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Original Article

The neoadjuvant chemotherapy responses and survival rates of patients with different molecular subtypes of breast cancer

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Abstract: Objective: The purpose of this study was to evaluate the effect of neoadjuvant chemotherapy (NAC) on the responses and survival rates of patients with different molecular subtypes of breast cancer. Methods: A retrospective analysis was conducted on 284 breast cancer patients who underwent NAC in our hospital from January 2017 to January 2019. The patients were classified into the Luminal A (n=87), Luminal B (n=78), human epidermal growth factor receptor 2 positive (HER-2$^+$, n=66), and triple-negative (TN, n=53) breast cancer subtypes. The Ki67 expressions and clinical prognoses were compared among the patients in the four subtypes. Results: The complete response (CR) rates were significantly higher in the HER-2$^+$ and TN patients than they were in the Luminal A and Luminal B subtype patients (P<0.05). The HER-2$^+$ and TN breast cancer patients had significantly higher response rates (RR) than the Luminal B patients (P<0.05). The Ki67 expressions decreased significantly in the patients with the Luminal B, HER-2$^+$, and TN subtypes after NAC (P<0.05), with a greater decrease in the Ki67 expressions in the HER-2$^+$ and TN subtypes than in the Luminal B subtypes (P<0.05). The Ki67 levels decreased significantly in the patients with CR or PR compared to the stable disease (SD) and progressive disease (PD) patients (P<0.05). The HER-2$^+$ patients had remarkably higher distant metastasis rates, compared to the patients with the Luminal A and B subtypes (P<0.05). Conclusion: Statistical differences were found in the pathological responses and survival rates in the patients with the different molecular subtypes of breast cancer after the NAC treatment. The HER-2$^+$ or TN breast cancer patients had higher pathological response rates, which may be closely related to their decreased Ki67 expressions. Interestingly, the HER-2$^+$ breast cancer patients also showed a higher distant metastasis rate, which warrants further analysis.

Keywords: Breast cancer, Ki67, HER-2, neoadjuvant chemotherapy, pathological remission, long-term prognosis

Introduction

Breast cancer, the second most common malignancy among women in China, is also the tumor with the highest mortality rate that endangers the physical wellbeing and quality of life of women worldwide [1]. Breast cancer is a highly heterogeneous disease at the molecular level. Traditionally, it can be classified into four molecular subtypes: Luminal A, Luminal B, human epidermal growth factor receptor 2-positive (HER-2$^+$), and triple-negative (TN), based on differences in the estrogen (ER), progesterone (PR), HER2, and Ki67 expressions [2]. Advances in molecular biology have provided researchers and practitioners with the genetic tools needed for molecular typing, thus laying the foundation for personalized treatment [3]. Neoadjuvant chemotherapy (NAC), also known as preoperative chemotherapy, is given systemically in the early stages of treatment to control the tumor size and reduce the risk of postoperative metastasis. NAC has been increasingly administered to breast cancer patients, with a well-documented clinical effectiveness [4]. However, the subtypes differ in their cellular morphology and molecular characteristics, with notable variations in the pathological responses to NAC and the prognoses [5]. Currently, there has been no systematic comparison made of the relationship between NAC application and the responses/survival rates of patients with different molecular subtypes of breast cancer [6]. Accordingly, we retrospec-

tively analyzed 284 breast cancer patients who underwent NAC in our hospital, to provide an evidence-based reference for the clinical application of NAC.

Subjects and methods

General data

A retrospective analysis was conducted on 284 female breast cancer patients treated in the Department of Breast Surgery of our hospital from January 2017 to January 2019. This study strictly complied with the requirements of the ethics committee, with an ethics committee approval number of 2016-12-11.

Inclusion and exclusion criteria

Inclusion criteria: (1) Female patients with ranging in age from 18 to 75 years old. (2) Patients with clinically confirmed stages II or III breast cancer [7]. (3) Patients undergoing elective radical mastectomies under NAC and general anesthesia. (4) Patients with no history of breast cancer or breast cancer treatment before the NAC treatment. (5) Patients with complete medical records and intact follow-up records for at least two years.

