Review Article

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Evaluation of overall survival and disease-free survival of adjuvant chemotherapy and hormone therapy in patients with breast cancer

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ABSTRACT

Background: This study evaluated the effect of adjuvant chemotherapy and hormone therapy on overall survival and disease-free survival in patients with breast cancer with hormone receptor-positive, HER2-negative tumors without lymph node involvement.

Methods: Breast cancer patients with hormone receptor-positive, HER2-negative, and no lymph node involvement were included in this retrospective cohort study. Patient records were used to collect data on sex, age, time of disease onset, tumor subtype, tumor size, grade, lymphovascular and perineural involvement, ki67, and treatment protocols. Patients were divided into 2 groups: Patients who received both adjuvant chemotherapy and hormonal therapy and patients who received hormonal therapy only. Disease-free survival index (DFS) and overall survival index (OS) were evaluated.

Results: Sixty-seven female patients were enrolled in this study. Of them, 68.2% received both adjuvant chemotherapy and hormonal therapy and 31.6% received hormonal therapy only. During follow-up, recurrences occurred in 8 patients. The 3-year and 5-year DFS were 93.4% and 90%, respectively. The 3-year and 5-year DFS was 94% and 92%, respectively, in patients who received both adjuvant chemotherapy and hormonal therapy, and 91% and 85%, respectively, in patients who received hormonal therapy. None of the factors studied affected the 3-year and 5-year DFS. The 3-year and 5-year DFS OS were 98.6% and 96.9%, respectively

Conclusion: Adjuvant chemotherapy in patients with breast cancer with hormone receptor-positive, HER2-negative, and no lymph node involvement compared with similar patients receiving hormone therapy alone had no significant difference in disease-free survival index and overall survival index.

Keywords: breast cancer; disease-free survival index; overall survival index

INTRODUCTION:

Breast cancer is the most common cancer diagnosed in the world and the leading cause of death in women. Several factors are associated with an increased risk of breast cancer but half of the patients with breast cancer have no specific risk factors except for age or gender. Increasing advances in the management of breast cancer has been shown to improve patient survival and prognosis. Despite extensive research over the last two decades on the classification, risk factors identification, early diagnostic methods, and treatment protocols, still a high percentage of patients experience metastatic disease associated with breast cancer. At the time of diagnosis, patients are mainly in one of the following three groups: The first group consists of patients that didn't make a profit from any adjuvant treatments such as endocrine and chemotherapy or immunotherapy. This small group of patients mostly experience metastases and therefore does not experience an improvement in survival. The second group is patients who had good survival even without adjuvant treatment. However, the third group is those patients who derive benefits from adjuvant therapy that leads to improvement in survival and prognosis. However, in almost all patients, it is not possible to predict the time of initial diagnosis of metastasis, and sometimes it is difficult to diagnose the best time to start adjuvant treatment to have optimal effectiveness. Many prognostic factors including nodal condition and tumor size described the risk and classification of the disease. It is shown that breast cancer has a variety of subtypes, especially completely different gene expression profiles, and Molecular markers improve treatment accuracy and aid in subtyping breast cancers.[1] [2-5]

In 2011, four different subtypes of breast cancer were identified which include luminal A, Luminal B subtypes with HER2 negative and HER2 positive, triple-negative, and overexpressing HER2. Based on the available guidelines, systemic therapies have been suggested for these subtypes, including only endocrine treatment for luminal A, endocrine therapy and chemotherapy for luminal B HER2 negative, chemotherapy and anti-HER2 treatment for overexpressing HER2 type, and chemotherapy for triple-negative subtypes.[6] [7-9]

