Original Research   **Open Access**

Concurrent radiation therapy and docetaxel in adjuvant treatment of locally advanced breast cancer

Samy M. Algizawy[1*], Hoda H. Essa[1] and AbdelNaser S. Zaid[2]

*Correspondence: samyalgiz@yahoo.com

CrossMark
← Click for updates

[1]Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt.
[2]Department of General Surgery, Faculty of Medicine, Assiut University, Egypt.

Abstract

Purpose: To assess the safety and efficacy of the use of concurrent radiation therapy and docetaxel in adjuvant treatment oflocally advanced breast cancer (LABC).

Patients and methods: Between February 2009 and January 2013, 62 patients with LABC who underwent primary mastectomy or neoadjuvant chemotherapy (FEC) followed by mastectomy at Assiut University Hospitals were entered into this trial. Three to five weeks after mastectomy or after the last dose of adjuvant FEC, patients were given concurrent chemoradiotherapy. Weekly intravenously docetaxel (30 mg/m²) was given over 9 weeks.

Results: The median follow-up for all patients is 32 months (range 12–63). Forty-eight patients (77.4%) remain alive, 12 patients (19.4%) died due to breast cancer, and 2 (3.2%) from other nonrelated causes. The 3-year rate of local recurrence free survival (LRFS) and disease free survival (DFS)were 93.8% (95% CI, 87.8-99.8%) and 70.2% (95% CI, 58.8-81.6%, Figure 1) respectively. The 3-year overall survival rate was 89.4% (95% confidence interval [95% CI], 81.7-97.1%; Figure 2). Four (6.4%) patients experienced locoregional recurrence as the first site of recurrence and 22 (35.5%) patients developed distant metastases. Acute toxicities were moderate during concomitant chemoradiotherapy. Five patients (8.1%) had grade 3-4 radiation dermatitis. Grade 3-4 radiation pneumonitis developed in 2 patients. Long-term toxicity was rare.

Conclusion: Concurrent docetaxel and radiotherapyis an acceptable adjuvant regimen for patients withLABC. Although it does not apparently improve local control and/or survival, it shortened total treatment time, and was well tolerated.

Keywords: Concurrent radiation therapy, docetaxel, breast cancer

Introduction

Locally advanced breast cancer (LABC) and inflammatory breast cancer refer to a diverse and heterogeneous group of breast cancers. Patients with these cancers include those with operable disease at presentation (AJCC clinical stage T3 N1M0), inoperable disease at presentation (AJCC clinical stage T4 or N2 to 3M0), and inflammatory breast cancer (AJCC clinical stage T4dN0 to N3M0) [1]. This group represents only 2% to 5% of all breast cancers in the United States (1) while in Egypt, patients usually present with advanced stage of cancer [2].

Compared to patients with early breast cancer, patients with LABC are at a significantly higher risk of local recurrence and distant metastases and have a worse overall survival. According to Tumor, Nodes, Metastases (TNM) stage, five-year relative survival rates by stage for patients presenting with stage I, IIA, IIB, IIIA, IIIB, and IV disease were 95, 85, 70, 52, 48, and 18 percent, respectively [3]. Current guidelines recommend primary surgery or neoadjuvant therapy followed by surgery. Mastectomy remains the standard of care for most patients with locally advanced disease, but breast-conserving surgery can be

considered for carefully selected patients. Adjuvant radiation to the breast, chest wall, and draining lymphatics should be offered to all patients with clinical stage III disease [4].

The optimal way to integrate chemotherapy and radiation therapy (RT) after breast surgery for patients with breast cancer remains unknown [5]. However, the current standard is chemotherapy followed by whole-breast-irradiation (WBI). The delay of RT induced more frequent local recurrences [6-8]. From pooled data of 10 retrospective studies, delaying RT in favour of chemotherapy increased the risk of local relapse to 16% from 6% [9]. Concurrent treatment allows RT and chemotherapy to start temporally, shortens the duration of therapy, and potentially improves local control via the radiation sensitizing effects of chemotherapy [10].

Anthracyclines and taxanes are the backbone of most modern breast chemotherapy regimens. Anthracycline-based concurrent chemoradiotherapy (CCRT) has been associated with serious skin and cardiac toxicity [11]. The concurrent use of taxanes and WBI seems feasible. Taxanes are mitotic inhibitors that stabilize microtubules by promoting their assembly and preventing depolymerization [12,13]. After exposure to the taxanes, cells are arrested in the G2/M phase of the cell cycle, which is known to be the most radiosensitive phase of the cell cycle [14,15]. Docetaxel has been studied in combination with radiation in other solid tumors with favorable results. In phase II trials, the most commonly used schedule with concomitant radiation was docetaxel at 20 to 30 mg/m² per week [16].

