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Original article

# Evaluation of Concurrent Adjuvant Chemotherapy Paclitaxel and Radiotherapy in Breast Conserving Management of Early Breast Cancer

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## ABSTRACT

**Background:** Breast cancer is the commonest malignancy affecting women. Today, Breast conserving surgery (BCS) plus radiation therapy is the standard treatment for early Breast Cancer as a loco-regional treatment modality. BCS provides much better cosmetic effect, compared to radical treatments; it provides the same level of overall survival as seen in patients treated with mastectomy. The proper sequence of delivering chemotherapy and radiotherapy is not established yet. Current standard treatment sequence is chemotherapy followed by radiotherapy.
**Aim:** Assess tolerability of patients by following up acute side effects associated with concurrent chemotherapy and radiotherapy. Assess cosmetic outcome.
**Methods:** This prospective study was carried in Clinical Oncology and Nuclear Medicine Department in Zagazig University Hospitals. It included 18 patients with early breast cancer, operated with BCS then received 4 cycles AC then received Whole breast radiotherapy concurrent with paclitaxel.
**Results:** Patients in this study found the concurrent administration of paclitaxel with whole-breast irradiation to be tolerable, all patients completing the treatment protocol. Overall acute toxicity is absent in 88.9 % of patients with only mild skin reaction, mild GIT symptoms and accepted cardiac and pulmonary evaluation. Also, cosmoses were good and acceptable by patients with 88.9 % of patients found that the cosmetic outcome is good
**Conclusion:** Concurrent chemoradiotherapy with paclitaxel is a good option for patients with early-stage breast cancer as it delivers optimum protocol of treatment with shortening of overall time of treatment with acceptable and tolerable side effects and good cosmoses.
**Keywords:** breast cancers; radiotherapy; AC; paclitaxel.

## INTRODUCTION

Breast cancer is the commonest malignancy affecting women, accounting for 29 % of all female cancers and the second cause of cancer death in women after lung cancer **[1].** Breast cancer is the most common cancers in female in Egypt (32%) estimated using the results of the National Population-Based Registry Program of Egypt **[2].** On the other hand, mortality rate from breast cancer has declined dramatically due to the use of adjuvant treatment protocols, systemic chemotherapy, and radiotherapy, which are now used for their established benefit in local control of disease (radiotherapy)**,** Prevention of distant metastases (chemotherapy) **[3].**

Today, Breast conserving surgery (BCS) plus radiation therapy is the standard treatment for early

Breast Cancer as a loco-regional treatment modality. It is a safe and preferred therapeutic option in early breast cancers, because it provides the same level of overall survival as seen in patients treated with mastectomy with much better cosmetic effect, compared to radical treatments **[4]**.

The proper sequence of delivering chemotherapy and radiotherapy is not established yet. Current standard treatment sequence is chemotherapy followed by radiotherapy **[5]**. Anthracycline (AC)-based regimens showed significant superiority compared with other chemotherapy regimens as adjuvant treatment, studies demonstrated that the addition of taxanes to an AC-based regimen improved disease-free survival (DFS) and overall survival (OS) in high-risk patients with early breast cancer **[6].** Paclitaxel is a taxane binds to tubulin, the protein component of microtubules, simultaneously promoting their assembly and disassembly to form stable, nonfunctional microtubules **[7]**. Stabilization of microtubules blocks cells in the M phase of the cell cycle, inhibiting cell division and causing cell death **[8]**. Paclitaxel also acts as a radio sensitizing agent by blocking cells in the G2 phase **[9].** The use of adjuvant paclitaxel after Anthracycline-based chemotherapy will result in delay in the start of radiation therapy after breast-conserving surgery. Some studies have found that a delay in initiating radiation therapy to complete course of chemotherapy was associated with a statistically significantly increased rate of local recurrence and a delay of 6 months was associated with a statistically significantly lower overall survival rate **[10].** Concurrent chemo-radiotherapy (CCRT) is not the standard protocol of treatment in case of breast cancer; it has the advantage of shortening the duration of therapy by allowing RT and CT to start at the same time and may improve local control via the radiation-sensitizing effects of Chemotherapy **[11]**. Concurrent administration of CT and RT seems to be another option for patient treated by breast conserving surgery, but the toxicity remains questionable **[12].** The aim of this study was to assess tolerability of patients to concurrent chemotherapy and radiotherapy and to assess the cosmetic outcome.

