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Time to Start Adjuvant Systemic Treatment in Breast Cancer; a Retrospective Cohort Study

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Abstract

Background: According to the World Health Organization (WHO), early diagnosis of cancer was associated with increasing rates of survival for cancers as breast, cervix, mouth, larynx, colon, rectum and skin. Still the optimal time to start adjuvant treatment after definitive surgery is uncertain

Aim of study: to evaluate the impact of delay to start adjuvant treatment in different biologic subtypes of breast cancer on treatment outcomes as regard response, failure free survival (FFS).

Patients and methods: It involved 107 patients with nonmetastatic breast cancer presented to clinical oncology department, Assiut university hospital from January 2011 to December 2012, and were eligible for adjuvant systemic treatment, The time from surgery to the start of 1st cycle of adjuvant systemic treatment was calculated, then this time was divided into three time intervals; ≤30 days, >30 - ≤60 days, and >60 days.

Results: 41.1%, 45.8%, 13.1% of patients received adjuvant treatment within 30 days, <30-60 days, and more than 60 days respectively, the median failure free survival was 50±2.104 months (95% CI=45.877-54.125) and was significantly decreased with increasing the time but not significantly differed between different time intervals in the whole study patients, nor in different biologic subtypes except luminal B, patients started early adjuvant treatment, relapsed late with significant effect of different time intervals on the time to relapse, local and distant relapses (P<0.000, P<0.001, P<0.02).

Conclusion: Adjuvant systemic treatment for breast cancer should be initiated as early as possible better within 30 days of surgery because of significant poor effect of delay to initiate adjuvant treatment on FFS and TTR.

Keywords: breast cancer, systemic chemotherapy, survival, response, time to adjuvant treatment

1. Introduction

Globally, breast cancer is the most common malignancy in females, developing countries account for approximately 50% of all breast cancer incidences and more than 60% of mortalities annually (Jemal et al., 2011).

In developing countries; delay in diagnosis and treatment has mainly been attributed to deficient human and financial resources to supply different screening programs subsequently early diagnosis and treatment (Unger-Saldaña, 2014).

According to the World Health Organization (WHO) (Organization, 2007), early diagnosis of cancer was associated with increasing rates of survival for different cancers including breast cancer.

According to the National Breast and Cervical Cancer Early Detection Program (NBCCEDP); there should be no more than 60 days between detection of a suspicious lesion on mammogram and breast tissue diagnosis, and no more than 60 days between diagnosis and initiation of treatment (Richardson et al., 2010).

In a study done by Gagliato Dde et al. (Gagliato et al., 2014) to compare survival (OS, RFS, DRFS,) outcomes among women with breast cancer stages I-III and were categorized into three groups according to time to start adjuvant chemotherapy: ≤ 30, 31 to 60, ≥ 61 days and found that start of chemotherapy ≥61 days after surgery was associated with poor distant relapse free survival among patients with stage II (DRFS: hazard ratio [HR],

1.20; 95% CI, 1.02 to 1.43) and poor overall survival, relapse free, and distant relapse free survival in patients with stage III (OS: HR, 1.76; 95% CI, 1.26 to 2.46; RFS: HR, 1.34; 95% CI, 1.01 to 1.76; and DRFS: HR, 1.36; 95% CI, 1.02 to 1.80) breast cancer. Patients with triple-negative breast cancer (TNBC) treated with systemic chemotherapy, and those with HER2 neu –positive tumors treated with trastuzumab and started treatment ≥ 61 days after surgery had worse survival (HR, 1.54; 95% CI, 1.09 to 2.18 and HR, 3.09; 95% CI, 1.49 to 6.39, respectively) compared with those who started treatment within 30 days after surgery (Organization, 2007).

