Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for stage II or III breast cancer

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Abstract.

Background: Radiation therapy after breast conserving surgery is a standard part of treatment for invasive breast cancer [12].. The authors found that delay in radiotherapy after surgery translated to increase in local recurrence.

Methods: This study included included 46 female patients with stage II-III (31patient stage II and15 Stage III) breast cancer who underwent conservative surgery. Then received 4 cycles of (AC) of doxorubicin (60 mg/ m2) and cyclophosphamide (600 mg/m2) intravenously every 21 days followed by 4 cycles of paclitaxel (175 mg/m2) intravenously over3 h, with actual body weight used to calculate surface area. Paclitaxel was administered every 21 days beginning 21 to 28 days after the fourth cycle of AC. Radio- therapy was delivered concurrent with the first 2 cycles of paclitaxel, with Day 1 of radiation coinciding with Day 1 of Cycle 1 of paclitaxel.

Results: Median age was 48 years: 60% of patients <50 years, most patients had stage II disease, and Grade II was the most common one. Invasive ductal carcinoma was reported in 94% and hormone receptors were positive in of p78.26% of patients. After median follow-up of 25 months, 2 year DFS was 93.5%, all patients were alive and ipsilateral local recurrence was reported in 2.2% only. 50% and 19.6% had Grade I and II acute skin toxicity respectively. At 12 months, grades (I) were reported as(26%) and no grade II skin toxicity was observed. telangiectasia, (34.7%) Grade I and completely disappeared after 24 month. Hyperpigmentation (6.5%,) Grade I. and also completely disappeared after 24 month. (Subcutaneous fibrosis, and lymphedema (13%-19.6) respectively while at 24 months grade II only reported as 6.5%lymphedema. Acute radiation pneumonitis reported as 8.7%grade I and 4.3% grade II while chronic pulmonary fibrosis reported as 6.5% grade I and 2.2% grade II. Only 1 patients (8.%) developed more than 10% drop in the left ventricular ejection fraction (LVEF).

Conclusion: The results of our study suggest there are no increased acute or late toxicities with comparable DFS and local control rates affiliated. with the concurrent use of radiotherapy with paclitaxel as prescribed .Large randomized trials and long term follow up are needed to confirm these favorable findings .

Key words: Breast cancer ,Concurrent radio-chemotherapy, Toxicity.

Introduction: Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012 (second most common cancer overall). This represents about 12% of all new cancer cases and 25% of all cancers in women [1]. The standard treatment is surgical excision of the primary breast tumor by lumpectomy or mastectomy [19] [20]... After surgery, systemic therapies and radiation are planned based on the pathologic features of the tumor, to achieve the maximal DFS and overall survival (OS) [2]. In higher-risk patients the standard treatment is to deliver chemotherapy first, then RT Although this approach is accepted, the right sequence of treatment is still a point of debate . In the adjuvant setting, systemic therapy and radiotherapy may be given sequentially, concurrently, or in a sandwich technique (that is radiotherapy, given between cycles of chemotherapy). But there is 10 retrospective studies proved that delaying in radiotherapy until completing cycles of chemotherapy lead to increase in local relapse from16% to 6%.Also, given radiotherapy more than 8 weeks after surgery may lead to duplication in local recurrence rate [3]. On the other hand some trial like CALGB which evaluate doxorubicin and cyclophosphamide with or without paclitaxel there. Patients who received paclitaxel delayed from initiation of radiation about 7-month. Five-year local-recurrence rates were 9.7% in women who received doxorubicin and cyclophosphamide compared with 3.7% in those who received the same regimen with paclitaxel[4]. **.So** this debate push use to evaluate the effect of concurrent use of both radio chemotherapy on recurrence rate and to evaluate it is safety. Taxanes may be a good choice for concurrent approach than CMF because of its properties in radio sensitization in several sites eg. Lung, Head and neck and esophagus[5] [16] [17].

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Patients and Methods

We enrolled 46 women diagnosed with Stage II or III, pathologically confirmed node-positive, invasive breast cancer in a Phase II, prospective, single-arm trial from May 2014 to September 2016.All patients underwent staging according to the American Joint Committee on Cancer criteria. Eligibility criteria included performance status of 0 or 1; normal cardiac function defined as left ventricular ejection fraction of 52% or greater as determined by echocardiogram; and normal hematopoietic, hepatic, and renal function. Patients with distant metastases at diagnosis or who had previously been treated with chemotherapy or breast RT were excluded. Patients underwent breast-conserving surgery involving either lumpectomy or a quadrantectomy and an ipsilateral axillary dissection as primary therapy according to surgeon, and margins were reviewed to ensure freedom from tumor.

