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The Survival of Patients with Triple Negative Breast Cancer Undergoing Chemotherapy Along With Lifestyle Change Interventions

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ABSTRACT

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Background: The survival of patients with triple-negative breast cancer subtype undergoing chemotherapy along with weight management, physical activity, and diet was examined. In addition, the relationship between the Overall Survival (OS) of patients and the expression of P53 and Ki 67 was investigated.

Methods: The study was conducted on 110 patients admitted to oncology clinics between October 2009 and July 2018. The patients underwent five chemotherapy cycles, including Docetaxel, Epirubicin, and Cyclophosphamide once every 21 days followed by two cycles of Epirubicin, Cyclophosphamide, and 5-Fluorouracil. The patients also received guidelines for physical exercise, diet, and lifestyle change.

Results: The median and mean follow-ups were 52.3 and 45.6 months respectively. Eight patients were metastatic and 103 were under adjuvant therapy, 13 of whom had relapses. The median relapse-free survival and mean OS were 44.4 months and 49.2 months, respectively. OS for P53-negative patients was 64.2 months, eight patients relapsed in the P53-positive group, and two relapsed in the P53-negative group. Survival was more favorable in the negative group ($P=0.021$). The mean DFS in the P53-negative group was 96.1% and 76.3% in the P53-positive group, suggesting a more favorable status in the P53-negative group. Out of 110 patients, 20 died and 90 are still alive.

Conclusion: Combining physical exercise, diet, and lifestyle change with chemotherapy increases the chance of a better response to treatment and a reduction in the rate of relapse during the first three years. The survival rate was better in p53-negative patients.

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INTRODUCTION

It is estimated that in 2019 in the United States, 268,600 new cases of breast cancer were recorded

making it the most common cancer after skin cancer in women.¹ Among the risk factors for breast cancer are aging, mutations, reproductive history, dense breasts, and family history of breast cancer. Some risk factors can be changed, for example, physical activity, being overweight or obese after menopause, and taking hormones. However, *BRCA1* and *BRCA2* gene

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mutations on chromosomes 17 and 13 accounts for 5% to 10% of all cases of breast cancer.^{2,3}

Classification of breast cancer based on histological profiling into the following five distinct subtypes provides an insight into therapeutic strategies. These subtypes are luminal A; IHC (the histology includes tumors that are estrogen and progesterone receptor positive); HER-2 negative and low-grade histology; luminal B (includes tumors that are estrogen receptor; and HER-2 positive (progesterone receptor negative in IHC and higher grade in histology compared to those with Luminal A). Luminal B is likely to benefit from chemotherapy and hormone therapy after the end of chemotherapy and Herceptin therapy, HER-2 Neu rich; this type includes tumors that are based on IHC are progesterone receptor and estrogen receptor are negative, but HER-2 positive, Basal-like; this type, which is also called triple-negative breast cancer (TNBC), includes tumors that are ER, PR and HER-2 negative and accounts for 10-15% of breast cancers⁴, and are associated with an unfavorable prognosis.⁵

The cancer is more common in younger women and African-American and Hispanic women who carry a germline mutation of the *BRCA1* gene.^{3,6} The target population of the present study consisted of patients with triple-negative breast cancer subtype undergoing chemotherapy with conventional drugs including Docetaxel, Epirubicin, Cyclophosphamide, and 5-Fluorouracil. An important risk factor for breast cancer is a lifestyle. One of the goals of our study is to challenge the lifestyle of patients treated, and to reduce adverse effects on the prognosis of breast cancer.

Major factors of lifestyle involved in breast cancer prognosis include diet, for instance, food low in vitamin D, food prepared at high temperatures such as fast food and barbecue, diets high in fat and sugar and low in vegetables, low levels of physical exercise, and being overweight. Patients were recommended to

change their sedentary lifestyle into an active one.⁷ To reduce the effects of certain factors with an adverse effect on the prognosis of breast cancer, patients were given a series of recommendations, including using a diet containing more vitamin D, not using foods prepared at high temperatures such as fast food and barbecue, not using diets containing high fat and sugar, consuming a lot of vegetables, and having significant physical activity. The present study aimed to assess patients' responsiveness to treatments and overall survival and the effects of Ki67 and P53 on relapse-free survival and overall survival of patients.