Still the optimal time to start adjuvant treatment after definitive surgery is uncertain; the study of Nurgalieva et al. (Nurgalieva et al., 2013) concluded that survival was significantly poor for those started adjuvant chemotherapy more than 3 months after surgery while Jara Sanchez et al. (Jara, et al., 2007) detected that no significant effect on disease free survival (DFS) and 5-year OS for those started adjuvant chemotherapy less than 3 weeks, 3-6 wks, 6-9 wks and more than 9 wks.

We aimed to evaluate the impact of delay to start adjuvant treatment in different biologic subtypes of breast cancer on the treatment outcomes namely response, failure free survival (FFS), and time to relapse (TTR).

2. Patients and Methods

This is a retrospective single centre review study that was carried out at clinical oncology department, Assiut University Hospital. It involved 107 patients with nonmetastatic breast cancer presented to this department from January 2011 to December 2012, and were eligible for adjuvant systemic treatment whether chemotherapy ± hormonal therapy or hormonal therapy alone (T≥0.5 cm, N+), age≥18 years, whether premenopausal or postmenopausal, any sex, and all patients had underwent mastectomy (modified radical mastectomy (MRM), breast conservative surgery (BCS), simple mastectomy, or lumpectomy).

The time from surgery to the start of 1st cycle of adjuvant systemic treatment was calculated, then this time was divided into three time intervals; ≤30 days, >30 - ≤60 days, and >60 days.

All patients' files were evaluated for:

History, clinical examination, Pathology, TNM stage, grade, radiologic imaging for detection of relapse, most of these images were multisclice CT with contrast of chest and pelvi-abdomen, gadolinium contrasted MRI of brain and spine, and bone scan.

Estrogen and progesterone receptors status, HER2 neu status, Ki-67, and biologic subtypes

Type of 1st line treatment, and the time of 1st cycle away from the date of surgery was calculated.

Response, time to relapse (TTR), and 5-year failure free survival (FFS)

3. Statistics

5-year FFS was calculated from the time of pathological diagnosis till evidence of any failure whether progression, local relapse or distant relapse or death within 5 years after diagnosis. Response was determined based on RECIST 1.1, and complete response (CR) declared disappearance of the target lesions in the breast and axilla and axillary lymph nodes should be <10mm each, partial response (PR) decrease in the summated targets ≥30%, and disease progression (DP) increase in the sum of target lesions ≥20%.

Descriptive data were presented as mean, median, standard deviation (SD), percentages. Chi-Square test was used for the relation between time and biologic subtypes, response, and local and distant relapse. Anova test for the relation between different time intervals and FFS. Kaplan-Meier for calculation of different FFS according to time and biologic subtypes, the results were considered significant at $P< 0.05$.

4. Results

This study was a retrospective cohort review of 107 patients with breast cancer stages I - III who were decided to receive systemic treatment chemotherapy ± hormonal treatment or hormonal treatment alone, and presented to clinical oncology department during the period from January 2011 to December 2012 and were evaluated for a duration of 5 years.

The median age was 50 years, male gender represented 2.8%, Rt side was a little bit more than Lt side, IDC was found in 86% of patients compared to 10% of ILC, T2 was more predominant in 55.1% of pts, followed by T3, T1, and T4, N2 was reported in 34.6%, followed by N3, N2, and N0, positive ER, positive PR, and negative Her2neu were found in 66.4%, 60.7%, and 69.2%, the commonest biologic subtype in this study was luminal A followed by Her2 neu, luminal B, and triple negative, 45.8% of pts received systemic treatment in the interval of >30 to ≤60 days, 41.1% of pts received treatment within 30 days, and the remaining 13.1% of pts received it more than 60 days. DP occurred to 4.7% of pts, PR in 4.7%, and CR in 90.7% to 1st line treatment (table 1).

