Impact of delayed Radiotherapy on outcome of breast cancer patients after Breast-Conservative Surgery. A Retrospective Analysis; Mansoura Experience

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Abstract:

Background: Breast cancer is the second most prevalent type of cancer and the most common cancer among women. The gold standard in the treatment of breast cancer is postoperative radiation following breast-conserving surgery (BCS). The optimal timing to begin postoperative radiation therapy (RT) is still up for debate.

Objective: The purpose of the study is to determine if the gap between BCS and postoperative RT has any impact on the frequency of local or distant relapses and overall survival in female patients with breast cancer.

Patients and Methods: Following the scheduling of radiation, we split the 302 female patients into two groups: ≤180 days and >180 days, and retrospectively examined the clinical data. The Fisher exact test, the χ2test or dummy variables were used to determine if the two groups had an unbalanced distribution of prognostic and treatment variables. The Kaplan-Meier survival analysis and a restricted mean survival time (RMST) were used to assess local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OAS). After correcting for known confounding variables, multivariate Cox regression was performed to test for the independent effect of time of RT. The typical median time of follow-up was 6.5 years.

Results: There were statistically significant differences in the distribution of pathological stage, chemotherapy regimens, timing of the initiation of chemotherapy (neoadjuvant or adjuvant), and total dose of radiation. We were unable to find a relation between the time interval and the probability of local relapse at the 6.5-year median time of follow-up (p = 0.285 and 0.259) in both the univariate and multivariate analyses. When radiation was begun later than recommended, the DMFS and OAS univariate analyses revealed no influence on outcome (p = 0.3445 and p = 0.249, respectively), and the multivariate analysis supported this finding (p = 0.578 and p = 0.487, respectively).

Conclusion: Our findings demonstrate that there is no relationship between the scheduling of postoperative RT and the chance of local relapse, distant metastasis, or progression of overall survival in our groups.

Keywords: Timing, Radiotherapy, breast cancer, breast conservative surgery Local relapse, Distant metastases, Survival

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Introduction:

The global burden of breast cancer in females, including incidence and mortality, is increasing and rising in several countries. Breast cancer is the second most prevalent type of tumor and the most common cancer among females. In 2018, around 2.1 million new instances of female breast cancer were diagnosed worldwide, accounting for nearly one-fourth of all cancer cases in women. It is the fifth cause of cancer death overall and is the commonest cause of cancer death in women in developed countries, and it is the 2nd common cancer in developed countries following lung cancer [1].

In Egypt, breast cancer is the most common female cancer accounting for 32% of all cancers and the 2nd most common cancer nationwide following liver cancer. According to the statistics of Egypt's population-based National Cancer Registry Program, it impacted approximately 36 females per 100,000 inhabitants between 2008 and 2011. According to the same

research, breast cancer accounts for 33% of cancer diagnoses in women in Lower Egypt's Damietta governorate [2].

According to several studies, the mortality rate for breast cancer has decreased as a result of early detection and advancements in cancer therapy[3]. In a randomized clinical trial Milan I involving 701 patients with early breast cancer, patients were grouped into Halsted's mastectomy, Quadrantectomy, Radiotherapy, Axillary treatment (QUART), and there was no difference in overall survival between the two groups [4].

After BCS, RT diminishes the risk of local recurrence by half and cancer-specific mortality by a sixth [5].

Randomized clinical trials have shown that WBRT after BCS for early as well as locally advanced tumor after neoadjuvant chemotherapy (NACT) improves local control and breast cancer survival, and has been recognized as the standard of care in breast-conserving therapy (BCT) (BCS and postoperative RT) for non-metastatic breast cancer for over two decades [6].

The ideal moment to begin postoperative RT has not yet been determined. The formation of radio resistance and the growth of clonogenic cells in the tumor bed could theoretically occur if RT is delayed in administration after surgery [7]. In observational studies, delays of >8–12 weeks appear to increase the risk of local relapse, but the findings are conflicting. Additionally, there are no phase III studies about the ideal gap between operation and RT. [5].

The long-term follow-up of 302 women who received WBRT after BCS for stage I-IIIa breast cancer was retrospectively examined in this research. The goal was to look into the correlations between postoperative RT wait times and local relapse, distant metastases, and overall survival.