The Luminal A subtype is the most common molecular subtype, This subtype is a type of hormone receptor-positive (+ HR, HER2 negative) and the expression of the Ki-67 marker is less than 10%. From a clinical point of view, patients with the luminal A subtype have a good prognosis and treatment with endocrine adjuvant therapy, but regarding the response to adjuvant chemotherapy in these patients and improving their survival, there are many questions. Also, patients with the luminal B subtype, which accounts for about 20% of breast cancer cases which includes ER + with and without HER2 genomic expression have a favorable prognosis by the adjuvant chemotherapy treatment, however, the effects of treatments type on the patient survival are still in doubt. Therefore, in the present study, we evaluate overall survival and disease-free survival for years in breast cancer patients with hormone receptor-positive, HER2 negative, and no axillary lymph node involvement with and without adjuvant chemotherapy.[10-13]

Methods:

GIn this retrospective cohort study, we investigate patients with hormone receptor-positive and HER2 negative and without axillary lymph node involvement who underwent breast cancer surgery from the the year 2013 to 2021. Exclusion criteria were in situ breast cancer (such as ductal carcinoma in situ), receiving neoadjuvant treatment, loss to follow-up, other breast cancer subtypes, metastatic breast cancer, axillary lymph node involvement, tumor size more than 2 cm, and age over 70 years.

Based on patients' records, basic and underlying characteristics including patient age, age of diagnosis, tumor subtype, underlying features of the tumor including tumor size and grade, number of lymph node involvement and perineural involvement, and treatment protocols were extracted. Patients with positive hormone receptors and negative HER2 without the involvement of axillary lymph nodes with tumor size equal to or less than 2 centimeters were in-

cluded in the study. All patients underwent conventional endocrine therapy.

Patients were divided into two groups based on receiving adjuvant chemotherapy treatment. Patients were followed at the clinic or by telephone and two indexes including the disease-free survival index (DFS) as well as the overall survival index (OS) evaluated. DFS would be the time interval between the diagnosis time and the first recurrence time of the disease in the form of breast cancer spreading to the chest, the opposite breast, or the local lymph nodes and OS would be the time interval between diagnosis and death for any reason.

Data were analyzed by using SPSS software. Quantitative variables were described by means and standard deviations and qualitative variables were described with Numbers and percentages. To determine the statistical difference in qualitative parameters between patients Chi-Square and Fisher's exact tests were used. For analysis, of patient survival, the Kaplan-Meier method was used and for assessment of independent factors on patient survival, the Cox proportional hazard models were used.

Results:

The records of patients who were referred to the cancer clinic of Imam Khomeini Hospital in Tehran between 2013 and 2021 were reviewed. Cases with defects in various fields such as patient pathology, patient symptoms at the beginning of diagnosis, type of treatment regimens, and follow-up of patients were not included in the study. Finally, 76 patients were included in the statistical analysis, of which 51 patients (68.4%) received chemotherapy and 10 patients (31.6%) did not receive chemotherapy and only received hormonal drugs.

The mean age of patients was 51±9.2 years old. Average KI67 and tumor size in pathology were 15.2±10.08 and 1.5±0.4 cm, respectively.

The patient's characteristics showed in Table 1.

During follow-up, 8 patients experienced recurrence. The 3-year and 5-year disease-free survival (DFS) was 93.4% and 90%, respectively. The 3-year and 5-year DFS in patients who received adjuvant chemotherapy were 94% and 92%, and also in patients who didn't receive adjuvant chemotherapy were 91% and 85%. The effects of different factors showed in Table 2.

It should be noted that during follow-up, 3 patients

Table 1. Characteristics of patients include age, tumor size, Ki67, grade, PNI, LVI

characteristic		Total patients (%)	No ACT	ACT
Age	<50	37 (48.7)	12 (50)	25 (48.1)
	≥50	(51.3) 39	12 (50)	27 (51.9)
Tumor size	<1cm	7 (9.2)	7 (29.20)	0 (0)
	≥ 1cm	69 (90.8)	17 (70.8)	52 (100)
Ki67	<10	20 (26.3)	9 (37.5)	11 (21.2)
	≥ 10	56 (73.3)	15 (62.5)	41 (78.8)
Grade	1	24 (31.6)	12 (50)	12 (23.1)
	≥ 2	52(68.4)	12 (50)	40 (76.9)
PNI	no	52 (68.4)	22 (91.7)	30 (57.7)
	Yes	24 (31.6)	2 (8.3)	22 (42.3)
LVI	No	49 (64.5)	20 (83.3)	29 (55.8)
	yes	27 (35.5)	4 (16.7)	23 (44.2)

