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Studying the Influence of Time to Initiate Chemotherapy on Survival in Non-Metastatic Breast Cancer

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Abstract: **The adjuvant chemotherapy in breast cancer has an established role in the management, it is administered a few weeks after breast surgery. However, there is no evidence about the optimum time of initiation of treatment.**

Aim: To evaluate the influence of timing of initiation of the adjuvant chemotherapy over survival in non-metastatic breast cancer.

Materials and Methods: This retrospective study was conducted at Oncology Department, Tishreen university Hospital in Lattakia, Syria. The study enrolled breast cancer patients (from 2010 to 2013) with stages I–III, treated with surgery and adjuvant chemotherapy. Data were gathered about prognostic factors such as age, tumor size, histological grade, lymph nodes involvement, hormonal receptor status and human epidermal growth factor 2 . The time interval between surgery and initiation of chemotherapy, and dates of relapse and death were recorded. Patients were assigned in three groups according to the surgery-chemotherapy interval: < 4 weeks, 4-8 weeks, >8 weeks.

Results: The study enrolled 299 patients, with a mean age of 53.6 years (age range: 32 – 82 years) . IDC was the most common breast cancer type (90%), the rest of cases were ILC (10%). 93.6% of study patients had mastectomy, 6.4% had partial breast surgery. Positive estrogen receptor breast cancer represented the most cases (75.5%) . 32.3% of cases were Her2 positive. There were no differences in 5-year overall survival (OS), according to the timing of initiation of adjuvant chemotherapy. Longer delay of initiation of adjuvant chemotherapy (<4 weeks versus >8 weeks) and moderate delay (<4 weeks versus 4-8 weeks) significantly decreased the DFS (HR of 2.7; 95% CI, 1.7 – 4.2) and (HR of 1.61 ; 95% CI, 1.18 – 2.2) respectively .

We further investigated the effect of time to adjuvant chemotherapy on disease free survival according to subtypes. Earlier initiation of adjuvant chemotherapy was associated with better5 – year DFS in patients with ER+/Her2- and ER-/Her2+ tumors.

Conclusion: Longer delay of adjuvant chemotherapy was associated with worse Disease free survival and early initiation of adjuvant chemotherapy should be performed for patients with some aggressive tumor subtypes.

Keywords: **breast cancer, adjuvant chemotherapy, timing of chemotherapy, overall survival.**

1. INTRODUCTION

Breast cancer is the most common malignancy in females , and the second most common cause of cancer deaths in women after lung cancer in developed countries, but in developing countries is the leading cause of cancer deaths in women [1] [2]. The treatment of breast cancer requires the cooperation of many specialists such as surgeon, oncologist , radiation oncologist , radiologist and pathologist. In addition, a plastic surgeon may be involved in rebuilding the breast tissue if the patient's breast is removed.

Breast cancer prognosis is determined by a wide range of clinical and pathological factors such as axillary lymph nodes involvement , which is the most important prognostic factor [3]. Estrogen receptors are an important marker . Positive estrogen receptor (ER +) Breast cancers tend to have a good histological differentiation and they are the main indication of hormonal therapy and represent a better prognosis [4] [5]. Human epidermal growth factor receptor – 2 (Her-2) positivity represents a bad prognosis , as it is associated with more aggressive and chemically resistant tumors [6]. There is a consensus on the significance of tumor size when measured microscopically and not grossly. The smaller the tumor, the better the prognosis . There is no significant prognostic difference between invasive ductal carcinoma and invasive lobular carcinoma, but some studies suggest that invasive ductal carcinoma responds better to chemotherapy. The greater the tissue grade (Nottingham score) [7], the worse the prognosis.

Chemotherapy has a key role in breast cancer management and has become a standard clinical practice. It increases the disease free survival (DFS) and the overall survival (OS) in patients with or without axillary lymph nodes involvement. Chemotherapy is usually given after several weeks of breast surgery. There is no evidence of the ideal timing for initiating chemotherapy after breast surgery. Results differ between studies made to determine the effect of the timing of initiation of postoperative chemotherapy over breast cancer prognosis .

In a study published in the Journal of Clinical Oncology in 2014, 6827 patients from the Anderson Cancer Center in Texas were included (Gagliato et al) [8] , OS and DFS were studied, patients were divided by the timing of initiation of chemotherapy after surgery into 3 groups: ($\leq$ 30 days, 31- 60, $\geq$ 61 days) . The study found that initiation of chemotherapy after $\geq$ 61 days was associated with worse results in breast cancer patients with stage II and III . Patients with triple-negative tumor type and Her2 positive tumors treated with Trastuzumab had bad results when starting the treatment $\geq$ 61 days after surgery . They confirmed that early initiation of postoperative chemotherapy is particularly beneficial for patients with stage III, triple-negative tumor type and Her2 positive tumors. This may be due to the intense aggressiveness and tendency to infiltrate of these patterns.

Another study published in the Journal of Oncology in 2006 included 2594 patients with stage I and II breast cancer at the British Columbia Center between 1989-1998 (Lohrisch et al) [9] , OS and DFS rates were studied ,patients were divided by the timing of initiation of chemotherapy after surgery into 4 groups: ($\leq$ 4 weeks, 4-8, 8-12, >12-24 weeks) . No effect over the OS or DFS rates was found regardless of the timing of initiation of chemotherapy.

Based on the importance of determining the optimal time to initiate chemotherapy in breast cancer, this study was conducted to investigate the effect of the timing of initiation of chemotherapy after breast surgery over the disease free survival rate and overall survival rate within 5 years in the various subsets of non-metastatic breast cancer in patients attending Oncology Department at Tishreen University Hospital in Lattakia.