Exclusion criteria: (1) Patients with distant metastasis determined using adjuvant tests, or patients who had received any prior anti-tumor-related therapy. (2) Patients who were pregnant or lactating. (3) Patients with inoperable tumors even after NAC. (4) Patients comorbid with severe organ dysfunction or immune system-related diseases.

Treatment

All the patients underwent NAC after admission using the TEC (docetaxel, epirubicin, and cyclophosphamide) regimen: Docetaxel 75 mg/m^2, iv drip, d1; (2) Epirubicin 90 mg/m^2, iv drip, d1; (3) Cyclophosphamide 500 mg/m^2, iv drip, d1. One chemotherapy cycle lasted for 21 days, and the efficacy was assessed three cycles after the surgery. The pathological specimens were retained.

Molecular subtyping

Breast cancer samples were collected using core needle biopsies. Immunohistochemical staining for ER, PR, and HER-2 was used to identify the patient subtypes. For the ER and PR staining, the nuclear-positive stained cell count ≥1% were considered positive and the nuclear-positive stained cell counts less than 1% were considered negative. For the HER-2 staining, the nuclear-positive stained cell count ≥50% were considered strongly positive (+++), the counts 25%-50% were considered positive (++), the counts 1-25% were considered weakly positive (+), and the counts <1% were considered negative (-). Weakly positive (+) and negative (-) immunoreactions were considered to indicate no HER-2 overexpression, and the strongly positive (+++) immunoreactions were considered to indicate HER-2 overexpressions. The positive (++) immunoreactions were confirmed using fluorescence in situ hybridization (FISH), with FISH+ considered to indicate HER-2 overexpression and FISH- considered to indicate no HER-2 overexpression. The Ki67 expressions were determined using immunohistochemistry before and after the NAC, with a high Ki-67 expression defined as ≥14% of tumor nuclei staining positive, and a low expression defined as <14% positive. Breast cancer molecular subtype classification: Luminal A was defined as having at least one positive for ER and PR, with no HER-2 overexpression and a low Ki67 expression. A total of 87 cases were classified as Luminal A (30.63%). Luminal B included two types: type I: having at least one positive for ER and PR, with no overexpression of HER-2 and a high expression of Ki67. Type II: having at least one positive for ER and PR, with and overexpression of HER-2 and any expression of Ki67. A total of 78 cases were classified as Luminal B (27.46%). The HER-2$^+$ subtype must be negative for both ER and PR and have an HER-2 overexpression, with any Ki67 expression. A total of 66 cases were classified as HER-2$^+$ (23.24%). The triple-negative (TN) subtype must be negative for both ER and PR, with no HER-2 overexpression or any Ki67 expression. A total of 53 cases were classified as TN (18.66%). The cells were considered Ki67 positive when the nucleus staining changed from light yellow to brownish yellow. A total of 10 fields of 400 magnification were randomly observed, using the 500 cells per field technique. The proportion of the Ki67 positive cells to the total number of the cells was calculated. Low Ki67 expressions were indicated when the number of Ki67 positive cells was 0-20%, and a high Ki67 expression was indicated when the number of positive cells >20%.

Table 1. Comparison of the clinicopathological characteristics of patients with different molecular subtypes of breast cancer

Index	Luminal A (n=87)	Luminal B (n=78)	HER-2$^+$ (n=66)	TN (n=53)	Z/χ^2	P
Age (year)					1.567	0.667
≤35	28	24	23	13		
>35	59	55	43	40		
Primary tumor diameter (cm)					3.862	0.277
≤5	66	59	44	33		
>5	21	19	22	19		
TNM stage					1.96	0.923
II a	46	44	37	29		
II b	20	19	12	10		
III	21	15	17	14		
Menstruation					0.42	0.936
Pre-menopausal	63	56	48	36		
Post-menopausal	24	22	18	17		