ACT = Patients got adjuvant chemotherapy

Table 2. Effect of different factors including age, tumor size, KI67, grade, PNI, LVI, and ACT.

characteristic	3-year DFS		5-year DFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.02 (0.92-1.12)	0.67	0.99 (0.91-1.08)	0.94
Tumor size	1.94 (0.22-16.52)	0.54	2.4 (0.37-15.75)	0.35
Ki67	0.99 (0.91-1.09)	0.97	1.04 (0.93-1.07)	0.90
Grade	0.92 (0.39-2.14)	0.85	0.89 (0.17-4.63)	0.89
PNI	1.86 (0.2-16.6)	0.57	1.08 (0.21-5.61)	0.92
LVI	0.79 (0.1-4.78)	0.80	0.67 (0.15-3.02)	0.60
ACT	1.44 (0.24-8.66)	0.68	1.61 (0.36-7.23)	0.52

died. The 3-year-old and 5-year-old OS were 98.6% and 96.9%, respectively. The 3-year-old and 5-year-old OS in patients who receive adjuvant chemotherapy were 98% and 95.4%, and also in patients who didn't receive any adjuvant chemotherapy was 100%. As only 3 patients died during this study, the effect of mentioned factors on OS was not possible.

Discussion:

Breast cancer is the leading cause of cancer death worldwide, and distant recurrences are common and represent the leading cause of death in breast cancer.

micrometastatic breast cancer., breast cancer cells that have left the breast and local lymph nodes but have not yet formed obvious metastases, is treated with adjuvant therapy.

Even in those at low risk of recurrence, adjuvant systemic therapies, including endocrine therapy, anti-HER2 therapy, and chemotherapy, are beneficial in reducing the risk of distant and local recurrence.

Regardless of age, nodal status, or estrogen receptor status (ER), adjuvant chemotherapy prolongs disease-free survival (DFS) and overall survival (OS).

However, systemic chemotherapy treatment appear to be most beneficial for patients with triple-negative and HER2-positive breast cancer.

Incidentally, when choosing the best treatment plan for adjuvant chemotherapy in HER2-negative patients, recommended treatment suggestions should be based on, recurrence risk, potential toxicity, and comorbidities.

In this study, overall survival and disease-free survival were studied in patients with breast cancer with receptor-positive hormone and HER2-negative and no lymph nodes who got chemotherapy compared to those who did not. There was no factor affecting 3-year and 5-year DFS and OS in this study. And adjuvant chemotherapy makes no difference from hormone therapy.

In the same study, 136 patients with luminal A breast cancer were studied, with 104 patients have got chemotherapy and 32 patients having received only hormone therapy. DFS in the 10 -years was 85 % in the chemotherapy group and 96 % in the non -chemotherapy group and OS was 88 % in the chemotherapy group and 100 % in the non -chemotherapy group.

In another similar study, 140 patients with luminal A breast cancer were studied, with 116 patients have got only hormone therapy and 24 patients having received only chemotherapy. DFS in the 10 -years was 84 % in the chemotherapy group and 95 % in the non -chemotherapy group and OS in the 10- years was 94 % in the chemotherapy group and 97 % in the hormone therapy group which the difference was not meaningful like our study.[14]

In another study performed on 1580 patients with luminal A type, 878 patients were in group N0, of which 322 patients received hormone therapy and 556 patients received adjuvant chemotherapy. OS and DFS (5 years) were not significantly different between the two groups.[14 15]

