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Factors Affecting Pathologic Complete Remission in Patients with Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer Receiving Neoadjuvant Chemotherapy

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Breast cancer · Chemotherapy · Response

Abstract
Introduction: Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is associated with improvement in survival outcomes. This study evaluated the pCR in patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer after NAC. ***Methods:*** We evaluated 417 patients who were diagnosed with invasive breast cancer and treated with NAC followed by curative surgery between January 2007 and December 2020 and analyzed the pCR for HR-positive and HER2-negative breast cancer. ***Results:*** The median age at the time of surgery was 45.4 years, and 9.1% of patients (38 of 417) with HR-positive/HER2-negative status had pCR. Among patients with HR-positive/HER2-negative breast cancer, patients with single HR-positivity had a 20.2% pCR rate, and patients with double HR-positivity had a 4.4% pCR rate. Patients with a high Ki-67 index exhibited a higher pCR rate than those with a lower Ki-67 index (14.5% vs. 3.2%). Patients with single HR-positive and high Ki-67 values exhibited a significantly higher pCR rate than those with double HR-positive and low Ki-67 values (27.8% vs. 2.1%; $p < 0.001$). ***Conclusion:*** NAC could improve prognosis in patients with HR-positive/HER2-negative breast cancer with a single HR-positive and high Ki-67 values.

Introduction

Neoadjuvant chemotherapy (NAC) has been established as a standard treatment for patients with locally advanced breast cancer and operable breast cancer [1]. To

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avoid aggressive surgery, it is preferable to perform minimal surgery as the first approach, which is associated with fewer problems and lower morbidity after NAC [2, 3]. The response to NAC in patients with breast cancer predicts the prognosis for patients; therefore, a pathologic complete response (pCR) to NAC is more likely to be associated with improved outcomes.

The pCR rate with NAC is higher in patients with HER2-positive breast cancer and triple-negative breast cancer. Furthermore, NAC in HR-positive and HER2-negative breast cancer cases is associated with a lower percentage of achieving pCR compared with that in other breast cancer cases [4]. Patients who achieve pCR have significantly higher overall survival and disease-free survival rates compared to those with residual tumors [5]. Therefore, the indication for NAC in HR-positive and HER2-negative breast cancers with lower pCR rates is currently controversial.

Initiating NAC for breast cancer cases with a low probability of pCR after NAC may result in unnecessary treatment. Therefore, it is important to determine the success rate of NAC by separating patients with low probability from those with high probability in HR-positive and HER2-negative breast cancer. We investigated factors that were predictive of pCR and established a mechanism for calculating the probability of pCR after NAC based on HR-positive and HER2-negative breast cancer subtypes and their correlation with the pCR rate.

Table 1. Patient demographic and clinical characteristics (n = 417)

Variables	n (%)
BMI	24.16±7.14
Age of diagnosis	44.91±10.19
ER	
Positive	403 (96.6)
Negative	14 (3.4)
PR	
Positive	287 (75.7)
Negative	92 (24.3)
Ki-67	
Low (≤20)	187 (44.8)
High (>20)	230 (55.2)
Clinical tumor stage	
cT1	21 (5.0)
cT2	221 (53.0)
cT3	160 (38.4)
cT4	15 (3.6)
Clinical nodal stage	
cN0	16 (3.8)
cN1	117 (28.1)
cN2	188 (45.1)
cN3	96 (23.0)
Menopause	
Yes	203 (48.7)
No	214 (51.3)
pCR	
Yes	38 (8.1)
No	379 (91.9)

Materials and Methods

We evaluated 417 patients who were diagnosed with invasive breast cancer and treated with NAC followed by curative surgery between January 2007 and December 2020 and analyzed the pCR rate for HR-positive/HER2-negative breast cancer cases. Patients were included in the study if they met the following criteria: (1) completion of the planned dosage and cycle of NAC and (2) had undergone breast-conserving surgery or mastectomy and axillary surgery.