Table 2. A clinical efficacy analysis of the different breast cancer subtypes

	CR	PR	SD	PD	RR
Overall (n=284)	70 (24.65)	147 (51.76)	54 (19.01)	13 (4.58)	217 (76.41)
Luminal A (n=87)	14 (16.09)	55 (63.22)	15 (17.24)	3 (3.45)	69 (79.31)
Luminal B (n=78)	6 (7.69)	44 (56.41)	23 (29.49)	5 (6.41)	50 (64.10)
HER-2$^+$ (n=66)	24 (36.36)	30 (45.45)	9 (13.64)	3 (4.55)	54 (81.82)
TN (n=53)	26 (49.06)	18 (33.96)	7 (13.21)	2 (3.77)	44 (83.02)

Patient follow-up

Post-operative telephone follow-ups were conducted every two months for a total of 24 months. Corresponding treatments were administered to the patients with recurrences or distance metastases. Symptom-free survival, overall survival, and the occurrence of adverse effects during the follow-up were recorded for all the subtypes.

Clinical response evaluation

The clinical response was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR: complete disappearance of all tumor foci. PR: a 50% or more significant reduction in the maximum bidirectional product compared to the original tumor. SD: a reduced maximum bidirectional product lower than 50% but greater or equal to 25% compared to the original tumor. PD: a reduction of less than 25% in the maximum bidirectional product compared to the original tumor. The overall effective response rate was taken as the sum of the CR and PR patients.

Statistical analysis

The statistical analysis and image rendering of the collected data were done using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 8.0, GraphPad Software Inc., La Jolla, CA, USA), respectively. The measurement data are presented as the (mean ± SE) and analyzed using t-tests for statistical significance. The count data are expressed as (n, %) and analyzed using chi-square tests for statistical significance. The survival of the patients with different molecular subtypes of breast cancer was visualized using Kaplan-Meier curves. All the statistical tests were two-tailed, and $P<0.05$ was considered statistically significant.

Results

Clinicopathological comparisons among the different subtypes

As shown in **Table 1**, there were 87 cases of Luminal A, 78 cases of Luminal B, 66 cases of HER-2$^+$, and 53 cases of TN. The patients with

Table 3. The toxic and side effects of the breast cancer subtypes

	Grade III-IV Leukopenia	Severe nausea and vomiting	Oral ulceration	Total toxic and side effects
Overall (n=284)	43 (15.14)	34 (11.97)	13 (4.58)	90 (31.69)
Luminal A (n=87)	16 (18.39)	12 (13.79)	4 (4.60)	32 (36.78)
Luminal B (n=78)	12 (15.38)	8 (10.26)	3 (3.85)	23 (29.49)
HER-2$^+$ (n=66)	8 (12.12)	8 (12.12)	4 (6.06)	20 (30.30)
TN (n=53)	7 (13.21)	6 (11.32)	2 (3.77)	15 (28.30)
χ^2				1.556
P				0.669

Table 4. Ki67 (%) expressions in the different breast cancer subtypes

	Before treatment	After treatment	t	P
Overall (n=284)	39.25±20.48	22.36±17.28	10.62	0.001
Luminal A (n=87)	7.25±2.77	8.58±7.28	1.593	0.113
Luminal B (n=78)	41.25±23.28	24.36±16.39	5.239	0.002
HER-2$^+$ (n=66)	48.56±20.58	28.15±21.04	5.634	0.003
TN (n=53)	52.36±29.84	30.25±25.33	4.112	0.001
F	36.489	25.565		
P	0.001	0.002		

