

The Survival of Patients with Triple Negative Breast Cancer with Chemotherapy Along with Lifestyle Change Interventions in Survivors

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Abstract

Background: The present study was conducted to examine the survival of patients with triple negative breast cancer subtype undergoing current chemotherapy and along with implanting weight management, physical activity and diet in breast cancer survivorship.

Patients and methods: The present study was conducted on 110 patients admitted to the oncology clinics of Talaghani Hospital of Kermanshah University of Medical science between October 2009 and July 2018. Patients started 5 chemotherapy cycles, including docetaxel, epirubicin and cyclophosphamide once every 21 days, and then two cycles of epirubicin and cyclophosphamide, ending with fluorouracil. Also recommend patients for physical exercise, diet and lifestyle change.

Results: The median and mean follow-up was 52.3 and 45.6 months respectively. 8 patients were metastatic and 103 were under adjuvant therapy, 13 of whom had relapses. Median relapse-free survival and mean overall survival were 44.4 months and 49.2 months, in respective order of the total of 110 patients, 20 died and 90 still live.

Conclusion: Along with recommendations for physical exercise, diet and lifestyle change, combination chemotherapy increases hopes for a better response to treatment and a reduction in the rate of relapse during the first three years.

Keywords: Triple negative breast cancer; Current chemotherapy; Physical exercise; Diet and lifestyle change

gene mutations, on chromosomes 17 and 13, account for 5% to 10% of all women with breast cancer [2-3]. Classification of breast cancer based of the histological profiling into the following five distinct subtypes provide insight into therapeutic strategies: luminal A; IHC and histology this subtype includes tumors that are estrogen and progesterone receptor positive, HER-2 negative and have a low-grade histology, luminal B; this type 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 are likely to benefit from chemotherapy and hormone therapy after end chemotherapy and herceptin therapy, HER-2 positive; this type includes tumors that based IHC are progesterone receptor and estrogen receptor 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 cancers [4]. And are associated with an unfavorable prognosis [5]. It is more common among younger women, African-American and Hispanic women and who carry a germ line mutation of the *BRCA-1* gene [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 fluorouracil. To reduce the effects of certain factors with an adverse effect on the prognosis of breast cancer, patients were given a series of advices. Major factors involved in breast cancer prognosis include diet (for instance, food low in vitamin D, prepared at high temperatures, such as barbecues, high in fat and sugar and low in vegetables), physical exercise (low levels of it have an adverse effect) and lifestyle (patients were recommended to change their sedentary lifestyle into an active one) [7]. 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.

Introduction

It is estimated that in 2019 in United State, 268,600 new cases of breast cancer will occur in women and making it the most common cancer after skin cancer in women [1]. A number of risk factors for breast cancer that can be mentioned include: getting older, genetic mutations, reproductive history, having dense breasts, family history of breast cancer that these things cannot be changed. A number of risk factors can be changed, for example: not being physically active, being overweight or obese after menopause, taking hormones. However, BRCA and BRCA-1

Materials and methods

We have entered the study 110 consecutively patients with TNBC from October 2009 until July 2018 at oncology clinics of Kermanshah University of Medical Science (KUMS). These centers are referral centers for patients from Kurdistan, Elam, Lorestan, and Hamadan provinces in IRAN. They were followed

from the time of diagnosis to the time of recurrence, then to follow-up to death. The established histomorphological factors patients with TNBC such as pathological tumor size, tumor type, nodal status and hormonal receptor and HER-2 status were identified from the database of the department of Pathology of KUMS and from the documentation in the patients' file. Tumors were classified as IHC stains score 0 if no membrane staining or incomplete faint membrane staining less than $\leq 10\%$ of invasive tumor cells was observed, an IHC score 1+ if an incomplete faint membrane staining was detected in more than 10% of invasive tumor cells, an IHC score 2+ if weak or incomplete circumferential membrane staining was observed in more than 10% of invasive tumor cells and complete and circumferential membrane staining that is intense and within $\leq 10\%$ of invasive tumor cells. For establish patient with score 2 in IHC recommends Fluorescence in Situ Hybridization (FISH). In IHC with score 3+ tumor displays complete, intense circumferential membranous staining in more than 10% of tumors cells. The cells were stained for Ki67 and P53. Patients underwent 5 chemotherapy cycles, including docetaxel $80\text{mg}/\text{m}^2$, epirubicin $80\text{ mg}/\text{m}^2$ and cyclophosphamide $500\text{ mg}/\text{m}^2$ once every 21 days with G-CSF support, and then two cycles of epirubicin $90\text{ mg}/\text{m}^2$ and cyclophosphamide $600\text{ mg}/\text{m}^2$ and 5-fluorouracil $600\text{ mg}/\text{m}^2$ with G-CSF support. Over the 21-day period, all patients were monitored for treatment complications, particularly for fever and febrile neutropenia, and were hospitalized if necessary. After completing the 7 chemotherapy cycles, qualified patients were referred for radiotherapy and then checked at regular intervals of 3 months up to a year, and afterwards every 6 months, for potential relapses, and were also reminded of the advices previously given regarding interferences with Lifestyle that could have a potentially negative effect on prognosis and assessed on their compliance with the advices. The following are recommended to patients: Attain and maintain an ideal weight throughout life. Especially for those who are overweight or obese, limit consumption of high calories foods. Participate in in regular physical activity. Be as thin as possible throughout life don't be under ideal weight. Adults should participate in in at least exercise 360 min/week or vigorous intensity activity at least 4 day/week, or a combination of both during the week. Eat a diet rich in whole grains and high in vegetable. Limit consumption of fast foods, sugar-sweetened drinks, red and processed meat. Avoid smoking and other exposure to tobacco [8].