This research aims to:

- Determine the demographic, clinical and histological characteristics of breast cancer patients included:(age, tumor size, lymph node involvement , histological type, histological grade, hormone receptor and Her2 receptor status , and the type of surgery .

- Determine the time interval between surgery and initiation of chemotherapy.

- Determine the patients outcomes and prognosis within 5 years of diagnosis of the disease.

- Determine DFS and OS within 5 years.

- Study the relationship between the period of time between surgery and chemotherapy on the one hand, and DFS and OS on the other.

Study population:

This is a retrospective study conducted in Oncology Department at Tishreen University Hospital during the period between march 2017 –march 2018.

Inclusion criteria:

- Patients diagnosed with non-metastatic breast cancer (stage I-II-III). - Patients who are surgically treated either by mastectomy or partial breast surgery.

- Chemically treated patients after surgery (adjuvant chemotherapy).

Exclusion criteria:

- Breast cancer in males.

- Patients with stage IV breast cancer .

- Lack of full information regarding: tumor details in size, histological grade, hormonal receptor and Her2 status .

- Failure to document the time between surgery and chemotherapy.

- Lack of information documenting patients' condition after 5 years of diagnosis in terms of recurrence or death.

- Patients who received pre-operative chemotherapy (neoadjuvant chemotherapy).

- Patients who received hormonal therapy alone without chemotherapy.

The final study sample consisted of 299 patients diagnosed with non-menstrual breast cancer from those who underwent the surgery and received chemotherapy .

2. METHODS AND MATERIALS

Back to the archive of patients diagnosed with non-metastatic breast cancer, who underwent surgery and chemotherapy after that, and who met the inclusion criteria of the study, in the Department of Oncology at the University of October between 2010-2013.

Information on prognostic factors was collected and documented as follows:

Age of patients: We divided the patients by age into two groups, patients younger than 40 years and patients aged 40 years and above.

Tumor size: We classified patients according to the size of the tumor and its infiltration to the skin and chest wall into 4 groups according to the TNM system [10]:

T1: tumor maximum diameter $\leq$ 2 cm

T2: tumor maximum diameter >2 cm but $\leq$ 5 cm

T3: tumor maximum diameter > 5 cm

T4: tumor of any size, with direct spread to the chest wall, or just the skin

Lymph node involvement: We classified patients with lymph nodes injury to 4 groups as follows:

N0: No local lymph nodes involvement

N1: 1 – 3 lymph nodes involved

N2: 4 – 9 lymph nodes involved

N3: $\geq$ 10 lymph nodes involved

Histological type of breast cancer

Histological grade of breast cancer: We classified patients according to the histological score of breast cancer Nottingham Histologic Score [7] into three groups: Grade I (G1) , Grade II (G2) , and Grade III (G3) .

Hormonal and human epidermal growth factor -2 receptors status: We classified patients according to the state of the hormonal and Her2 receptors status into 4 groups:

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ER + / Her2 +

ER + / Her2 –

ER - / Her2 +

ER - / Her2 –

Type of surgical operation: We classified patients into two groups: Complete mastectomy and partial breast surgery .

Period of time between surgery and chemotherapy: We classified patients into 3 groups: < 4 weeks , 4 - 8 weeks , and > 8 weeks

Results and outcomes of the treatment were reviewed within 5 years of diagnosis of cancer. Recurrence, type of recurrence and the interval in which it occurred were documented , as well as documentation of the deaths within 5 years and the time interval during which they occurred.

Statistics:

The analysis was carried out using SPSS (version 20) and Excel 2010. The predictive value less than 0.05 (P value <0.05) was considered statistically significant. To characterize the sample in the descriptive variables: We relied on the percentages and graphs (Pie chart) and Bar chart. In continuous quantitative variables: Scattering parameters (mean, standard deviation, domain) were used.

For the statistical relations test, we used the following statistical methods:

Basal differences in the pathological variables between the groups were tested using the Chi-square test and expressed as "X2" for the class variables.

We calculated the disease free disease (DFS): from the date of surgery (not surgical diagnostic biopsy) and until the occurrence of any of the following: recurrence in any place, second primary breast tumor, or Death.

Overall Survival (OS): From the date of surgery until death for any reason or to the last follow-up visit.

The Kaplan-Meier method was used for 5-year DFS and 5-year OS for 95% confidence interval (95% CI) for all patients according to the date of initiation of post-operative chemotherapy, As well as according to tumor characteristics (tumor size, lymph node injury, tumor receptor condition).

The categories were compared using the log-rank method.

3. RESULTS

The study included 299 patients, with mean age of 53.6 ± 10.7 years, ages ranged from 32 to 82 years.

The mean time interval between surgery and initiation of chemotherapy was 25.8 ± 12 days, ranging from 6 - 90 days. 184 patients (61.5%) received chemotherapy in < 4 weeks after surgery, 107 patients (35.8%) in 4-8 weeks after surgery, and 8 patients (2.7% %) in > 8 weeks of surgery.

Table (1) shows the clinical, histological, and pathological characteristics of breast cancer patients.