## PATIENTS AND METHODS

This prospective study was conducted in the Clinical Oncology and Nuclear Medicine Department, Zagazig University from September 2019 to December 2020. Approval was taken from the research ethical committee of Faculty of Medicine, Zagazige university. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans and written consent was taken from patients included in the study.

### *Inclusion Criteria*

Age more than 18 years old, pathologically proven invasive breast carcinoma, early breast cancer patient's operated by breast conservative surgery stage (I, II, IIIA), all patients received 4 cycles of adjuvant chemotherapy AC, ECOG performance status = 0 – 1, normal CBC, normal liver & renal function tests, accepted ECHO and free metastatic workup.

### *Exclusion criteria*

Patients with stage IV disease, contraindications to radiotherapy or chemotherapy, patient underwent MRM, and uncontrolled systemic disease.

### *Study design*

Extended phase I clinical trial.

### *Operational Design*

For all study patients, the following data was reported; medical history, clinical examination includes general and local examinations. Bilateral mammography and ultrasonography were done. Pathological diagnosis based on histopathological specimens was done. Plain X-ray or chest computed tomography (CT) with contrast was done if indicated. Pelvi-abdominal U/S or CT pelvi-abdomen with contrast was also done if indicated. Bone scintigraphy was requested if indicated. Echocardiography was done for all patients to document ejection fraction and to exclude any pre-existing cardiac issues. Regarding laboratory investigations, complete blood picture, liver function tests, kidney function tests as a requirement for chemotherapy and tumor markers include CA15-3 and CEA were requested.

### *Surgery*

All patients underwent breast conserving surgery.

### *Chemotherapy*

Patients received adjuvant chemotherapy 4 cycles AC (Adriamycin 60 mg/m$^2$ + cyclophosphamide 600 mg/m$^2$) followed by:

Paclitaxel 175 mg/m$^2$ every 3 weeks for 4 cycles, concurrent with 3D Conformal radiotherapy, and starting of radiotherapy is with first dose of paclitaxel.

***Radiotherapy***

Dose of radiotherapy 50Gy/25Fr in 5 weeks, 5 days a week by use of opposed tangential fields to the whole Breast and\ or regional lymph nodes (by Elekta Precise Release 2.12 powered by Precise Plan Release 2.12-477.08 silicon graphic workstation (CPU ID: 17626888860)) followed by Boost of 10Gy/5Fr given to the tumor bed by electron beam with energy according to depth of tumor (9Mev, 12Mev).Tumor bed was delineated using preoperative clinical data, cavity seroma, or scar.

***Treatment plan of radiotherapy***

Immobilization of all patients were done by using a breast board, followed by CT scanning with slices thickness of 5mm start at 5 mm intervals from top of thyroid notch to 5 cm below contralateral inframammary fold. CT images then transferred to treatment planning system. Delineation and contouring included the GTV, and relevant organs-at-risk (OARs) were according to the Radiation Therapy Oncology Group (RTOG) recommendations (edition 2010).