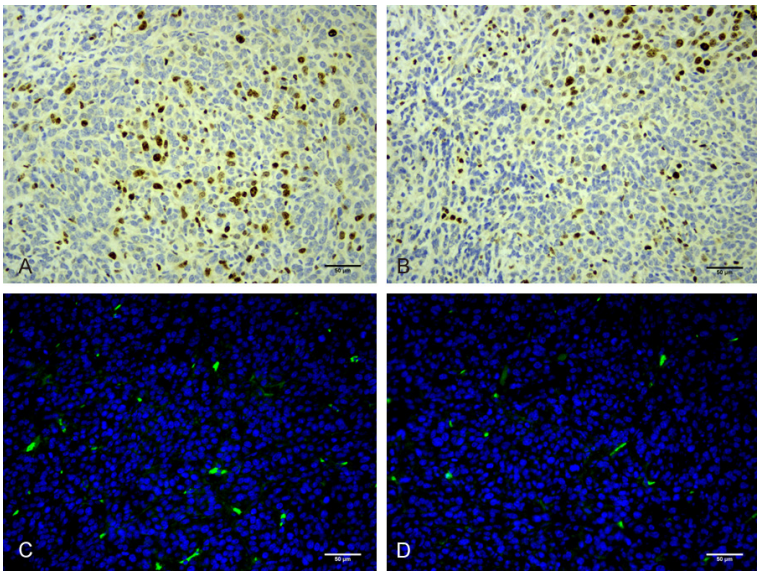

Figure 1. The overall Ki67 expression levels before and after treatment. Note: (A and C) High expressions of overall Ki67 before treatment; (B and D) Low expressions of overall Ki67 after treatment (original magnification: ×200).

the different subtypes were similar in terms of age, primary tumor diameter, TNM stage, and menstruation (P>0.05).

Clinical efficacy analysis of the different subtypes

As shown in **Table 2**, the overall CR rate was 24.65% (70/284) across all subtypes. The CR rates for the Luminal A, Luminal B, HER-2$^+$, and TN groups were 16.09% (14/87), 7.69% (6/78), 36.36% (24/66), and 49.06% (26/53) respectively. The overall response rate (RR) was 76.41% (217/284) across all the subtypes. The RR rates for the Luminal A, Luminal B, HER-2$^+$, and TN groups were 79.31% (69/87), 64.10% (50/78), 81.82% (54/66), and 83.02% (44/53) respectively. The CR was significantly higher in the HER-2$^+$ and TN groups than it was in the Luminal A and B subtype groups (P<0.05). The RR was significantly higher in HER-2$^+$ and TN subtype groups than it was in the Luminal B group (P<0.05).

Toxic and side effects of different subtypes

As shown in **Table 3**, the overall incidence of toxicity was 31.69% (90/284). The toxicity incidence rates in the Luminal A, Luminal B, HER-2$^+$, and TN groups were 36.78% (32/87), 29.49% (23/78), 30.30% (20/66), and 28.30% (15/53) respectively, with no statistical significance among the four subtypes (P=0.669).

Ki67 (%) expression changes

As shown in **Table 4** and **Figures 1-5**, the mean Ki67 expression (%) decreased significantly in the patients with Luminal B, HER-2$^+$, and TN post-NAC regimens (all P<0.001), but it showed insignificant changes in the Luminal A patients (P=0.113). A total of 153 patients, including 35

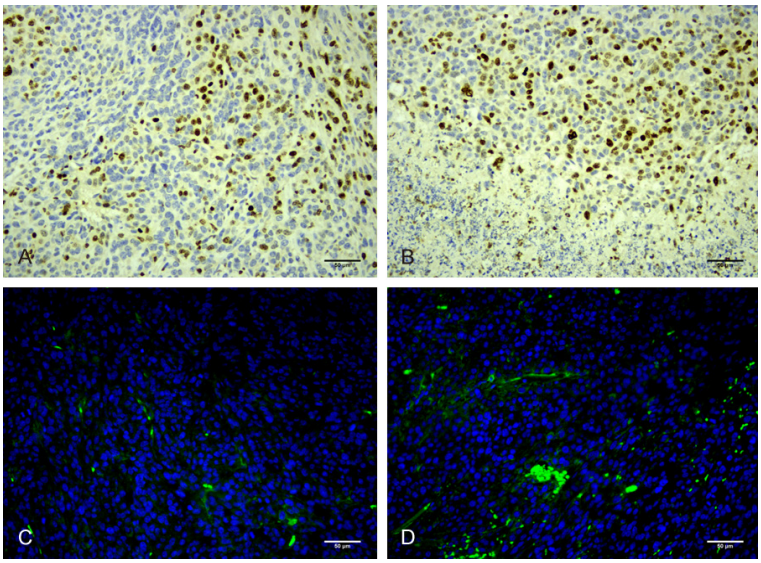

Figure 2. Ki67 expressions in the patients with luminal A breast cancer before and after the treatment. Note: (A and C) Low Ki67 expression in patients with luminal A breast cancer before treatment; (B and D) High Ki67 expression in patients with luminal A breast cancer after the treatment (original magnification: ×200).

