Surgery Open Science 15 (2023) 19–25

Contents lists available at ScienceDirect

Surgery Open Science

journal homepage: www.journals.elsevier.com/surgery-open-science

Research Paper

Neoadjuvant chemotherapy response, disease-free survival, and overall survival of breast cancer in a single institution

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ARTICLE INFO

Keywords:
Breast cancer
Chemotherapy regimen
Disease-free survival
Chemotherapy response
Overall survival

ABSTRACT

Background: Breast cancer is the most common malignancy among women worldwide. Previous studies have shown factors influencing breast cancer patients' survival, including histopathological grading, stage, histopathological type, hormone receptors, and the number of mitotic images. This study aimed to determine the survival rate in breast cancer patients based on neoadjuvant chemotherapy (NAC) response and regimen.

Methods: This was an observational analytic study with a retrospective design. The population was breast cancer patients at our institution who had undergone NAC. Kaplan–Meier analysis using the log-rank method was used to determine the level of survivability (overall survival [OS] and disease-free survival [DFS]) of patients based on chemotherapy response and regimen.

Results: The NAC overall response rate of breast cancer patients was 93.17 %, whereas the non-response rate was 6.83 %. Significant differences existed in the DFS of patients by chemotherapy response ($p = 0.010$). Patients with a complete response had a mean survival of 71.37 ± 2.92 months, those with progressive disease had a mean survival of 64.80 ± 15.58 months, and overall patients had a mean survival of 68.56 ± 10.452 months. Patients with a complete response had a mean recurrence time of 69.54 ± 7.48 months; this was 57.53 ± 19.06 months in those with progressive disease, for an overall time of 65.41 ± 13.81 months. No significant difference existed between the NAC regimens in OS and DFS ($p = 0.901$ and $p = 0.798$, respectively).

Conclusion: Generally, the response to NAC in breast cancer was very good. The DFS rates were significantly different from the chemotherapy response but not from the NAC regimen.

Introduction

Breast cancer is the most common malignancy among women worldwide [1]. According to the World Health Organization, in 2020, >2.3 million women were diagnosed with breast cancer worldwide and 685,000 breast cancer died [2]. Invasive breast cancer affects one out of every eight women in the United States (12.4 %) at some point in their lives. In 2022, an estimated 287,850 women in the United States will be diagnosed with invasive breast carcinoma, while 51,400 will be diagnosed with breast cancer in situ [3]. In Indonesia, breast cancer has an incidence of 16.7 % and is the leading cause of death at 11.0 % [4].

Women with an initial diagnosis of breast cancer have an excellent prognosis and survival rates today. Despite substantial advances in breast cancer research over the last 20 years, a large proportion of patients will acquire metastatic illness. Unfortunately, metastatic breast cancer has not yet been cured [5]. TNM stage, histopathological type, histological grade, hormone receptors, and the number of mitotic pictures are prognostic variables that affect the survival of breast cancer patients, according to the consensus of the College of American Pathologists in 1999. The cancer stage reveals the extent to which breast cancer has spread. The TNM (tumor, node, metastasis) approach is used to report the cancer stage according to the American Joint Committee on Cancer Staging. It ranges from stage I to stage IV. Stage III cancer has a 5-year life expectancy of 86 %, and it changes with each stage [5–7].

This study aimed to determine the survival rate of breast cancer patients based on the stage and regimen of NAC at our institution as reference data to better evaluate, detect, and treat breast cancer.

Methods

This was an observational analytic study with a retrospective design. The population of this study was all patients diagnosed with breast

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https://doi.org/10.1016/j.sopen.2023.07.016
Received 17 July 2023; Received in revised form 20 July 2023; Accepted 26 July 2023
Available online 27 July 2023
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Table 1
Characteristics of participants.