Table 1. The clinical characteristics of 107 patients eligible for systemic treatment

characteristics	No	% from total number
Age: Mean	49.3925	
Median ± SD	50.0 ± 1.05846	
Min-max.	24-70	
Gender: Male	3	2.8%
Female	104	97.2%
Site: Rt side	54	50.5%
Lt side	53	49.5%
Pathology:		
IDC	92	86%
ILC	11	10.3%
Mixed ILC& IDC	1	0.9%
Mucinous carcinoma	3	2.8%
Staging: T		
T1	19	17.8%
T2	59	55.1%
T3	21	19.6%
T4	8	7.5%
Staging: N		
Nx	7	6.5%
N0	27	25.2%
N1	37	34.6%
N2	17	15.9%
N3	19	17.8%
Estrogen receptor status		
ER +ve	71	66.4%
ER –ve	36	33.6%
Progesterone receptor		
PR +ve	65	60.7%
PR –ve	42	39.3%
Her2neu		
+ve	33	30.8%
-ve	74	69.2%
Grade:		
G1	18	16.8%
G2	69	64.5%
G3	20	18.7%
Biologic subtype:		
Luminal A	37	34.6%
Luminal B	22	19.6%
Her2neu +ve	32	30.8%
Triple negative	16	15%
Time of start adjuvant treatment after surgery:		
≤ 30 days	44	41.1%
>30-≤60 days	49	45.8%
>60 days	14	13.1%
Types of surgery		
MRM	93	86.9%
BCS & axillary clearance	9	8.4%
Simple mastectomy	3	2.8%
Lumpectomy	2	1.9%
Adjuvant treatment		
chemotherapy ± hormonal	97	90.65%
chemotherapy ± trustuzumab	2	1.9%
hormonal treatment alone	8	7.47%
Response		
CR	97	90.7%
PR	5	4.7%
DP	5	4.7%

LT=left, RT=right, ER=estrogen receptor, PR=progesterone receptor, IDC=infiltrating ductal carcinoma, ILC=infiltrating lobular carcinoma, BCS=breast conservative surgery, CR=complete response, PR=partial response, DP=disease progression.

Relation between time of adjuvant treatment and response

No significant effect of the time to adjuvant treatment on the response to this treatment (P=0.415) as shown in

table 2.

Table 2. Relation between the time and response

Response	Time			Significance
Total number (107)	≤ 30 days	30-60	> 60	*P< 0.05*
CR	42	43	12	
% from total number	39.3%	40.2%	11.2%	
PR	0	4	1	NS
% from total number	0%	3.7%	0.9%	P=0.415
DP	2	2	1	
% from total number	1.9%	1.9%	0.9%	

NS= nonsignificant

PR and DP can be explained as some patients didn't undergo radical surgery (and so couldn't be considered disease free at the time of adjuvant therapy, even if clinically free), some had lumpectomy or simple mastectomy and others had inadequate axillary evacuation.

Relation between the time and FFS.

The 5-year OS was 66.35% for the whole group, and it was 34.57%, 24.29%, and 7.47% for those started within 30 days, 30-60 days and >60 days and the result was significant (P<0.005).

The median FFS ± SD = 50 ±2.104 months with 95% confidence interval (CI=45.877-54.123) for the whole study group (figure 1).

FFS was significantly lower with increasing time (r=-0.380, P<0.000), but it didn't significantly differ between these time intervals (P=0.467) (Figure 2).