Results

Patients' mean age was 55.3 years and their median follow-up was 52.3 months with 95% 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. 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. At the time of diagnosis, 8 patients showed evidence of metastasis, with 3 cases in the bone, 4 cases in the liver and 1 case in the lung. Out of the 110 patients, 51 met the criteria for radiotherapy and underwent the procedure. Paget's disease was observed in 5 patients. Invasive ductal-lobular carcinoma was observed in only 2 patients. IHC for P53 was performed on 99

out of the 110 patients, but failed for 11 due to technical problems, and out of the remaining 99 patients, P53 staining was negative in 53 and positive in 44. IHC staining for Ki67 was performed on 52 patients only and not on 57 patients because failed due to technical problems.

Levels above 10% (the cut-off point) were considered positive. 38 patients (73%) came out positive from the staining and 14 came out negative. Patients' staging was based on the ACC system: Stage I: 6 patients (6.9%); stage IIA: 25 patients (22.5%); stage IIB: 35 patients (31.5%); stage IIIA: 31 patients (27.9%); stage IIIB: 2 patients (1.8%); stage IIIC: 3 patients (2.7%); and stage IV: 8 patients (7.2%).

Patients were also grouped based on their age: 22 (20%) in the 25-35 age group, 41 (37.27%) in the 35-45 age group, 32 (28.8%) in the 46-55 age group and 15 (13.5%) in the over-56 age group. Mean relapse time was 33.3 months (10 months at minimum and 62 months at maximum). 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 (total of 103 out of 110), relapse occurred in 13 patients, of which 4 cases had it in the bone, 2 in the brain, 2 in the lung and 5 in the liver 4 of the 103 patients (3.6%) experienced local relapse at the site of surgery. Of the 103 patients, 86 (83%) did not experience relapses. Of the 8 patients with metastasis (stage 4), 7 died and one with lung metastasis is in remission.

Ultimately, 20 patients died and 90 still live. One relapsed case of pulmonary metastasis recovered and still lives. At the end of the statistical analysis phase, one other patient experienced brain and bone metastases and is currently receiving treatments and was 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 was 55.72 months and median OS 66.5 months).

Overall survival for P53-negative patients was 64.2 months (mean OS was 44.28 months and median OS 36.4 months). 8 patients relapsed in the P53-positive group and 2 relapsed in the P53-negative group. Survival was more favorable in the negative group ($p=0.021$) (Figure 1). 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).

Fifty-two patients were assessed in terms of Ki67, 14 of who turned out negative and 38 positive. In the Ki-67-positive group, 2 of the total of 38 patients relapsed and ultimately died, and in the Ki-67-negative group, 3 of the total of 14 patients' relapsed and ultimately 3 patients of this group died.

The relationship between DFS and overall survival was assessed. In the Ki-67-negative group, the mean OS was 64.152 months and the median OS was 62.067 months. In the Ki-67-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 Ki-67 and relapse was assessed. Relapse occurred in 2 patients from the Ki-67-positive group and 2 from the Ki-67-negative group; however, the relationship was not significant ($p=0.201$).

A total of 5 patients died, 2 of whom belonged to the Ki-67-negative group and 3 to the Ki-67-positive group; however, this relationship was not significant ($p=0.11$).

The overall survival total patients are shown in Survival outcomes in all patients (110 patients) are shown in Figure 4.