Patients and Methods:

We analyzed data concerning 302 patients with breast cancer (BC) who underwent WBRT with conventional fractionation at our institution between December 2010 and December 2016. All patients had invasive breast cancer-T1-T3, N0-2, M0 breast cancer, and underwent BCS (quadrantectomy ± sentinel lymph node biopsy and/or axillary dissection). Following surgery, they all underwent WBRT using an isocentric technique with two tangential fields, which was followed in 71.19% of instances by a boost on the tumor bed. For WBRT, a median dose of 40 Gy (with a range of 40–42.5 Gy) was administered five times a week. According to the ICRU 50 recommendations, the dose was given at the isocenter, and the CTV (clinical target volume) was set at a 95% isodose level. A 6 MV photon beam was used to deliver the dosage to the breast; an electron or photon beam with a 9 Gy median dose was used to deliver the dose to the tumor bed (range 8-20). Most of the patients received chemotherapy either neoadjuvant (3.6%) or adjuvant (83.4%), only (8.9%) did not receive chemotherapy for postmenopausal with early-stage T1-2 N0-1, age or comorbidities. In 79.47% of patients, hormone therapy (HT) was given (28.8% Aromatase Inhibitors (AIs), 43.7% Tamoxifen, and 7 % Tamoxifen then AIs). Protocols or guidelines regarding risk factors were not officially used to condition the waiting list for breast cancer patients. The overall waiting list for beginning RT and the delay in referring to the RT facility were the main factors influencing the amount of time that passed.

Our institution's ethics committee gave its approval for this study.

Statistical analysis:

We conducted a retrospective analysis of clinical data for 302 women who received treatment from 2010 to 2016 and were split into two groups based on the duration of RT: ≤ 180days and >180days. The 2 tests, the Fisher exact test, or dummy variables were used to determine whether there was an unbalanced distribution of prognostic and therapy factors between the two groups. LRFS, DMFS, and OAS were estimated with the Kaplan–Meier method, restricted mean survival time, and multivariate Cox regression was used to test for the independent effect of timing of RT after adjusting for known confounding factors. The level of significance was considered statistically significant for the analysis when p was ≤ 0.05.

Results:

In terms of the timing of BCS and the start of RT, patients are divided into two groups: The first group measured less than 180 days including 111 patients, while the second group measured more than 180 days including 191 patients.

Patients' characteristics are demonstrated in Table 1. The mean age at presentation among the studied group was 48.8 years (range; 17-78 years). We had 111 patients in the 1st group with mean age 49.5 years and 191 patients in the 2nd group with mean age 48.5 years. 139 patients (46.0%) were premenopausal,59 (53.2%) of them were in the 1st group while, 116 patients (38.4%) were postmenopausal with 78 (40.8%) of them were in the 2nd group and 47 patients (15.6%) were perimenopausal with no statistical significance between 2 groups.

289 patients (95.7%) had an ECOG performance status score of 1. Hypertension was the most common associated co-morbidity. The mean of the BMI was 38.0 with no significant distribution between 2 groups.

Tumor pathological characteristics

As illustrated in Table 2 approximately 239 patients (79.1%) had a pathological stage I and II diseases, 95 (85.6%) were in the 1st group whereas 144 (75.4%) were in the 2nd group; 63 patients (20.8%) had a pathological stage IIIa disease; 16 patients (14.4%) were in the 1st group, whereas 47 patients (24.6%) were in the 2nd group. The distribution of patients between the 2 groups was statistically insignificant p-value 0.036.

283 patients (93.7%) had malignant invasive tumors of ductal origin ;103 patients (92.8%) were in the 1st

group and 180 patients (94.2%); 15 patients (5%) had invasive lobular cancer with no statistically significant distribution between 2 groups.

Only 5 patients (1.7%) had positive margins, and all of them belonged to the second group. The majority of tumors were properly excised with sufficient margins. In 61 individuals (20.2%), associated intraductal cancer was discovered.

75 patients (24.8%) showed positive Her2neu staining, while 222 patients (73.5%) had tumors that were hormone receptor-positive with no statistically significant distribution between 2 groups.

By applying the 20% criterion, Ki67 was found to be low (20%) in 152 patients (13.6%) and high (>20%) in 150 patients (23.5%) with no statistically significant distribution between 2 groups.

Although the majority of the patients had luminal like tumors (Luminal A in 133 patients and Luminal B in 86 patients), only 19.5% of the patients had more aggressive tumors (Her2neu enriched in 23 patients (7.9%) and triple negative in 36 patients (11.9%) with no statistically significant distribution between two groups P-value is 0.489.