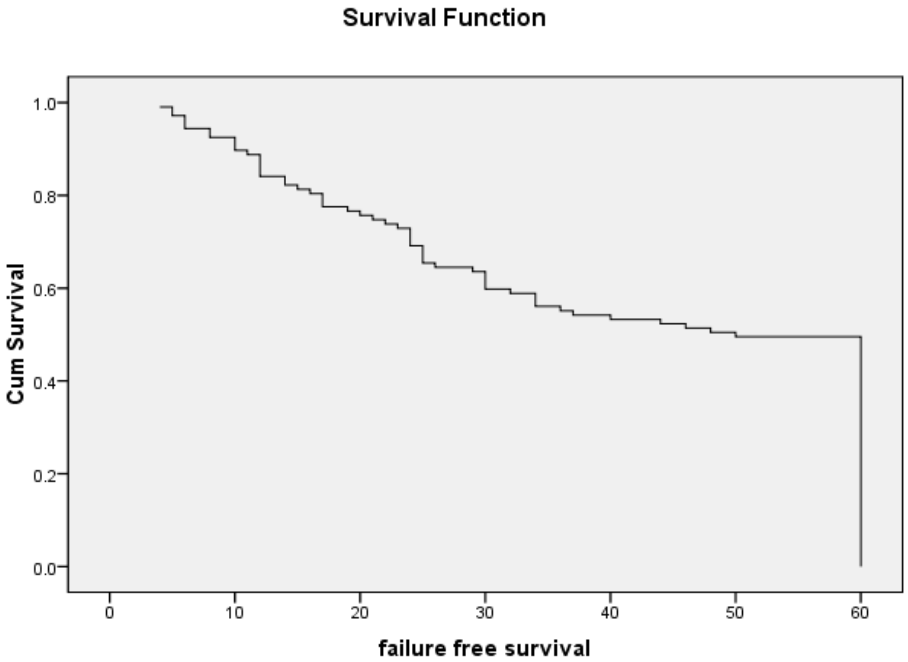

Figure1. 5-year failure free survival for 107 breast cancer patients

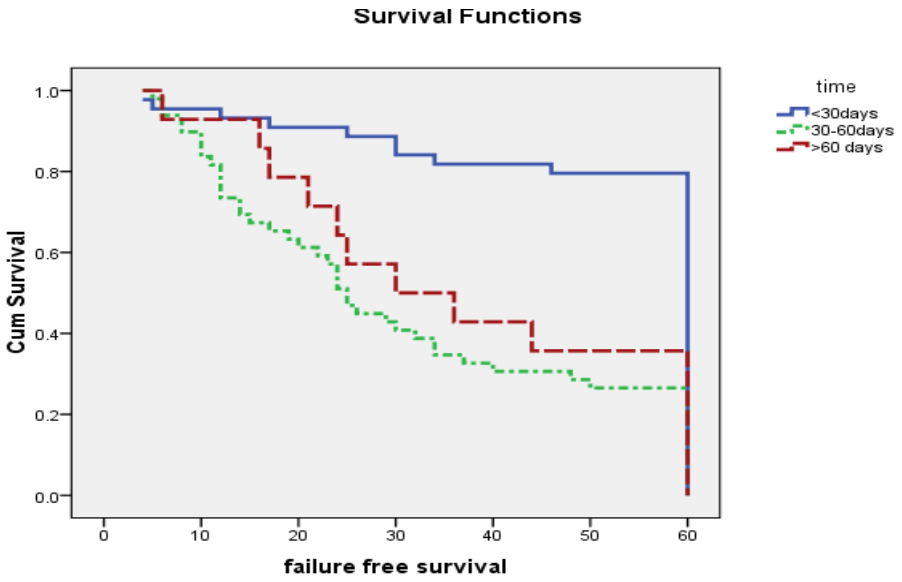

Figure 2. The median FFS for those started treatment ≤30 days was 60 months, while for those started it within >30-60 days was 25 ±1.747 months (95% CI= 21.567-28.424), and for those received treatment more than 60 days was 30 ±10.290 months (95% CI= 9.832-50.168), and the results was significantly better for those received treatment ≤30 days (P<0.000)

Subgroup analysis of FFS within each biologic subtype of breast cancer wasn't affected by the time intervals except in luminal B (P<0.002).

For luminal A the median FFS was 60 months Figure 3.

For luminal B; the median FFS was 36.0 ±14.071 (95% CI=8.420-63.580) and it was significantly higher for those started treatment ≤30 days (P<0.002) Figure 4.

For Her2 neu; the median FFS was 30 ±3.508 (95% CI=23.125-36.875) Figure 5.

For triple negative; the median FFS was 21 ±2.667 (95% CI=15.773-26.227), Figure 6.

