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The Effect of Neoadjuvant vs Adjuvant Chemotherapy on Final Outcome of Patients with Triple Negative Breast Cancer

Najmeh Dabbagh[1], Hooman Riazi[1], Maryam Khayamzadeh[1], Alireza Negahi[1], Mahnaz Akbari[1], Mohammad Esmail Akbari[1]*

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Abstract

Background: Triple negative breast cancer (TNBC) accounts for about 10% to 20% of breast cancers, does not respond to endocrine treatment, and is more aggressive. Two chemotherapy methods suggested include neoadjuvant chemotherapy (NAC), performed before surgery, and adjuvant chemotherapy (AC), performed after surgery. In order to determine whether the choice of chemotherapy method has any impact on patients' outcome, the present study aimed to compare the overall survival (OS) and disease-free survival (DFS) of TNBC patients with a 10-year follow-up.

Methods: The present study aimed to investigate the effect of neoadjuvant versus adjuvant chemotherapy on the final outcome of patients with TNBC. Women with TNBC stages II and III who referred to the Cancer Research Center of Shahid Beheshti University of Medical Sciences during 2000 and 2020 were included (N = 237) and visited or called by phone to obtain their consent and complete their information. The participants were categorized into 2 groups according to the treatment protocol they received; one group received NAC (N = 85) and the other group received AC (N = 188); patients' age, tumor's grade and stage, lymphovascular invasion (LVI), DFS, and OS were compared between the 2 treatment types. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp) was used. All tests were 2-sided and *P* values < 0.050 were considered statistically significant.

Results: The frequency of pathologies, LVI, and type of surgery was not different between the groups ($p = 0.543$, $p = 0.352$, $p = 0.935$), while the frequency of age categories and tumor grade was significantly different between the groups ($p = 0.003$, $p = 0.001$). Ten-year OS and DFS were not different between the groups ($p = 0.771$, $p = 0.506$). The Multivariate Cox analysis results showed clinical stage, pathologic grade, age >70, and LVI as significant predictors of death.

Conclusion: These results showed that the choice of chemotherapy method, performed before or after surgery, does not influence the 10-year OS and DFS of TNBC patients.

Keywords: Breast Cancer, Triple Negative Breast Cancer, Neoadjuvant Therapy, Chemotherapy, Adjuvant, Disease-Free Survival, Survival Rate

Conflicts of Interest: *None declared*
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Introduction

Breast cancer is the most common type of cancer worldwide with an incidence of about 2.1 million women worldwide in 2018; it is the first cause of cancer-related death among women (1). The national databases of Iran report its incidence at 33.21 per 100,000 women, mortality rate of 14.2 per 100,000, and 5- and 10-year survival rate of 81% and

Corresponding author: *Dr Mohammad Esmail Akbari, me-akbari@sbmu.ac.ir*

[1.] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

↑What is "already known" in this topic:
TNBC is one of the uncommon types of breast cancer with a greater aggressiveness and no response to endocrine treatment. Chemotherapy is recommended as the most appropriate treatment, which can be performed either before surgery, named as neoadjuvant chemotherapy or after surgery, adjuvant chemotherapy.

→What this article adds:
Both of the chemotherapy methods resulted in acceptable and similar five- and ten-year overall and disease-free survival rates in women with triple-negative breast cancer, which shows the appropriateness of physician's choice for the type of chemotherapy.

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77%, respectively (2, 3). Despite the decreasing trend in Europe (4), the mortality rate of breast cancer vary according to disease characteristics, such as stage, grade, lymphovascular invasion (LVI), metastasis, and type of breast cancer (5).

Risk stratification and treatment choice depend predominantly on the tumor's characteristics, especially the molecular subtypes (6). About 10% to 20% of cases are negative for the 3 receptors (estrogen, progesterone, and human epidermal growth factor receptor 2), known as triple-negative breast cancer (TNBC), the treatment of which is more challenging; chemotherapy is considered the main treatment in these patients (7).

TNBC is more common in younger women and some races, like African American and Hispanic women (consisting about 40% of all breast cancer types) (8). Some variants are biologically more aggressive, have higher risk of lymphocytic infiltration, distant metastases, high grade, and large tumors; thus, the patients' prognosis remain poor (9), while some suggest that TNBC respond to chemotherapy better than other subtypes. Chemotherapy can be given to the patients either before surgery, known as neoadjuvant chemotherapy (NAC), aimed to reduce the tumor size and lymph node involvement to make it more operable, or after surgery, known as adjuvant chemotherapy (AC) (10). Some have suggested that NAC can improve patients' survival, especially in cases with pathologic complete response (PCR) (11-13), while the meta-analysis of randomized clinical trials has indicated no difference in distant metastasis and mortality rates between these 2 types, although NAC resulted in a higher rate of local metastasis (14). Due to the discrepancies in the results of previous studies and the lack of evidence in this regard in our country, the present study aimed to compare the overall survival (OS) and disease-free survival (DFS) of TNBC patients with a 10-year follow-up.