In the International Breast Cancer Study 4,105 patients

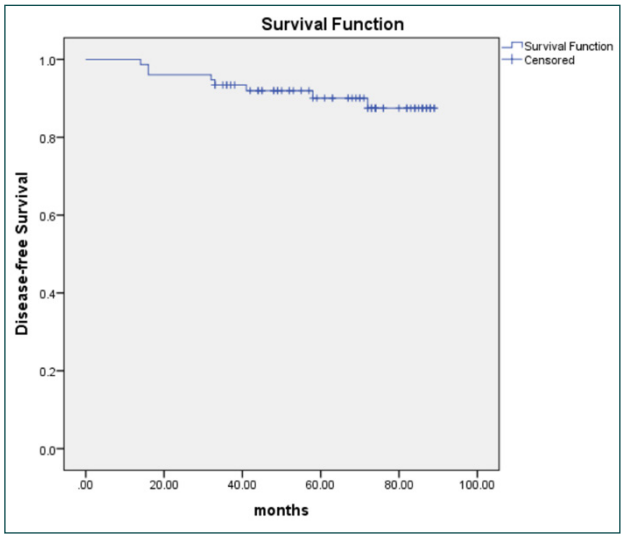

Figure 1. disease-free survival in studied patients

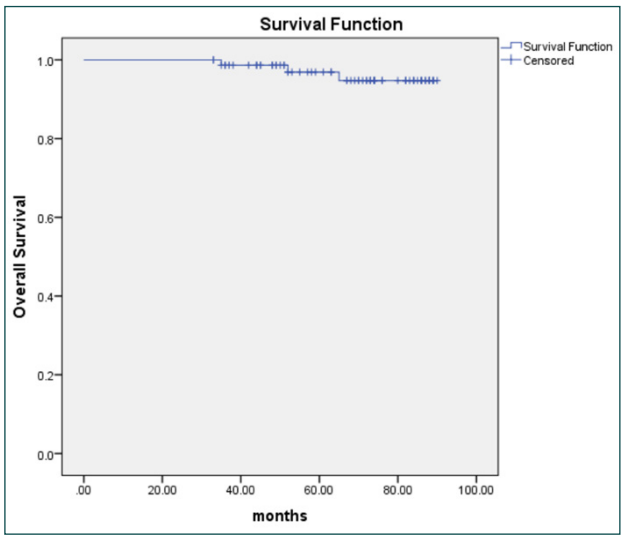

Figure 3. the overall survival rate

have studied with Annualized hazards, disease-free survival, and overall survival for ER-positive patients for the entire group, the annualized hazard of recurrence was highest during the first 5 years (10.4%), with a peak between years 1 and 2 (15.2%) in patients with estrogen receptor (ER) – positive disease compared to ER-negative patients. However, beyond 5 years, patients with ER-positive disease had higher hazards (5 to 10 years: 5.4% v 3.3%; 10 to 15 years: 2.9% v 1.3%; 15 to 20 years: 2.8% v 1.2%; and 20 to 25 years: 1.3% v 1.4%; P < .001) so patients with ER-positive disease had a higher chance of