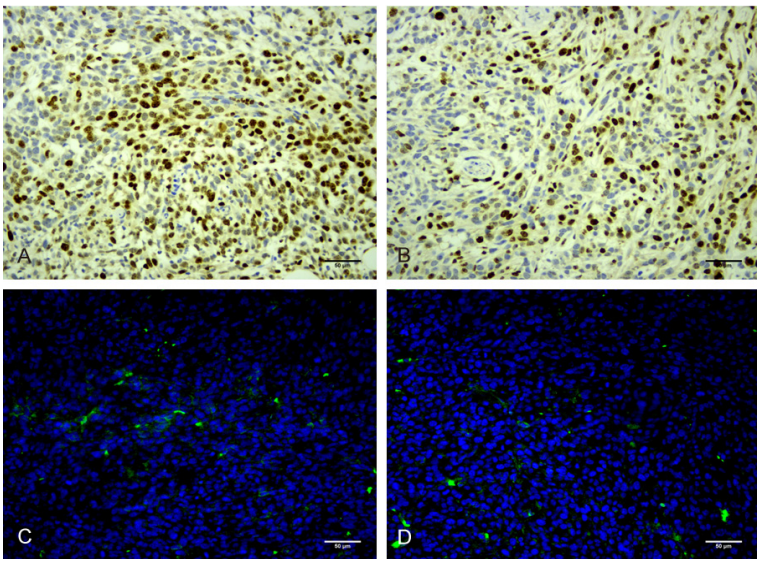

Figure 3. The Ki67 expressions in the patients with luminal B breast cancer before and after the treatment. Note: (A and C) High Ki67 expressions in the patients with luminal B breast cancer before the treatment; (B and D) Low Ki67 expressions in the patients with luminal B breast cancer after the treatment (original magnification: ×200).

Luminal A patients, 37 Luminal B patients, 42 HER-2$^+$ patients, and 39 TN patients, showed declined Ki67 expressions after NAC (P<0.001). Our pairwise comparisons revealed a greater Ki67 decline in the HER-2$^+$ and TN subtypes than in the Luminal A and B subtypes (P<0.05; **Table 5**).

The Ki67 expressions and the clinical efficacy in the different molecular breast cancer subtypes

As shown in **Table 6**, the Ki67 expressions decreased in the 138 patients with CR and PR after NAC, and in the 15 patients with SD and PD. The decrease in the Ki67 expressions in the CR and PR patients was remarkably greater than it was in the SD and PD patients (P<0.05).

Comparison of the long-term prognoses

As shown in **Table 7**, the total local recurrence rate for all subtypes was 4.58% (13/284) during the 2-year follow-up. The local Luminal A, Luminal B, HER-2$^+$, and TN subtype recurrence rates were 5.75% (5/87), 2.56% (2/78), 4.55% (3/66), and 5.66% (3/53), respectively, with no significant differences among the four subtypes (P=0.768). The total incidence of distant metastasis was 9.15% (26/284) across all the subtypes. The Luminal A, Luminal B, HER-2$^+$, and TN subtype distant metastasis rates were 5.75% (5/87), 3.85% (3/78), 18.18% (12/66), and 11.32% (6/53) respectively, without any statistically significant differences (P=0.014). The incidence of distant metastasis in the HER-2$^+$ subtype was significantly higher than it was in the Luminal A and B subtypes (P<0.05). The mortality rate was 4.58% (13/284) across all the subtypes, and the individual rates were 2.30% (2/87), 2.56% (2/78), 9.09% (6/66), and 5.66% (3/53) for the Luminal A, Luminal B, HER-2$^+$, and TN subtypes respectively, with no significant difference among the subtypes (P=0.211). The progression-free survival curves and total survival curves for the four subtypes are shown in **Figure 6**.