Methods

All patients who referred to the Cancer Research Center of Shahid Beheshti University of Medical Sciences (SBMU) during 2000 and 2020 and were diagnosed with TNBC were considered as the study population. The protocol of the study was approved by the ethics committee of the Cancer Research Center of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.CRC.REC.1399.034).

Of 3210 patients with breast cancer without ductal carcinoma in situ, the results of IHC showed TNBC in 372 cases (11.58%), included into the study. Patients with TNBC stage I and IV (N = 99) were excluded from the study (as patients with stage I did not require chemotherapy and all patients with stage IV were scheduled for chemotherapy); therefore, 273 patients with TNBC stage II or III consisted the final sample of the present study. The researcher visited or called the patients, explained the study objectives to the patients or their family members, and asked for their consent for participation. After obtaining a verbal consent from the patients or their parents (in case the patient passed away), the researcher asked about the missing information. The recorded information included patients' age, tumor's grade and stage, LVI, date of diagnosis, and date of recurrence or death (for estimation of OS and DFS) for each patient. OS was defined as the time from the date of diagnosis until the date of the last follow-up or death (due to any reason). Disease-free survival (DFS) was defined as the time from the date of diagnosis until the date of recurrence. Also, PCR of NAC was recorded according to the results of pathologic report.

The participants were categorized into 2 groups according to the chemotherapy protocol they received, selected by the surgeon according to the disease stage (tumor's size, breasts' size, and lymph node involvement); group 1 received NAC before surgery (N = 85) and group 2 received AC after surgery (N = 188). Chemotherapy regimen was similar in both groups and included a combination of taxane- and anthracycline-based regimens. The type of surgery included breast conserving surgery (BCS) or modified radical mastectomy (MRM), decided by the surgeon, according to tumors and breasts' size, as well as patients' conditions. The groups were similar in terms of lymph node involvement.

Statistical Analysis

Results of the categorical variables were described by percentage and compared between the 2 groups using a chi square test. Age was the only numeric variable in this study that had a normal distribution; thus, it was presented by mean ± standard deviation and compared between the 2 groups using an independent samples t test. The Kaplan Meier method was used for estimation of OS and DFS and the log-rank test for comparison of the survival rates between the 2 study groups (NAC and AC). Prognostic factors affecting the survival rate were predicted by applying the Cox proportional hazard model. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp) was used. All tests were 2-sided and P values 0.05 were considered statistically significant.

Results

Among 273 women, 85 received NAC before surgery and 188 AC after surgery. Mean ± syandard deviation of participants' age was 42.93 ± 12.14 and 47.97 ± 11.73 years, respectively. The frequency of pathologies, LVI, disease stage, and type of surgery were not different between the groups ($p = 0.543$, $p = 0.352$, $p = 0.891$, $p = 0.$935), while the frequency of age categories and tumor grades were significantly different between the groups (P = 0.003 and $p =$ 0.001; Table 1). The majority of patients in AC group had grade III (63.8%), while more than half of the NAC group had grade II cancer (p = 0.001; Table 1). In NAC group, 6 patients in clinical stage II and 4 patients in clinical stage III had PCR.

The Kaplan Meier estimation of 5 and 10-year OS and DFS showed no significant difference between the groups (Figs. 1 and 2).

Five-year OS for NAC and AC were estimated at 79% and 84% and 10-year OS at 79% and 72%, respectively (p = 0.771) (Fig. 1). Five-year DFS for NAC and AC were estimated at 90% and 88% and 10-year DFS at 90% and

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Table 1. Comparing Tumors Characteristics and Type of Surgery Between the 2 Groups

Variable	Categories	Adjuvant Chemotherapy (n=188)	Neoadjuvant Chemotherapy (n=85)	*P* value*
Pathology	IDC	137 (72.9%)	69 (81.2%)	0.543
	IDC/DCIS	39 (20.7%)	11 (12.9%)	
	ILC	10 (5.3%)	5 (5.9%)	
	IDC/ILC	1 (0.5%)	0	
	ILC/DCIS	1 (0.5%)	0	
Stage	2	120 (63.8%)	53 (62.4%)	0.891
	3	68 (36.2%)	32 (37.6%)	
Grade	1	8 (4.3%)	7 (8.2%)	0.001
	2	60 (31.9%)	44 (51.8%)	
	3	120 (63.8%)	34 (40%)	
Lymphovascular invasion	Positive	52 (27.7%)	19 (22.4%)	0.352
	Negative	136 (72.3%)	66 (77.6%)	
Type of Surgery	BCS	134 (71.3%)	61 (71.8%)	0.935
	MRM	54 (28.7%)	24 (28.2%)	
Age Groups	<40	51 (27.1%)	43 (50.6%)	0.003
	40-49	62 (33%)	19 (22.4%)	
	50-59	44 (23.4%)	15 (17.6%)	
	60-69	22 (11.7%)	4 (4.7%)	
	≥70	9 (4.8%)	4 (4.7%)	

*The results of the chi square test.
Abbreviations: IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; BCS, breast conserving surgery; MRM, modified radical mastectomy.