Treatment Characteristics

Treatment characteristics are illustrated in Table 3 and 4. 295 patients (97.68%) had a wide local excision (lumpectomy) of their tumors. Complete quadrant excision was performed on 7 patients (2.3%). (quadrantectomy). Only 7 patients (2.3%) underwent oncoplastic surgery with the goal of cosmetic improvement. SLNB was found in 10 patients (3.3%). Adjuvant chemotherapy wasn't planned in 29 patients (9.6%); 17 patients (15.3%) were in the first group, while 12 patients (6.3%) were in the second group. 252 patients (83.4%) received adjuvant chemotherapy;81 patients (73.0%) were in the 1st group while 171 (89.5%) patients were in the 2nd group. 11 patients received neoadjuvant chemotherapy 6 (5.4%) patients were in the 1st group whereas 5 (2.6%) were in the 2nd group with significant p value between two groups < 0.001

The majority of patients (115; 38.1%) received anthracycline-containing chemotherapy (Doxorubicin and Cyclophosphamide) and antimetabolite (Fluorouracil), while others (82; 27.2%) received a sequential regimen of anthracycline-based chemotherapy combined with antimetabolite followed by single-agent taxane. 56 patients (18.5%) received anthracycline based then taxanes while 20 patients (6.6%) received anthracycline only. By $\chi 2$ test there was statistically significant difference p-value <0.001 regarding regimens of chemotherapy between the two groups so dummy variables ware created. Dummy variables revealed only significant between the groups who received anthracycline-based chemotherapy followed by single-agent taxane p-value 0.003. Adjuvant trastuzumab was planned for 75 patients with positive Her2-neu expression; 23 patients were in the first group, and only 6 (27.27%) received 12-month target therapy. whereas 52 patients with positive Her2-neu expression were in the second group; only 17 (32.07%) patients received target therapy for 12 months.

Tamoxifen was prescribed for 132 patients (43.7%) while AIs were prescribed for 87 patients (28.8%). As a switch strategy, 21 patients (7.0%) received Tamoxifen followed by AIs, with statistically insignificant distribution between the two groups.

Radiotherapy treatment Characteristics

RT was planned to start around 4–8 weeks (56 days) postoperatively if the patients weren't eligible for adjuvant treatment or after completion of adjuvant chemotherapy with the same duration, but it was limited by many factors like wound healing, delay in referral to our department, completion of adjuvant chemotherapy, and a long waiting list. However, the median time to start RT, defined as the time between BCS and the start of the RT, was 210 days (range: 30- 390). The median of the total RT dose was 40 Gy, with significant distribution p-value $\leq$ 0.001 between the two groups, and the median of the boost dose was 9 Gy with insignificant p-value between 2 groups Table 5. According to the RT regimen, the overall treatment time was planned to be 20–25 days in terms of total dose. However, only 75 patients had a gap range from 1week to 4 weeks.

The median time of follow-up

Defined as the median time between diagnosis and last follow-up, it was 6.5 years (range: 1 year–12 years). Following RT, patients underwent evaluations every two months for the first two years, every six months for the next five years, and then annually after that.

Disease-free survival (DFS)

Overall, we found 18 patients (6%) had local recurrence; out of them, 5 patients in the 1st group (≤180 days) and 13 patients in the 2nd group (>180 days).

33 patients had distant metastasis (10.9%); out of them, 11 patients were in the 1st group (≤180 days) and 22 patients in the 2nd group (>180 days).

As illustrated in Figure 1 the Kaplan–Meier curve for LRFS found $\chi 2[1] = 1.176$. There was no statistically significant correlation between the onset of RT and local recurrence p-value 0.285 [HR 1.69, 95% CI: 0.6536- 4.3872] in comparison the 2nd group to 1st group.

Restricted mean survival time at point of 5 years for LRFS in relation to the timing of RT illustrated in Table 6 [HR 1.2546, CI: -0.6337- 3.1430] and insignificant P-value 0.1928 in comparison of the 1st group to the 2nd group.

Using Cox regression multivariate for correction confounding factors tumor stage and tumor molecular subtype in relation to LRFS adjusted HR was 1.84 [95% CI: 0.6390- 5.2738] for the 2nd group compared to the 1st group, with insignificant P-value 0.259 between the two groups, as illustrated in Table 9.