***Treatment evaluation***

Chemotherapy toxicities were assessed before every cycle by clinical examination, laboratory investigations, patient complaints put into consideration (according to Common Terminology Criteria for Adverse Events). Radiotherapy toxicity and tolerability was assessed weekly and at the end of treatment and every 3 months for one year according to follow up protocol of breast cancer. Breast cosmeses was assessed by the RTOG and Harvard criteria. The cosmeses was assessed before initiation of radiotherapy, weekly during radiotherapy, at end of radiotherapy, and one month after radiotherapy, then every 3 months. This was done by patient (subjective) and physician (objective) and by comparing it with the contralateral untreated breast. Breast size, shape, texture, scar was recorded. Radiation pneumonitis was evaluated by symptoms, signs, and X-ray when needed. ECHO was done before initiation of treatment then follow up at 3, 6, and 9 months.

***Statistical analysis***

All data were collected, tabulated, and statistically analyzed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA). Continuous variables were expressed as the mean (average) ± SD & median (range), and the categorical variables were expressed as a number (percentage).

## RESULT

Basic Characteristics of patients are outlined in table (1); median age was 42 years (range 28 – 65 years). 72.2% of patient were premenopausal, 16% were postmenopausal. BSA range from (1.7-2.2). Half of patients had right breast. Tumor characteristics as illustrated in table (1); 88.9 % of patients had stage II breast cancer and all of them had adequate number of dissected lymph nodes (more than 10 lymph node dissected). Thirteen patients are hormonal positive and all of them are HER-2 negative. Chemotherapy tolerability of patients illustrated in table (2); thirteen patients developed grade I nausea and vomiting but was tolerated, five patients developed grade I neuropathy but was tolerated by medical treatment, four patient developed bone pain only one of them had severe bone pain which was relieved by use of analgesics (NSAIDS)**,** and two patients developed grade I anemia that treated with medical treatment (bone marrow support). None of patients developed neutropenia or neutropenic fever. Only one patient had delayed chemotherapy cycle (3$^{rd}$ cycle) due to severe bone pain.

The mean whole breast dose 49.3Gy and mean dose of ipsilateral lung 6.6GY and V20 of ipsilateral lung 10.2%, mean heart dose 2.5Gy, and V40 was 5.2%.

Radiotherapy tolerability and overall toxicity and cosmoses illustrated in table (3); eight patients developed grade I breast pain, three patients developed grade II breast pain which is tolerated and resolved after end of radiotherapy course. Nine patients developed dry desquamation during course of radiotherapy but didn't cause radiotherapy interruption, 50% of patients developed grade III hyper- pigmentation which then improved by time during follow up, and only four patients developed grade I breast edema with self-resolution. Only one patient had delayed radiotherapy due to acute radiation dermatitis in the form of breast pain, edema, dry desquamation. In general, overall acute toxicity is accepted and tolerable and cosmoses is accepted by physician and patients. Echo was done

for all patients before initiation of treatment then follow up every 3 months and its values remain in accepted values.

There is a significant correlation between irradiated breast volume and breast pain at the end of radiotherapy course (p-value = 0.029) but no significant correlation between irradiated breast volume and radiotherapy toxicity in regular follow up at 3,6,9, and 12 months.

Statistical analysis of results showed that there is no correlation between breast size and radiotherapy toxicity at end of radiotherapy course and during regular follow up and no significant correlation between breast size and overall toxicity and cosmetic outcome.

Median Body surface area for patients included in our study is 2 (1.7-2.2), statistical analysis of result shows no significant correlation between BSA and radiotherapy toxicity during regular follow up at 3,6,9, and 12 months. Also, no significant correlation between BSA of patients and overall acute toxicity and cosmetic outcome.