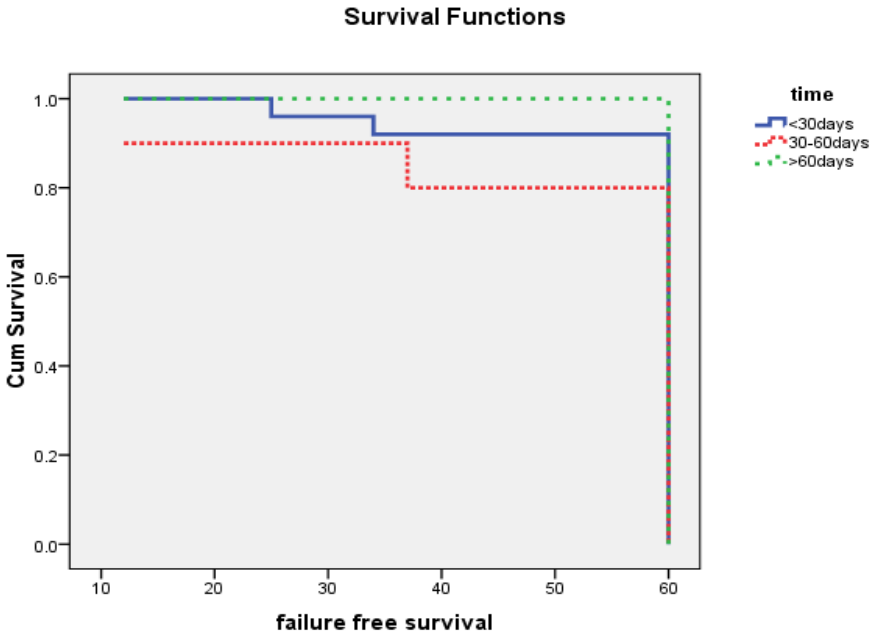

Figure 3. FFS among 37 pts with luminal A according to time of start adjuvant treatment, the median FFS was 60 months and not affected by the time to chemotherapy (P=0.476).