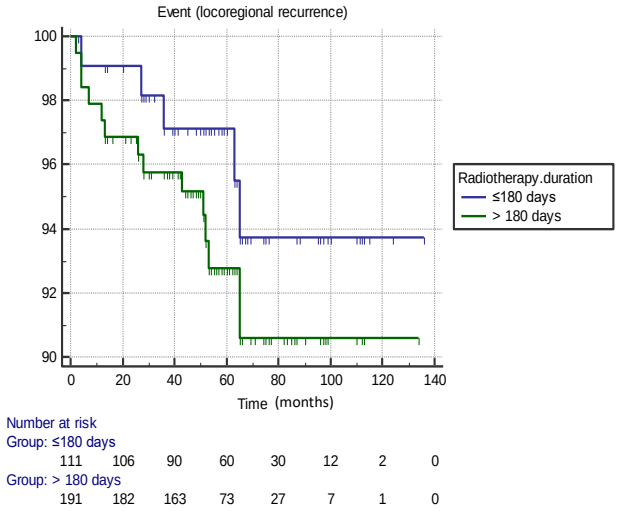

Figure (1): Kaplan-Meier loco regional recurrence among the studied groups

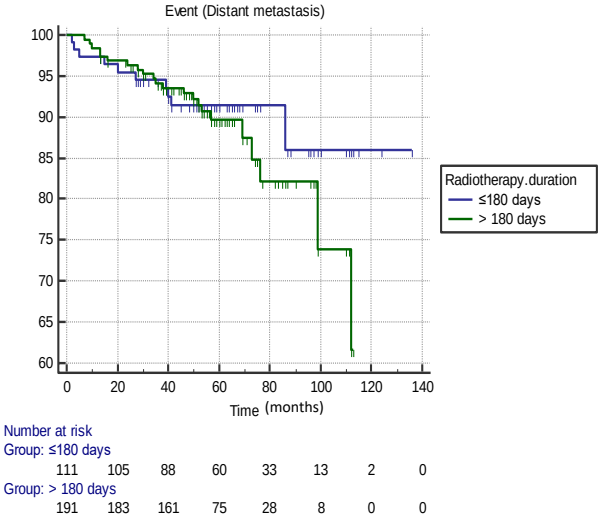

Figure (2): Kaplan-Meier distant metastasis among the studied groups

The Kaplan-Meier curve for DMFS between two groups of RT delay had no significant p-value of 0.3445, as demonstrated in Figure 2. With restricted mean survival time at 5 years for DMFS in relation to the timing of RT [HR 0.4492, CI; -2.1255- 3.0239] P-value 0.7324 during comparing of the 2nd group to the 1st group. The restricted mean survival time at 5 years for DMFS is illustrated in Table 7.

When corrected for pathological stage, molecular subtype, and chemotherapy timing from surgery and regimens in relation to DMFS, the adjusted HR of the 2nd group in comparison to the 1st group was 1.239 [95% CI: 0.5819-2.6395] and a p-value of 0.578 as illustrated in Table 9.

Overall survival

Kaplan-Meier disease OAS among the studied groups showed $\chi 2[1] = 1.324$ with [HR 0.5063, 95% CI: 0.1589 - 1.6134] comparing the 2nd group to the 1st group. We found no statistically significant relationship between the onset of RT and OAS, with a p-value of 0.249 (Figure 3).

With Restricted Mean Survival Time at 5 years [HR 0.4472, CI: -0.7019- 1.5963] with a statistically insignificant p-value of 0.446 when comparing the 2nd group to the 1st group (Table 8).

With adjusting confounding factors OAS regarding timing of RT adjusted HR of the 2nd group 0.6569 [95% CI: 0.2011- 2.1455] with insignificant p-value 0.4865 as illustrated in Table 9.

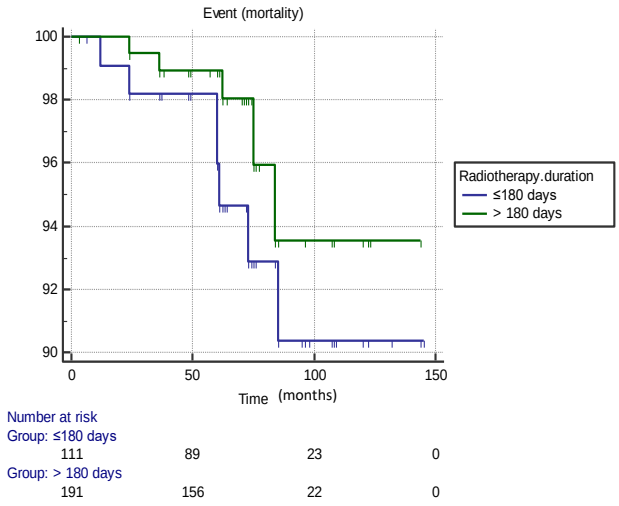

Figure (3): Kaplan-Meier overall survival among the studied groups.

