Long-term follow-up of patients who received concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for stage II or III breast cancer at South Egypt Cancer Institute

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Abstract:

Background: Adjuvant chemotherapy administration before breast irradiation decreases the risk of systemic recurrence, However, delaying the administration of radiotherapy after surgery could result in higher local failure. Concurrent chemoradiotherapy may yield better local control with minimal toxicity.

Methods: This retrospective study included 46 female patients with stage II or III breast cancer who underwent breast conservative surgery. Adjuvant chemotherapy administered was 4 cycles of AC (Doxorubicin 60 mg / m^2 and Cyclophosphamide 600 mg / m^2) followed by 4 cycles of Paclitaxel (175 mg / m^2) given intravenously every 3 weeks. Adjuvant radiotherapy was given concurrently with the first 2 cycles of paclitaxel. The radiotherapy dose delivered was 50 Gy/ 25 fractions / 5 weeks to the whole breast with a tumor bed boost of 16 Gy. Regional lymphatics were included when indicated.

Results: In this study, the median follow-up period was 61 months, disease-free survival (DFS) was 86.6 %, overall survival was 89%, local recurrence was reported in only 2 patients (4.3%), and distant metastasis was reported in 4 patients (8.7%). There was no grade 2 or 3 toxicities 6 weeks after finishing radiotherapy. Late skin toxicity (telangiectasia, hyperpigmentation, and subcutaneous fibrosis) was assessed and showed that after 60 months of radiotherapy, most patients had grade 0 toxicity with no grade 2 or 3 toxicity. Cosmesis was evaluated and after 60 months of radiotherapy, 20 (46.5%) patients scored good, 15 (34.9%) excellent, 7 (16.3%) fair, and only one patient (2.3%) showed poor cosmesis. Regarding pulmonary toxicity, only 2 patients developed grade 3 acute radiation pneumonitis and as for chronic lung toxicity after 60 months of radiotherapy, 37 patients (86%) were grade 0 and had no grade 3 toxicity. Cardiac toxicity was evident in only 3 patients (6.5%). Regarding lymphedema, most patients that showed lymphedema were grade 1.

Conclusion: Our results confirm the efficacy and safety of concurrent paclitaxel with radiotherapy after AC chemotherapy in breast cancer patients in terms of acute and late toxicity and disease control.

Keywords: Breast cancer, concurrent chemoradiotherapy, toxicity

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Introduction:

Chemotherapy (CT) and radiotherapy (RT) have well-established roles in the management of high-risk and early-stage breast cancer. The ideal sequence for these therapeutic elements to be used is not yet confirmed. When adjuvant CT is given before RT, some retrospective analyses of earlier CT regimens have revealed higher rates of local recurrence, while others have revealed no increased risk. [1]

Adjuvant RT is postponed further as the adjuvant CT course is extended, adding to the overall treatment period. Longer therapy length unquestionably affects patients' lives and convenience, even though its impact on outcomes may be debatable. Therefore, the question

becomes whether giving RT sooner in the course of treatment is safe and effective. Although frequently linked to an increase in toxicity, Concurrent chemoradiotherapy (CCRT) has been extensively studied in various disease sites and is viable. [2–3] This practical approach has the benefit of reducing the overall treatment time, as well as the potential to boost RT's biological effectiveness and produce a synergistic effect on tumor management. [4]

Data supporting the addition of taxane CT to anthracycline-based regimens started to emerge about 20 years ago, especially in node-positive breast cancer. Such regimens have been demonstrated to improve overall survival (OS) and disease-free survival (DFS) (1). Also, early breast cancer patients who received taxanes in conjunction with CT experienced an increase in survival. [5]

CCRT in breast cancer started early with the CMF regimen. After 94 months of follow-up, there was a 4% local recurrence and a reasonable amount of local toxicity. [6] Two multicenter trials comparing concurrent with sequential therapy were conducted after that. The first is the Acrosein trial, which uses RT together with six cycles of CNF (cyclophosphamide, novantrone, and fluorouracil). The second involves a French study that substitutes epirubicin with Novantrone. They had no impact on DFS or OS but they both demonstrated an increase in local control. [7,8,9]