Characteristic	n (%)
Age (years)	
21–30	13 (4.67)
31–40	58 (20.86)
41–50	97 (34.89)
51–60	88 (31.65)
61–70	18 (6.47)
71–80	2 (0.72)
> 80	2 (0.72)
Tumor size (T)	
T1	2 (0.72)
T2	6 (2.16)
T3	36 (12.95)
T4	234 (84.17)
Lymph node stage (N)	
N0	76 (27.34)
N1	69 (24.82)
N2	89 (32.01)
N3	44 (15.83)
TNM Stage	
II	17 (6.12)
IIIa	26 (9.35)
IIIb	190 (68.35)
IIIc	45 (16.18)
Histopathology	
IDC	182 (65.47)
ICM	60 (21.58)
ADC	17 (6.12)
ILC	7 (2.52)
Mucinous carcinoma	5 (1.79)
Metaplastic carcinoma	4 (1.44)
Other	3 (1.08)
Grade	
High	55 (19.78)
Intermediate	195 (70.14)
Low	28 (10.07)
Subtype	
Luminal-A	86 (30.94)
Luminal-B	27 (9.71)
HER-2	90 (32.37)
Triple-negative	75 (26.98)
Location	
Right	154 (55.40)
Left	112 (40.29)
Bilateral	12 (4.31)
NAC regimen	
FAC	99 (35.61)
TC	63 (22.66)
TAC	77 (27.70)
AC/T	18 (6.47)
GC	19 (6.83)
NF	2 (0.72)

Abbreviations: IDC, invasive ductal carcinoma; ICM, invasive carcinoma; ADC, adenocarcinoma; ILC: invasive lobular carcinoma; HER-2, Human epidermal growth factor receptor-2; FAC, cyclophosphamide, doxorubicin, and 5-fluorouracil; TC, docetaxel and cyclophosphamide; TAC, paclitaxel, doxorubicin, and cyclophosphamide; AC/T, doxorubicin, cyclophosphamide, and docetaxel; GC, gemcitabine and carboplatin; NF, vinorelbine and capecitabine.

Table 2
Cumulative response to neoadjuvant chemotherapy.

RECIST criteria	n (%)	Response	%
CR	7 (2.52)	Positive	93.17
PR	252 (90.65)		
SD	13 (4.68)	Negative	6.83
PD	6 (2.15)		

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

Table 3
Neoadjuvant chemotherapy response based on regimen.

NAC regimen/RECIST criteria		n	Response	n (%)
FAC	CR	3	Positive	93 (93.94)
	PR	90		
	SD	3	Negative	6 (6.06)
	PD	3		
TC	CR	1	Positive	57 (90.48)
	PR	56		
	SD	4	Negative	6 (9.52)
	PD	2		
TAC	CR	3	Positive	74 (96.10)
	PR	71		
	SD	3	Negative	3 (3.90)
	PD	0		
AC/T	CR	0	Positive	17 (94.44)
	PR	17		
	SD	1	Negative	1 (5.56)
	PD	0		
GC	CR	0	Positive	16 (84.21)
	PR	16		
	SD	2	Negative	3 (15.79)
	PD	1		
NF	CR	0	Positive	2 (100)
	PR	2		
	SD	0	Negative	0 (0)
	PD	0		

Abbreviations: FAC, cyclophosphamide, doxorubicin, and 5-fluorouracil; TC, docetaxel and cyclophosphamide; TAC, paclitaxel, doxorubicin, and cyclophosphamide; AC/T, doxorubicin, cyclophosphamide, and docetaxel; GC, gemcitabine and carboplatin; NF, vinorelbine and capecitabine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4
Neoadjuvant chemotherapy response based on subtype.

Subtype / RECIST criteria		n	Response	n (%)
Luminal-A	CR	1	Positive	77 (89.53)
	PR	76		
	SD	7	Negative	9 (10.47)
	PD	2		
Luminal-B	CR	1	Positive	27 (100)
	PR	26		
	SD	0	Negative	0 (0)
	PD	0		
HER-2	CR	3	Positive	85 (94.44)
	PR	82		
	SD	2	Negative	5 (5.56)
	PD	3		
Triple-negative	CR	2	Positive	70 (93.33)
	PR	68		
	SD	4	Negative	5 (6.67)
	PD	1		

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HER-2, Human epidermal growth factor receptor-2.