Table (1): Patients' characteristics among the studied groups

Patients' characteristics	Total (n=302)	Less than 6 m (n=111)	More than 6 m (n=191)	statistics	P value
Age/ years					
Mean ± SD	48.79±10.35	49.47±10.99	48.4±9.97	t-value0.862	0.389
Menopausal status					
Premenopausal	139 (46.0%)	59 (53.2%)	80 (41.9%)	χ^2 3.715	0.156
Perimenopausal	47 (15.6%)	14 (12.6%)	33 (17.3%)		
Postmenopausal	116 (38.4%)	38 (34.2%)	78 (40.8%)		
Comorbidities	95 (31.5%)	37 (33.3%)	58 (30.4%)	χ^2	0.592
HTN	84 (27.8%)	31 (27.9%)	53 (27.7%)	0.287	0.973
DM	32 (10.6%)	14 (12.6%)	18 (9.4%)	0.001	0.385
				0.753	
marital status					
Married	285 (94.4%)	104 (93.7%)	181 (94.8%)	0.166	0.946
Single	7 (2.3%)	3 (2.7%)	4 (2.1%)		
Widow	10 (3.3%)	4 (3.6%)	6 (3.1%)		
Residence					
Rural	240	79 (71.2%)	161(84.3%)	7.409	0.007
Urban	62	32 (28.8%)	30 (15.7%)		
Performance status (PS)					
0	13 (4.3%)	7 (6.3%)	6 (3.1%)	-	0.192
1	289 (95.7%)	104 (93.7%)	185 (96.9%)		
BMI Mean ± SD	38.00±8.87	37.7±10.99	36.48±8.99	t-value	0.321
				0.995	
BMI category					
Underweight	7 (2.3%)	4 (3.6%)	3 (1.6%)		
Normal weight	22 (7.3%)	9 (8.1%)	13 (6.8%)		
Overweight	40 (13.2%)	13 (11.7%)	27 (14.1%)	-	0.603
Obese G1	62 (20.5%)	19 (17.1%)	43 (22.5%)		
Obese G2	72 (23.8%)	25 (22.5%)	47 (24.6%)		
Obese G3	99 (32.8%)	41(36.9%)	58 (30.4%)		

Table (2): Tumor characteristics among the studied groups

Tumor characteristic	Total (n=302)	Less than 6 m (n=111)	More than 6 m (n=191)	Statistics	P value
T stage					
T1	113 (37.4%)	55 (49.5%)	58 (30.4%)	-	0.003
T2	183 (60.6%)	54 (48.6%)	129 (67.5%)		
T3	6 (2.0%)	2 (1.8%)	4 (2.1%)		
histological type					
IDC	283 (93.7%)	103 (92.8%)	180 (94.2%)	-	0.649
ILC	15 (5%)	7 (6.3%)	8 (4.2%)		
Another types	4 (1.3%)	1 (0.9%)	3 (1.6%)		
Grade					
GI	11 (3.6%)	5 (4.5%)	6 (3.1%)	-	0.836
GII	200 (66.2%)	73(65.8%)	127 (66.5%)		
GIII	91 (30.1%)	33 (29.7%)	58 (30.4%)		
LVI					
No data	240(79.5%)	90 (81.1%)	150 (78.5%)	0.285	0.867
Negative	27(8.9%)	9 (8.1%)	18 (9.4%)		
Positive	35(11.6%)	12 (10.8%)	23 (12%)		
PNI					
No data	276 (91.4%)	107 (96.4%)	169 (88.5%)	-	0.036
Negative	13 (4.3%)	3 (2.7%)	10 (5.2%)		
Positive	13 (4.3%)	1(0.9%)	12 (6.3%)		
LN stage					
N0	148 (49%)	53(47.7%)	95 (49.7%)	0.112	0.946
N1	130 (43%)	49 (44.1%)	81 (42.4%)		
N2	24 (7.9%)	9 (8.1%)	15 (7.9%)		
Pathological stage					
Early (I-II)	239 (79.1%)	95 (85.6%)	144 (75.4%)		0.036
Advanced (IIIa)	63 (20.9%)	16 (14.4%)	47 (24.6%)		
ER					
No data	4 (1.3%)	0 (0.0%)	4 (2.1%)	-	0.368
Negative	76 (25.2%)	30 (27.0%)	46 (24.0%)		
Positive	222 (73.5%)	81 (73.0%)	141 (73.8%)		
PR					
No data	4 (1.3%)	0 (0%)	4 (2.1%)	-	0.444
Negative	85 (28.1%)	32 (28.8%)	53 (27.7%)		
Positive	213 (70.5%)	79 (71.2%)	134 (70.2%)		
HER2					
No data	20 (6.6%)	8 (7.2%)	12 (6.2%)		
Negative	207(68.5%)	83 (74.75%)	124 (64.92%)		0.122
Positive	75 (24.8 %)	20 (18%)	55 (28.7%)		
KI67					
Low index	152(50.3%)	50(45%)	102 (53.4%)	1.962	0.161
High index	150(49.7%)	61 (55%)	89 (46.6%)		
Molecular subtype					
No data	24 (8.0%)	11 (9.90%)	13 (6.8%)		
luminal	219 (72.5%)	80 (72.07%)	139 (72.77%)		0.489
her2enrich	23 (7.6%)	7 (6.3%)	16 (8.37%)		
TNBC	36 (11.9%)	13 (11.7%)	23 (12.0%)		
Margins					
Negative	297 (98.3%)	111 (100%)	186 (97.4%)	-	0.162
Positive	5 (1.7%)	0 (0.0%)	5 (2.6%)		
Associated intraductal carcinoma					
No data	217 (71.9%)	77 (69.4%)	140 (73.3%)	$\chi 2$ 0.576	0.750
Negative	24 (7.9%)	10 (9%)	14 (7.3%)		
Positive	61 (20.2%)	24 (21.6%)	37 (19.4%)		