Later Paclitaxel was added to the concurrent regimen either weekly or every three weeks with greater toxicity. [9] Brustein et al. (2006) examined the effects of Paclitaxel combined with RT on 40 patients. It compared the 60 mg/m^2 dose of paclitaxel given every week with the 175 mg/m^2 dose given every 21 days (16 vs 24 patients). Pneumonitis incidence was lower with the three-weekly regimen (8% vs. 25%), making it more tolerable. [10]. Pneumonitis cases were absent in a second study by Chen et al. (2012) utilising the three-weekly regimen, and 4.7% of cases had grade III skin damage. [1] Using taxanes with RT has a sensitising effect, which is beneficial. As a mitotic inhibitor, it keeps the cells in the radiosensitive G2/M phase. [11]

The feasibility and tolerability of CCRT were evaluated in this retrospective study at the South Egypt Cancer Institute RT department with a particular focus on the patient's cosmetic outcomes.

Patients and Methods:

The records of 46 patients who received concurrent paclitaxel and radiotherapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for stage II or III breast cancer between 1 May 2014 to September 2016 at the Department of Radiotherapy, South Egypt Cancer Institute, Assiut University, Egypt were revised, then the patients followed up till the end of December 2021. The following criteria were previously used to enroll patients: female gender, age ≥ 18 years old with normal functioning cardiac, renal, and pulmonary functions, ECGO performance status 0-1, patients with histopathologically proven carcinoma of the breast, patients with stage II or III breast cancer (AJCC 2010) who underwent breast conservative surgery and received CCRT. All patients with stage I or IV breast cancer, patients who received adjuvant CT other than AC, patients with prior irradiation to the thoracic region, pregnant or lactating patients, and patients with serious comorbid diseases such as chronic obstructive pulmonary disease were excluded from this study. [12]

Treatment

Before beginning treatment, all these 46 patients from the South Egypt Cancer Institute got a thorough physical examination, a routine blood count, biochemistry, and a contrast-enhanced CT scan of the chest and abdomen.

a- Surgery

All patients underwent breast conservative surgery either lumpectomy or quadrantectomy and an ipsilateral axillary dissection as primary therapy according to the surgeon and margins were reviewed to ensure freedom from the tumor.

b- Chemotherapy

All patients received 4 cycles of CT, consisting of doxorubicin and cyclophosphamide (AC) [60 mg/m^2 and 600 mg/m^2 respectively] and 4 cycles of paclitaxel [175 mg/m^2] administered every 3 weeks after surgery.

c- Radiotherapy

After 4 cycles of AC, RT was started in 3 to 4 weeks and was given concurrently with the first and second cycles of paclitaxel. Patients were treated with a linear accelerator using lateral and medial tangential fields to a dose of 50 Gy / 25 fractions / 5 weeks. Patients who had 4 or more involved axillary nodes or any number of involved axillary nodes with extracapsular extension had lymph node irradiation. Extra axillary RT was administered when Level I and II nodes were not removed, or less than 10 nodes were eliminated during axillary dissection. It was also administered when there was gross residual disease in the axilla. After lymph node dissection the axilla was not specifically targeted for cases of extracapsular extension. Supra and infraclavicular lymph nodes were irradiated per Radiation Therapy Oncology Group (RTOG) atlas contouring. Unless radiologically enlarged, internal mammary nodes did not receive radiation. The total whole breast RT dose is 50 Gy in 25-fractions 2Gy per fraction and 16 Gy for the boost. 6 MV photon beam is the energy used for the whole breast RT. Also, for the boost, we used a 6 MV photon beam.