METHODS

The study was approved by the regional Ethical Committee at the University of Medical Sciences. The study population was patients with TNBC. The sampling method was convenience and sequential. In total, 110 patients with TNBC entered the study from October 2009 until July 2018 at the oncology clinics of Kermanshah University of Medical Science. These centers are referral centers for patients from Kermanshah, Kurdistan, Ilam, Lorestan, and Hamadan provinces in Iran. The patients were followed-up from the time of diagnosis until the time of the last statistical work of the article. The established histopathological factors in patients with TNBC such as pathological tumor size, tumor type, nodal status, hormonal receptor, and HER-2 status were identified from the database of the Department of Pathology and the documentation in the patient's file. Data were analyzed using the SPSS 16 statistical software and reported as crosstabulation, frequency (percentage), median, mean (\pm standard deviation), and confidence interval (CI). The Kaplan-Meier method and curve were used to calculate and present overall survival (OS) and relapse-free survival (DFS) for patients.

The tumors were classified as IHC stains Score 0, Score 1+, Score 2+, and Score 3+ (Table 1).

Table 1. HER 2/neu scoring in breast cancer

Score	Activity	Result
0	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of the percentage of tumor cells stain	Negative
2+	Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of the percentage of tumor cells stained	Equivocal
3+	cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of the percentage of tumor cells stained	Positive

*For established patients with a score of 2 in IHC recommends fluorescence *in situ* hybridization (FISH).

The cells were stained for Ki67 and P53. Chemotherapy regimens and chemotherapy courses are listed in Table 2 over 21 days.

During this period, all patients were monitored for treatment complications, particularly for fever and

febrile neutropenia, and hospitalized if necessary. After completing the seven chemotherapy cycles, qualified patients were referred for radiotherapy and then checked at regular intervals of three months up to a year, and afterward every six months, for



potential relapses. The patients were also reminded of the pieces of advice previously given regarding interferences with a lifestyle that could have a

potentially negative effect on prognosis and assessed on their compliance with the bits of advice.

Table 2. Chemotherapy regimens and chemotherapy courses

chemotherapy	Drug	Drug	Drug	Over the 21 days
5 cycles	docetaxel 80 mg/m ²	epirubicin 80 mg/m ²	cyclophosphamide 500 mg/m ²	once every 21 days with G-CSF support
2 cycles	epirubicin 90 mg/m ²	cyclophosphamide 600 mg/m ²	5-fluorouracil 600 mg/m ²	with G-CSF support

At the time of writing the proposal, the authors did not include the initial check of the vitamin D3 level although it would be much better to determine this. However, in the second year of the follow-up, along with routine tests for patients, the level of vitamin D3 was checked, and recommendations related to vitamin D3 were given if necessary.

Several patients may have followed some of these recommendations to some extent before being diagnosed with breast cancer. The following points were recommended to patients: attain and maintain an ideal weight throughout life. Especially for those who were overweight or obese, they were advised to limit consumption of high-calorie foods, be as thin as possible throughout life while avoiding losing too much weight and being under ideal weight, and participate in regular physical activity. The patients were advised to have at least 60 minutes/day walking for six days per week or moderate to intensive physical activity for five days per week. They were also advised to eat a diet rich in whole grains and high in vegetables, limit consumption of fast foods, sugar-sweetened drinks, and red and processed meat, and avoid smoking and other exposure to tobacco. In practice, it was not possible to evaluate whether the patients followed our recommendation.

On every visit, these recommendations would be repeated for the patients, and the patients would be asked if they had paid attention to these recommendations. The participants responded that they followed these recommendations as much as possible. We do not know how many people had a healthy lifestyle before this recommendation, and this was not assessed. However, the aim was to ensure that these people continued to live a healthy lifestyle after being diagnosed with cancer.

RESULTS

Patients' mean age was 55.3 years and their median follow-up was 52.3 months with 95% CI between 39.1 months and 65.4 months. Their mean follow-up was 45.6 months with 95% between 45.6 months and 55.3 months. Overall, 108 patients were female (98.2%) and 2 (1.8%) were male. In 57 of the

patients (50.4%), the tumor was on the right side, and in 53 (49.6%), on the left. The demographic characteristics of the patients are shown in Table 3. The mean relapse time was 33.3 months (10-62 months). The median relapse time was 30 months, and in 95% of the patients, relapse occurred from month 10.3 to month 61.8.