Table (3): Type of surgery among the studied groups

Type of surgery	Total (n=302)	Less than 180 days (n=111)	More than 180 days (n=191)	Statistics	P value
WLE and ALND	278 (92.1%)	102 (91.9%)	176 (92.1%)	-	0.48
WLE and SLND	10 (3.3%)	4 (3.6%)	6 (3.1%)		
WLE and ALND with reconstruction	7 (2.3%)	0 (0.0%)	7 (3.7%)		
Quadrantectomy and ALND	7 (2.3%)	5 (4.5%)	2 (1.0%)		

Table (4): Systemic therapy among the studied groups

Systemic therapy	Total (n=302)	Less than 180days (n=111)	More than 180days (n=191)	Statistics	P value
Timing of chemotherapy					
No chemotherapy	29 (8.9%)	17(15.3%)	12 (6.3%)	-	0.001
Neoadjuvant	11 (3.6%)	6 (5.4%)	5 (2.6%)		
Adjuvant	252(83.4%)	81 (73.0%)	171(89.5%)		
Neoadjuvant and Adjuvant	10 (3.3%)	7 (6.3%)	3 (1.6%)		
Regimens of Chemotherapy					
-Anthracycline and antimetabolite	115(38.1%)	53(47.7%)	62(32.5%)	Dummy variables	0.010
-Anthracycline and antimetabolite then taxanes	82(27.2%)	25(22.5%)	57(29.8%)		0.182
-Anthracycline then taxanes	56(18.5%)	11(9.9%)	45(23.6%)		0.003
-Anthracycline alone	20(6.6%)	5(4.5%)	15(7.9%)		0.340
-No chemotherapy	29(9.6%)	17(15.3%)	12(6.3%)		0.014
Hormonal therapy					
-Tamoxifen	132(43.7%)	54 (48.6%)	78 (40.8%)	2.185	0.535
-AI	87 (28.8%)	30 (27.0%)	57 (29.8%)		
-Tam then AI (switch)	21 (7.0%)	8 (7.2%)	13 (6.8%)		
Target therapy in HER2 +ve patients (Trastuzumab)				0.037	0.848
No	53(70.67%)	17(32.07%)	36(67.92%)		
Yes	22(29.33%)	6(27.27%)	16(72.72%)		

Table (5): Radiotherapy characteristics among the studied group

Radiotherapy characteristics	Total (n=302)	Less than 6 m (n=111)	More than 6 m (n=192)	Statistics	P value
Total dose (Gy) Median (Min-Max)	40 (40-42.5)	40 (40-42.5)	40 (40-50)	Z= -3.709	≤ 0.001
Boost (Gy) Median (Min-Max)	9 (8-20)	10 (8-20)	9 (8-20)	Z= -1.264	0.206
Gap in weeks Median (Min-Max)	0 (0-4)	0 (0-4)	0 (0-4)	Z= 2.280	0.023

Table (6): RMST at time 5yrs for LRFS regarding timing of RT

Factor	Mean	95% CI for the mean
≤180 days	58.937	57.691 to 60.183
> 180 days	57.682	56.264 to 59.101
Overall	58.146	57.136 to 59.157

Table (7): RMST at 5yrs for DMFS regarding timing of RT

Factor	Mean	95% CI for the mean
≤180 days	56.779	54.628 to 58.930
> 180 days	57.228	55.813 to 58.643
Overall	57.066	55.872 to 58.261

Table (8): RMST at 5yrs for OAS regarding delay from RT

Factor	Mean	95% CI for the mean
≤180 days	59.236	58.177 -60.296
> 180 days	59.684	59.239- 60.128
Overall	59.519	59.038- 60.000

Table (9): Adjusted proportional hazard regression results

Timing of RT	HR (95 % CI)	P value
LRFS		
≤180days	1	0.2592
>180days	1.8358 (0.6390 - 5.2738)	
DMFS		
≤180days	1	0.5781
>180days	1.239(0.5819 -2.6395)	
OAS		
≤180days	1	0.4865
>180days	0.6569(0.2011 –2.1455)	

Discussion:

Combining BCS and RT is a mainstay option in the multimodality treatment of breast cancer, with optimal long-term local control, mild toxicity, a good cosmetic outcome, and survival rates comparable to mastectomy [8]. Adjuvant WBRT yields a local failure rate of 3–15% depending on the patient cohort and variables such as intrinsic risk factors, type of surgery, and follow-up time [9].