Assessment and follow up

Patients were examined before RT, weekly during treatment, after 6 weeks of RT, 3 months after RT then after 12,24,36,48, and 60 months of RT. They were evaluated for disease recurrence and different toxicities (skin, subcutaneous tissue, lymphedema, cardiac and pulmonary toxicity). The required investigations were done accordingly, any suspicious lesion was subjected to biopsy, and also during the follow-up, patients were

subjected to mammography/ sonomamography/ CT/ MRI chest wall (in selected patients) to evaluate any local recurrence. Distant metastases were evaluated by both clinical and imaging examinations. Acute skin toxicity was graded based on RTOG acute toxicity scale. Late skin toxicity (telangiectasia and hyperpigmentation) and late subcutaneous toxicity (fibrosis) were graded using the RTOG/EORTC late radiation morbidity scoring scheme.

Cosmetic outcomes were subjectively assessed by the patients themselves and scored excellent, good, fair, and poor. Cardiac toxicity: all left-sided patients were assessed by echocardiography before starting treatment and once at 3 months after finishing RT. The fall of more than 10% ejection fraction (EF) was considered significant. Pulmonary toxicity: all patients were evaluated by chest X-ray and CT chest was carried out for symptomatic patients with negative chest X-rays. Acute pulmonary toxicity was graded according to the RTOG acute radiation lung morbidity scoring criteria. Chronic lung toxicity was scored using the RTOG/EORTC late radiation morbidity scoring scheme. Lymphedema: By measuring the arm circumference on both sides, all patients were evaluated for ipsilateral arm lymphedema.

Statistical analysis

SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22 was used for all statistical calculations. Quantitative data were statistically described in terms of mean ± SD and median (range) when not normally distributed. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. The Friedman test was used for comparing categorical data over time. Kaplan-Meier's method with log-rank test was used for OS and PFS analysis. The P-value is always 2 tailed set significant at 0.05 level.

Results:

The present study is a five-year retrospective study aimed to evaluate the efficacy and safety of the late effect of concurrent paclitaxel and breast RT, in addition, to assessing its associated late toxicity among breast cancer patients who attended South Egypt Cancer Institute, Assiut. This study included those 46 female patients with stage II - III (31 patients with stage II and 15 patients with stage III) who previously enrolled in the period from the 1st of May 2014 up to September 2016. [12] We retrospectively reviewed all files of those patients and then followed them up to the end of December 2021.

The demographic and clinical characteristics of the studied participants were summarized in Table 1. Their mean age was 47.26 ± 11.39 and ranged from 28 up to 70 years old, 30 patients (65.2%) were aged less than 50 years old, and 16 patients (34.8%) were aged ≥ 50 years old. [12]

More than half of the studied cases (73.9%) suffered from right-sided breast cancer. 31 patients (67.4%) have tumor grade 1, 14 patients (30.4%) have tumor grade 2, and only one case (2.2%) has tumor grade 3. The majority of the studied cases had infiltrating-ductal carcinoma which was documented in 43 cases (93.5%). Regarding the tumor size, 29 cases (63.0%) had T1, 15 cases (32.6%) had T2, and two cases (4.3%) had T3. For nodal metastasis, 32 cases (69.6%) had N1, eight cases (17.4%) had N2, and six cases (13.0%) had N3. 31 patients (67.4%) had stage II and 15 patients (32.6%) had stage III. Regarding the hormonal status among the studied participants; 36 (78.3%) had positive hormonal receptors, while ten cases (21.7%) had negative hormonal receptors, and eight cases (17.4%) had her2neu overexpression.