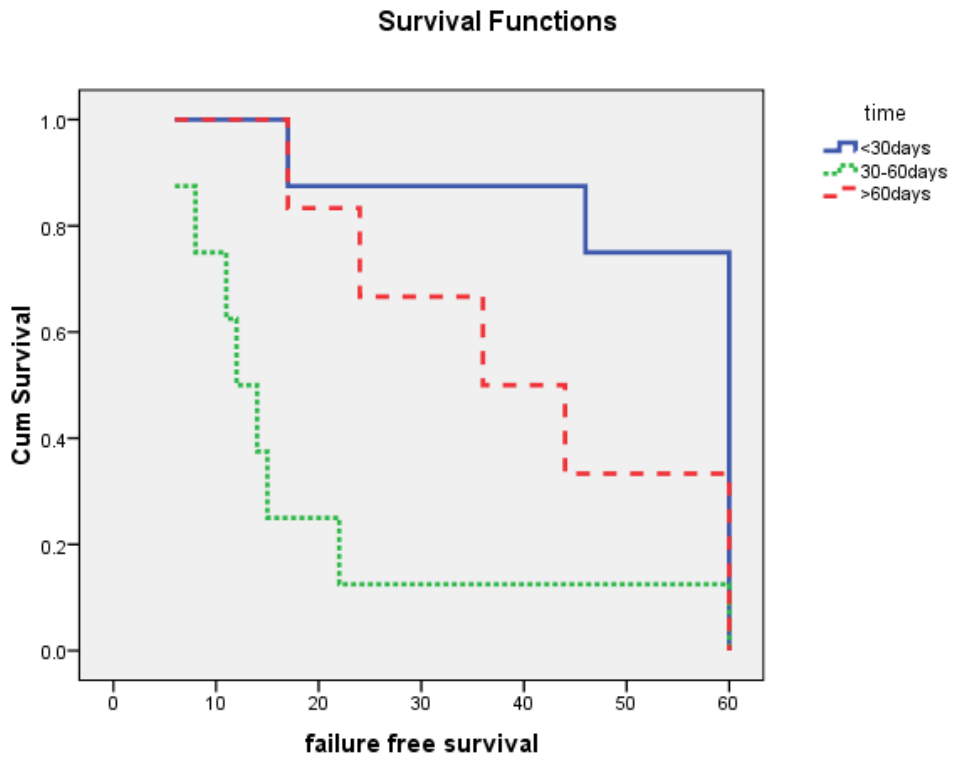

Figure 4. FFS among 22 pts with luminal B according to time of start adjuvant treatment, the median FFS was 60 m, 12 m, 36 m, for those started treatment ≤30 d, 30-60 d, >60 d, respectively (P<0.002)

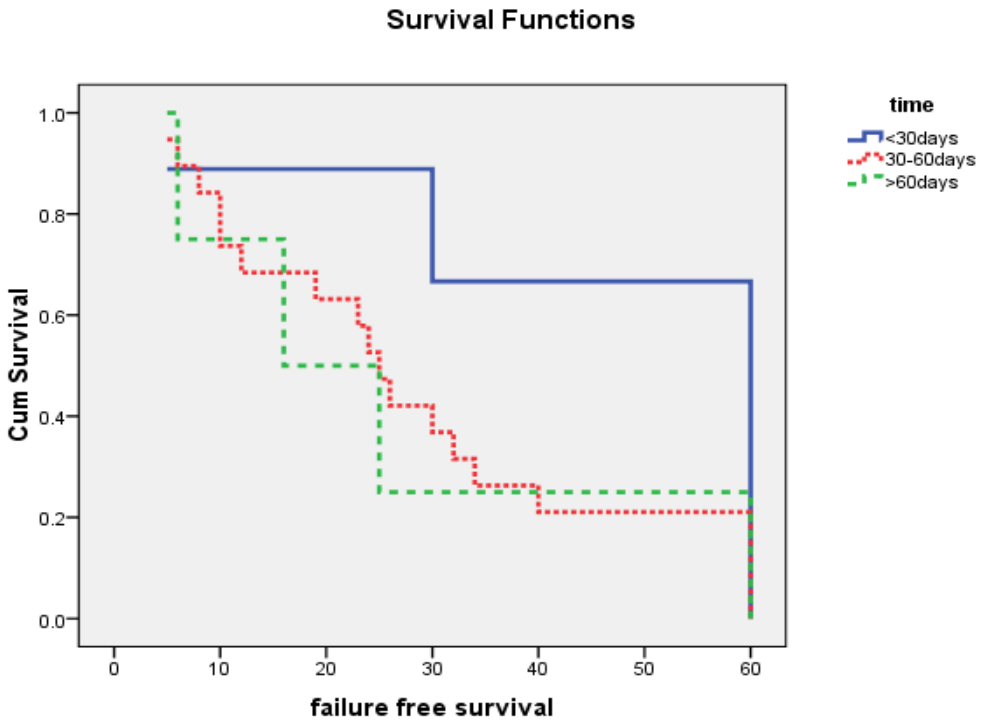

Figure 5. FFS among 32 pts with Her2neu according to time of start adjuvant treatment, the median FFS was 60 m, 25 m, 16 m, for the same time groups but it was nonsignificant (P=0.07).