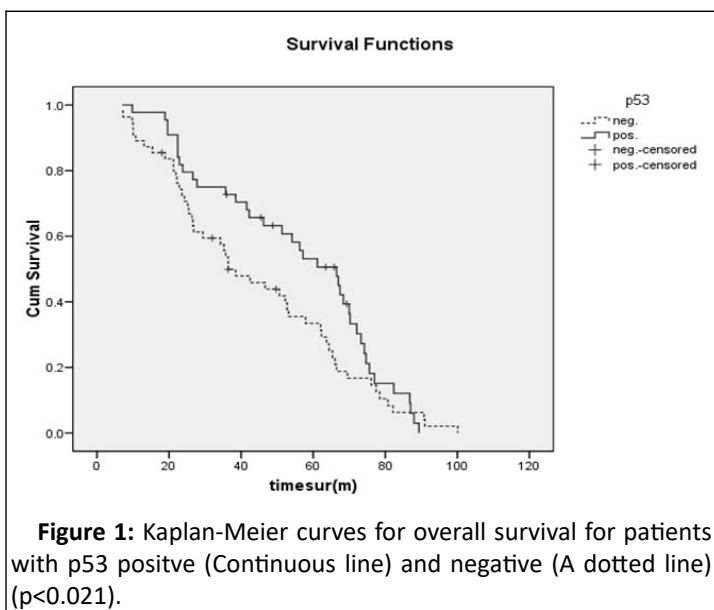


Figure 1: Kaplan-Meier curves for overall survival for patients with p53 positive (Continuous line) and negative (A dotted line) ($p<0.021$).

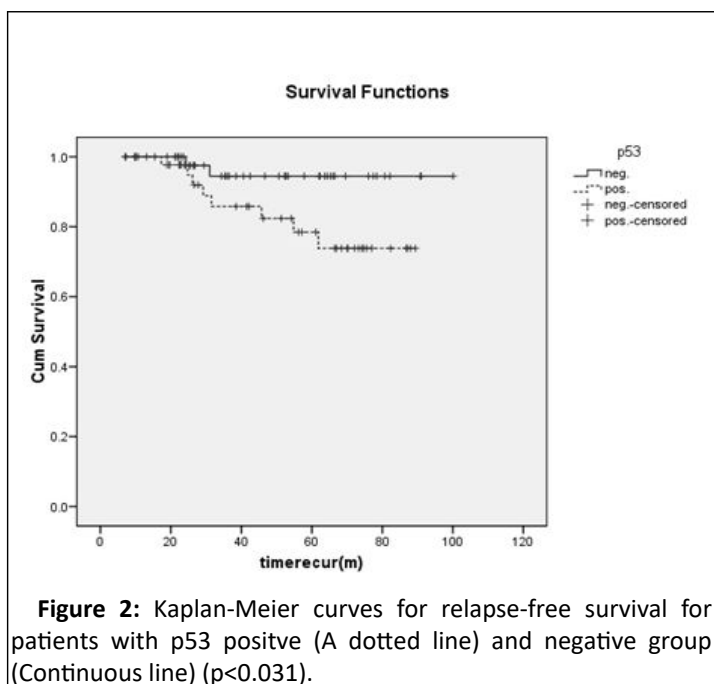


Figure 2: Kaplan-Meier curves for relapse-free survival for patients with p53 positive (A dotted line) and negative group (Continuous line) ($p<0.031$).

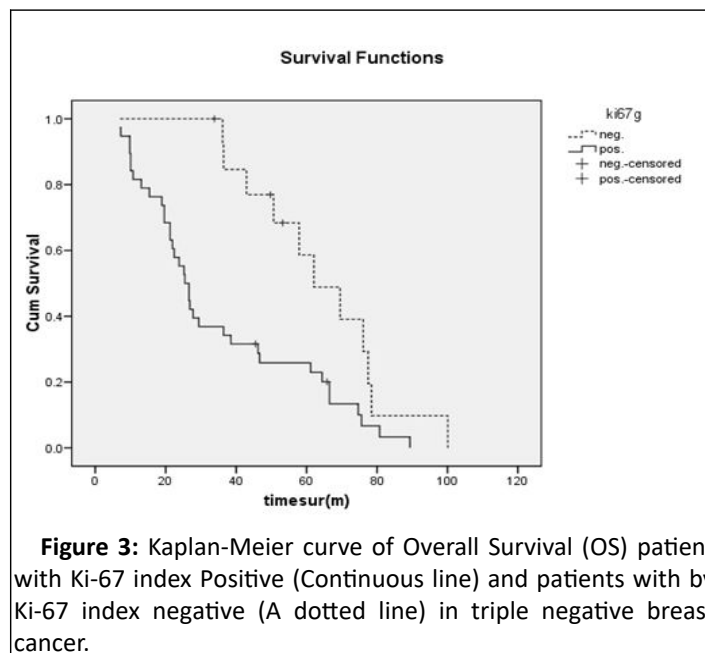


Figure 3: Kaplan-Meier curve of Overall Survival (OS) patient with Ki-67 index Positive (Continuous line) and patients with by Ki-67 index negative (A dotted line) in triple negative breast cancer.