Most patients received anthracycline- and/or taxane-based regimens. These regimens included anthracycline plus cyclophosphamide, followed by anthracycline- and taxane-based approaches. The clinical stage was evaluated using breast magnetic resonance imaging or breast ultrasonography. The following definitions were used in the assessments: (1) cN0 indicated normal axillary lymph nodes or absence of enlarged axillary lymph nodes on breast ultrasonography or magnetic resonance imaging; (2) axillary pCR (pN0) indicated absence of micrometastatic or macrometastatic nodal disease in sentinel lymph node biopsy or axillary lymph node dissection; (3) breast pCR was defined as absence of invasive breast cancer (ypT0 or ypTis) on final pathologic results; and (4) single HR-positive status was defined as estrogen receptor (ER)-positive/progesterone receptor (PR)-negative or ER-negative/PR-positive cases, and double HR-positive status was defined as ER-positive/PR-positive cases.

All radioactive and/or 0.8% indigo carmine dye lymph nodes and palpable lymph nodes were removed as sentinel lymph nodes. Most patients underwent breast and axillary surgery within 1 month of completing NAC. The type of breast surgery was selected based on the location and size of the breast tumor. ER and PR statuses were determined using the Allred scoring system, and a positive result was defined as a total score of ≥3. HER2 3 + reactions were considered positive, whereas 0 and 1 + reactions were considered negative. If 2 + results were obtained, silver-enhanced in situ hybridization was performed to determine whether the patient was HER2-positive. Ki-67 expression levels are shown as the percentage of cells with positive nuclear staining among the total number of tumor cells. ER status, PR status, HER2 status, and Ki-67 expression level of the specimens obtained via biopsy or surgery were evaluated. We used the immunohistochemical results of the core needle biopsy specimens to analyze the response to NAC.

Proportions were compared between groups using the χ^2 test, and two-sided 95% binomial confidence intervals were calculated for the estimated proportions. Statistical significance was set at a p value <0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows version 23 software (IBM Corp., Armonk, NY, USA). This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (IRB file No. 2017-09-051).

Table 2. Comparisons of patients treated with NAC according to pCR

Variables	PCR (*n* = 38)	No PCR (*n* = 379)	*p* value
Age of diagnosis	43.66±10.98	45.03±10.11	0.429
ER			<0.001
Positive	31 (81.58)	372 (98.15)	
Negative	7 (18.42)	7 (1.85)	
PR			0.002
Positive	20 (52.63)	287 (75.73)	
Negative	18 (47.37)	92 (24.27)	
Ki-67			<0.001
Low (≤20)	6 (15.79)	181 (47.76)	
High (>20)	32 (84.21)	198 (52.24)	
Clinical tumor stage			0.004
cT1	3 (7.89)	18 (4.75)	
cT2	29 (76.32)	192 (50.66)	
cT3	6 (15.79)	154 (40.63)	
cT4	0 (0.00)	15 (3.96)	
Clinical nodal stage			0.200
cN0	3 (7.89)	13 (3.43)	
cN1	13 (34.21)	104 (27.44)	
cN2	17 (44.74)	171 (45.12)	
cN3	5 (13.16)	91 (24.01)	

Table 3. Breast pCR-, axillary pCR-, or both pCR-associated Ki-67 and HR status

	Breast pCR			Axillary pCR			Both pCR		
	yes (*n* = 46)	no (*n* = 371)	*p* value	yes (*n* = 138)	no (*n* = 279)	*p* value	yes (*n* = 38)	no (*n* = 379)	*p* value
Ki-67			<0.001			0.023			<0.001
Low (≤20)	7 (15.22)	180 (48.52)		51 (36.96)	136 (48.75)		6 (15.79)	181 (47.76)	
High (>20)	39 (84.78)	191 (51.48)		87 (63.04)	143 (51.25)		32 (84.21)	198 (52.24)	
HR			<0.001			<0.001			<0.001
Single	27 (58.70)	97 (26.15)		57 (41.30)	67 (24.01)		25 (65.79)	99 (26.12)	
Double	19 (41.30)	274 (73.85)		81 (58.70)	212 (75.99)		13 (34.21)	280 (73.88)	
HR and Ki-67			<0.001			<0.001			<0.001
Single and high	24 (52.17)	55 (14.82)		45 (32.61)	34 (12.19)		22 (57.89)	57 (15.04)	
Double and low	4 (8.70)	138 (37.20)		39 (28.26)	103 (36.92)		3 (7.89)	139 (36.68)	

Results

The median age of the patients at the time of surgery was 44.9 years. The clinicopathological characteristics of the patients are shown in Table 1, and comparisons between the pCR and the non-pCR groups are shown in Table 2 pCR was associated with ER status, PR status, Ki-67 index, and initial clinical tumor stage. Breast pCR was achieved in 11.0% (46 patients), axillary pCR in 33.1% (138 patients), and pCR for both was achieved in 9.1% (38 patients) of patients who underwent surgery after NAC.