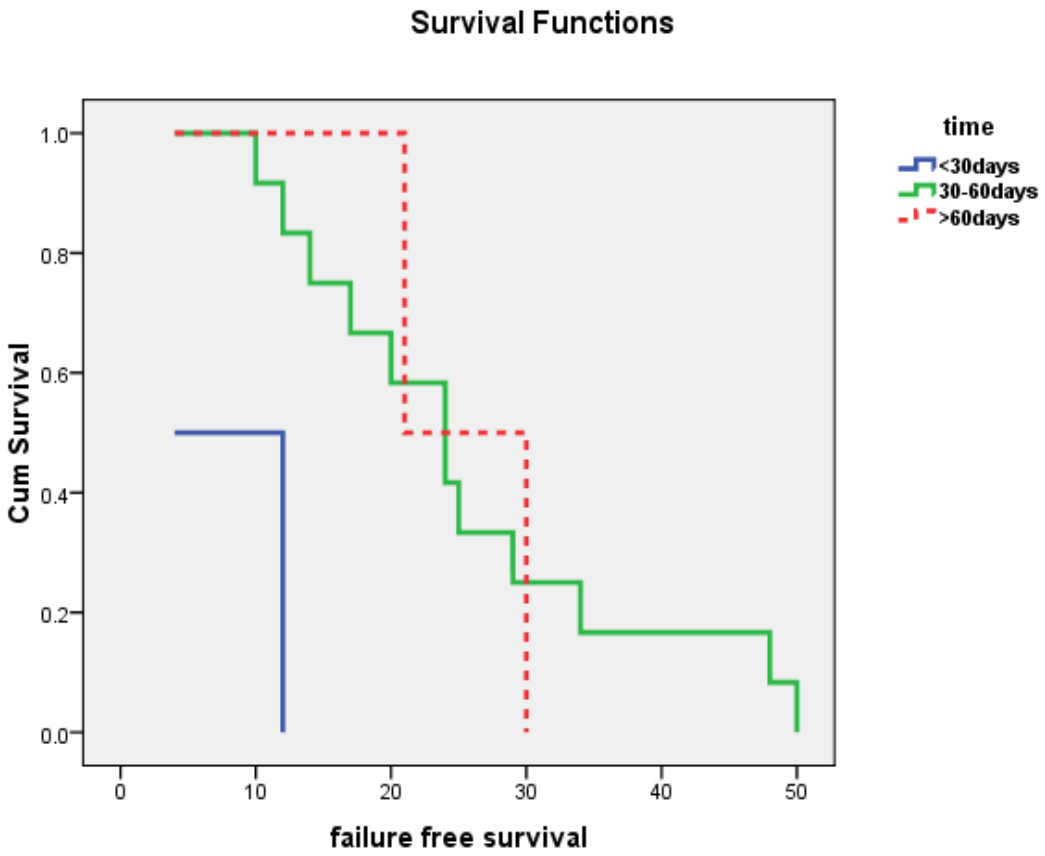

Figure 6. FFS among 16 pts with triple negative according to time of start adjuvant treatment, the median FFS was 4 m, 24 m, 21m for the same time groups and it was nonsignificant (P=0.20).

Relation between time and pattern of relapse:

Time to relapse (TTR) was significantly longer for those started treatment ≤30 days than those started 30-60 days and >60 days (P<0.000), local and distant relapses significantly occurred in those started adjuvant treatment at a time > 30 days than those ≤30 days (P<0.001, P<0.02 respectively), higher number of patients who received treatment within 30-60 days suffered from relapse and this could be explained as most patients within this time were Her2neu and triple negative, table 4.

Table 4. Relation between time and patterns of relapse

time	Relapse							
	Time to relapse				Local relapse		Distant relapse	
	<5 ys		≥5 ys		Total No=24		Total No=43	
≤30 days	9	20.5%	35	79.5%	2	1.9%	11	10.28%
>30-≤60 days	36	73.5%	13	29.5%	17	15.9%	24	22.43%
>60 days	9	64.3%	5	35.5%	5	4.7%	8	7.48%
significance	P<0.000				P<0.001		P<0.02	

5. Discussion

Worldwide; breast cancer still persisted as the most common cancer in females, although the incidence rates in developed countries remained stable since 2003 (Siegel et al., 2015). But these rates still were higher among developed countries than developing countries while death rates were higher among the later than the former (Jemal et al., 2011).