**Table 1:** Clinicopathological characteristics of the studied breast cancer patients (N=18).

| Clinicopathological characteristics | The studied breast cancer patients (N=18) | |
|---|---|---|
| | Number | Percent |
| **Age (years)** | | |
| **Mean±SD** | 43.88 ± 9.61 | |
| **Median (Range)** | 42 (28 – 65) | |
| **Menopausal status** | | |
| **Premenopausal** | 13 | 72.2% |
| **Perimenopausal** | 2 | 11.1% |
| **Postmenopausal** | 3 | 16.7% |
| **Affected side** | | |
| **Right breast cancer** | 9 | 50% |
| **Left breast cancer** | 9 | 50% |
| **Site of tumor** | | |
| **Upper outer quadrant** | 15 | 83.3% |
| **Lower outer quadrant** | 3 | 16.7% |
| **T stage** | | |
| **T1** | 1 | 5.6% |
| **T2** | 14 | 77.8% |
| **T3** | 3 | 16.7% |
| **N stage** | | |
| **N0** | 9 | 50% |
| **N1** | 7 | 38.9% |
| **N2** | 2 | 11.1% |
| **Clinical AJCC stage** | | |
| **Stage II** | 16 | 88.9% |
| **Stage III** | 2 | 11.1% |
| **Stage IIA** | 8 | 44.4% |
| **Stage IIB** | 8 | 44.4% |
| **Stage IIIA** | 2 | 11.1% |
| **IHC staining** | | |
| **ER positive** | 13 | 72.2% |
| **PR positive** | 12 | 66.7% |
| **HER2 positive** | 0 | 0% |

Continuous variables were expressed as the mean (average) ± SD & median (range).
Categorical variables were expressed as a number (percentage).

**Table 2:** Treatment tolerability among the studied breast cancer patients (N=18).

| Chemotherapy tolerability | The studied breast cancer patients (N=18) | |
|---|---|---|
| | Number | Percent |
| **Leukopenia/Neutropenia** | | |
| **G0** | 18 | 100% |
| **G1** | 0 | 0% |
| **G2** | 0 | 0% |
| **G3** | 0 | 0% |
| **Anemia** | | |
| **G0** | 16 | 88.9% |
| **G1** | 2 | 11.1% |
| **G2** | 0 | 0% |
| **G3** | 0 | 0% |
| **Nausea/vomiting** | | |
| **G0** | 4 | 22.2% |
| **G1** | 13 | 72.2% |
| **G2** | 1 | 5.6% |
| **G3** | 0 | 0% |
| **Alopecia** | | |
| **G0** | 0 | 0% |
| **G1** | 18 | 100% |
| **G2** | 0 | 0% |
| **G3** | 0 | 0% |
| **Neuropathy** | | |
| **G0** | 13 | 72.2% |
| **G1** | 5 | 27.8% |
| **G2** | 0 | 0% |
| **G3** | 0 | 0% |
| **Bone pain** | | |
| **Absent** | 14 | 77.8% |
| **Present** | 4 | 22.2% |
| **Chemotherapy interruption** | | |
| **No** | 16 | 88.9% |
| **Yes** | 2 | 11.1% |
| **Radiotherapy interruption** | | |
| **No** | 17 | 94.4% |
| **Yes** | 1 | 5.6% |

Categorical variables were expressed as a number (percentage).

**Table 3:** Radiotherapy toxicity among the studied breast cancer patients (N=18).

| Radiotherapy toxicity | End of RT (N=18) | | 3rd month (N=18) | | 6th month (N=18) | | 9th month (N=18) | | 12th month (N=18) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % |
| **Breast pain** | | | | | | | | | | |
| **G0** | 7 | 38.9% | 18 | 100% | 18 | 100% | 18 | 100% | 18 | 100% |
| **G1** | 8 | 44.4% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G2** | 3 | 16.7% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G3** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Dry skin** | | | | | | | | | | |

