions used the 1% limit. Using 10% cut-off value would result in an increase in the ratio of sPR-positive phenotype. 3. Both false-negative ER status or false-positive PR status can lie behind the finding of an sPR-positive immunohistochemistry result. Cserni, G and his collaborators reevaluated the ER and PR status in the sPR-positive patients by IHC with a 1% cut-off for positivity, and found that only 0.43% were sPR positive. In our research, the SEER database uses a 1% cut-off for positivity, and the ratio of sPR positive was 0.76%, which was in keeping with reevaluated proportion. Thus, it can be seen that sPR-positive phenotype is very rare.

**Fig. 3** Chemotherapy benefits in different HoR status phenotypes in the PSM cohort with her-2 negative breast cancer. The patients with sER positive phenotype could not benefit from chemotherapy with \( P=0.052 \) (B), while patients with sPR positive and dHoR negative phenotypes benefited significantly from chemotherapy both with \( P<0.001 \) (C and D).
and should be carefully diagnosed in clinic. Since different immunohistochemical processes, ER or PR antibody and cut-off value for ER/PR positivity could all have an impact on the diagnosis of sPR-positive subtype breast cancer, we should keep these factors consistent in future studies about this particular subtype breast cancer. The data of this study came from SEER database, which uses a 1% cut-off for positivity, but the other two factors could not be determined to be the same. This is a defect of this study.

In our study, compared with sER-positive and dHoR-positive subtypes, sPR-positive subtype had more aggressive biological behavior and worse prognosis (Fig. 1; Table 2). When considering the causes of sPR-positive breast cancer, the mechanisms are quite complicated [19, 25–27]. The secondary loss of ER is one of the hypotheses. Higher estrogen levels in premenopausal females could downregulate the expression of ER protein [26]. Previous studies showed that patients with sPR-positive phenotype were more diagnoses in young, who have a relatively higher estrogen level. What’s more, patients with sPR-positive phenotype were more often with her-2 positive [17, 21] and higher grade [20], which were consistence with our study.

In this study, we identified eligible female patients with her-2-negative breast cancer from SEER to explore the outcomes of patients with sPR-positive phenotype. Our results showed that patients with sPR-positive phenotype had unfavorable prognosis which was similar with patients dHoR-negative phenotype, which was consistent with other studies [20, 22, 28]. We have investigated detail clinicopathologic features of sPR-positive phenotype and found that the majority of sPR-positive breast cancer occurred in younger women with poorly differentiated and late-stage tumors and were rarely of classical lobular type. Besides, the study of Rakha showed that sPR-positive phenotype was more frequently associated with biomarkers of poor prognosis such as positive 53 and basal cytokeratin and reduced E-cadherin expression [20]. All above suggested that sPR-positive phenotype is a more aggressive phenotype.

Perou and his co-authors [29] identified four breast cancer subtypes: the basal-like, HER2-enriched, luminal-A, luminal-B and the normal-like breast cancer. Majority of sPR-positive tumors tend to be lower mRNA level of ESR1 and basal-like molecular subtype according to Ethier’s study (N = 31, 58.49%) [12] and Itoh’s study (N = 13, 65%) [18]. Compared with luminal subtypes, patients with basal-like subtype had a poorer survival [30–35] and benefited least from tamoxifen endocrine therapy [36, 37]. Besides, patients with basal-like subtype benefited better from chemotherapy

![Table 4](image)

| Author       | Year | Nation            | Original Her-2 | Number of sPR positive | Luminal-A (%) | Luminal-B (%) | Basal-like (%) | HER2-enriched (%) | Normal-like (%) |
|--------------|------|------------------|----------------|------------------------|---------------|---------------|----------------|------------------|----------------|
| Ethier       | 2018 | Canada and Spain | Negative       | 23                     | 12 (52.17)    | 4 (17.39)    | 3 (13.04)    | 4 (17.39)        | –               |
| Schroth      | 2016 | Germany          | Unknown        | 15                     | 4 (26.67)    | 1 (6.67)    | 8 (53.33)    | 1 (6.67)         | 1 (6.67)        |
| Ke-Da Yu     | 2015 | China            | Negative       | 53                     | 9 (16.98)    | 7 (13.21)    | 31 (58.49)   | 4 (7.55)         | 2 (3.77)        |
| Total        | –    | –                | –              | 91                     | 25 (27.47)   | 12 (13.19)   | 42 (46.15)   | 9 (9.89)         | 3 (4.41)        |
with paclitaxel and anthracycline than luminal subtypes [32, 38–40]. Aleix’s study highlighted the higher chemotherapy sensitivity of basal-like subtype [34]. Above all, these results suggest that sPR-positive breast cancer might tend to be more sensitive to chemotherapy and less effective in endocrine therapy. Furthermore, these speculations could be confirmed in our study. The Kaplan–Meier and interaction analyses of chemotherapy in different HoR status revealed that patients with sPR-positive phenotype could benefit more from chemotherapy when compared with sER-positive and dHoR-negative phenotypes. The particular mechanism of the highly sensitive to chemotherapy of sPR-positive phenotype is still unclear. We speculate that it might be related to inadequate chemotherapy to the patients with sPR-positive phenotype. What’s more, the HRD vividly showed that sPR-positive breast cancer suffered a high death risk at the initial 1–2 years. Above all, we proposed that patients with sPR positive should be given more intense chemotherapy just like dHoR negative at the beginning.

The study of Bardou, V. J and his co-authors showed that patients with sPR-positive phenotype, compared with dHoR positive and sER positive, had the worst prognosis when received systemic endocrine therapy in the database of Project Program [41]. Davies’s study also revealed that 1236 patients with sPR-positive breast cancer did not benefit from 5 years of tamoxifen endocrine therapy with P = 0.35 [42]. These results showed that sPR-positive breast cancer had less sensitivity of endocrine therapy.

According to the HRD, for sPR-positive patients, the risk of tumor death was decreased to nearly zero after 5 years. On the contrary, the HRD of dHoR-positive and sER-positive patients were both continued to stabilize in relatively high levels during the follow-up time. Therefore, for patients with sPR positive, it is advisable to de-escalate rather than highlight the endocrine therapy, and for dHoR-positive and sER-positive patients the escalating endocrine therapy might be more necessary to reduce the risk of recurrence or tumor death in the later time.

In conclusion, patients with sPR-positive and her-2-negative phenotype had similar prognosis with triple-negative phenotype. Patients with sPR-positive phenotype had higher sensitivity of chemotherapy and lower response to endocrine therapy. In future clinical trials of breast cancer concerning endocrine therapy, patients with sPR positive should be treated with caution or even be excluded. However, further prospective studies referring to response of sPR-positive breast cancer to endocrine therapy are recommended.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-022-02158-0.

Funding The study was supported by the Grant from the major program of the Jinhua Municipal Science & Technology Bureau (Grant number 2019-3-004) and the key program of the Jinhua Municipal Science & Technology Bureau (Grant number 2014-3-008).

Declarations

Conflict of interest All authors have declared no conflicting interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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