In this study; patients who started adjuvant treatment early after surgery had better failure free survival than those started more than 30 days.

Many researchers encouraged early initiation of treatment and proved that delaying of treatment more than 90

days was associated with poor survival outcomes (Nurgalieva et al., 2013; McLaughlin et al., 2012; Elmore et al., 2012).

Alkis et al (Alkis et al., 2011), concluded that patients started adjuvant chemotherapy up to 44 days had a significantly better OS than more than 44 days.

Ghany D (Ghany, 2012) investigated the impact of the time to start adjuvant chemotherapy after surgery and found that delay of adjuvant chemotherapy more than 3 weeks after definitive surgery in premenopausal females with early breast cancer and negative ER was associated with poor survival.

Nurgalieva et al (Nurgalieva et al., 2013), proved that survival was significantly worse for those started adjuvant chemotherapy more than 3 months than those less than 3 months in patients with stages I, II, III breast cancer.

The time at which adjuvant systemic treatment should be started was debatable, as most of studies examined mainly the impact of time delaying between diagnosis and definitive surgery.

A systematic analysis of 33 studies done by Williams (Williams, 2015) to evaluate the impact of treatment delay on prognosis and survival; 11 studies defined treatment interval as the time interval between diagnosis and the start of first treatment whether surgery, chemotherapy, radiation, or hormonal therapy, Ten studies defined it as the interval between the date of surgery and the first date of radiation, Six other studies defined it as the time between surgery and first cycle of chemotherapy treatment, one study simply defined it as the interval between surgery and treatment, while five studies did not provide any definition of the interval delay used in their assessment, also these studies differed in their determination of the time interval used; some defined it in days, others in weeks, and others in months, 13 studies proved that there was a significant effect of time delay on survival, recovery and recurrence, while the remaining reported no effect.

In addition to the significant impact of time delay on FFS in this study, also time delay was associated with significantly higher local and distant relapse and shorter time to relapse and this was comparable to Gagliato Dde M et al, that found initiation of chemotherapy ≥61 days after mastectomy was associated with significantly worse relapse free survival in stages II and III breast cancer (stage II, DRFS: HR 1.20; 95% CI=1.02-1.43, stage III, RFS:HR, 1.34; 95% CI=1.01-1.76, and DRFS, HR, 1.36; 95% CI=1.02-1.80).

Chevaz-MacGregor et al defined delayed time to chemotherapy (TTC) as >90 days between surgery and 1st dose of chemotherapy and found that longer TTC was associated with worse OS and breast cancer-specific survival, especially those with triple-negative.

Subgroup analysis in this study demonstrated that the median FFS in patients with luminal A wasn't affected by the time to systemic treatment, in luminal B; the median FFS was significantly better for those ≤30 days (the median FFS was 5-ys, 1-y, 3-ys for those started ≤30, 30-60, >60 days, P<0.002), in Her2 neu; there was a trend for better median FFS but non significant for those also started ≤30 days (the median FFS was 60 m, 25 m, 16 m, for ≤30, 30-60, >60 days respectively, P=0.07), and lastly patients with triple negative showed no significant effect of the time on the median FFS and this could be explained by the small sample size which was incomparable to Chavez-MacGregor M (Chevaz-MacGregor, et al., 2016) that demonstrated longer TTC in patients with Her2 neu and triple negative was associated with worse survival outcomes.

However, this study was an observational study and there was some bias in registering the actual time delay, also it couldn't be extended to before 2011 as Ki-67 and Her2neu were not determined, and it was a unicenteric evaluation hence the small sample size, it should be done in multiple centers and continued follow up was advisable to determine the accurate impact of time delay on overall survival.

6. Conclusion

Adjuvant systemic treatment for breast cancer should be initiated as early as possible better within 30 days of surgery because of significant poor effect of delay to initiate adjuvant treatment on FFS and TTR.

Conflict of interest

The authors disclosed no conflict of interest

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