Radiation: Patients lied in the supine position on a wing wedged board with the ipsilateral arm raised to the degree that allows treatment fields to be easily applicate . Radiopaque wires and markers were used to locate palpable breast tissue and visible surgical scars. Three tattoos were made on the thoracic skin to enable patient repositioning during treatment CT simulation was used for the localization and determination of the target volumes, organ at risk, and the field arrangement. The CT scans were done from the level of the larynx to the upper abdomen with both lungs were included and the scan thickness was 5 mm. The Whole Breast Clinical Target Volume (WB-CTV) included the glandular breast tissue and did not extend to cover the pectorals major, the ribs or the skin. The Whole Breast Planning Target Volume (WB-PTV) was generated by the addition of a 5 mm margin around the WB-CTV considering the presence of nearby organs at risk (OARs) while for the cranial and caudal directions a 10 mm margin was used The heart and ipsilateral lung were considered OARs. The heart was contoured from the pulmonary trunks superiorly to its base and included the pericardium. The major blood vessels were excluded. The ipsilateral lung was contoured in all its extension Treatment plans for the whole breast were generated using two opposed tangential beams. Beam weighting, gantry angles, wedges, and beam energies were determined to achieve optimal dose conformity and homogenous dose distribution as well as maximal avoidance of the heart and ipsilateral lung. supraclavicular L.N treated in patients who had 4 or more involved axillary nodes or any number of involved axillary nodes with extracapsular extension. Additional axillary radiation was given when axillary dissection was inadequate, defined as Level I and II nodes not resected or fewer than 10 nodes removed, and was also given when there was gross residual disease in the axilla. The axilla was not specifically targeted for cases of extra capsular extension after lymph node dissection. Internal mammary nodes were not specifically targeted. In those patients receiving supraclavicular nodal irradiation. The total whole breast radiation dose is 50Gy in 25-

fractions 2Gy per fraction. And 16 Gy for the boost The energy used for the whole breast radiotherapy is 6 MV photon beam .The energy used to the boost is 6 MV photon beam also.

Assessment and Follow up:

Patients were followed weekly during treatment and up to 6 weeks for assessment of acute toxicity and then every 3 months up to 2 years for evaluation of the late radiation toxicity, disease free survival and local control. The RTOG scoring system for radiation reactions was used to score radiation toxicity [6]. Late skin toxicities (telangiectasia and hyperpigmentation) and late subcutaneous toxicities (fibrosis) were graded using the modified late effects on normal tissues scoring system (LENT/Soma Tables .Cosmetic outcomes were subjectively assessed by the patient's their selves and scored as excellent, good, fair, and poor. All left sided patients were assessed by echocardiography before starting treatment and once at three months after finishing the radiation treatment [7]. Local DFS was calculated from date of diagnosis of ipsilateral tumor recurrence in the operated breast or overlying skin.

Statistical analysis: Data was analyzed using Graph pad Prism version 5. Univariate factors were analyzed using the chi-square test for categorical variables and differences were considered statistically significant at $P<0.05$.

Results:

Patient's characteristics: In our study the median age of our patients was 48 years with age ranged from 28to 70 years, 65.2% (n= 30) of patients were < 50 years of age, 67.4% (n=31) had grade 2 disease, and 93.4% (n=43) had infiltrating ductal carcinoma. 63%(n=29) of patients had T1 disease while 32.6 %(n=15) had T2 and 4.3%(n=2). The histopathological examination of the dissected axillary lymph nodes revealed that 69.5%(n=32) of patients had N1,17.4%(n=8)had N2and 13% (n=6)had N3.It was found that all patients (n=46) had negative surgical margins. Regarding the hormonal receptors, our present study showed that 78.26%(n=36) of patients had positive hormonal receptors and 21.73%(n=10) had negative hormonal receptors. All patients (n=46) received four cycles of cyclophosphamide (600 mg\m2) and doxorubicin (60mg\m2) and paclitaxel (175 mg\m2) delivered every 3 weeks .Radiotherapy was concurrent with first 2 cycles of paclitaxel .According to the laterality, 26% (n=12) of patients suffered from left side breast cancer and 73.9% (n=34) suffered from right breast cancer. Finally regarding the Her 2/new over-expression, it was found that 17.4%(n=8) of the patients had overexpression of the Her 2/new receptors while 82% (n=38)of the patients did not show Her 2/new over-expression.