Breast pCR, axillary pCR, and pCR for both were associated with Ki-67 levels and HR-positive status, and these results are summarized in Table 3. Ki-67 levels and single HR-positive status were associated with a significant difference in achieving pCR (breast and axillary). Moreover, 9.1% of patients (38 of 417) with HR-positive/HER2-negative status achieved pCR. Three of 142 patients with breast cancer with double HR-positive and low Ki-67 levels achieved both pCR outcomes, and 22 of 79 patients with single HR-positive and high Ki-67 levels achieved both pCR outcomes. Patients with single HR-positive and high Ki-67 levels exhibited a significantly

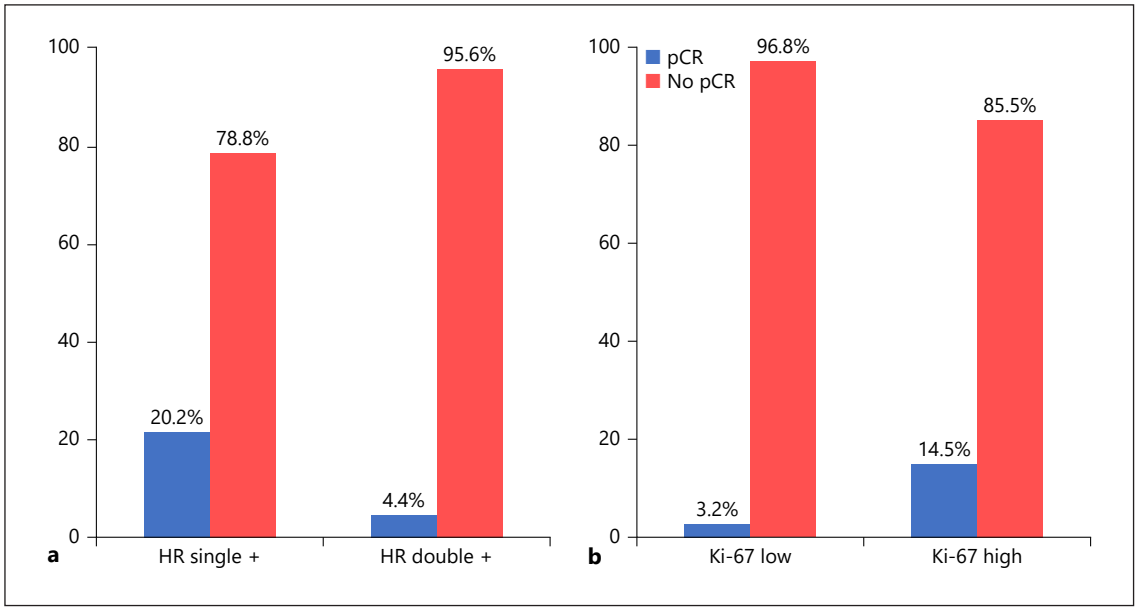

Fig. 1. Correlation between HR-positive and Ki-67 levels with pCR. **a** pCR rate associated with single or double HR-positive status. **b** pCR rate associated with Ki-67 status.