Table 1: Demographic and clinical characteristics of the studied patient's cohort (n=46). [12]

Variable name	N	(%)
Age (years)		
• Mean ± SD	47.26 ± 11.39	
• Median (range)	46 (28 – 70)	
Age groups		
• < 50 years	30	(65.2)
• ≥ 50 years	16	(34.8)
Breast side		
• Right	34	(73.9)
• Left	12	(26.1)
Tumor grade		
• Grade 1	31	(67.4)
• Grade 2	14	(30.4)
• Grade 3	1	(2.2)
Histology		
• IDC	43	(93.5)
• ILC	3	(6.5)
T stage		
• T1	29	(63.0)
• T2	15	(32.6)
• T3	2	(4.3)
N stage		
• N1	32	(69.6)
• N2	8	(17.4)
• N3	6	(13.0)
Tumor stage		
• Stage 2	31	(67.4)
• Stage 3	15	(32.6)
Hormonal status		
• Negative	10	(21.7)
• Positive	36	(78.3)
HER2		
• Negative	38	(82.6)
• Positive	8	(17.4)

ICD: infiltrating duct carcinoma: ILC: infiltrating lobular carcinoma. Quantitative data are presented as mean ± SD and median (range), and qualitative data are presented as number (percentage).

Disease relapse, Disease-free survival, and Overall survival

In our study, locoregional recurrence occurred in 2 patients (4.3%), 1 patient (2.2%) at the operative bed, and 1 patient (2.2%) at the axillary lymph nodes. Distant metastases were reported in 4 patients (8.7%), lung metastasis occurred in 2 patients (4.3%), bone metastasis occurred in 1 patient (2.2%) and liver metastasis occurred in 1 patient (2.2%). The development of loco-regional recurrence and distant metastasis among the studied patients was shown in Table 2.

Table 2: The development of loco-regional recurrence and distant metastasis among the studied of the studied patient's cohort (n=46).

	N	(%)
Loco-regional recurrence	2	(4.3)
At the operative bed	1	(2.2)
At axillary lymph nodes	1	(2.2)
Distant metastasis	4	(8.7)
Lung	2	(4.3)
Bone	1	(2.2)
Liver	1	(2.2)

Qualitative data are presented as numbers (percentages).

The median follow-up duration of the 46 breast cancer patients was 61 months (range, 30 to 68 months). During follow-up, 4/46 patients (8.7%) died because of tumor recurrence or metastasis. According to Kaplan-Meier analysis, after the 68-month OS rate was 89.0%. A total of 6/46 patients (13.0%) developed tumor recurrence. The median time to tumor recurrence was 61 months (range, 30 to 68 months). According to Kaplan-Meier analysis, the DFS rate after 68 months was 86.6%. DFS and OS curves of the studied breast cancer cases were shown in Figures 1 and 2, respectively. As shown in Table 3 factors affecting OS were T stage P value 0.004, N stage P value 0.001, and tumor stage P value 0.04. Factors affecting DFS were tumor grade P value 0.000, T stage P value 0.009, N stage P value 0.000, and tumor stage P value 0.004.