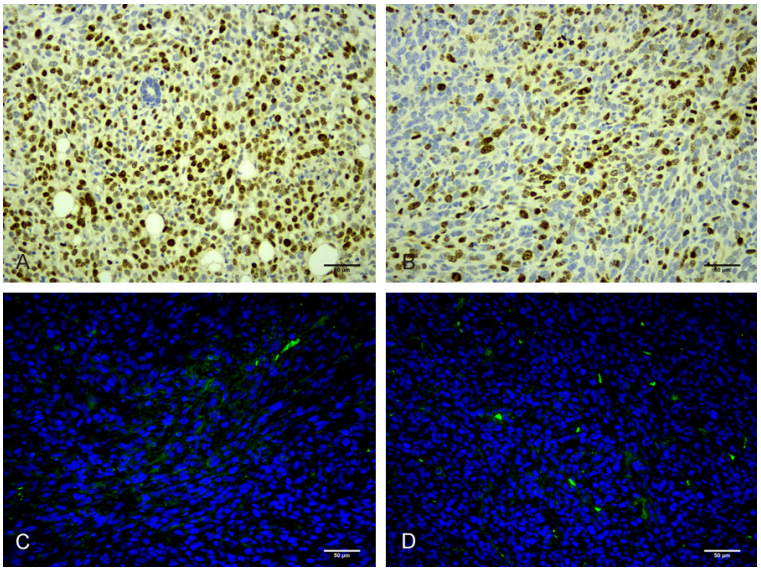

Figure 4. Ki67 expressions in patients with HER-2$^+$ breast cancer before and after the treatment. Note: (A and C) High Ki67 expressions in the patients with HER-2$^+$ breast cancer before the treatment; (B and D) Low Ki67 expressions in the patients with HER-2$^+$ breast cancer after the treatment (original magnification: ×200).

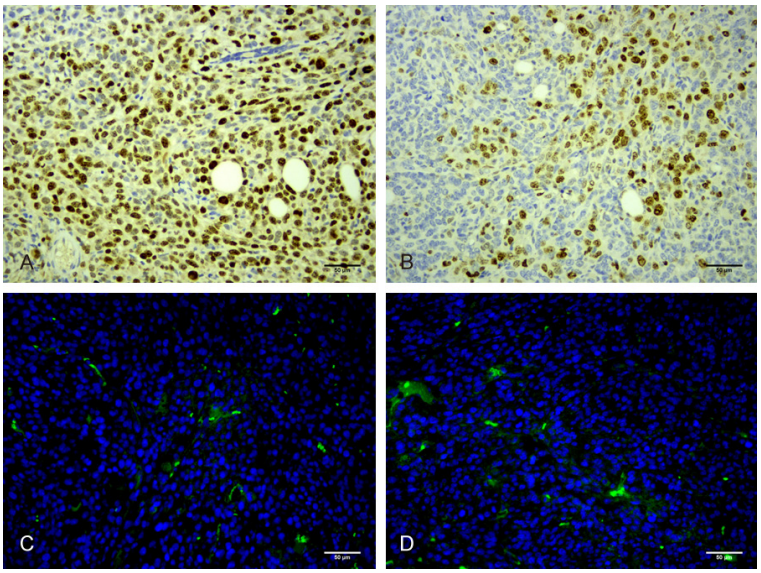

Figure 5. The Ki67 expressions in patients with TN breast cancer before and after the treatment. Note: (A and C) High Ki67 expressions in the patients with TN breast cancer before the treatment; (B and D) Low Ki67 expressions in patients with TN breast cancer after the treatment (original magnification: ×200).