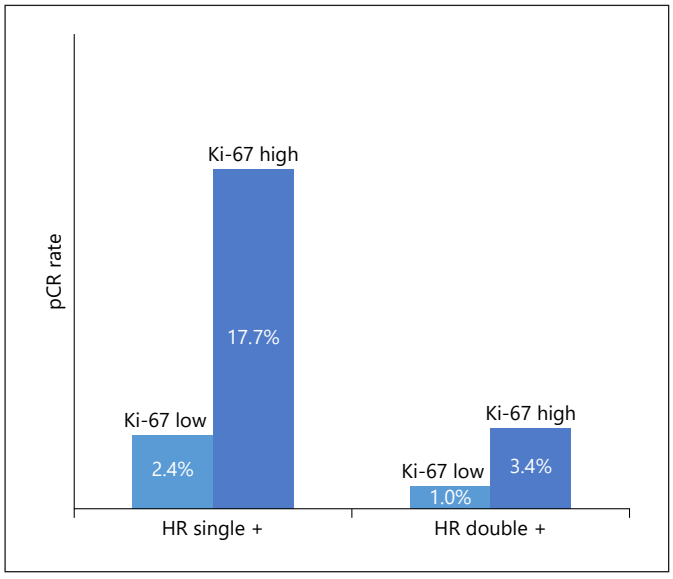

Fig. 2. pCR rate associated with Ki-67 status in patients with single or double HR-positive status.

higher pCR rate than those with double HR-positive and low Ki-67 levels (27.8% vs. 2.1%; $p < 0.001$).

Figure 1 shows the correlation between HR (single or double)-positive and Ki-67 levels and pCR. Among patients with HR-positive/HER2-negative breast cancer, patients with single HR-positive status had a pCR rate of 20.2%, and patients with double HR-positive status had a pCR rate of 4.4%. Patients with high Ki-67 levels exhibited higher pCR rates than those with low Ki-67 levels (14.5% vs. 3.2%). In patients with single HR-positive status, patients with high Ki-67 levels achieved a pCR rate of 17.7%, and patients with low Ki-67 levels achieved a pCR rate of 2.4%. In double HR-positive cases, patients with high Ki-67 levels achieved a pCR rate of 3.4%, and patients with low Ki-67 levels had a pCR rate of 1.0% (Fig. 2).

Discussion

NAC in HR-positive/HER2-negative breast cancer does not accurately predict and has been associated with a low percentage of pCR; however, predicting pCR is important for understanding and improving oncologic outcomes and identifying patients for whom aggressive surgery, such as mastectomy and axillary lymph node dissection, could be provided as a treatment option. We retrospectively studied data collected from a database of patients with HR-positive/HER2-negative breast cancer and assessed clinicopathological characteristics to estimate factors that can affect axillary or breast pCR. Our study showed an extremely low rate of pCR in patients who presented with double HR-positive and low Ki-67

levels. Moreover, for HR-positive/HER2-negative breast cancers, chemotherapy can be omitted due to Oncotype DX or MammaPrint tests [6, 7]. NAC in patients with breast cancer with a low probability of pCR after NAC may result in unnecessary and aggressive treatment for these patients. Therefore, it is important to study the subjects and assess the value of NAC by separating those with low probability from those with high probability. Our study showed that an average of 9.1% of the patients (38 of 417) with HR-positive/HER2-negative status achieved pCR. Patients with double HR-positive and low Ki-67 levels only had a 2.1% pCR rate. Based on these results, initiating NAC is questionable as the best practice for these patients.

Several studies have evaluated post-NAC results based on HER2-positive or triple-negative breast cancer status [8–10]. Some studies have indicated that axillary pCR is associated with a biological subtype, initial clinical tumor stage, clinical nodal stage, and breast pCR [4]. Our study showed that breast cancer with a single HR, high Ki-67 status, and initial lower clinical tumor stage was associated with pCR in HR-positive/HER2-negative breast cancer cases. For cases identified during the initial clinical tumor stage, small tumors <2 cm were excluded from NAC in patients with HR-positive/HER2-negative breast cancer; therefore, additional comparisons were not necessary and were omitted. Alison et al. [11] showed that breast pCR rates were lower (12.7%) in patients with HR-positive/HER2-negative breast cancer. Our study showed that 9.1% of patients with all HR-positive/HER2-negative status achieved pCR. However, patients with single HR-positive and high Ki-67 levels exhibited a pCR rate of 27.8%.