Variables		Number of cases	Percent (%)
Age	< 40 years old	20	% 6.7
	≥ 40 years old	279	%93.3
Tumor histological type	IDC	269	%90
	ILC	30	%10
Primary tumor size	T1	55	%18.4
	T2	159	%53.2
	T3	66	%22
	T4	19	%6.4

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Lymph nodes involvement	N0	85	%28.4
	N1	69	%23.1
	N2	89	%29.8
	N3	56	%18.7
Surgery	Mastectomy	280	%93.6
	Partial breast surgery	19	%6.4
Histological differentiation	Grade 1	18	%6
	Grade 2	188	%62.9
	Grade 3	93	%31.1
Tumor receptor status	ER+/ HER2-	66	%22
	ER+/ HER2+	160	%53.5
	ER- / HER2+	31	%10.3
	ER- / HER2-	42	%14.2

There was no significant difference in the clinical, histological, and pathological characteristics of breast cancer patients among different groups classified by the chemotherapy initiation period as shown in Table 2.

Table (2): Relationship between variables and time intervals

Variables		< 4 weeks		4 – 8 weeks		> 8 weeks		X^2- test	P-value
		N	%	N	%	N	%		
Age	< 40 years old	16	%8.7	4	%3.7	0	%0	3.253	0.196
	≥ 40 years old	168	%91.3	103	%96.3	8	%100		
Tumor histological type	IDC	168	%91.3	93	%87	8	%100	2.36	0.307
	ILC	16	%8.7	14	%13	0	%0		
Primary tumor size	T1	34	%18.5	18	%16.8	3	%37.5	3.125	0.793
	T2	100	%54.3	56	%52.3	3	%37.5		
	T3	38	%20.7	26	%24.3	2	%25		
	T4	12	%6.5	7	%6.6	0	%0		
Lymph nodes involvement	N0	47	%25.5	38	%35.5	0	%0	9.136	0.16
	N1	40	%21.7	27	%25.2	2	%25		
	N2	58	%31.5	27	%25.2	4	%50		
	N3	39	%21.3	15	%14.1	2	%25		
Surgery	Mastectomy	170	%92.4	102	%95.3	8	%100	1.538	0.463
	Partial breast surgery	14	%7.6	5	%4.7	0	%0		
Histological differentiation	G1	13	%7	4	%3.7	1	%12.5	3.702	0.447
	G2	116	%63	69	%64.5	3	%37.5		
	G3	55	%30	34	%31.8	4	%50		
Tumor receptor status	ER+/ HER2+	44	% 24	21	%19.6	1	%12.5	11.76	0.067
	ER+/ HER2-	106	%57.6	49	%45.8	5	%62.5		
	ER- / HER2+	14	%7.6	17	%15.9	0	%0		
	ER- / HER2-	20	%10.8	20	%18.7	2	%25		

During the 5-year follow-up period, 105 patients (35%) experienced recurrence . Ie, the number of patients who completed 5 years of follow-up without the recurrence is 194 patients. **The 5 -Year DFS is 65% (95% CI: 0.59 - 0.7).**

Table (3) shows a 5-year survival comparison between patients according to the starting time of chemotherapy. Figure (1) shows the Kaplan-Meier plot of 5-year DFS according to the period of initiation of chemotherapy.

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Table (3): 5 –year DFS according to time intervals between chemotherapy and surgery

Outcomes after 5 years of following	< 4 weeks	4 – 8 weeks	> 8 weeks	P (log-rank)
Total number	184	107	8	0.007
Recurrence	51	48	6	
No Recurrence	133	59	2	
5-year DFS	%72.2	% 55	%25	
95% CI	0.65 – 0.78	0.45 – 0.64	0.04 – 0.64	

Table (4) shows a comparison of the effect of chemotherapy initiation time on 5 – year disease free survival .

Table (4): Chemotherapy timing effect on 5 –year DFS

	< 4 weeks VS 4-8 weeks		P –value	< 4 weeks VS > 8 weeks		P –value
	HR	%95 CI		HR	%95 CI	
5-year DFS	1.61	1.18 – 2.2	0.002	2.7	1.7 – 4.2	<0.0001