Table (1): patient's characteristics

Variable	No.	%
1.Age at time of diagnosis:		
<50 years	30	65.2%
>50 years	16	34.8%
Range	28-70 years.	
Median	46years.	
2.Laterality:		
RT side	34	73.9%
LT side	12	26%
3.Quadrant site		
UO (upper outer)	20	43.4%
UI (upper inner)	6	13%
LO (lower outer)	10	21.7%
LI (lower inner)	6	13%
CE (central)	4	8.6%
4.Tumor grade		
Grade 1	31	67.4%
Grade 2	14	30.4%
Grade 3	1	2%
5.Tumor histopathology		
IDC (infiltrating ductal carcinoma)	43	**93.4%**
ILC (infiltrating lobular carcinoma)	3	6.5%

6.T stage: **T1** **T2** **T3**	 29 15 2	 63% 32.6 4.4%
7.Node stage: N1 N2 N3	 32 8 6	 69.5 17.4 13
8.Hormonal Positive Negative	 36 10	 78.26% 21,73%
9.Her 2 new Over-expression: Yes NO	8 38	17.4% 82%

Disease relapse and DFS: In our study, the local relapse was reported in one patient (2.2%) , bone metastasis reported in one patient (2.2%) as well as liver metastasis reported in another patient (2.2%) at 15, 18, and 21 months of disease free interval (DFI) respectively The median follow up period was 25 months ranged, from 25 to 28 months and the median DFS is 25 months ranged from 15 to 28 months and the 2 year DFS was 93.5%(fig 1)Univariate analysis for the factors that may affect the DFS including the age (P value 0.357, Hazard ratio of 1.353, and 95% Cl of(0.711-2.574), TNM staging (P value0.901, Hazard ratio of 0.959, and 95% Cl of (0.497-1.850), and hormonal receptor status (P value 0.388, Hazard ratio of 0.763, and 95% Cl of(0.413-1.410) showed no factor of them has significant effect on the patient DFS as shown in table (2).

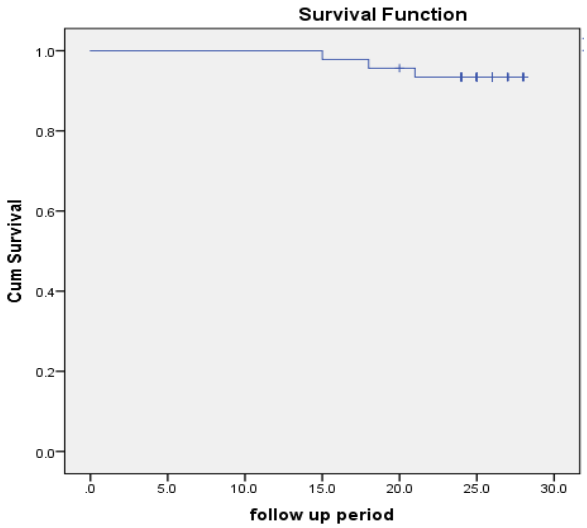

Figure (1): the DFS for all patients

Table (2): Univariate analysis of the 2 years DFS:

Variable		2 year DFS %	P value	Hazard Ratio (HR)	95% Cl of Ratio
Age at diagnosis		90% 100 %	0.357	1.353	0.711- 2.574
TNM staging		97% 87%	0.901	0.959	0.497- 1.850
Hormonal status		96.2% 90 %	0.388	0.763	0.413- 1.410

In figure 3, the 2 years DFS rates were 90% and 100 % for patients with<50 years and those with >50 years of age respectively (P value > 0.05).