Evidence indicates that the Ki-67 levels are low during G1 and early S-phase and progressively increase to reach a maximum level during mitosis [12]. Some studies have shown that Ki-67 expression is associated with cell proliferation, and high Ki-67 levels in breast cancer tissue have been considered a poor prognostic factor and a good predictive factor for response to chemotherapy [13–15]. Most studies have identified a high Ki-67 proliferation rate as a predictive factor for a higher rate of pCR after NAC [15, 16]. However, currently, there is no standard index for classifying Ki-67 expression as high or low; therefore, many studies have used different indices to classify Ki-67 levels. One study adopted a cutoff value of 20% to distinguish between low and high Ki-67 expression [17]. Other studies have suggested 25% or 12% as the cutoff standard, which are the same values noted in our study, to classify low or high Ki-67 expression [18, 19]. In our study, high and low Ki-67 levels were divided based on a cutoff value of 20%. Patients with high Ki-67 levels exhibited a pCR rate of 14.5%, while those with low Ki-67 levels showed a pCR rate of 3.2%.

HR-positive subtypes account for more than 80% of invasive breast cancers, and treatment approaches for these subtypes are associated with better disease-free and overall survival outcomes. However, some studies have shown that single HR-positive breast cancer may have less favorable profiles and outcomes than those of double HR-positive breast cancer [20–22]. Christine et al. [23] showed that, compared with the ER-positive/PR-positive group, the ER-positive/PR-negative and ER-negative/PR-positive groups were more likely to be diagnosed with high-grade cancer (16.0% vs. 34.2% and 80.0%; $p < 0.001$) and have lymphovascular invasion (17.9% vs. 19.6% and 23.0%; $p < 0.001$). In this study, single HR-positive cases had a pCR rate of 20.2%, and double HR-positive cases had a pCR rate of 4.4%. Moreover, patients with ER-positive/PR-negative breast cancer were more likely to have the basal-like subtype according to the PAM50 method and the ER-negative/HER2-negative subtype among the three-gene subtypes [24]. It can be thought that these characteristics affect pCR rate.

Although our study was performed in three comprehensive cancer institutions and the number of patients was relatively small, our study included patients with HR-positive and HER2-negative results who were treated with NAC. To date, only a limited number of studies have assessed the clinical value of NAC in such patients. Therefore, the results from the small number of patients in this study are meaningful and allow us to confidently draw important conclusions regarding the treatment of HR-positive and HER2-negative breast cancer cases with NAC. Furthermore, this study was not a prospective randomized clinical trial, and for that reason, the distribution of patients was uneven and may have influenced the results of regional control.

In conclusion, we found that patients with double HR-positive breast cancer had worse pCR rates than those with a single HR-positive phenotype. Furthermore, patients with breast cancer with low Ki-67 levels had worse outcomes than those with high Ki-67 levels. These findings may impact decisions regarding NAC treatment. These results suggest that patients with HR-positive/HER2-negative breast cancer with single HR-positive and high Ki-67 levels should consider NAC. However, in patients with HR-positive/HER2-negative breast cancer with double HR-positivity and low Ki-67 levels, NAC should be considered again.

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Statement of Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (IRB file No. 2017-09-051).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