During the follow-up of patients in stages 1, 2, and 3 (102 out of 110), systemic and local relapses occurred in 16 patients (Table 2). Out of the 102 patients, 86 (84.3%) did not experience relapses and out of the eight patients with metastasis (stage 4), seven died and one with lung metastasis is in remission. Ultimately, 20 patients died and 90 are still alive. One relapsed case of pulmonary metastasis was recovered and still lives. At the end of the statistical analysis, one patient experienced brain and bone metastases and is currently under treatment and excluded from the statistical analyses. The relationship between overall survival and P53 was assessed. Overall survival for P53-positive patients was about 35.3 months (mean OS = 55.72 months and median OS = 66.5 months). Overall survival for P53-negative patients was 64.2 months (mean OS = 44.28 months and median OS = 36.4 months). Eight patients relapsed in the P53-positive group and two relapsed in the P53-negative group. Survival was more favorable in the negative group (P=0.021) (Figure 1).

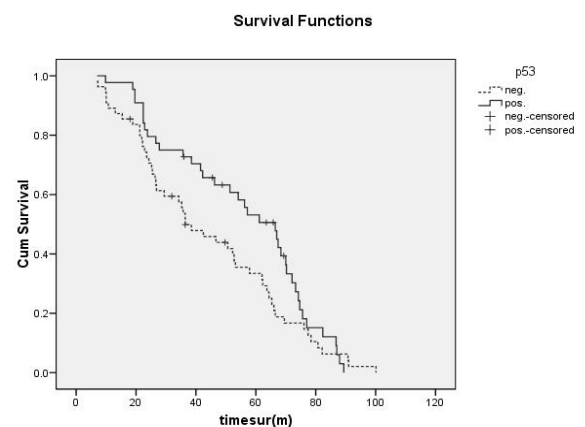


Figure 1. Kaplan-Meier curves for overall survival for patients with p53 positive (Continuous line) and negative (A dotted line) (P<0.021)

**Table 3.** The frequency (percentage) distribution of the patients' characteristics

Variables	Strata	Frequency	Percent
ACC System	Stage I	6	5.5
	Stage IIA	25	22.7
	Stage IIB	35	31.8
	Stage IIIA	31	28.2
	Stage IIIB	2	1.8
	Stage IIC	3	2.7
	Stage IV	8	7.3
	Total	110	100.0
P53 and Relapse*	Negative	53	54.1
	Positive	44	45.9
	Total	98	100.0
Ki-67 and Relapse**	Negative	38	73.1
	Positive	14	26.9
	Total	52	100.0
Age group (year)	25-34	22	20.0
	35-44	41	37.3
	46-54	32	29.1
	55+	15	13.6
	Total	110	100.0
Relapse in Stages I, II, III)	Systemic Relapse Brain	2	1.96
	Systemic Relapse Bone	4	3.92
	Systemic Relapse Liver	5	4.90
	Systemic Relapse Lung	2	1.96
	Local Relapse	3	2.94
	Metastasis at Diagnosis	8	7.85
	None	78	76.47
	Total	102	100.0
Death	Yes	20	18.2
	No	90	81.8
	Total	110	100.0

* P Value for OS/DFS=0.021, Failed for 12 due to technical problems

** Levels above 10% (the cut-off point) were considered positive, P Value for OS/DFS=0.11, Failed for 58 due to technical problems.

The relationship between DFS and P53 was also assessed, and the mean DFS in the P53-negative group was 96.1% and 76.3% in the P53-positive group, suggesting a more favorable status in the P53-negative group (Figure 2).

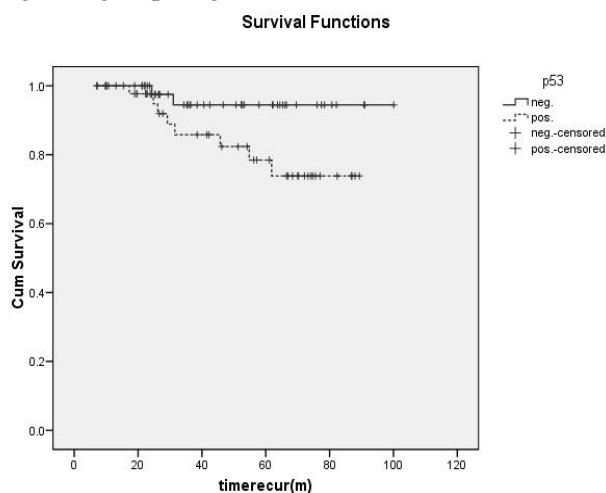


Figure 2. Kaplan-Meier curves for relapse-free survival for patients with p53 positive (A dotted line) and negative group (Continuous line) ($P < 0.031$).