| Radiotherapy toxicity | End of RT (N=18) | | 3rd month (N=18) | | 6th month (N=18) | | 9th month (N=18) | | 12th month (N=18) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % |
| **G0** | 8 | 44.4% | 18 | 100% | 18 | 100% | 18 | 100% | 18 | 100% |
| **G1** | 9 | 50% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G2** | 1 | 5.6% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G3** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Hyper-pigmentation** | | | | | | | | | | |
| **G0** | 0 | 0% | 0 | 0% | 8 | 44.4% | 9 | 50% | 13 | 72.2% |
| **G1** | 0 | 0% | 10 | 55.6% | 9 | 50% | 9 | 50% | 5 | 27.8% |
| **G2** | 9 | 50% | 8 | 44.4% | 1 | 5.6% | 0 | 0% | 0 | 0% |
| **G3** | 9 | 50% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Induration/ fibrosis** | | | | | | | | | | |
| **G0** | 16 | 88.9% | 15 | 83.3% | 17 | 94.4% | 17 | 94.4% | 17 | 94.4% |
| **G1** | 2 | 11.1% | 3 | 16.7% | 1 | 5.6% | 1 | 5.6% | 1 | 5.6% |
| **G2** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G3** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Edema** | | | | | | | | | | |
| **G0** | 14 | 77.8% | 18 | 100% | 18 | 100% | 18 | 100% | 18 | 100% |
| **G1** | 4 | 22.2% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G2** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **G3** | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |

Categorical variables were expressed as a number (percentage).

**Table 4:** Overall toxicity and cosmetic outcome of the studied breast cancer patients (N=18).

| Overall toxicity and cosmetic outcome | The studied breast cancer patients (N=18) | |
|---|---|---|
| | Number | Percent |
| **Overall acute toxicity** | | |
| **Absent** | 16 | 88.9% |
| **Present** | 2 | 11.1% |
| **Overall late toxicity** | | |
| **Absent** | 18 | 100% |
| **Present** | 0 | 0% |
| **Cosmetic at 12 months by patient** | | |
| **Good** | 16 | 88.9% |
| **Excellent** | 2 | 11.1% |
| **Cosmetic at 12 months by physician** | | |
| **Good** | 5 | 27.8% |
| **Excellent** | 13 | 72.2% |

Categorical variables were expressed as a number (percentage).

## DISCUSSION

Breast cancer is the most common cancer in women and, over 1.5 million women (25% of all women with cancer) are diagnosed with breast cancer every year around the world **[13].** Although breast cancer incidence has risen during the past decades, mortality has decreased due to efforts of screening, early detection, increased awareness, and great development in treatment options **[14].** Early breast cancer treatment involves combination of local modalities [surgery, radiotherapy], systemic anticancer treatments (Chemotherapy+\- hormonal +\- targeted therapies) **[15]**. Today, BCS with radiotherapy is the preferred local treatment option for most of early breast cancer cases that provide local control of disease with good cosmoses **[15].** Although administration of adjuvant CT before RT has become a tradition practice in women with

early-stage breast cancer who undergo breast conservative surgery, the optimum sequencing of CT and RT still controversial. Several retrospective reports have suggested that delaying the initiation of RT for more than six months after surgery might increase the risk of locoregional recurrence **[16]**. Some believes that delay chemotherapy for initiation of radiotherapy may increase distant metastasis **[17]**.

Although, most believe that current sequencing of delivering chemotherapy then radiotherapy is the optimum option to decrease toxicity, we try in present study to encourage the concurrent option for delivering CT - RT as it helps in delivering optimum protocol of treatment without delay, decrease hospital visits, and have a biological synergy effect that can increase the efficacy of the treatment **[18].** At era of COVID-19 pandemic, we need to contribute to the statement of the World Health Organization (WHO) "to stop, contain, control, delay and reduce the impact of this virus at every opportunity". This translates into minimizing exposure and burden to both patients and healthcare providers without compromising oncological outcome, by minimizing the number of hospital visits with the goal of taking care of breast cancer patients by providing appropriate treatment within the shortest period of time and according to established guidelines **[19].** In the adjuvant setting, CCRT has been previously investigated using concurrent CMF with most observed toxicities were moist desquamation and pneumonitis **[20]** Also using anthracyclines, the most observed toxicities were hematological and cutaneous toxicity **[21].**