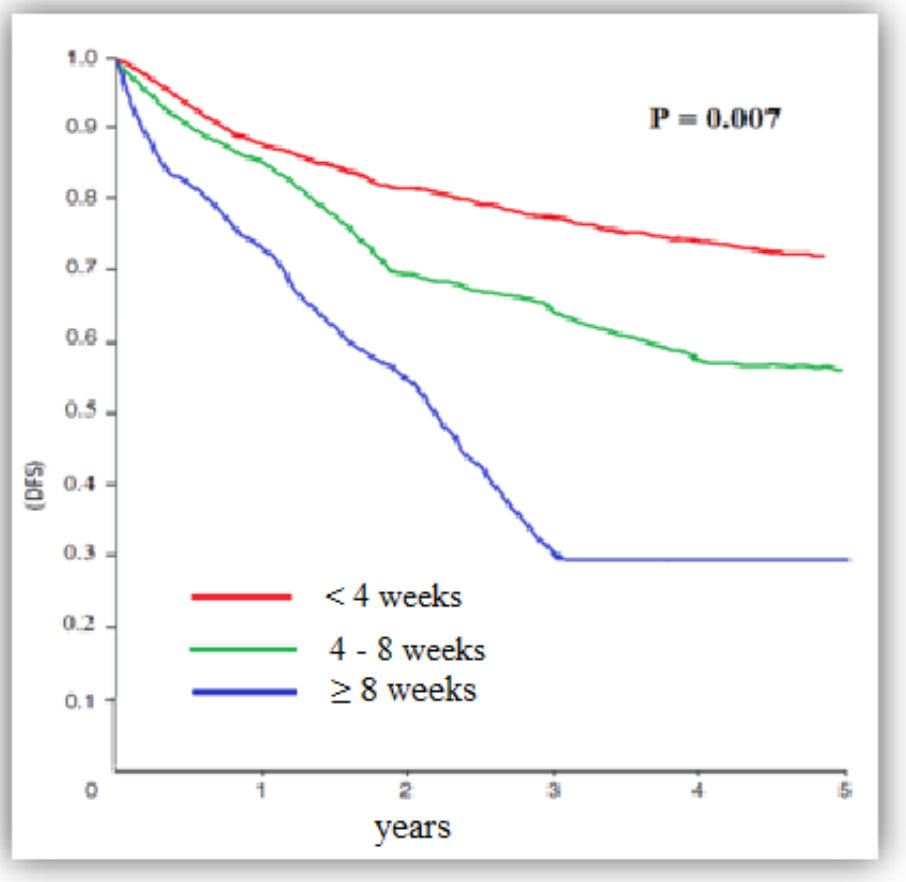

Figure (1) the Kaplan-Meier plot of 5-year DFS according to the period of initiation of chemotherapy

57 patients (19%) died during the 5 years follow-up period . That is , 242 patients remained alive after 5 years of diagnosis of breast cancer and therefore a **5-year OS is 81% (95% CI: 0.76- 0.85).**

Table (5) shows a comparison of 5-year OS among patients by the start-up time of chemotherapy. Figure (2) shows the Kaplan-Meier plot of 5-year OS according to the period of initiation of chemotherapy.

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Table (5): 5 –year OS according to time intervals between chemotherapy and surgery

Outcomes after 5 years of following	< 4 weeks	4 – 8 weeks	> 8 weeks	P (log-rank)
Total number	184	107	8	0.251
Death	31	23	3	
No Death	153	84	5	
5-year OS	%83.2	%78.5	%65.5	
95% CI	0.76 – 0.88	0.69 – 0.85	0.26 – 0.89	

Table (6) shows a comparison of the effect of chemotherapy initiation time on 5 – year overall survival .

Table (6): Chemotherapy timing effect on 5 –year OS

	< 4 weeks VS 4-8 weeks		P –value	< 4 weeks VS ≥ 8 weeks		P –value
	HR	%95 CI		HR	%95 CI	
5-year OS	1.275	2 – 0.78	0.32	2.22	5.75 – 0.86	0.098

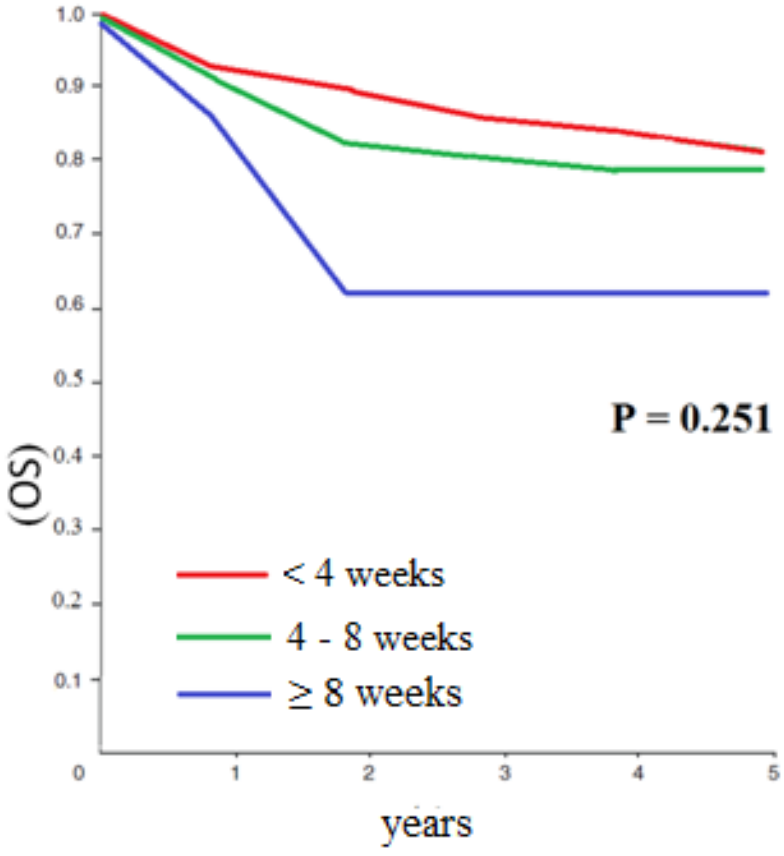

Figure (2) the Kaplan-Meier plot of 5-year OS according to the period of initiation of chemotherapy

The effect of tumor size at diagnosis, lymph nodes involvement and tumor receptor status were studied over both 5-year DFS (Table 7) and 5-year OS (Table 8)

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Table (7): 5-year DFS according to tumor size, lymph nodes involvement and tumor receptors status

Variables		Number of cases	Recurrence cases	5-year DFS	95% CI	P (log-rank)
Tumor size	T1	55	7	%87.2	0.74 – 0.94	0.0000
	T2	159	40	%74.8	0.67 – 0.81	
	T3	66	42	%36.3	0.25 – 0.49	
	T4	19	16	%15.7	0.04 – 0.4	
Lymph nodes involvement	N0	85	20	%76.5	0.65 – 0.84	0.0042
	N1	69	21	%69.5	0.57 – 0.79	
	N2	89	35	%60.6	0.49 – 0.7	
	N3	56	29	%48.2	0.34 – 0.61	
Tumor Receptors status	ER+/ HER2-	160	42	%73.7	0.66 – 0.8	0.000
	ER+/ HER2+	66	16	%75.7	0.63 – 0.85	
	ER- / HER2+	31	21	%32.3	0.17 – 0.51	
	ER- / HER2-	42	26	%38	0.24 – 0.54	