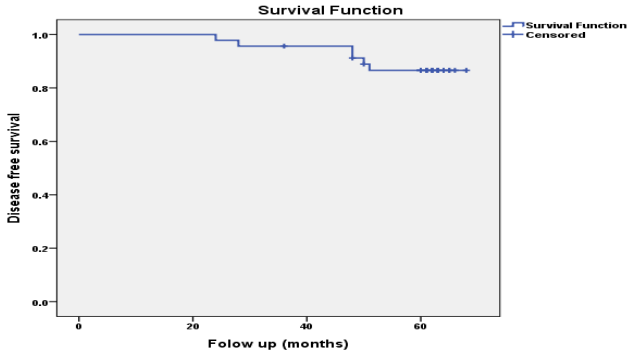

Figure 1: Disease-free survival curve of the studied breast cancer cases

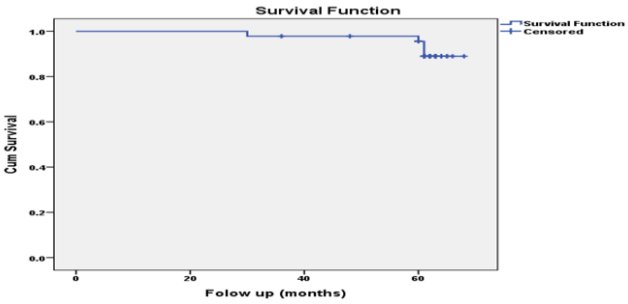

Figure 2: Overall survival curve of the studied breast cancer cases

Toxicity

The acute skin toxicity was previously assessed at the end of RT and 6 weeks after finishing the treatment. Acute grade 2 and 3 skin toxicity occurred in 9 (19.6%) and 3 patients (6.5%), respectively at the end of RT treatment, but after 6 weeks of RT, there was no grade 2 or 3 toxicity. [12]

Late skin toxicity (telangiectasia, hyperpigmentation, and subcutaneous fibrosis) was assessed 12, 24, 36, 48, and 60 months after finishing the treatment and showed that after 60 months of RT, most patients had grade 0 toxicity with no grade 2 or 3 toxicity. The incidences and grades of hyperpigmentation, subcutaneous fibrosis, and telangiectasia in the studied breast cancer cases were shown in Tables 4, 5, and 6, respectively.

Cosmesis was evaluated and after 60 months of RT 20 patients (46.5%) scored good, 15 (34.9%) excellent, 7 (16.3%) fair, and only one patient (2.3%) showed poor cosmesis. The incidence and grades of cosmesis of the studied breast cancer cases were shown in Table 7. Regarding pulmonary toxicity, only 2 patients developed grade 3 acute radiation pneumonitis within 3 months after treatment [12] and as for chronic lung toxicity after 60 months of RT, 40 (93%) patients were grade 0 and had no grade 3 toxicity. The incidence and grades of chronic radiation-induced pneumonitis in the studied breast cancer cases were shown in Table 8. The cardiac toxicity was evaluated by measuring the left ventricular ejection fraction at baseline and 3 months after radiotherapy 3 patients (6.5%) only developed cardiac toxicity. The development of cardiac toxicity in the studied breast cancer cases was shown in Table 9. As for lymphedema after 60 months of RT out of 43 remaining patients, 40 patients (93%) were grade 1, and 3 patients (7%) were grade 2 with no grade 3 lymphedema. The incidence and grades of lymphedema in the studied breast cancer cases were shown in Table 10.

Table 3: Overall survival and disease-free survival according to clinic-pathological details of the studied breast cancer cases (n=46).

	OS Estimate ± SE	P value	DFS Estimate ± SE	P value
Age groups		0.330		0.978
• < 50 years	96.7 ± 3.3		86.7 ± 6.2	
• ≥ 50 years	93.8 ± 6.1		86.5 ± 8.9	
Tumor grade		0.673		**0.000**
• Grade 1	96.7 ± 3.3		89.9 ± 5.5	
• Grade 2	92.9 ± 6.9		85.7 ± 9.4	
• Grade 3	100.0 ± 0.0		***	
T stage		**0.004**		**0.009**
• T1	100.0 ± 0.0		96.6 ± 3.4	
• T2	85.6 ± 9.5		69.6 ± 12.9	
• T3	100.0 ± 0.0		***	
N stage		**0.001**		**0.000**
• N1	100.0 ± 4.6		93.5 ± 4.4	
• N2	100.0 ± 0.0		100.0 ± 0.0	
• N3	66.7 ± 19.2		33.3 ± 19.2	
Tumor stage		**0.048**		**0.004**
• Stage 2	100.0 ± 4.6		96.6 ± 3.4	
• Stage 3	86.7 ± 8.8		66.7 ± 12.2	
Hormonal status		0.116		0.070
• Negative	88.9 ± 10.5		67.5 ± 15.5	
• Positive	97.2 ± 2.7		91.5 ± 4.7	
HER2		0.696		0.247
• Negative	94.6 ± 3.7		89.0 ± 5.2	
• Positive	100.0 ± 17.9		75.0 ± 15.3	

One case with tumor grade 3 and T3 showed local recurrence and its follow-up ended at 30 months.