cancer who received multimodal therapy (surgery, chemotherapy, hormonal therapy, and targeted therapy) in Dr. Wahidin Sudirohusodo Makassar, Indonesia, from 2014 to 2018. The inclusion criteria were age 20 years or over when diagnosed with breast cancer and complete laboratory and histopathological examinations. The exclusion criteria were breast cancer patients with psychotic disorders, incomplete medical record data, stage IV breast cancer patients, and patients who could not be contacted or were lost to follow-up. The criteria for patients receiving neoadjuvant chemotherapy (NAC) are all stage III breast cancer patients, all early-stage breast cancer patients with HER2 or triple-negative subtypes, and several other indicators, such as high-grade cancer and high Ki-67 value.

Medical record data taken as research data included age at diagnosis of breast cancer, TNM stage, neoadjuvant type, response to therapy based on RECIST criteria, subtype, histopathological grading, tumor

Table 5
Neoadjuvant chemotherapy response based on stage.

Stage / RECIST criteria		n	Response	n (%)
II	CR	1	Positive	16 (94.10)
	PR	15		
	SD	1	Negative	1 (5.90)
	PD	0		
IIIa	CR	3	Positive	26 (100)
	PR	23		
	SD	0	Negative	0 (0)
	PD	0		
IIIb	CR	2	Positive	175 (92.10)
	PR	173		
	SD	11	Negative	15 (7.90)
	PD	4		
IIIc	CR	1	Positive	42 (93.33)
	PR	41		
	SD	1	Negative	3 (6.67)
	PD	2		

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

location, overall survival (OS) for 72 months, and disease-free survival (DFS) for 72 months.

Chemotherapy response

The classification of chemotherapy response used was based on the RECIST criteria [8], with complete response (CR) classified as primary tumor disappearance, partial response (PR) classified as a decrease in tumor size of at least 30 % of the initial lesion, progressive disease (PD) classified as an increase in tumor size of at least 20 % of the initial lesion, and stable disease (SD) not classified as partial or progressive.

Neoadjuvant chemotherapy regimens

NAC regimens were in accordance with clinical and laboratory assessments to provide the proper chemotherapy regimen according to the patient's condition. The regimen given was a combination of several types of chemotherapy, such as FAC (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and 5-fluorouracil 500 mg/m^2 repeated at 21-day intervals), TAC (paclitaxel 175 mg/m^2, doxorubicin 50 mg/m^2,