Discussion

Since the 1970s, NAC has been administered to patients with locally advanced breast cancer unsuitable for surgical resection, to reduce the tumor size and enable surgery on previously inoperable tumors. Today, NAC has become an essential component of the comprehensive treatment of breast cancer [8-10], with the following advantages [11]: (1) It can shrink the tumor size and reduce the invasiveness of the surgical procedures and surgical trauma. (2) It allows tumor downstaging to create the conditions for radical surgery and breast-conserving surgery. (3) It reduces the risk of tumor cell dissemination during surgical operations. (4) It contributes to evaluating tumor drug sensitivity to provide a reference for postoperative chemotherapy. Previous studies have shown that NAC can significantly prolong a patient's symptom-free survival and elevate the overall survival rates compared with postoperative adjuvant chemotherapy. Breast cancer is a highly collective term describing multiple types of malignant tumors. Accordingly, discussions on the effective prognosis and chemotherapy regime should focus on the specific molecular subtype [12]. In clinical practice, breast cancer is divided into four subtypes based on the ER, PR, HER-2, and Ki67 levels. This classification enables the determination of the biological characteristics of the tumor and the prediction of the clinical risk [13-15]. However, discussions regarding the tumor response to NAC and patient survival following NAC treatment remain controversial.

In this study, 284 breast cancer patients administered NAC in our hospital were retrospectively analyzed. The patients included 87 Luminal A, 78 Luminal B, 66 HER-2$^+$, and 53 with TN. Ki67 is a nuclear antigen with an

Table 5. The Ki67 (%) expression changes

Ki67	Decrease	No decrease
Overall (n=284)	153	131
Luminal A (n=87)	35	52
Luminal B (n=78)	37	41
HER-2$^+$ (n=66)	45	21
TN (n=53)	39	14
χ^2	21.52	
P	0.005	

Table 6. The Ki67 expressions and the clinical efficacy in the different breast cancer subtypes

Ki67 Changes	Clinical Response	
	CR+PR	SD+PD
Decrease	138	15
No decrease	79	52
χ^2	34.98	
P	0.001	

Table 7. A comparison of the recurrence and metastasis among the different breast cancer subtypes

	Local recurrence	Distant metastasis	Death
Overall (n=284)	13 (4.58)	26 (9.15)	13 (4.58)
Luminal A (n=87)	5 (5.75)	5 (5.75)	2 (2.30)
Luminal B (n=78)	2 (2.56)	3 (3.85)	2 (2.56)
HER-2$^+$ (n=66)	3 (4.55)	12 (18.18)	6 (9.09)
TN (n=53)	3 (5.66)	6 (11.32)	3 (5.66)
χ^2	1.139	10.62	4.514
P	0.768	0.014	0.211

expression profile closely related to the cell cycle proliferation-related phases G1, G2, and S; hence, research on Ki67 in breast cancer has captured great attention in academia [16]. It is well-established that high cell proliferations are positively correlated with Ki67 expression: an elevated Ki67 expression indicates a high invasion and a poor prognosis, but a low Ki67 expression indicates a higher breast cancer survival rate [17]. Hence, the Ki67 expression shows great potential in evaluating the proliferation and biological activity of cancer cells, so it is of great significance for the formulation of treatment plans and prognoses [18]. In the present study, the mean Ki67 expressions were reduced significantly in the patients with the Luminal B, HER-2$^+$, and TN subtypes. Additionally, the decrease in the Ki67 expression was significantly greater in the HER-2$^+$ and TN subtypes than it was in the Luminal A and B subtypes. These results indicate that the NAC regimen can significantly reduce the Ki67 expressions in patients with the Luminal B, HER-2$^+$, and TN Ki67 subtypes, especially in the patients with HER-2$^+$ or TN. The Ki67 reduction in the patients with CR or PR was significantly greater than it was in the patients with SD or PD, indicating that Ki67 can be an independent predictor of the clinical efficacy of NAC, and this is consistent with previous research [19]. In this study, CR in patients with the HER-2$^+$ and TN subtype was significantly higher than it was in the patients with the Luminal A or B subtypes; the response rates of the patients with the HER-2$^+$ and TN subtypes was also significantly better than it was in the patients with the Luminal B subtype. The 2-year symptom-free survival rates of the Luminal A, Luminal B, HER-2$^+$, and TN patients were 88.51%, 93.59%, 77.27%, and 83.02% respectively, and the overall survival rates were 97.70%, 96.20, 90.91%, and 94.34%, respectively. Previous studies have shown that the Luminal A subtype enjoys the most favorable prognosis and TN the worst [20]. However, in the present study, the HER-2$^+$ subtype showed significantly decreased Ki67 levels and the highest clinical efficacy after NAC, and the worst prognosis. This result indicates that Ki67 is related to clinical efficacy but not to long-term patient prognosis, so it may be attributed to the relatively shorter follow-up time. Further research on the specific mechanism is needed. In addition, this study is a retrospective study, and only the relevant data of the patients treated with NAC were analyzed. Moreover, due to ethical considerations, our hospital routinely used NAC for treatment; hence, the breast cancer patients who did not undergo NAC treatment were not included in this study, so further investigation is warranted to confirm whether NAC affects the clinical efficacy and survival of the patients with different molecular subtypes.