Table 4: Incidence and grades of hyperpigmentation in the studied breast cancer cases (n=46).

Hyperpigmentation	N	Grade 0		Grade 1		Grade 2		Grade 3	
After 12 months of radiotherapy	46	36	(78.3)	9	(19.6)	1	(2.2)	0	(0.0)
After 24 months of radiotherapy	46	40	(87.0)	5	(10.9)	1	(2.2)	0	(0.0)
After 36 months of radiotherapy	46	41	(89.1)	4	(8.7)	1	(2.2)	0	(0.0)
After 48 months of radiotherapy	44	38	(86.4)	5	(11.4)	1	(2.3)	0	(0.0)
After 60 months of radiotherapy	43	40	(93.0)	3	(7.0)	0	(0.0)	0	(0.0)
P value (overtime)					**0.051**				

Qualitative data are presented as numbers (percentages). Significance defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Table 5: Incidence and grades of subcutaneous fibrosis in the studied breast cancer cases (n=46).

Subcutaneous fibrosis	N	Grade 0		Grade 1		Grade 2		Grade 3	
After 12 months of radiotherapy	46	33	(71.7)	8	(17.4)	5	(10.9)	1	(2.3)
After 24 months of radiotherapy	46	33	(71.7)	12	(26.1)	1	(2.2)	1	(2.3)
After 36 months of radiotherapy	46	30	(65.2)	15	(32.6)	1	(2.3)	0	(2.2)
After 48 months of radiotherapy	44	27	(61.4)	16	(36.4)	0	(0.0)	0	(0.0)
After 60 months of radiotherapy	43	40	(93.0)	3	(7.0)	0	(0.0)	0	(0.0)
P value (overtime)					**<0.001**				

Qualitative data are presented as numbers (percentages). Significance defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Table 6: Incidence and grades of telangiectasia in the studied breast cancer cases (n=46).

Telangiectasia	N	Grade 0		Grade 1		Grade 2		Grade 3	
After 12 months of radiotherapy	46	42	(91.3)	3	(6.5)	1	(2.2)	0	(0.0)
After 24 months of radiotherapy	46	43	(93.5)	2	(4.3)	1	(2.2)	0	(0.0)
After 36 months of radiotherapy	46	43	(93.5)	2	(4.3)	1	(2.2)	0	(0.0)
After 48 months of radiotherapy	44	41	(93.2)	2	(4.5)	1	(2.3)	0	(0.0)
After 60 months of radiotherapy	43	42	(97.7)	1	(2.3)	0	(0.0)	0	(0.0)
P value (overtime)					0.287				

Qualitative data are presented as numbers (percentages). Significance defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Table 7: Incidence and grades of cosmesis of the studied breast cancer cases (n=46).

Cosmesis	N	Fair		Good		Excellent		Poor	
After 24 months of radiotherapy	46	9	(19.6)	15	(32.6)	15	(32.6)	7	(15.2)
After 36 months of radiotherapy	46	11	(23.9)	19	(41.3)	15	(32.6)	1	(2.2)
After 48 months of radiotherapy	44	9	(20.5)	19	(43.2)	15	(34.1)	1	(2.3)
After 60 months of radiotherapy	43	7	(16.3)	20	(46.5)	15	(34.9)	1	(2.3)
P value (overtime)					**0.038**				

Qualitative data are presented as numbers (percentages). Significance is defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Table 8: Incidence and grades of chronic radiation-induced pneumonitis in the studied breast cancer cases (n=46).