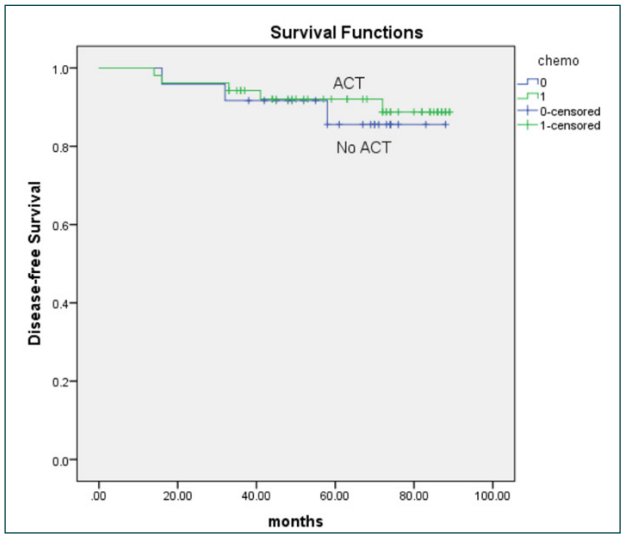

Figure 2. disease-free survival in adjuvant chemotherapy received by patients

recurrence. Despite our study, DFS and OS 5 years were 90 % and 96.9% in ER-positive patients. So according to this study, patients with ER-positive breast cancer had a significant recurrence rate during follow-up and should follow up more than 5 years despite our study.[16]

In another study, 7635 patients underwent surgery for breast cancer. And the 5-year DFS was worse in the non-endocrine therapy group (78%) than the endocrine therapy group (95%) in the T1c stage. However, there was no significant difference in DFS between the ET and the non-ET groups in T1a like in our study and T1b patients (ET 96% vs non-ET 93%) breast cancer. Despite our study, the OS of the patients was better in endocrine therapy in the T1c group, but the same as we, OS had no difference in the T1a and T1b groups.

In the other study about 207404 cases of Luminal A type breast cancer in the early stage were studied, and divided into a chemotherapy group and a non-chemotherapy group. The cumulative risk curve and survival time of the two groups were compared. And the same as our result there was no significant difference in chemotherapy treatment decision unless for N1mi staging of lymph node metastasis. in which adjuvant chemotherapy should be considered. [17]

Despite our study, in the other study, 464 patients under age 40 who underwent adjuvant chemotherapy had

more unfavorable features, and the results were not agreeable with our study like significant OS benefits from aCT. But, DFS did not reach statistical significance in their group. [18]

A retrospective study included 1054 luminal breast cancer patients with lymph node metastasis, Overall survival (OS) and disease-free survival (DFS) were compared between patients in the short and long time interval for adjuvant chemotherapy. Like our study, there was no difference in OS and DFS between patients with long and short TI but it has shown that age, N stage, and tumor size were significant predictors of DFS. A short TI was associated with better DFS than a long TI. but in small tumors like ours, there was no significant difference in DFS even when a lymph node was involved. So the size of the tumor role an important play in DFS rather than short or long time intervals. [19 20]

In another study, chemotherapy was studied in pre-menopausal and post-menopausal patients with early-stage luminal breast cancer and it showed that pre-menopausal patients had a higher risk stratification and should receive more through therapy rather than hormone therapy alone. Like our study, it said that in lower-risk patients hormone therapy must be sufficient.[21] [20]

In our trial, some limitations should be acknowledged. The study closed early and the planned sample size was not reached, so the statistical power is reduced , on the other hand , the heterogeneity of some molecular aspects such as the intensity and strength of hormonal receptors and the different grade and vascular invasion of tumors can lead to some minor changes in the power of study . By the way, choosing the best adjuvant chemotherapy treatment plans should be based on the Recurrence risk, possible toxicity, and Comorbidities. [22 23]

Conclusion:

In conclusion, according to other studies, other factors like classic clinicopathologic features and newer gene expression assays can help in making a treatment decision, rather than the factors we consider in our study. and also the longer surveillance(more than five years) may help the treatment decision by differing in the DFS and OS.

Declarations:

1. Funding: No funding was used to support this study

2. Conflicts of interest/Competing interests: The authors declare that there is no conflict of interest to declare.

3. Ethics approval: In this study, no additional costs were imposed on the patients. We maintained the patient's privacy, and their written consent was obtained.

4. Consent to participate: The patients had consented to participation in this article.

5. Consent for publication: The participants had consented to the publication of this article.

6. Availability of data and material: The data that support the findings of this study are available from the corresponding author, [EK], upon reasonable request.

7. Code availability (Not applicable)

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