Fifty-two patients were assessed in terms of Ki67, 14 of whom turned out to be negative and 38 positive. In the Ki67-positive group, two of the total 38 patients relapsed and ultimately died, and in the Ki67-negative group, three of the total 14 patients relapsed, and ultimately three patients of this group died. The relationship between DFS and overall survival was assessed. In the Ki67-negative group, the mean OS was 64.152 months and the median OS was 62.067 months. In the Ki67-positive group, the mean DFS was 35.25 months and the median DFS 25.43 months; however, the relationship was not statistically significant ($P = 0.33$) (Figure 3).

The relationship between Ki67 and relapse was assessed. Relapse occurred in two patients from the Ki67-positive group and two from the Ki67-negative group; however, the relationship was not significant ($P = 0.201$). A total of five patients died, two of whom belonged to the Ki67-negative group and three to the Ki67-positive group; however, this relationship was not significant ($P = 0.11$). The overall survival of all patients is shown in survival outcomes for all patients (110 patients) in Figure 4.

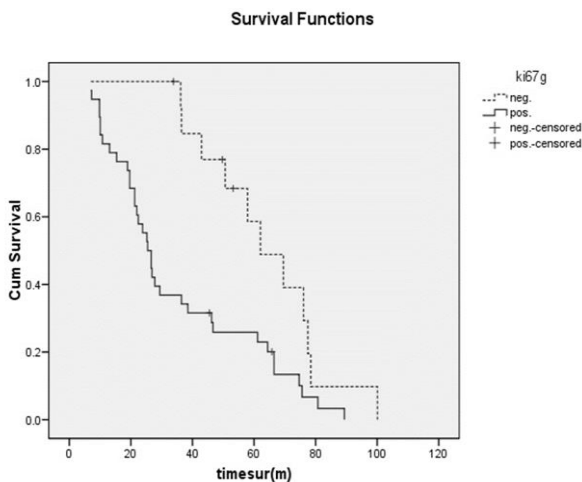


Figure 3. Kaplan-Meier curve of overall survival (OS) patients with a Ki-67 index Positive (Continuous line) and patients with a Ki-67 index negative (A dotted line) in triple-negative breast cancer.

The relationship between Ki67 and relapse was assessed. Relapse occurred in two patients from the Ki67-positive group and two from the Ki67-negative group; however, the relationship was not significant ($P=0.201$). A total of five patients died, two of whom belonged to the Ki67-negative group and three to the Ki67-positive group; however, this relationship was not significant ($P=0.11$). The overall survival of all patients is shown in survival outcomes for all patients (110 patients) in Figure 4.

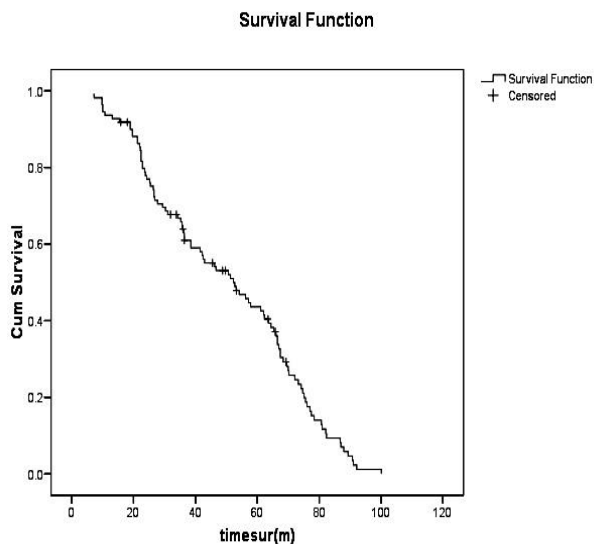


Figure 4. The OS curve of patients with TNBC from October 2009 to September 2018

DISCUSSION

A relative improvement is evident in the disease outcome of patients with Triple Negative Breast Cancer (TNBC) within the past 20 years.^{4,6,8,9} TNBC is chemotherapy-sensitive and these patients appear to benefit from chemotherapy, and despite the