Chronic radiation pneumonitis	N	Grade 0		Grade 1		Grade 2		Grade 3	
After 12 months of radiotherapy	46	33	(71.7)	11	(23.9)	2	(4.3)	0	(0.0)
After 24 months of radiotherapy	46	33	(71.7)	11	(23.9)	2	(4.3)	0	(0.0)
After 36 months of radiotherapy	46	33	(75.0)	11	(25.0)	2	(4.7)	0	(0.0)
After 48 months of radiotherapy	44	34	(77.3)	10	(22.7)	0	(0.0)	0	(0.0)
After 60 months of radiotherapy	43	40	(93.0)	3	(7.0)	0	(0.0)	0	(0.0)
P value (overtime)					**<0.001**				

Qualitative data are presented as numbers (percentages). Significance defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Table 9: Development of cardiac toxicity in the studied breast cancer cases (n=46).

Cardiac toxicity	N	(%)
No	43	(93.5)
Yes	3	(6.5)

Qualitative data are presented as numbers (percentages).

Table 10: Incidence and grades of lymphedema in the studied breast cancer cases (n=46).

Lymphedema	N	Grade 0		Grade 1		Grade 2		Grade 3	
At the end of radiotherapy	46	0	(0.0)	38	(82.6)	5	(10.9)	3	(6.5)
After 3 months of radiotherapy	46	0	(0.0)	36	(78.3)	10	(21.7)	0	(0.0)
After 12 months of radiotherapy	46	0	(0.0)	40	(87.0)	4	(8.7)	2	(4.3)
After 24 months of radiotherapy	46	0	(0.0)	43	(93.5)	3	(6.5)	0	(0.0)
After 36 months of radiotherapy	46	1	(2.2)	39	(84.8)	6	(13.0)	0	(0.0)
After 48 months of radiotherapy	44	0	(0.0)	40	(90.9)	4	(9.1)	0	(0.0)
After 60 months of radiotherapy	43	0	(0.0)	40	(93.0)	3	(7.0)	0	(0.0)
P value (overtime)					0.051				

Qualitative data are presented as numbers (percentages). Significance defined by $p < 0.05$. During the study period, three cases were lost to follow-up.

Discussion:

Several retrospective studies have shown an increase in locoregional recurrence if the initiation of RT is delayed after surgery, with some even going so far as to say that postponing CT in favor of RT can raise the chance of distant metastasis and, as a result, lower survival. [1]

The 5-year DFS and OS in a study by Chen et al. in node-positive breast cancer following conservative therapy receiving concurrent paclitaxel and RT were 88% and 93%, respectively. [1] In another study by Ibrahim et al. conducted in node-positive stage II-III breast cancer after definite surgery receiving concurrent therapy there were no local recurrence and the OS and the DFS were 95% and 92.5% respectively. [11] After undergoing conservative surgery, the improvement in local control was comparable to a meta-analysis done by Huang et al. on operable breast cancer. The study compared CCRT and sequential CRT in terms of local and OS in the adjuvant setting. The odds of surviving without a local recurrence for 5 years increased significantly (OR: 0.39, 95% CI: 0.2-0.75, P=0.005) but there was no significant change in OS (OR: 0.62, 95% CI: 0.35-1.11, P=>0.05). [13]

Others have shown no increase in the risk of local recurrence when RT is given after completion of adjuvant CT [14-15] including National Surgical Adjuvant Breast and Bowel Project B-28. [16] where local recurrence at 5 years was 4.3% with AC and 4.7% with AC-paclitaxel. Prolonged treatment courses can also affect the patient's convenience. Briefly, the ideal sequencing of adjuvant RT and CT in breast cancer is not yet confirmed. So, the question is whether adjuvant RT and paclitaxel CT could be given safely concurrently after adjuvant AC CT in women with Stage II or III breast cancer. This study allowed earlier delivery of RT without delaying systemic CT. The extensive use of CCRT has not been commonly used because of the fear of the resulting toxicity. [1]