Table (8): 5-year OS according to tumor size , lymph nodes involvement and tumor receptors status

Variables		Number of cases	Death cases	5-year OS	95% CI	P (log-rank)
Tumor size	T1	55	5	%90	0.79 – 0.96	0.0000
	T2	159	19	%88	0.81 – 0.92	
	T3	66	20	%69.6	0.56 – 0.8	
	T4	19	13	%31.5	0.13 – 0.56	
Lymph nodes involvement	N0	85	9	%89	0.8 – 0.94	0.001
	N1	69	10	%85.5	0.74 – 0.92	
	N2	89	18	%79.7	0.69 – 0.78	
	N3	56	20	%64	0.5 – 0.76	
Tumor Receptors status	ER+/ HER2-	160	20	%87.5	0.81 – 0.92	0.0197
	ER+/ HER2+	66	12	% 81.8	0.7 – 0.89	
	ER- / HER2+	31	10	%67.7	0.48 – 0.82	
	ER- / HER2-	42	15	% 64.2	0.47 – 0.78	

The effect of tumor size at diagnosis, lymph nodes involvement and tumor receptor status were studied over both 5-year DFS (Table 7) and 5-year OS (Table 8)

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Table (9): Comparing survival according to some prognostic markers

	(5 –year DFS)			(5 –year OS)		
	HR	%95 CI	P value	HR	%95 CI	P value
T1 VS T2	1.97	0.94 – 4.1	0.07	1.4	0.56 – 3.6	0.45
T1 VS T3	5	2.4 – 10.2	<0.0001	3.6	1.45 – 9	0.0057
T1 VS T4	6.6	13.5 – 3.2	<0.0001	8.2	3.36 – 20	<0.0001
N0 VS N1	1.21	0.7 – 2	0.7	1.36	0.58 – 3.1	0.46
N0 VS N2	1.57	0.99 – 2.4	0.053	1.9	0.9 – 4	0.08
N0 VS N3	2	1.31 – 3.2	0.0017	3.37	1.6 – 6.8	0.0008
ER+/ HER2- VS ER+/ HER2-	0.93	0.56 – 1.5	0.8	1.38	0.71 – 2.6	0.337
ER+/ HER2- VS ER- / HER2+	1.94	1.26 – 2.97	0.002	3.63	2.1 – 6.1	> 0.0001
ER+/ HER2- VS ER- / HER2-	1.83	1.22 – 2.75	0.0032	2.36	1.3 – 4.3	0.004

We studied the effect of chemotherapy timing on prognosis according to tumor receptors status (Table 10), age (Table 11), tumor size (Table 12), lymph node involvement (Table 13) and histological grade (table 14) .

Table (10): Chemotherapy timing effect on survival according to tumor receptors status

Tumor receptors status \ Chemotherapy timing		< 4 weeks	4 – 8 weeks	> 8 weeks
ER+/ HER2-	Total number	106	49	5
	Recurrence cases	23	16	3
	Death cases	12	6	2
	5 – year DFS	%78.3	%67.3	%40
	5 – year OS	%88.7	%87.7	%60
ER+/ HER2+	Total number	44	21	1
	Recurrence cases	9	6	1
	Death cases	6	5	1
	5 – year DFS	%79.5	%71.4	%0
	5 – year OS	%86.3	%76.2	%0
ER- / HER2+	Total number	14	17	0
	Recurrence cases	8	13	-
	Death cases	4	6	-
	5 – year DFS	%42.8	%23.5	-
	5 – year OS	%71.4	%64.7	-
ER- / HER2-	Total number	20	20	2
	Recurrence cases	11	13	2
	Death cases	9	6	0
	5 – year DFS	%45	%35	%0
	5 – year OS	%55	%70	%100

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Table (11): Chemotherapy timing effect on survival according to patients age at diagnosis

Patient age \ Chemotherapy timing		< 4 weeks	4 – 8 weeks	> 8 weeks
< 40 years	Total number	16	4	0
	Recurrence cases	9	3	-
	Death cases	7	1	-
	5 – year DFS	%43.7	%25	-
	5 – year OS	%56.2	%75	-
≥ 40 years	Total number	168	103	8
	Recurrence cases	42	45	6
	Death cases	24	20	3
	5 – year DFS	%75	%56.3	%25
	5 – year OS	%85.7	%80.5	%62.5

Table (12): Chemotherapy timing effect on survival according to primary tumor size

Tumor size \ Chemotherapy timing		< 4 weeks	4 – 8 weeks	> 8 weeks
T1	Total number	34	21	0
	Recurrence cases	4	3	-
	Death cases	3	2	-
	5 – year DFS	%71.6	%85.7	-
	5 – year OS	%91.1	%90.4	-
T2	Total number	100	53	6
	Recurrence cases	17	18	4
	Death cases	10	7	2
	5 – year DFS	%83	%66	%33.3
	5 – year OS	%90	%86.7	%66.6
T3	Total number	40	24	2
	Recurrence cases	22	19	2
	Death cases	13	6	1
	5 – year DFS	%45	%21	%0
	5 – year OS	%67.5	%75	%50
T4	Total number	10	9	0
	Recurrence cases	8	8	-
	Death cases	6	7	-
	5 – year DFS	%20	%11.1	-
	5 – year OS	%40	%22.2	-

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Table (13): Chemotherapy timing effect on survival according to lymph nodes involvement