In the course of treating breast cancer, the time between BCS and postoperative RT can vary considerably. Patient compliance and socioeconomic status, the regional distribution of RT facilities, increasing waiting lists, patient characteristics, and cancer could all be contributing factors in this variation (age, prognostic factors, presence of comorbidities, etc.)[10] and surgical complications (slow wound healing, inflammation, or infections). Additionally, over the past few decades, the duration of the RT waiting period has dramatically grown [11, 12] owing to a rise in the demand for radiation therapy.

In 44 studies comprising 26231 patients, a systematic review was carried out by Chen et al. [13], with the majority of the studies focusing on breast cancer or head and neck cancer. This study found statistically insignificant difference between patients who received chemotherapy and those who did not (no chemotherapy HR 1.11; 95% CI, 0.94-1.33; with chemotherapy HR 1.11; 95% CI, 1.03-1.19), and it was found that delaying the start of RT increased the risk of local breast cancer recurrence. Breast cancer patients were not significantly more likely to develop distant metastases in any site if RT was delayed (HR per month of delay: 1.04, 95% CI, 0.98–1.09). A significant correlation between the number of fatalities per month of delay and OS was not observed either (HR of deaths per month of delay: 1.06, 95% CI, 0.97–1.16).

According to a study by Caponio et al. [5]., three categories were created based on the timing of RT: ≤60, 61-120, and >120 days, using retrospective clinical data analysis on 615 women treated from 1984 to 2010. There were statistically significant differences in the age distribution, type of hormone treatment, and year of diagnosis. They failed to find a significant relationship between the time interval and the chance of local relapse at the 15-year follow-up ($p = 0.09$ for both the univariate and multivariate analyses). The DMFS and the DFS univariate analysis showed a decreased outcome when RT was started early ($p = 0.041$ and 0.046, respectively), but the multivariate analysis did not support this finding ($p = 0.406$ and $p = 0.102$, respectively) [5] .

According to a study by Zheleva V. et al. on 285,291 patients diagnosed with invasive breast cancer from 2004 to 2012, Patients with stage III disease with ≥4 positive lymph nodes after mastectomy and stage I–III disease after BCS were found to be compliant with RT administration within 365 days of diagnosis. In the BCS cohort, 89.4% of patients got timely RT, improving OAS in comparison to those who did not (HR 0.47, 95% CI 0.45- 0.49). OAS was high with delayed RT relative to no RT (HR 0.64, 95% CI 0.56-0.74), but low with timely RT (HR 1.37, 95% CI 1.19-1.58) [14].

The efficacy of locoregional radiation therapy in patients who underwent definitive surgery and adjuvant systemic therapy was investigated through a systematic review of randomized trials[15]. Thirteen trials had recurrence data accessible. The odds ratio for any recurrence was found to be 0.69 (95% CI, 0.58- 0.83; $p = 0.00004$) after radiation treatment. The timing of

radiation therapy (6 months versus >6 months since the start of systemic treatment) showed a treatment impact on multivariate analysis (p = 0.03). The findings of this meta-analysis were in line with those of earlier research, demonstrating that locoregional treatment not only reduced local failure but also enhanced DFS and OS [16-18].

Our research looked at the relationship between postoperative RT delay and the occurrence of DFS, and OAS in patients with breast cancer treated with BCS with or without chemotherapy, hormonal therapy, or target therapy.

We conducted a retrospective analysis of clinical data pertaining to 302 women who were treated from 2010 to 2016, split into two groups based on the date of the RT delay from BCS (group 1; ≤180 days, group 2;>180 days).

The distribution between the two groups was significant in pathological stage, regimens of chemotherapy, timing of starting the chemotherapy either neoadjuvant or adjuvant and total dose of RT.

Adjuvant chemotherapy wasn't planned in 29 patients (9.6%) due to postmenopausal status with early-stage T1-2N0 breast cancer or presence of comorbidities.

Regarding target therapy 75 patients were candidate for adjuvant Trastuzumab, but only 22 patients received the treatment. This may be due to difficulty in obtaining governmental support during certain periods or a small tumor size less than 1 cm.

75 patients had a gap range from 1 week to 4 weeks. Reasons for the gap were breakdowns in the RT machines and may be due to radiation-induced breast dermatitis.

Our experience found DFS was better in the 1st group (≤ 180 days) but failed to detect a significant correlation between BCS-to-RT time interval and DFS in breast cancer patients in the 1st group (≤ 180 days).