The present study addressed the use of concurrent radiation therapy and docetaxel in adjuvant treatment of locally advanced breast cancer.

Patients and methods

Between February 2009 and Jan. 2013, 62 patients with locally advanced breast cancer who underwent primary modified radical mastectomy (MRM) or neoadjuvant chemotherapy followed by MRMat Assiut University Hospitals were entered into this pilot prospective trial. Patients should fulfill the following criteria.

Inclusion criteria

- Histological diagnosis of invasive adenocarcinoma of the breast.
- AJCC clinical stage III at presentation.
- Age ≥18 and ≤70 years old.
- Performance status (Karnofsky index) ≥ 80.
- Complete stage workup during the 4 weeks prior to the start of treatment. All patients must have baseline measurements of breast and nodallesions. All patients must have a bilateral mammogram, computed tomography (CT)-scan of the chest and abdomen and echocardiography. If there was bone pain, and/or alkaline phosphatase elevation, a bone scintigraphy was mandatory.
- Laboratory results (within 14 days prior to the start of adjuvant treatment): Hematology: neutrophils ≥1.5x10^9/l; platelets ≥100x10^9/l; hemoglobin ≥10 mg/dl; Hepatic

function: total bilirubin ≤1 upper normal limit (UNL); SGOT and SGPT ≤2.5 UNL; alkaline phosphatase ≤2.5 UNL. Renal function: creatinine ≤175 umol/l (2 mg/dl).

Exclusion criteria

- Prior radiotherapy for breast cancer.
- Bilateral invasive breast cancer.
- Pregnant or lactating women.
- Any M1 tumor.
- Pre-existing grade ≥2 motor or sensorial neurotoxicity (National Cancer Institute Common Toxicity Criteria version 2.0 [NCI CTC v-2.0]).
- Any other serious medical pathology, such as congestive heart failure; unstable angina; history of myocardial infarction during the previous year or high risk arrhythmias.

Treatment plan

Patients who didn't receive neoadjuvant chemotherapy were given the same regimen in the adjuvant sitting. Neoadjuvant or adjuvant chemotherapy used in this study represented a standard anthracycline-based regimen. It consisted of three cycles of intravenous 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²) administered every three weeks (FEC) [17].

Three to five weeks after mastectomy or after the last dose of adjuvant FEC, patients were given concurrent chemoradiotherapy. Weekly intravenously(IV) docetaxel (30 mg/m²) was given over 9 weeks, with daily external beam radiation therapy (RT) administered concurrently during the first five to six weeks.RT started the day of the first docetaxel cycle and was given at least 2 hours after finishing docetaxel infusion. All patients were premedicated with IV dexamethasone 8 mg, ondansetron 8 mg IV, and ranitidine 50 mg IV infusion 30 minutes before chemotherapy.

Radiation therapy technique

The target volumes included treatment to the chest wall and draining lymphaticswhen indicated. The supraclavicular nodal regionwas treated in patients who had 4 or more involved axillary nodes orany number of involved axillary nodes with extracapsular extension. Additional axillary radiation was given when axillary dissectionwas inadequate, defined as Level I and II nodes not resected orfewer than 10 nodes removed, and was also given when there wasgross residual disease in the axilla. The axilla was not specifically targeted for cases of extracapsular extension after lymph node dissection. Internal mammary nodes were not specifically targeted. Patients were immobilized with their ipsilateral arm abducted (90 to 120 degrees) and externally rotated. Patients were placed on a 10- to 15-degree angle board to flatten the slope of the chest wall in the region of the sternum. The border between the chest wall and the supraclavicular fields is typically placed at the bottom of the clavicular head. Treatment portals consisted of opposing tangential fields using 6- to 10-MV photons. The lateral border of this field was matched to the photon tangent fields that were

created with matched nondivergent deep and cranial borders. A nondivergent cranial border was created through rotation of the couch, and a nondivergent deep border was achieved by overrotating the gantry or a half-beam block. The collimators were rotated to match the chest wall slope, and any volume that extended into the supraclavicular field is blocked. These fields were matched to a supraclavicular/axillary apex field. All patients were planned with two-dimensional planning. All chest wall radiation fields were designed to avoid irradiating the heart. Initial fields and target volumes were treated to a total dose of 50 Gy in 25 fractions over 5 weeks. For patients with skin involvement a 5–10-mm bolus was applied for 50% of the dose every other day to cover skin and dermal lymphatics.