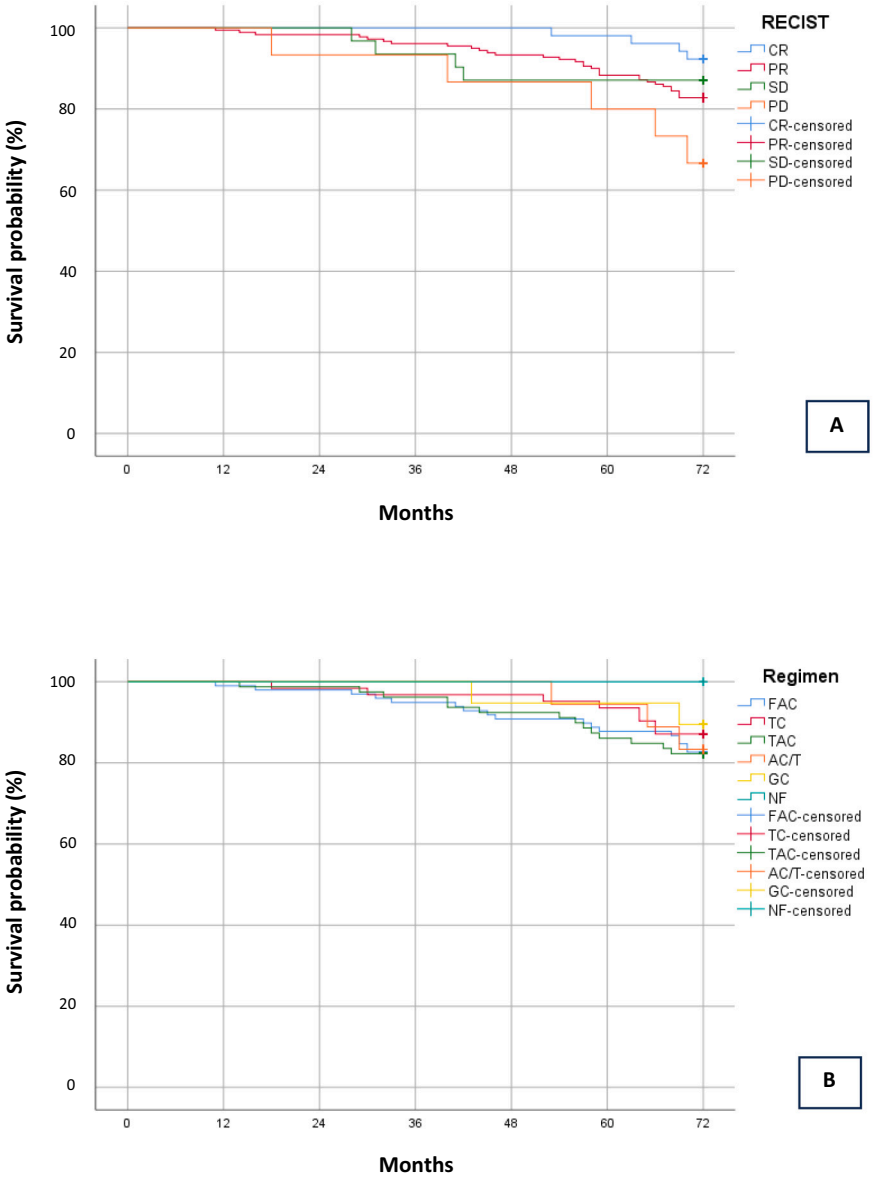

Fig. 1. Overall survival based on chemotherapy response (A); overall survival based on chemotherapy regimen (B) using Kaplan–Meier analysis.

Table 6
OS and DFS based on therapeutic response and breast cancer stage.

Characteristic	Mean OS ± SD (months)	p-Value	Mean DFS ± SD (months)	p-Value
Chemotherapy response				
CR	71.37 ± 2.92	0.084	69.54 ± 7.48	0.010
PR	68.28 ± 10.82		65.01 ± 13.92	
SD	67.29 ± 12.64		64.65 ± 16.75	
PD	64.80 ± 15.58		57.53 ± 19.06	
Total	68.56 ± 10.45		65.41 ± 13.81	
NAC regimen				
FAC	67.81 ± 12.09	0.901	65.07 ± 14.66	0.798
TC	69.47 ± 9.10		66.31 ± 12.87	
TAC	67.86 ± 11.08		64.43 ± 15.00	
AC/T	70.39 ± 4.68		65.00 ± 12.63	
GC	70.32 ± 6.65		68.05 ± 8.48	
NF	72.00 ± 0.00		72.00 ± 0.00	
Total	68.56 ± 10.45		65.41 ± 13.81	

Abbreviations: OS, overall survival; DFS, disease-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FAC, cyclophosphamide, doxorubicin, and 5-fluorouracil; TC, docetaxel and cyclophosphamide; TAC, paclitaxel, doxorubicin, and cyclophosphamide; AC/T, doxorubicin, cyclophosphamide, and docetaxel; GC, gemcitabine and carboplatin; NF, vinorelbine and capecitabine.

and cyclophosphamide 500 mg/m^2, repeated at 21-day intervals), TC (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2, repeated at 21-day intervals), AC/T (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, and docetaxel 100 mg/m^2, repeated at 21-day intervals), GC (gemcitabine 1000 mg/m^2 given on day 1 and day 8 and carboplatin 400 mg/m^2, repeated at 21-day intervals), and NF (vinorelbine 25 mg/m^2 given on day 1 and day 8 and capecitabine 1650–2000 mg/m^2 given from day 1 to day 14, repeated at 21-day intervals).

Statistical analysis

Data were collected and statistically analyzed using SPSS version 22 (Armonk, NY, USA: IBM Corp.). Data were analyzed as univariate and bivariate, and univariate analysis was conducted to determine the distribution of patient characteristic data. Kaplan–Meier analysis using the log-rank method (Mantel–Cox) was used to determine differences in patient survivability based on stage and response to NAC.