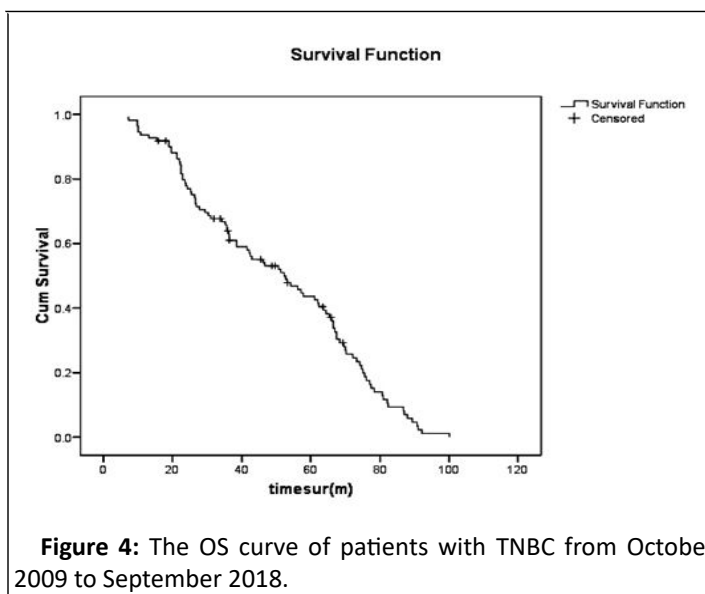


Figure 4: The OS curve of patients with TNBC from October 2009 to September 2018.

Discussion

A relative improvement can be noticed in the disease outcome of patients with Triple Negative Breast Cancer (TNBC) within the past 20 years [9]. 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 techniques, 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, they often take an aggressive form, and the likelihood of relapse and death due to the disease is higher in the first 3 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 Ki-67 and P53 receptors is high at the tumor level, which comprises poor prognostic factors in breast cancer. Ki-67 overexpression is likely associated with a larger tumor size and the involvement of axillary lymph nodes [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 but 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. Many epidemiologic studies show that post-diagnosis exercise may associate with improved OS among women with TNBC [14]. The American Cancer Society and the National Comprehensive Cancer Network has a number of dietary recommendations and weight and physical activity adjustments in cancer patients along with other recommendations [15-16]. Many studies suggest that a healthy lifestyle may reduce the risk of breast cancer and better breast cancer prognosis [17]. Evidence suggests that physical activity and weight management has a role in breast cancer prevention and can improve survival in patient with breast cancer and 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 [18-19]. Also Evidence has shown that inactivity is a risk factor for breast cancer and death from the disease [20]. Despite our knowledge of the above, we have little information on how weight loss and physical activity can reduce breast cancer risk or in improving outcomes in individuals diagnosed with breast cancer [21]. Most recent trials are evaluating impression of interventions such as diet, weight loss, and physical activity in the relapse and survival of patients with breast cancer. The results of research success-trial were presented at the San Antonio Breast Cancer Symposium 2018 [22] showed participants who completed the study had a low relapse rate and mortality. We need recommendations for patients to lose weight in obese people and plan for physical activity. Recommendations to patients about physical activity were either vigorous activity or household activities or walking [23]. In the present study, patients were advised to have at least 60 minutes/day walking for 6 day per week or moderate to intensive physical activity 5 days per week. 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, such as Douq (diluted yoghurt), yoghurt, fish (twice a week), vegetables (5 days a week) and no barbecues. Moreover, obese patients are advised to lose weight [24-27]. Patients with a BMI over 30 are advised to reduce their BMI by reducing their waistline. Review of literature shows that a BMI over 25 is associated with a poor prognosis [28-29]. These patients are therefore advised to use low-fat and low-sugar diets since high-cholesterol diets may induce vasculogenesis [30]. In the analysis of patients in the present study, 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

influential factors: First, the stage of disease (a substantial proportion of patients in the present study were in stages 1,2 and 3); second, the 4 drugs used (epirubicin, taxotere, cyclophosphamide and 5-E-U); and third, advices 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 the survival of P53-negative patients. In the present study, Ki-67 was not associated with a poor prognosis, which might have been due to the low number of IHC performed for Ki-67.

Conclusion

Unlike genetic factors affecting prognosis in triple negative patients that cannot be interfered with, interfering with environmental and acquired factors might actually improve patients' prognosis. The high level of visceral metastasis in these patients necessitates their constant follow-up and surveillance during the first few years at shorter intervals, especially in the case of P53-positive patients, because survival rates might increase with the early diagnosis and aggressive treatment of relapsed patients. To conclude, TEC is an acceptable treatment regimen.

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