Lymph node involvement \ Chemotherapy timing		< 4 weeks	4 – 8 weeks	> 8 weeks
N0	Total number	57	25	3
	Recurrence cases	10	8	2
	Death cases	4	5	0
	5 – year DFS	%82.4	%68	%33.3
	5 – year OS	%92.9	%80	%100
N1	Total number	39	30	0
	Recurrence cases	10	11	0
	Death cases	7	3	0
	5 – year DFS	%74.3	%63.3	-
	5 – year OS	%82	%90	-
N2	Total number	54	32	3
	Recurrence cases	16	17	2
	Death cases	10	7	1
	5 – year DFS	%70.3	%46.8	%33.3
	5 – year OS	%81.4	%78.1	%66.6
N3	Total number	34	20	2
	Recurrence cases	15	12	2
	Death cases	10	8	2
	5 – year DFS	%55.8	%40	%0
	5 – year OS	%70.5	%60	%0

Table (14): Chemotherapy timing effect on survival according to tumor histological differentiation

Histological grade \ Chemotherapy timing		< 4 weeks	4 – 8 weeks	≥ 8 weeks
Grade 1	Total number	7	10	1
	Recurrence cases	1	2	1
	Death cases	0	2	1
	5 – year DFS	%85.7	%80	%0
	5 – year OS	%100	%80	%0
Grade 2	Total number	123	62	3
	Recurrence cases	30	29	2
	Death cases	19	10	1
	5 – year DFS	%75.6	%53.2	%33.3
	5 – year OS	%84.5	%83.3	%66.6
Grade 3	Total number	54	35	4
	Recurrence cases	20	17	3
	Death cases	12	11	1
	5 – year DFS	%62.9	%51.4	%25
	5 – year OS	%77.7	%68.5	%75

Table 15 compares groups of patients by the timing of initiation of chemotherapy over 5-year disease free survival according to the prognostic markers (tumor receptor status, age, primary tumor size, lymph node involvement, histological grade).

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Table (15): comparison of chemotherapy timing effect on 5-year DFS according to prognostic markers

Variables	< 4 weeks VS 4-8 weeks		P value	< 4 weeks VS > 8 weeks		P value
	HR	%95 CI		HR	%95 CI	
ER+/ HER2-	1.5	0.87 – 2.5	0.138	2.76	1.24 – 6.1	0.0129
ER+/ HER2+	1.39	0.57 – 3.4	0.46	4.8	2.7 – 8.7	<0.0001
ER- / HER2+	1.3	0.79 – 2.26	0.27	-	-	-
ER- / HER2-	1.18	0.7 – 1.9	0.52	1.8	1.2 – 2.7	0.0031
< 40 years old	1.33	0.65 – 2.71	0.428	-	-	-
≥ 40 years old	1.74	1.2 – 2.45	0.001	3	1.8 – 4.8	<0.0001
T1	1.21	0.3 – 4.9	0.785	-	-	-
T2	1.96	1.1 – 3.4	0.0216	3.92	1.9 – 7.9	0.0002
T3	1.43	1 – 2	0.0399	1.81	1.37 – 2.4	<0.0001
T4	1.1	0.775 – 1.6	0.59	-	-	-
N0	1.8	0.81 – 4	0.141	3.8	1.4 – 10.1	0.0075
N1	1.43	0.7 – 2.9	0.324	-	-	-
N2	1.79	1 – 3	0.029	2.25	0.91 – 5.5	0.077
N3	1.36	0.8 – 2.28	0.247	2.26	1.5 – 3.3	<0.0001
Grade 1	1.4	0.15 – 12.6	0.764	7	1.14 – 42.9	0.035
Grade 2	1.91	1.27 – 2.8	0.008	2.73	1.15 – 6.4	0.021
Grade 3	1.3	0.8 – 2.13	0.275	2	1 – 3.9	0.037

Table (16) compares groups of patients by the timing of initiation of chemotherapy over 5-year overall survival according to the prognostic markers (tumor receptor status, age, primary tumor size, lymph node involvement, histological grade).

Table (16): comparison of chemotherapy timing effect on 5-year OS according to prognostic markers

Variables	< 4 weeks VS 4-8 weeks		P value	< 4 weeks VS > 8 weeks		P value
	HR	%95 CI		HR	%95 CI	
ER+/ HER2-	1	0.43 – 2.7	0.86	3.5	1 – 11.7	0.039
ER+/ HER2+	1.7	0.6 – 5	0.3	7.3	3.4 – 15.4	<0.0001
ER- / HER2+	1.23	0.43 – 3.5	0.69	-	-	-
ER- / HER2-	0.66	0.29 – 1.5	0.33	3.6	0.02 – 4.8	0.44
< 40 years old	0.57	0.09 – 3.4	0.539	-	-	-
≥ 40 years old	1.35	0.79 – 2.3	0.265	2.62	0.99 – 6.9	0.05
T1	1.1	0.19 – 5.9	0.93	-	-	-
T2	1.32	0.5 – 3.27	0.54	3.33	0.93 – 11.9	0.064
T3	0.76	0.33 – 1.75	0.53	1.53	0.35 – 6.59	0.56
T4	1.29	0.7 – 2.39	0.4	-	-	-
N0	2.85	0.83 – 9.7	0.094	1.61	0.1 – 24.9	0.733
N1	0.55	0.15 – 1.9	0.365	-	-	-
N2	1.18	0.49 – 2.79	0.704	1.8	0.33 – 9.8	0.496
N3	1.36	0.64 – 2.87	0.420	3.4	2 – 5.7	<0.0001
Grade 1	3.63	0.2 – 65.8	0.382	12	0.72 – 19.7	0.082
Grade 2	1	0.51 – 2.1	0.9	2.15	0.41 – 11.2	0.361
Grade 3	1.41	0.7 – 2.8	0.972	1.12	0.19 – 6.6	0.896

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4. DISCUSSION

The exact timing of initiation of chemotherapy for the best benefit associated with survival remains controversial. Previous published clinical studies have not suggested the ideal time to start chemotherapy, and there is a significant variation in the time between surgery and initiation of chemotherapy.