78%, respectively ($p = 0.506$; Fig. 2).

The univariate cox proportional hazard model analysis performed on age categories, type of chemotherapy, type of surgery, clinical stage, pathologic grade, and LVI showed no significant difference between the hazard of the type of chemotherapy and surgery type; however, age categories, clinical stage, pathologic grade, and LVI showed significant differences between diverse categories. The Multivariate cox analysis, performed on the groups different on univariate analysis, showed significant differences between the hazard of various categories according to clinical stage, pathologic grade, and LVI. Prognosis was worse in the age group >70 years, compared with other age groups, while the hazards of other age groups were not different (Table 2). The mean duration of the follow-up was 59.13 months in AC group and 52 months in NAC group without significant differences between the groups ($p = 0.264$).

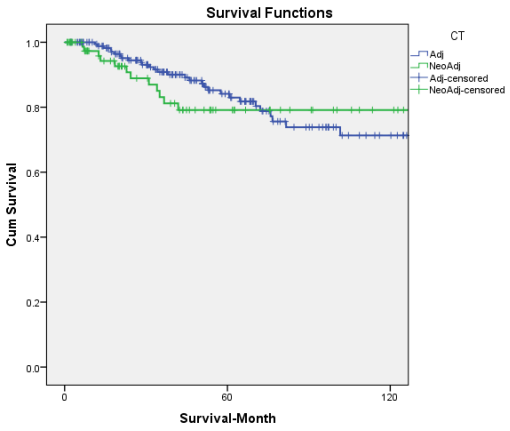

Fig. 1. Kaplan Meier estimate of 5- and 10-year overall survival in patients with triple negative breast cancer referring to the Cancer Research Center from 2000 to 2020, with comparison between patients who received adjuvant or neoadjuvant chemotherapy.

Discussion

In the present study, the results of the retrospective investigation of patients with breast cancer showed the prevalence of TNBC at 11.58%, which is consistent with the overall rate of 10% to 20%, reported previously (15) and the results of the study by Abdollahi et al in Tehran, reporting TNBC in 14% of cases (16), although the results of national registries in Iran have not reported breast cancer subtypes separately, as far as the authors are concerned (17-19).

TNBC is biologically more aggressive with a lower OS compared with non-TNBC patients (20). Chemotherapy is the mainstay of treatment for TNBC and patients with stages II and III can receive chemotherapy either before or after surgery, NAC or AC, according to the surgeon's preference and decision (21). For studying the effect of treatment type on patients' survival rates, we allocated the patients into 2 groups, according to the type of chemotherapy

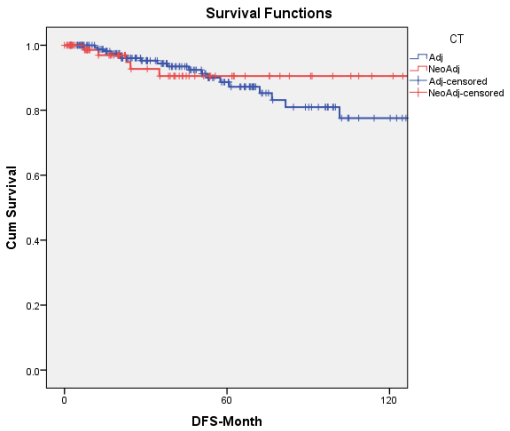

Fig. 2. Kaplan Meier estimate of 5- and 10-year disease-free survival in patients with triple negative breast cancer referring to the Cancer Research Center from 2000 to 2020, with comparison between patients who received adjuvant or neoadjuvant chemotherapy.