The first author, Hee Jun Choi, planned and wrote the manuscript. Other co-authors, Chang Shin Jung, Seungju Lee, and Seok Kyung Kang, played a role in the data collection and processing of this study. Other co-authors, Jun Ho Lee, Jeong Eon Lee, and Youn Joo Jung, played a role in the modulation and supervision of this study. The corresponding author, Hyun Yul Kim planned, revised, edited, and submitted the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287–312.
2 Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455–61.
3 Mittendorf EA, Caudle AS, Yang W, Krishnamurthy S, Shaitelman S, Chavez-MacGregor M, et al. Implementation of the american college of surgeons oncology group z1071 trial data in clinical practice: is there a way forward for sentinel lymph node dissection in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy? Ann Surg Oncol. 2014;21(8):2468–73.
4 Choi HJ, Ryu JM, Kim I, Nam SJ, Kim SW, Yu J, et al. Prediction of axillary pathologic response with breast pathologic complete response after neoadjuvant chemotherapy. Breast Cancer Res Treat. 2019;176(3):591–6.
5 Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol. 2005;23(36):9304–11.
6 Losk K, Freedman RA, Laws A, Kantor O, Mittendorf EA, Tan-Wasielewski Z, et al. Oncotype DX testing in node-positive breast cancer strongly impacts chemotherapy use at a comprehensive cancer center. Breast Cancer Res Treat. 2021;185(1):215–27.
7 Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375(8):717–29.
8 Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. neoadjuvant chemotherapy in triple negative breast cancer: correlation between androgen receptor expression and pathological response. Asian Pac J Cancer Prev. 2020;21(2):563–8.
9 Wu YT, Xu Z, Arshad B, Wu JS, Zhang K, Wu H, et al. Significantly higher pathologic complete response (pCR) after the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: evidence from a meta-analysis of randomized controlled trials. J Cancer. 2018;9(17):3168–76.
10 Santonja A, Sanchez-Munoz A, Lluch A, Chica-Parrado MR, Albanell J, Chacon JI, et al. Triple negative breast cancer subtypes and pathologic complete response rate to neoadjuvant chemotherapy. Oncotarget. 2018;9(41):26406–16.
11 Barron AU, Hoskin TL, Day CN, Hwang ES, Kuerer HM, Boughey JC. Association of low nodal positivity rate among patients with ERBB2-positive or triple-negative breast cancer and breast pathologic complete response to neoadjuvant chemotherapy. JAMA Surg. 2018;153(12):1120–6.
12 Brown DC, Gatter KC. Ki67 protein: the immaculate deception? Histopathology. 2002;40(1):2–11.
13 de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, Durbecq V, et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12, 155 patients. Br J Cancer. 2007;96(10):1504–13.
14 Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol. 2005;23(28):7212–20.
15 Jain P, Doval DC, Batra U, Goyal P, Bothra SJ, Agarwal C, et al. Ki-67 labeling index as a predictor of response to neoadjuvant chemotherapy in breast cancer. Jpn J Clin Oncol. 2019;49(4):329–38.
16 Alba E, Lluch A, Ribelles N, Anton-Torres A, Sanchez-Rovira P, Albanell J, et al. high proliferation predicts pathological complete response to neoadjuvant chemotherapy in early breast cancer. Oncologist. 2016;21(6):778–5.
17 Li XR, Liu M, Zhang YJ, Wang JD, Zheng YQ, Li J, et al. Evaluation of ER, PgR, HER-2, Ki-67, cyclin D1, and nm23-H1 as predictors of pathological complete response to neoadjuvant chemotherapy for locally advanced breast cancer. Med Oncol. 2011;28(Suppl 1):S31–8.
18 Nishimura R, Osako T, Okumura Y, Hayashi M, Arima N. Clinical significance of Ki-67 in neoadjuvant chemotherapy for primary breast cancer as a predictor for chemosensitivity and for prognosis. Breast Cancer. 2010;17(4):269–75.
19 Colleoni M, Viale G, Zahrieh D, Pruneri G, Gentilini O, Veronesi P, et al. Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. Clin Cancer Res. 2004;10(19):6622–8.

20 Van Asten K, Slembrouck L, Olbrecht S, Jongen L, Brouckaert O, Wildiers H, et al. prognostic value of the progesterone receptor by subtype in patients with estrogen receptor-positive, HER-2 negative breast cancer. Oncologist. 2019;24(2):165–71.
21 Rakha EA, El-Sayed ME, Green AR, Paish EC, Powe DG, Gee J, et al. Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype. J Clin Oncol. 2007;25(30):4772–8.
22 Bae SY, Kim S, Lee JH, Lee HC, Lee SK, Kil WH, et al. Poor prognosis of single hormone receptor- positive breast cancer: similar outcome as triple-negative breast cancer. BMC Cancer. 2015;15:138.
23 Dauphine C, Moazzez A, Neal JC, Chlebowski RT, Ozao-Choy J. Single hormone receptor-positive breast cancers have distinct characteristics and survival. Ann Surg Oncol. 2020;27(12):4687–94.
24 Li Z, Tu Y, Wu Q, Wang Z, Li J, Zhang Y, et al. clinical characteristics and outcomes of single versus double hormone receptor-positive breast cancer in 2 large databases. Clin Breast Cancer. 2020;20:e151–63.