This retrospective study included 299 patients with non-malignant breast cancer. The mean age of patients was 53.6 years, ages ranged from 32 to 82 years. Patients aged 40 years and above accounted for 93.3%.

The mean time interval between surgery and chemotherapy was 25.8 days for patients, ranging from 6 to 90 days. The study showed that 97.3% of non-malignant breast cancer patients in the Oncology Department at Tishreen University Hospital received adjuvant chemotherapy within two months of surgery. Most of the cancers (90%) were invasive ductal carcinoma (IDC), while invasive lobular carcinoma (ILC) accounted for the remaining 10%. The vast majority of patients (93.6%) underwent complete mastectomy and the rest(6.4%) had a partial breast surgery .

The majority of cancers (75.5%) were positive estrogen receptors , and Her2 positive tumors accounted for 32.2% . When patients were divided into 3 categories according to the starting date of postoperative chemotherapy (< 4 weeks, 4-8 weeks, >8 weeks), we did not find any significant difference in the prognostic clinical and pathological characteristics of breast cancer (age, tumor size, Histological type, histological grade, surgical type, hormonal receptor status) among the three groups (P> 0.05).

During the 5-year follow-up of patients , recurrence occurred in 35% of the patients and the 5 -Year DFS was 65% (95% CI: 0.59 - 0.7). 19% of the patients died and the overall survival rate for 5 years (5 - year OS) was 81% (95% CI: 0.76 - 0.85).

In the group of patients who received chemotherapy within < 4 weeks of surgery, 5-year DFS was 72.2%, and 5-year OS was 83.2%.

In the group of patients who received chemotherapy within 4 to 8 weeks of surgery, 5-year DFS was 55%, and5-year OS was 78.5%.

In the group of patients who received chemotherapy > 8 weeks of surgery: 5-year DFS was 5%, and 5-year OS was 62.5%.

The study showed a statistically significant relationship between the period of initiation of postoperative chemotherapy and 5-year DFS (P = 0.007) and non- significant relationship between the timing of initiation of chemotherapy and 5-year OS (P> 0.05).

Our study concluded that early initiation of chemotherapy (< 4 weeks after surgery) significantly reduces the recurrence rate within 5 years and also reduces mortality but not statistically significant compared with initiation of chemotherapy within 4-8 weeks and > 8 weeks of surgery.

The results of our study is consistent with Lohrisch et al. [9] in the United States in 2006.

The results of our study differ with other studies. In 2007, Sanchez et al. [11] in Spain showed no correlation between timing of chemotherapy after surgery and prognosis . There was no statistically significant relationship between the period of initiation of postoperative chemotherapy (1-3 weeks, 3-6 weeks, 6-9 weeks, >9 weeks) and DFS (P = 0.28). There was also no statistically significant association between the period of initiation of postoperative chemotherapy and overall survival (P = 0.138)

S Cold et al. [12] in Denmark in 2005 also noted that there was no relationship between the timing of initiation of chemotherapy after surgery and prognosis of breast cancer.

Our study showed that the size of the primary tumor at diagnosis as well as the lymph node involvement are of the most important predictive factors of recurrence and mortality.

The higher the size of the primary tumor at diagnosis, the higher the risk of recurrence and mortality, especially in T3 and T4 tumors according to TNM system. The higher the number of lymph node involvement , the higher the risk of recurrence and mortality .

The results of our study confirmed that the tumor receptors (hormonal receptors and Her -2 receptor) status affects the prognosis of breast cancer. Positive estrogen receptor/negative Her-2 receptor (ER+/Her2-) breast cancers had the best 5-year OS (87.5%) and second best 5-year DFS rate (73.7%) , (ER-/Her2+) cancers had the worst 5-year DFS rate (32.8%), and (ER-/Her2-) cancers had the worst 5-year OS (64.2%). There was no difference in 5-year DFS or 5-year OS between (ER+/Her2-) and(ER+/Her2+) cancers . Negative estrogen receptor breast cancers are associated with a worse prognosis compared to (ER+/Her2-) cancers (P <0.05) .

We studied the effect of the timing of initiation of chemotherapy on prognosis (5-year DFS and 5-year OS) in patient classified according to tumor receptor status : Our study showed that for different tumor receptor status, early initiation of chemotherapy (< 4 weeks after surgery) , improves the prognosis with no statistical significance compared to starting chemotherapy within 4-8 weeks.

Early initiation of chemotherapy (< 4 weeks after surgery) significantly improves the prognosis compared to delayed initiation of chemotherapy (>8 weeks) in all tumor types after classification according to tumor receptors except for (ER-/Her2-).

In the study of (Ke-Da Yu et al.) [13] in China in 2016, they found that when chemotherapy was given early , prognosis was improved in triple-negative and Her2+ breast cancers.

(Colleoni et al.) [14] showed that early initiation of chemotherapy improves prognosis in negative estrogen receptor breast cancers patients but not positive estrogen receptor cancers.

(Gagliato et al.) [8] in the United States in 2014 indicated that delayed chemotherapy initiation was accompanied by a worse prognosis in negative estrogen receptors breast cancer patients.