Results

The total number of breast cancer patients who underwent NAC and met the inclusion criteria was 278. The largest proportion was aged 41–50 (34.89 %), and the lowest was aged 71–80, and above 80 years were 0.72 % and 0.72 %, respectively. The analysis of tumor size (T) in the patient population revealed that the majority of cases were classified as T4 (84.17 %), followed by T3 (12.95 %), T2 (2.16 %), and T1 (0.72 %). The most common patient stage was stage IIIb (68.35 %), and stage II (6.12 %) was the least common. The most common histopathological type was invasive ductal carcinoma (IDC) (65.47 %). The most common histopathological grade was intermediate (70.14 %), and the least common was low-grade (10.07 %). The most common breast cancer subtype was HER-2 (32.37 %), and the least common was luminal-B (9.71 %). The most common tumor location was the right breast (55.40 %), followed by the left (40.29 %) and bilateral (4.31 %). The most common chemotherapy regimen given was FAC (35.61 %), and the least common was NF (0.72 %). The characteristics of the participants can be seen in Table 1.

The response to chemotherapy generally showed promising results, with a positive response rate of 93.17 % and a no response (negative response) rate of 6.83 % (Table 2). The chemotherapy response based on regimen, subtype, and stage can be seen in Tables 3 to 5.

Fig. 1 shows the Kaplan–Meier analysis using the log-rank (Mantel–Cox) OS rate based on chemotherapy response and regimen. This study showed a significant difference in chemotherapy response to survivability (p = 0.084). Patients with a CR (n = 7) had a mean survival of 71.37 ± 2.92 months, and patients with PD (n = 6) had a mean survival of 64.80 ± 15.58 months, with overall patients (n = 278) having a mean survival of 68.56 ± 10.45 months.

This study showed no significant difference between NAC regimens on patient survivability (p = 0.901; Table 6). Fig. 2 shows the Kaplan–Meier analysis using the log-rank method (Mantel-Cox) on the disease-free survival of patients. There was a significant difference in chemotherapy response to the patient's recurrence time (p = 0.010). Patients with CR had a mean recurrence time of 69.54 ± 7.48 months, and patients with PD had a mean recurrence time of 57.53 ± 19.06 months, with overall patients (n = 278) having a mean DFS of 65.41 ± 13.81 months. Based on the NAC regimen, there was no significant difference in the patients' recurrence time (p = 0.798; Table 6).

Discussion

In Indonesia, a country with a minimal health budget and a large population, the choice of type of breast cancer treatment is adjusted to the existing budget. The use of the latest chemotherapy response predictors, such as *MammaPrint*, Oncotype dx, etc. has yet to be covered by the national health system. Therefore, conventional chemotherapy still plays an important role in neoadjuvant and adjuvant therapy for breast cancer. It is essential for our country to evaluate the response to several currently used chemotherapy regimens. From our evaluation, it turned out that the overall response rate (complete and partial response) to chemotherapy was still reasonable at >90 %, while other studies were between 76.41 %–91 % [9–12]. However, the complete response rate in our study is lower than that of Sannachi et al. [13] with a result of 21 %. This is because >60 % of the patients come to our institution with locally advanced breast cancer. This behavior is related to socio-economic problems, healthcare access, health expenditure, rural residence, and breast cancer stigma [14–18]. It can be seen from the data that most of them come with T3 (12.95 %) and T4 (84.17 %), while T2 and T1 were only 2.158 % and 0.72 %, respectively. So with that large of a tumor, the chance for a complete response with 6× chemotherapy is less. This study provides an overview of the response rates of existing conventional regimens in the population of our country. This study proves that the existing regimen is still relevant for use.