In a prospective Phase I CT dose-escalation research, Burstein et al. [10] included 40 Stage II or III breast cancer patients who underwent concurrent RT and paclitaxel either once a week or every three weeks. 4 of 16 patients (or 25%) who received weekly paclitaxel at a dose of 60 mg/m^2 together with concurrent RT experienced dose-limiting toxicity (DLT). Three of the four instances of DLT in this trial were caused by Grade 2 and Grade 3 pneumonitis (n = 1 and n = 2, respectively) that necessitated the use of steroids. Patients who received RT alongside paclitaxel at dosages ranging from 135 to 175 mg/m^2 administered every 21 days, on the other hand, did not experience DLT. Nevertheless, Grade 2 pneumonitis occurring in 2 of 24 patients (8%) did not necessitate steroid therapy. Major radiation dermatitis was not detected in either arm. These results imply that concurrent therapy is feasible and more tolerable when paclitaxel is given every 21 days. Similar to this, a prospective study from William Beaumont Hospital examined 20 women who had concurrent paclitaxel (175 mg/m^2) administration every 21 days along with RT after adjuvant anthracycline-based CT. Patients who underwent modified radical mastectomy (MRM) and breast-conserving surgery were included. According to this study, 13 patients (65%) experienced cutaneous toxicity of Grade 2 or above, while 4 patients (20%) developed radiation pneumonitis. [17] In a retrospective study conducted at the Massachusetts General Hospital, Taghian et al. reported the incidence of radiation pneumonitis in lymph node-positive breast cancer patients who received paclitaxel as part of their adjuvant CT along with breast irradiation either concurrently or sequentially. In this study, 41 women received adjuvant paclitaxel and RT, with 21 receiving treatments concurrently and 20 receiving them sequentially. Radiation was associated with a 15% risk of pneumonitis in the group receiving concurrent paclitaxel, as compared with an incidence of 1% among patients not treated with paclitaxel concurrently. [18]

In another study by Chen et al concurrent RT and 175 mg/m^2 of paclitaxel every 21 days for 4 cycles were administered without causing significant toxicity, The concurrent administration of paclitaxel with whole breast RT was largely deemed tolerable by the study's participants, with 42 of 44 patients finishing the prescribed course of treatment. None of the 43 RT patients experienced acute skin toxicity that necessitated treatment interruption. Although long-term cosmesis was satisfactory and late skin toxicity was acceptable, the volume of irradiated breast tissue showed a brisk skin reaction as one could anticipate [1].

Our study did not reveal any severe toxicity that would have necessitated interrupting CCRT with paclitaxel (175 mg/m^2/three weeks). All acute and chronic skin toxicities were mild with only three patients showing grade III toxicity at the end of radiotherapy at boost areas, which showed rapid resolution without interference. Such findings support our protocol's dermatological safety. Due to the pulmonary toxicity of paclitaxel. [19] Radiation pneumonitis was assessed, most patients showed mild respiratory symptoms, and only 2 patients had grade 3 toxicity which required antitussive and steroid treatment. There are no significant cardiac issues or more cases of lymphedema.

Our protocol showed good local control as we reported 86.6 % 5-year DFS, 2 patients developed local recurrence, 4 patients developed distant metastasis and OS was 89 %. To demonstrate the projected survival advantages of CCRT in the adjuvant setting for breast cancer, longer follow-up on a greater number of patients is advised.

Conclusion:

Following breast-conserving surgery, concurrent paclitaxel CT and RT reduced the overall treatment time, resulted in excellent local control, was well tolerated without severe pulmonary toxicity, and had positive cosmetic results. Therefore, our study confirms the efficacy and feasibility of CCRT in stage II and III breast cancer following breast conservative treatment.

Ethical statement

Faculty of Medicine ethical committee at Assiut University in Egypt has evaluated and approved the study. Before being enrolled in the trial, each patient provided their informed permission.

List of abbreviations

DFS	Disease-free survival
CT	Chemotherapy
RT	Radiotherapy
CCRT	Concurrent chemoradiotherapy
OS	Overall survival
DFS	Disease-free survival
RTOG	Radiation Therapy Oncology Group
EF	Ejection fraction
SPSS	Statistical package for the social science
DLT	Dose-limiting toxicity
MRM	Modified radical mastectomy

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