Neoadjuvant chemotherapy, an emerging technique for the current clinical treatment of breast cancer, has gained wide recognition. It plays a pivotal role in increasing the breast cancer surgical resection rate, raising breast-conserving opportunities, prolonging patient sur-

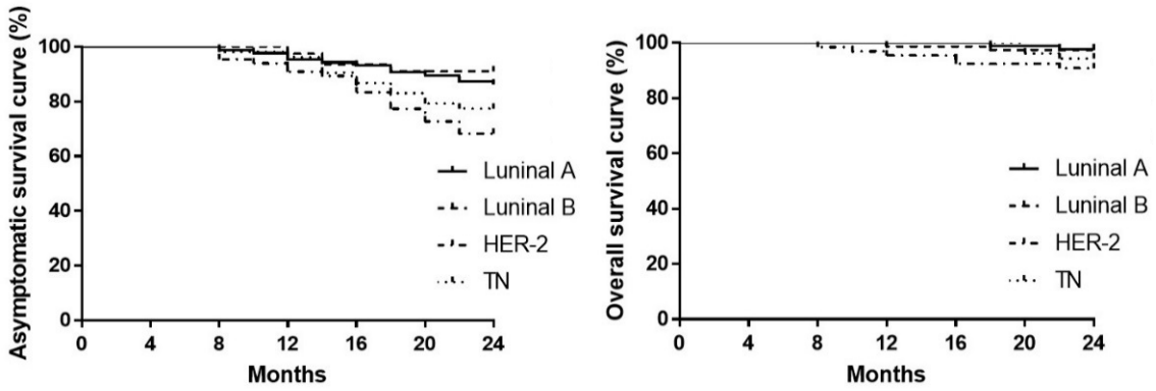

Figure 6. The progression-free survival and overall survival curves of the patients with different molecular subtypes of breast cancer. Note: The median progression-free survival was 13.9 months (95% CI: 10.452-30.741), and the median overall survival was 20.4 months (95% CI: 16.452-34.741).

vival, and improving prognosis. The molecular typing of breast cancer is a procedure based on immunohistochemistry, and it is characterized by its simple application and strong maneuverability. It has been widely used in clinical practice, replacing gene expression profile molecular typing, provides promising data on the formulation of NAC regimens and prognosis evaluation. It has been reported that the one-year disease-free survival rates of Luminal A and B types are similar (91.4%, 88.7%), and the molecular classification of breast cancer is related to the clinicopathological characteristics of breast cancer such as tumor size, TNM staging, and lymph node metastasis [21]. At present, it is believed that the Luminal A and B subtypes of breast cancer feature small tumor sizes and early clinical staging, which are more common in invasive ductal carcinoma and more sensitive to endocrine therapy, so the effective rate is higher [21]. However, the HER-2 and basal-like subtypes belong to the advanced stages, with poor cell differentiation, high degrees of malignancy, high possibilities of visceral and nervous system metastasis, and low disease-free survival, so it has become the theoretical basis for the correlation between the molecular classification and the prognosis of breast cancer.

Conclusion

In conclusion, we found differences in the post-NAC pathological responses and survival rates in patients suffering from different molecular subtypes of breast cancer. A higher pathological response rate was observed in the patients with the HER-2$^+$ and TN subtypes, which may be closely related to decreased Ki67 expressions after NAC. Interestingly, patients with the HER-2$^+$ subtype also showed a higher incidence of distant metastasis, the mechanism of which requires further exploration.

Disclosure of conflict of interest

None.

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