In this study, the cancer stage at diagnosis was a factor in evaluating survival time because it is an important prognostic factor and has been widely used in other studies [19,20]. The average survival time of breast cancer patients in this study was 68.56 months. This result is in line with a population-based study in Malaysia that found a mean OS time of 68.1 months among breast cancer patients, although other studies found a median survival time of 54 months [21,22]. In Indonesia, studies showing the survival of breast patients for 5 years have been reported; Wahyuni et al. showed that the probability of 5-year survival of breast cancer patients was 48 %, and the OS was 54 months [22]. However, a study by Sundquist et al. revealed a mean survival time between 13 and 33 months, depending on the type of treatment received [23].

Patients in this study had a mean survival period of 71.37 months for CR and 64.80 months for progressing disease. In a collaborative investigation, median survival durations for stage II, stage III, and stage IV breast cancer were 164 months, 53 months, and 17 months, respectively [24]. According to Andre et al. [23,25], the median survival time for metastatic breast cancer patients admitted to French cancer centers increased from 23 to 29 months.

Based on Kaplan–Meier analysis in this study, patients with CR had greater recurrence time than patients with PD, with the former having an DFS of 69.54 months, which was statistically significantly different (p = 0.010). This finding is in line with that of Laohavinij, who followed up breast cancer patients for 10 years and reported a median OS time of patients with metastases of 13.43 months [26]. Urru et al. found that an