Toxicity: The acute radiation dermatitis was assessed at the end of radiotherapy and at 6 weeks after finishing the treatment and it was noted that grade 3 skin was shown in 3 patients (6.5%) grade 2 skin toxicity was shown in 9 patients (19.6%) at the end of radiotherapy and disappeared after 6 weeks of treatment Factors that may affect the grade and the incidence of acute radiation dermatitis were studied and there were no significant differences (P value > 0.05) The incidence and the grades of telangiectasia at 12 and 24 months of follow up where there was no grade 3 telangiectasia at any time of follow. Grade 1 hyperpigmentation was reported in 4 patients and grade 2 in one patient at 12 months of follow up whereas only 3 patients showed grade 1 at 24 months of follow up .Grade 1 subcutaneous fibrosis was reported in 6 patients (13%) and grade 2 in 5 patients (10.9%) at 12 months of follow up whereas 11(23.9%) patients showed grade 1 at 24 months of follow up. Factors that may affect the grade and the incidence of subcutaneous fibrosis including the age(P value 0.41), laterality(P value 0.27), T N M staging (P value 0.13), and the hormonal receptor status(P value 0.208) were studied and there were no significant difference as Acute and chronic lung toxicity were reported , 6 patients only (13%) developed acute pneumonitis, 2 of them only(4.3%) received antitussive and steroid therapy (grade 2) within 3 months after treatment, while regard the chronic lung toxicity, only one patient(2.2%) who received treatment (grade 2) from 4 patient (8.7%) that developed the toxicity. Factors that may affect the grade and the incidence of acute lung toxicity including the age (P value 0.505) laterality(P value0.356)). T N M staging (P value 0, 622), and the hormonal receptor status(P value 0,06) were studied and there were no significant difference .The cardiac toxicity was evaluated by measuring the left ventricular ejection fraction at base line and at 3 months after radiotherapy. In our study we had only 1asymptomatic patients (8.3%) who showed drop more than 10% below the showing the grades and the incidence of cosmetic outcome that are graded using the four grades Harvard scale. Excellent and good cosmoses were reported in **35** patients **(76%)** while fair and poor cosmoses were reported in 1**1** patients only **(23.9%).** Different prognostic factors that may affect cosmoses including the age (P value **0.949),** laterality (P value **0.406),** TNM staging (P value **0.216),** and the hormonal receptor status (P value **0.149)** were studied and there were no significant difference

Discussion: several retrospective trial have shown that delaying radiotherapy after chemotherapy will increase local recurrence) [13] [14] [8]. .Thus we determine to examine if concurrent use of radiotherapy with adjuvant paclitaxel is safe and feasible or not in women with Stage II or III breast cancer after CBS and 4 cycles of AC(doxorubicin and cyclophosphamide**) [15] [18]**. This phase II trial allowed earlier delivery of radiation without affecting systemic therapy. Burstein et al. (2006) examined 40 patient with breast cancer after CBS(breast conserving surgery) and 4 cycles of AC to receive concurrent radio -chemotherapy 16 patients receive weekly paclitaxel(60 mg/m2) with radiotherapy and 24 patients to receive paclitaxel every 3 weeks (175 mg/m2) Dose-limiting toxicity was(25%)in patients who receive weekly paclitaxel 4 of 16 patients Grade 2 pneumonitis (n = 1) and Grade 3 pneumonitis (n = 2) treated by steroid accounted for 3 of the 4 of DLT in this trial and (8%) in those who receive paclitaxel every 3 weeks 2 of 24

(Grade 2 pneumonitis not requiring steroid therapy) [9]. Hanna et al .(2002)examine 20 patients both after CBS and MRM to receive concurrent paclitaxel with radiotherapy after 4 cycles of AC (20%) develop pneumonitis and (65%) had Grade 2 cutaneous toxicity or more the increased toxicity in this trial may be due to patient selection with 60% of patients under went MRM (modified radical mastectomy) [10] . Chen et al.(2012) also evaluate the same regimen in 44 women with Stage II or III, node-positive ,invasive breast cancer acute Grade 3 skin developed in 2 patients No cases of had pneumonitis requiring steroid and according cosmetic assessment 51.4% was excellent ,29,7% was good ,18,9%was fair and 0% was poor.(they Used the Harvard Scale for scoring of cosmoses, the cosmetic outcomes were graded into 4 grades, excellent, good, fair, and poor outcome) and there is two other small trial examine the same regimen with favraboule out come. [11] [21] [22] . In our study we did not observe excessive toxicity with concurrent radiation treatment and 175 mg/m2 of paclitaxel every 21 days for 4 cycles, reaffirming the findings of Burstein et al.(2006) and finding of Chen et al.(2012) . Unlike the findings of Hanna et al, (2002) 0nly 2 of our patients had grade 2 pneumonitis (4.3%) not requiring steroids and only 3 patients had grade 3 skin toxicity (6.5%). According cosmetic outcome that are graded using the four grades Harvard scale. Excellent and good cosmetic were reported in 35 patients (76%) while fair and poor cosmoses were reported in 11 patients only (23.9%)) .In our study DFS was 93.5% which is comparable to chen et al.(2012).

Conclusion: The results of our study suggest there are no increased acute or late toxicities with comparable DFS and local control rates affiliated with the concurrent use of radiotherapy with paclitaxel as prescribed. Large randomized trials and long-term follow-up are needed to confirm these favorable findings.

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