advances in the treatment of breast cancer and the emergence of biological and target therapy, chemotherapy regimens with standard factors are still the frontline treatment for them. Although women with TNBC often enter a period of remission in response to chemotherapy, the disease often takes an aggressive form, and the likelihood of relapse and death due to the disease is higher in the first three years following diagnosis compared to that in the other subtypes of breast cancer. After this period, the risk of relapse is reduced rather significantly compared to the PR and ER-positive subtypes. Patients with TNBC appear to be different from the other subtypes in terms of the presentation and expression of certain receptors. For instance, the expression of Ki67 and P53 is high at the tumor level, which constitutes poor prognostic factors in breast cancer. Ki67 overexpression is likely to be associated with larger tumor size and the involvement of axillary lymph nodes.^{5,10,11} Juny Su *et al.*¹⁰ showed that Ki67 can be an independent prognostic factor for DFS or OS rates in early-stage breast cancer patients. Breast cancer with high Ki-67 expression responds better to chemotherapy; however, visceral recurrence is high during follow-up.^{12,13} In the present study, patients received advice on increasing their physical exercise and changing their lifestyle from a sedentary one to an active one.¹⁴ Many epidemiologic studies have shown that post-diagnosis exercise may be associated with improved OS in women with TNBC.¹⁵ The American Cancer Society and the National Comprehensive Cancer Network have some dietary recommendations and weight and physical activity adjustments for cancer patients along with other recommendations.^{16,17}

Many studies have suggested that a healthy lifestyle may reduce the risk of breast cancer and lead to a better breast cancer prognosis.¹⁸ Evidence suggests that physical activity and weight management has a role in breast cancer prevention and can improve survival in patients with breast cancer. In addition, vigorous activity can even reduce the risk of relapse in PR and ER-negative breast cancer patients. Evidence suggests a link between obesity and breast cancer at the time of diagnosis as well as recurrence and mortality of patients.^{19,20} In addition, evidence has shown that inactivity is a risk factor for breast cancer and death due to the disease.²¹ Despite this, we have little information on how weight loss and physical activity can reduce breast cancer risk or improve outcomes in individuals diagnosed with breast cancer.²²

Most recent trials have evaluated the impression of interventions such as diet, weight loss, and physical activity in the relapse and survival of patients with breast cancer. The results of the research SUCCESS-



C trial were presented at the San Antonio Breast Cancer Symposium in 2018²³ and evidently, the participants who completed the study had a low relapse rate and mortality. In the present study, patients were advised to have at least 60 minutes/day walking for six days per week or moderate to intensive physical activity five days per week. We need recommendations to lose weight in obese people and plan for physical activity.²⁵

Recommendations to patients about physical activity were either vigorous activity or household activities or walking.²⁴ In some studies, physical activities were vigorous activities, which were not associated with reducing the risk of breast cancer.²⁶ Moreover, obese patients are advised to lose weight.²⁷⁻³⁰ Patients with a BMI over 30 are advised to reduce their BMI by reducing their waistline. A review of the literature showed that a BMI over 25 is associated with a poor prognosis.^{31,32} Early studies have shown that low levels of vitamin D at the time of diagnosis are associated with a high risk of relapse; patients are therefore advised to consume food high in calcium and vitamin D^{33,34,35} such as Doug (diluted yogurt), yogurt, fish (twice a week), vegetables (5 days a week) and no barbecues. However, In some studies, vitamin D consumption has not been associated with lowering the risk of breast cancer.^{36,37} In addition, in some studies, vegetable consumption has not been associated with reducing the risk of breast cancer.³⁶ These patients are therefore advised to use low-fat and low-sugar diets since high-cholesterol diets may induce vasculogenesis.^{38,39,40} Some studies have reported results identical to our findings.⁴¹

The rates of local relapse, systemic relapse, and mortality were lower in the first three years compared to other studies. Three unproven hypotheses were therefore proposed, suggesting different factors. First, the stage of disease (a substantial proportion of patients in the present study were in stages 1, 2, and 3); second, the four drugs prescribed (Epirubicin, Taxotere, Cyclophosphamide, and 5-E-U); and third,

pieces of advice about diet, lifestyle change, and physical activity. P53 was found to display an important role in the prognosis of the disease and the survival of P53-positive patients was also found to be lower than that of P53-negative patients. In the present study, Ki67 was not associated with a poor prognosis⁴², which might be due to the low number of IHC performed for Ki67.

CONCLUSION

The high level of visceral metastasis in these patients necessitates constant follow-up and surveillance during the first few years at shorter intervals, especially in the case of P53-positive patients. The reason for this is that survival rates might increase with the early diagnosis and aggressive treatment of relapsed patients. Patients with positive P53 expression had shorter survival. There was no difference in the survival rate of patients in the group with low and high Ki67. Relapse-free survival and overall survival in patients with TNBC in our study were significant, which can be due to the changes in lifestyle and diet in these patients. There is a need for studies with a larger sample group and a more accurate design.

ETHICAL CONSIDERATIONS

This study was approved by regional Ethical Committee (Ref. No.: IR.KUMS.REC.1398.750)

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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