During chemoradiotherapy, patients were evaluated weekly for acute toxicity and compliance with the protocol. Clinical examination and complete blood count were performed. An absolute granulocyte count of less than 1,500/mm³ or a platelet count of less than 100,000/mm³ beforeeach cycle resulted in a treatment delay of at least 1 week. Treatment was stopped if hematologic recovery took more than 5 weeks. No dose reductions were planned. RT was interrupted if grade 3 cutaneous or pulmonary toxicity occurred.

Concerning HER2 status, none of the patients with HER2 positive disease were treated with neoadjuvant or adjuvant trastuzumab, due to financial reason. All women who were shown to have estrogen receptor–positive and/or progesterone receptor-positive tumors were prescribed 20 mg daily of tamoxifen, which was started 3 weeks after the last dose of docetaxel.

The trial was approved by the ethics committee of the Faculty of Medicine, Assiut University, and allpatients provided a written informed consent.

Follow-up and end points
Patients were followed every three months for the first two years after the last cycle of adjuvant chemotherapy and thereafter every six months for 5 years. Mammography was performed annually. The primary end point was Disease free survival (DFS), defined as the time from enrolling in the study to the first treatment failure or death. Secondary end points were the incidence of adverse effects, local recurrence-free survival (LRFS) defined as the time from enrolling in the study to the first treatment locoregional relapseor death and overall survival (OS) calculated from the time of diagnosis to the time of the last follow-up visit or death.

Toxicity evaluation
Skin, lung and esophageal toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG) scale for acute and late effects. Other toxic side effects werescored according to National Cancer Institute Common Toxicity Criteria version 2.0 [NCI CTC v-2.0].

Statistical analysis
The Kaplan-Meier method was used to estimate the rates of DFS, LRFS, and OS. Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL).

Results
Patients and disease characteristics are summarized in **Table 1**. Sixty-two patients were recruited in this study, 46 (74.2%) of them underwent neoadjuvant FEC followed by MRM. All of the remaining 16 patients who underwent primary MRM received 3 cycles of adjuvant FEC. Patients in clinical stages IIIA, -B, and -C were 38.7%, 45.2%, and 16.1% respectively. No patients had inflammatory breast cancer. Underwent primary mastectomy or neoadjuvant chemotherapy followed by mastectomy. Estrogen receptor (ER)-positive expression was found in 56.5%, and in 54.8% for progesterone receptor (PgR). Low/moderate histological grade was 56.5, while high grade stood at 43.5%. Human epithelial growth factor receptor 2 (HER2) expression wasfound in 27.4%.

Treatment compliance
Thirty eight (61.3%) patients received supraclavicular irradiation, and a posterior axillary supplement was used in eleven(17.7%) patients. RT treatment had to be interrupted in 13 (21%) patients; 5 (8.1%) of them were due to skin toxicity grade 3, six were due to machine malfunctions and two due to patient choice. Two patients received less than 50 Gy.

Table 1. Patient and Tumor Characteristics.

Patient and Tumor Characteristics	No. of patients (%)
Age: median (range) months	51.5 (26-70)
Menopausal status:	
Pre/perimenopausal	32 (51.6)
Postmenopausal	30 (48.4)
T- stage	
T3	38 (61.3)
T4	24 (38.7)
N- stage	
N0	5 (8.1)
N1	19(30.6)
N2	23 (37.1)
N3	15 (24.2)
TNM stage	
IIB	15 (24.2)
IIIA	17 (27.4)
IIIB	20 (32.3)
IIIC	10 (16.1)
Grade	
I	5 (8.1)
II	30 (48.4)
III	27 (43.5)
Estrogen receptor	
Negative	27 (43.5)
Positive	35 (56.5)
Progesterone receptor	
Negative	28 (45.2)
Positive	34 (54.8)
HER2/neu	
Negative	39 (62.9)
Positive	23 (37.1)

Three patients (4.8%) of the whole group developed grade 1-2 hypersensitivity reactions to docetaxel (in the form of palpitation and chest pressure) and they were re-challenged successfully with slower rates of infusion. Three patients discontinued docetaxel after the third to sixth weekly doses due to grade III neuropathy.