The small number of breast cancer patients who received chemotherapy after > 8 weeks of surgery may be the cause of the unclear timing effect of chemotherapy on (ER-/Her2-) breast cancer patients .

In our study, no patient aged < 40 years had received chemotherapy after 8 weeks of surgery. There was no statistically significant difference in 5-year DFS or 5-year OS among patients aged < 40 years who received chemotherapy within 4 weeks compared to whom treated within 4-8 weeks of surgery. In breast cancer patients aged ≥ 40 years, initiation of chemotherapy within 4 weeks after surgery is associated with a 5-year DFS rate higher than initiation of chemotherapy within 4-8 weeks (P = 0.001) and higher than chemotherapy initiation After 8 weeks of surgery (P <0.0001), there was no statistically significant difference in the 5-year OS rates.

No patient with T1 breast cancer received chemotherapy after 8 weeks of surgery. There was no statistically significant difference in the 5-year DFS or 5-year OS among patients with T1 cancer who received chemotherapy within < 4 weeks compared to whom treated within 4-8 weeks of surgery.

In patients with T2 and T3 breast cancers, initiation of chemotherapy within < 4 weeks after surgery is associated with a 5-year DFS higher than initiation of chemotherapy within 4-8 weeks (P <0.05) and higher than chemotherapy initiation After 8 weeks of surgery (P <0.05), there was no statistically significant difference in 5-year OS.

No patient with T4 breast cancer had received chemotherapy after 8 weeks of surgery. There was no statistically significant difference in 5-year DFS or 5-year OS among patients with T4 cancer who received chemotherapy within 4 weeks compared to whom treated within 4-8 weeks of surgery.

Our study showed that in Grade 1 and Grade 3 breast cancers, there is no statistically significant difference in 5-yearDFS among patients who received chemotherapy within 4 weeks and who received treatment within 4-8 years weeks of surgery, while 5-year DFS was higher compared to those who received chemotherapy after > 8 weeks of surgery (P <0.05). There was no statistically significant difference in5-year OS between different groups. In Grade 2 breast cancer, the initiation of chemotherapy within 4 weeks after surgery was associated with a 5-year DFS higher than initiation of chemotherapy within 4-8 weeks (P = 0.008) and higher than initiation after > 8 weeks of surgery (P = 0.021), while there was no statistically significant difference in the 5-year OS among the different groups.

Our study showed that in breast cancer with N0, there was no statistically significant difference in the 5-year DFS among patients who received chemotherapy within 4 weeks and who received treatment within 4-8 weeks of surgery, while 5-year DFS is Higher than those who received chemotherapy after 8 weeks of surgery (P = 0.0075). No statistically significant difference in the 5-year OS was found among the different groups.

In breast cancer with N1, no patient had received chemotherapy after 8 weeks of surgery. There was no statistically significant difference in 5-year DFS or 5-year OS among patients who received chemotherapy within 4 weeks and compared to who received treatment within 4-8 weeks of surgery.

In breast cancer with N2, initiation of chemotherapy within 4 weeks after surgery was associated with a 5-year DFS higher than initiation of chemotherapy within 4 to 8 weeks (P = 0.029), while no significant difference was found compared to whom was treated after 8 weeks of surgery (P = 0.077). No statistically significant difference in the 5-year OS was found among the different groups. In breast cancer with N3, there was no statistically significant difference in the 5-year DFS among patients who received chemotherapy within 4 weeks and compared to whom were treated within 4 to 8 weeks of surgery, while 5-year DFS was higher than who received chemotherapy after 8 weeks of surgery (P <0.0001). There was no statistically significant difference in 5-year OS among patients who received chemotherapy within 4 weeks and who received treatment within 4-8 weeks of surgery, while 5-year OS was higher compared to those who received chemotherapy after 8 weeks of surgery (P <0.0001).

5. CONCLUSIONS

1. The vast majority of breast cancers in our patients are of invasive ductal carcinoma (IDC) (90%), positive estrogen receptor breast cancer counted of (75.5%) and Her2 positive breast cancer (32.2%).

2. The vast majority of patients (93.6%) underwent mastectomy . 97.3% of patients received adjuvant chemotherapy within 2 months of surgery.

3. During the 5 years follow-up period, 35% of the patients had recurrence and the 5 -Year DFS rate was 65%. 19% of patients had died and 5-year OS is 81%.

4 . The size of the primary tumor at diagnosis, lymph node involvement, and the status of tumor receptors are the most important prognostic factors in breast cancer.

5. Early initiation of chemotherapy (< 4 weeks after surgery) significantly reduces the recurrence rate within 5 years and also reduces mortality but not statistically significant compared with initiation of chemotherapy within 4-8 weeks and > 8 weeks of surgery.

6. Early initiation of chemotherapy (< 4 weeks) significantly improves prognosis compared with delayed initiation (>8 weeks) in all tumor types classified by tumor receptor except the pattern (ER-/Her-).

6. RECOMMENDATIONS

1. Since early initiation of chemotherapy (< 4 weeks) improves the 5-year DFS in breast cancer patients, we recommend starting chemotherapy during this time period.

2. One of the disadvantages of this study is the small number of patients who received chemotherapy > 8 weeks, so we recommend new studies on larger numbers of patients.

3. Further studies on the prognostic role of timing of chemotherapy according to the tumor receptors status are warranted due to differences in the results of our study on global studies.

4. We suggest future studies that will examine the role of hormonal therapy and Her2 targeted treatment and the timing of post-operative chemotherapy.

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