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Table 2. Cox Proportional Hazards Model for Overall Survival

Variable		Hazard Ratio (%95 CI)
Stage		
	2	1
	3	1.718(1.183-3.343)
Grade		
	1	1
	2	1.368(1.152-2.661)
	3	2.402(1.140-4.155)
LVI		
	Negative	1
	Positive	1.948(1.124-3.705)
Age Groups		
	<40	1
	40-49	1.678(0.739-3.810)
	50-59	1.448(0.545-3.338)
	60-69	1.235(0.030-1.866)
	=>70	9.130(2.732-19.510)

LVI: Lymphovascular invasion
CI: Confidence Interval

they received, decided by the physician and according to disease characteristics. The results of our study showed that OS and DFS of the 2 groups were not different, while the disease stage and tumor grade had significant effects on patients' OS, based on the results of the cox regression analysis. These results are in line with the results of a meta-analysis of 4756 women that indicated no difference in distant metastasis and mortality rates between these 2 types of chemotherapies in a median follow-up of 9 years (14). Nevertheless, in another meta-analysis of 36,480 TNBC patients, the results showed worse OS in NAC group, compared with AC, after a median follow-up of 4.12 years (HR = 1.59) (22), which is contrary to the results of the present study, although the duration of follow-up differed and we reported 10-year outcomes for all patients. Therefore, the results of studies are controversial in this regard. In the study on the National Cancer Database of the United States, the results indicated significantly worse 5-year OS in NAC versus AC patients (73.4% vs 76.8%) (13), which is close to that reported by the present study (79% and 84%). According to the results of studies, several factors play a role in patients' survival, variation of which can result in discrepancy in the results of studies.

The results of the present study showed that age was a significant predictor of patients' prognosis and patients aged >70 years old had a worse prognosis compared with other age groups. Also, disease stage and grade were significant predictors of patients' prognosis. These results are in line with the previous evidence referring to the worse prognosis in the elderly and in higher disease stage/grade (23); however, the main objective is focused on amendable factors (24). One of the factors that has been considered of significant importance in the patients' survival and recurrence is the PCR after NAC and it has been suggested that patients with PCR have a significantly better 5-year OS (11-13). In our study, only 10 patients in NAC group achieved PCR, which is significantly lower than that reported by previous studies; Xia et al reported PCR at 35% (22), Bagegni et al at 47.4% (13), and the American National Cancer 28% in NAC group (13). Another factor that can differ among the studies was the disease stage; for example, Clifton et al have included patients with stages I and II (25). LVI is another factor that affect OS of TNBC patients, based on the results of the cox regression analysis in our study. Mousavi et al showed that TNBC patients with positive LVI had 5.64-fold higher odds of death or recurrence (26). Therefore, a difference in LVI of the patients can justify the discrepancy of the results reported by the previous studies (11-14, 22). However, in our study, we showed that the frequency of LVI was not different between the groups (28.7% vs 21.8% in AC an NAC groups). Another factor that can vary among studies is the proportion of patients undergoing the 2 major types of surgeries, BCS, and MRM. In the present study, most patients in both groups underwent BCS (about 71%-72%) without a significant difference between the 2 groups. These results are similar to that reported by Golshan et al, indicating that about 70% underwent BCS after NAC (21). BCS is preferred due to the esthetic advantages and reducing the need for further margin excision, while the local recurrence is comparable to MRM (27, 28). Chen et al reported that TNBC patients who underwent BCS plus radiotherapy had a better OS compared with those who underwent MRM (29). Although in the present study the frequency of the 2 types of surgeries was not different between the 2 study groups and this factor did not influence our results, we believe that the difference in the frequency of surgical procedures performed among different studies could be a source of controversy in the results of OS.

In addition to the studies comparing the results of 2 chemotherapy methods, other Iranian studies have also reported 5-year OS and DFS of TNBC patients at 56% and 71% (30), 86.13% and 63.09% (26), and 88.1% and 74.1% (31), respectively. However, in the present study, we reported the 5-year OS at 79% and 84% and DFS at 90% and 88%, for NAC and AC, respectively. The discrepancy in the reported OS and DFS could also be attributed to the issues mentioned earlier.

One of the limitations of the present study was the retrospective nature of the study, which resulted in loss of some cases, because of the lack of access to the patients. Moreover, patients' enrollment into the study was not randomized and we included all patients who referred to our center by census method, according to the inclusion criteria. Also, the allocation of patients into the 2 groups was non-random, as this was a retrospective analysis and the treatment was based on the physician's choice. It has to be considered that the studied patients were selected among referrals to 1 center in 1 city, and thus generalizing the results to the whole population should be done with great caution.

Conclusion

These results showed that the choice of chemotherapy method, performed before or after surgery based on the physician's choice, does not influence 5- and 10-year OS and DFS of TNBC patients, and both methods resulted in acceptable OS and DFS. Therefore, the chemotherapy method should be chosen by the physician according to disease characteristics and medical conditions of each patient individually. Further studies are required in Iran for definite conclusion about this statement.

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Ethics Approval and Consent to Participate

The protocol of the study was approved by the Ethics Committee of Cancer Research Center of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.CRC.REC.1399.034). Each patient who enters the university affiliated hospitals is informed on sharing their data for future researches.

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Conflict of Interests

The authors declare that they have no competing interests.

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