18 patients (6.0%) had local recurrence, 5 patients in the 1st group (≤ 180 days) and 13 patients in the second group (>180 days). Thirty-three patients had distant metastasis (11.6%), eleven patients were in the 1st group (≤ 180 days), and twenty-two patients were in the 2nd group (>180 days).

The Kaplan–Meier method for LRFS found $\chi 2[1] = 1.176$. Statistically insignificant relationship between LRFS and timing of RT was found with p-value 0.285 and [HR 1.69, 95% CI; 0.6536- 4.3872] in comparing the 2nd group to 1st group.

RMST at 5 years for LRFS in relation to the timing of RT the mean was 58.937 [95% CI; 57.691- 60.183] in the 1st group and 57.682 [95% CI; 56.264- 59.101] in the 2nd group with [HR 1.2546, CI; -0.6337- 3.1430] and insignificant P-value 0.1928 in comparing the 1st group to 2nd group. Using Cox regression multivariate for correction confounding factors pathological stage, molecular subtype and chemotherapy regarding timing and regimens in relation to LRFS adjusted HR was 1.84 [95%CI; 0.6390 - 5.2738] for the 2nd group compared to 1st group with statistically insignificant P-value 0.259 between two groups.

Kaplan Meier curve for DMFS between two groups of RT delay had no statistically significant p-value 0.3445 $\chi 2[1] = 0.894$ [HR 1.4, CI; 0.69- 2.84] comparing 2nd group to 1st group. RMST at 5 years for DMFS in relation to the timing of RT the mean was 56.779 [95%CI; 54.628 – 58.930] in the 1st group and 57.228 [95%CI; 55.813- 58.643] in the 2nd group, [HR 0.4492, CI; -2.1255 - 3.0239] P-value 0.7324 in comparing 2nd group to 1st group. When corrected for pathological stage, molecular subtype and chemotherapy regarding timing and regimens in relation to DMFS the adjusted HR of the 2nd group in comparison to 1st group was 1.239 [95% CI; 0.5819 - 2.6395] and p-value 0.578.

OAS was better in the group who received RT ≤ 180 days; however, it didn't reach statistically significance p-value. Kaplan-Meier curve for OAS among the studied groups showed $\chi 2[1] = 1.324$ [HR 0.5063, 95% CI: 0.1589- 1.6134] comparing 2nd group to 1st group. We found no statistically significant relationship between the timing of RT and OAS p-value 0.249. Regarding RMST at 5 years was 59.236 [95% CI; 58.177- 60.296] in the 1st group whereas it was 59.684 [95%CI; 59.239- 60.128] in 2nd group. RMST at 5 years [HR 0.4472, CI; -0.7019- 1.5963] with statistically insignificant p-value 0.446 when comparing 2nd group to 1st group. After adjusting confounding factors OAS adjusted HR of the 2nd group 0.6569 [95% CI; 0.2011- 2.1455] with statistically insignificant p-value 0.4865. We also didn't find any statistically significant p-value when we use survival analysis tests to detect the impact of molecular subtypes, chemotherapy timing from surgery, and chemotherapy regimens on the events. The impact of pathological stage on DMFS was statistically significant with p-value 0.0193, but it didn't have impact on the other events (LRFS, OAS). This may be referred to small sample size and a limited number of events.

The multivariate analysis that took tumor molecular biology, pathological TNM stage, and chemotherapy regimens into account showed that the lack of significance was due to the failure to find a univariate relationship between the timing of RT and the events was not imputable to an uneven distribution of these two variables.

Although most of high-risk patients (positive LNs, unfavorable pathological type, high grade and unfavorable tumor biology) were found in the 2nd group >180 days, the local recurrence rate was not statistically significant compared to the other group. This may suggest that delayed RT more than180 days following surgery has no effect on local recurrence even in high-risk population.

Our population's sample size wasn't sufficient, and there were differences between the two groups in terms of pathological stage, whether chemotherapy was used as an adjuvant or neoadjuvant treatment, and total RT dose. The main drawbacks of our study were the lack of randomized design and the small number of events.

Conclusion:

The BCS-to-RT interval time and the chance of DFS or OAS were not correlated in our group of individuals.

However, due to the retrospective nature of the research and the small sample size of our population, our results should be confirmed by randomized studies or carefully chosen meta-analyses in order to close the clinical evidence gap regarding the ideal time period between BCS and RT.

Compliance with ethical standards:

Ethical approval was obtained from Institutional Research Board (IRB) at the Faculty of Medicine, Mansoura University, Egypt (MS.000000). All procedures were done in accordance with the current revision of Helsinki Declaration of medical research involving human subjects.

Conflict of interest:

The authors declare that no conflict of interest to disclose.

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