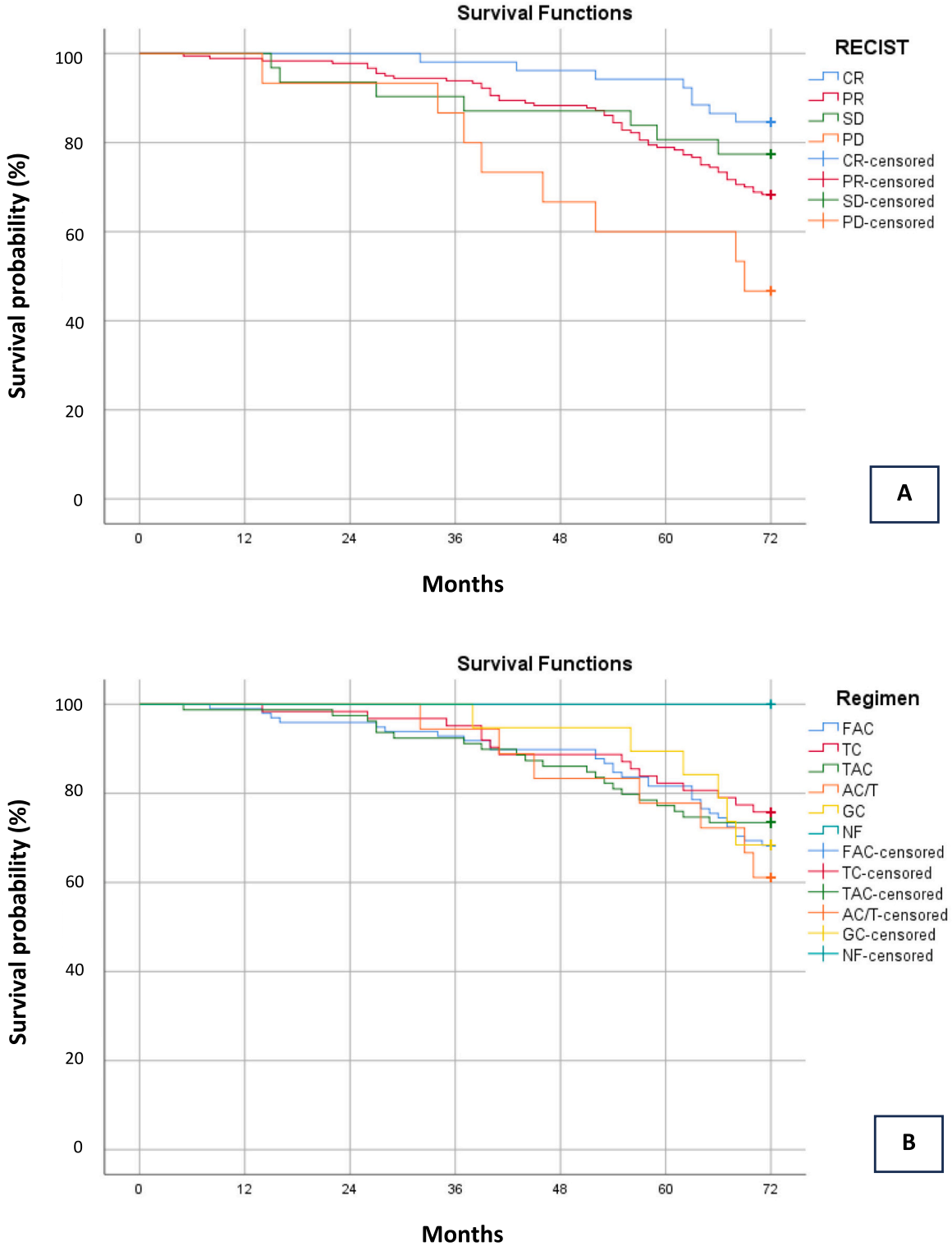

Fig. 2. Disease-free survival based on chemotherapy response (A) and chemotherapy regimen (B) using Kaplan–Meier analysis.

increase in staging at the diagnosis of triple-negative breast cancer was associated with a clear and substantial reduction ($p = 0.001$) in OS. Stage I had a 5-year OS of 93.9 %, stage II had a 5-year OS of 84.5 %, stage III had a 5-year OS of 57.2 %, and stage IV had a 5-year OS of 26.7 % [27]. This difference in survival could be attributed to changes in diagnosis staging due to discrepancies in screening, early cancer detection, and referral pathways. Differences in survival by stage reflect differences in staging accuracy, comorbidity, and treatment [19]. To improve survival outcomes, patients with large tumors should be treated with intensive chemotherapy and targeted therapy if the HER-2 status is positive [26].

Important prognostic factors related to OS in metastatic breast cancer patients are the type of first-line treatment, tumor size, and Eastern Cooperative Oncology Group (ECOG) score. The tumor size at the start

of treatment was also related to patient survival at 5 years because of tumor spread to the surrounding area. Wahyuni et al. showed that the probability of 5-year survival of breast cancer patients with a tumor size of <5 cm was 81 %, and for a tumor size of >5 cm, it was 24 %. When compared with a tumor size of <5 cm, the risk of death for a tumor size of >5 cm is 3.7 times as high [28,29].

In this study, patients with stage III breast cancer had a shorter OS and DFS, but the choice of NAC did not significantly affect OS or DFS. This is related to selecting a regimen according to the patient's clinical needs based on clinical and laboratory examinations. By knowing the response to therapy, patients who have a CR to chemotherapy should continue the treatment plan that has been established, with a transition to a non-cross-resistant regimen or continuing surgical intervention for operable disease in patients with progressing disease assessment. To choose the best surgical solution in each case, assessing the patient's response to therapy is also vital [30]. Nowadays, the primary tumor response to NAC is measured by changes in tumor size, and surgical specimens are histologically examined for many months following treatment. According to a previous study, patients who do not respond to the first chemotherapy often respond to subsequent systemic chemotherapy or radiotherapy [25,31].

This study has several limitations. The number of samples for each group was not equal, which could affect the study results. Additionally, there was a lack of follow-up; we know that follow-up is more useful to assess survival in support of appropriate management and diagnostics. Finally, in our country, the Social Security Agency of Health Insurance covers public health. In this insurance policy, trastuzumab can only be given to patients with metastases, and this insurance does not cover pertuzumab, so there was very little use of these chemotherapy drugs in our data.

Conclusion

In general, the response to NAC for breast cancer was very good. The cumulative positive response was greater than the negative response. The DFS rates were significantly different by chemotherapy response but not by NAC regimen. Further studies with a larger scale and follow-up will further support these findings for better management and diagnosis of breast cancer.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval

The Ethics Commission Faculty of Medicine, Hasanuddin University (Number: 1028/UN4.6.4.5.31/PP36/2019) approved this study with waiver of informed consent.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their data base and files for research work.

CRediT authorship contribution statement

Prihantono: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Muhammad Faruk:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Acknowledgement

The authors would like to thank Bayu Satria, MD for his language editing and Amirullah Abdi, MD for statistical review support.

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