This study showed that no severe toxicity caused due to use of concurrent paclitaxel (175 mg/m$^2$) and whole breast radiotherapy (50Gy + 10Gy boost to tumor bed). Otherwise, all toxicities are mild in the form of mild GIT symptoms (which type of GIT toxicity), grade I anemia which occur with all chemotherapeutic regimens. Although taxanes especially paclitaxel is known to cause chemotherapy induced peripheral neuropathy (11-87%) **[22]**,

In the present study, only five patients developed grade I CIPN which is tolerated and transient. Although Paclitaxel is known of its pulmonary side effects **[23]**, none of our patients' developed symptoms of pneumonitis that need interruption of radiotherapy or steroid treatment this may attributed to use of paclitaxel every 3 weeks not weekly and, also using 3D conformal system. A prospective Phase I study of 40 patients with Stage II or III breast cancer patients who received concurrent radiation with paclitaxel either weekly or every 3 weeks, showed that dose-limiting toxicity was reached in 4 of 16 patients (25%) who received weekly paclitaxel at 60 mg/m$^2$ per week with concurrent radiation and, grade 2 and grade 3 pneumonitis requiring steroid treatment. In contrast, toxicity was not encountered in patients who received concurrent radiation with paclitaxel at doses ranging from 135 to 175 mg/m$^2$ given every 21 days **[24]**. These findings suggest that concurrent treatment is feasible and better tolerated with paclitaxel administered every 21 days. In contrast to the finding of our study, a retrospective study of 76 patients, chemotherapy used was AC for 4 cycles (Doxorubicin 60 mg/m2, Cyclophosphamide 600 mg/m$^2$, day 1 every 21 days) followed by Paclitaxel 80 mg/m$^2$ per week for twelve weeks concurrent with radiotherapy of the affected breast showed that 9.2 % of patients developed interruption of RT treatment due to skin toxicity and dermatitis grades 3 and 4.17 % of patients had interrupted chemotherapy due to blood toxicities, asthenia and arthralgia **[25],** These findings favor the use of paclitaxel every 3 weeks.

A retrospective study showed that concurrent paclitaxel chemotherapy and radiotherapy after breast-conserving surgery shortened total treatment time, provided excellent local control, and was well tolerated" after a phase II study of 44 patients with node-positive Stage II and III breast cancer who underwent breast-conserving surgery and 4 cycles of doxorubicin (60 mg/m$^2$) & cyclophosphamide (600 mg/m$^2$) were followed by 4 cycles of paclitaxel (175 mg/m$^2$) delivered every 3 weeks, radiotherapy was concurrent with the first 2 cycles of paclitaxel, the breast received 39.6Gy in 22 fractions with a tumor bed boost of 14Gy in 7 fractions, (77.8%) of patient enrolled in this study had a mild skin reaction ranging from erythema to dry desquamation, (16.7%) of patients had a small to moderate area of moist desquamation, and (5.6%) had a large area of moist desquamation qualifying as grade 3 acute toxicity. No cases of ulceration, hemorrhage, and none of patients developed pneumonitis requires steroid therapy **[18]**, these finding similar to our results that patients only develop mild skin reaction but none of our patients develop moist desquamation. Patients in our study found the concurrent administration of paclitaxel with whole-breast irradiation to be tolerable, whole patients completing the treatment protocol. Overall acute toxicity is absent in 88.9 % of patients with

only mild skin reaction, mild GIT symptoms and accepted cardiac and pulmonary evaluation. Also, long-term cosmoses were good and acceptable by patients with 88.9 % of patients found that the cosmetic outcome is good, these finding are similar to results of **Abbas et al. 2017 [26].**

## CONCLUSION

Concurrent chemoradiotherapy with paclitaxel is a good option for patient with early-stage breast cancer as it delivers optimum protocol of treatment with shortening of overall time of treatment with accepted and tolerable side effects and good cosmoses.

## LIMITATIONS

More studies on a large number of patients with longer time of follow up is needed for better assessment of chronic side effects and estimation of DFS and OS.

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