Outcome and pattern of failure (Table 2)

The median follow-up for all patients is 32 months (range 12–63). Forty-eight patients (77.4%) remain alive,12 patients (19.4%) died due to breast cancer, and 2 (3.2%) from other nonrelated causes. The 3-year rate of LRFS and DFS was 93.8% (95% CI, 87.8–99.8%) and 70.2% (95% CI, 58.8–81.6%, **Figure 1**). The 3-year overall survival rate was 89.4% (95% confidence interval [95% CI], 81.7–97.1%; **Figure 2**). Four (6.4%) patients experienced locoregional recurrence as the first site of recurrence and 22 (35.5%) patients developed distant metastases. First sites of distant metastases were as follows: bone (16.1%), lung (6.4%), liver (4.8%) and brain (3.2%). Four patients had more than one recurrence site.

Toxicity

Both acute locoregional and Acute systemic toxicities were moderate during concomitant chemoradiotherapy. **Table 2** shows the incidences of grade 3/4 toxicities during concomitant chemoradiotherapy. Five patients (8.1%) had grade 3-4 radiation dermatitis. Grade 3-4 radiation pneumonitis developed in 2 patients.

Regarding docetaxel-induced systemic toxicity, seven patients (11.3%) developed grade 3-4 neutropenia, six (9.7%) had grade 3-4 anaemia and three (4.8%) had grade 3-4 thrombocytopenia. Grade 3-4 neuropathy occurred in three patients. There was no grade 3-4 gastrointestinal toxicity.

Long-term toxicity was rare. Skin pigmentation and telangectasia were recorded in 8.1%, and 3.2% of the study patients
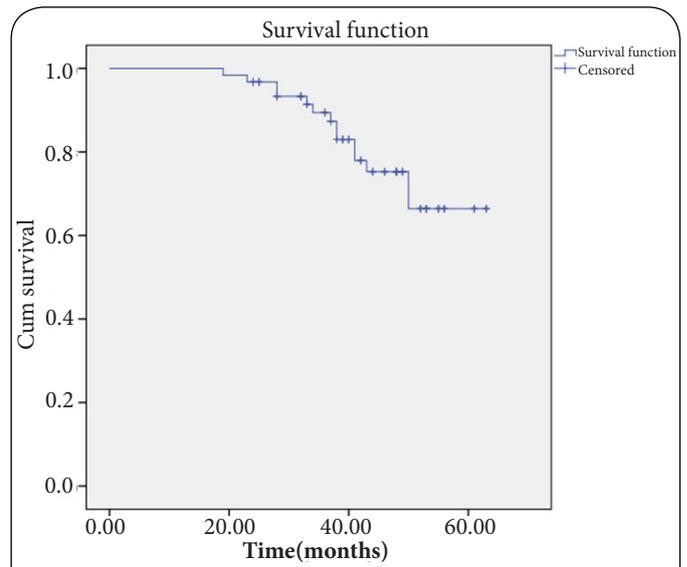

Figure 2. Overall survival of 62 patients with LABC receiving post-mastectomy concomitant Docetaxel and radiotherapy.

Table 2. Concomitant chemoradiotherapy-induced acute toxicity.

Toxicity	Number of patients (%)	
During concomitant chemoradiotherapy	All grades	Grades 3/4
Radiation dermatitis	48 (77.4%)	5 (8.1%)
Radiation pneumonitis	11 (17.7%)	2 (3.2%)
Anemia	24 (38.7%)	6 (9.7%)
Neutropenia	21 (33.9%)	7 (11.3%)
Thrombocytopenia	11 (17.7%)	3 (4.8%)
Neuropathy	10 (16.1%)	3 (4.8%)
Diarrhoea	6 (9.7%)	0
Esophagitis	6 (9.7%)	0
Febrile neutropenia	0 (0%)	0 (0%)

respectively. Each of radiation pneumonitis, and esophagitis were recorded in 3.2% of the study patients. There were no cases of subcutaneous fibrosis, brachial plexopathy or rib fracture.

Discussion

This trial was conducted to evaluate the impact of adjuvant concurrent RT and CT in locally advanced breast cancer.The main advantages of CCRT are: 1. delivering both treatments of CT and RT at same time; 2. Biologicalsynergy effect that can increase the efficacy of the treatment [18].

Early experiences with concurrent chemoradiation in early-stage breast cancer were evaluated in CMF-based chemotherapeutic regimens [19-22]. Although that treatment had an acceptable toxicity profile and a shortened overall treatment time, clinical benefit in terms of OS or DFS has not consistently been shown [11]. Moreover, CMF regimens are no longer commonly used. Since that initial experience, the feasibility of concurrent
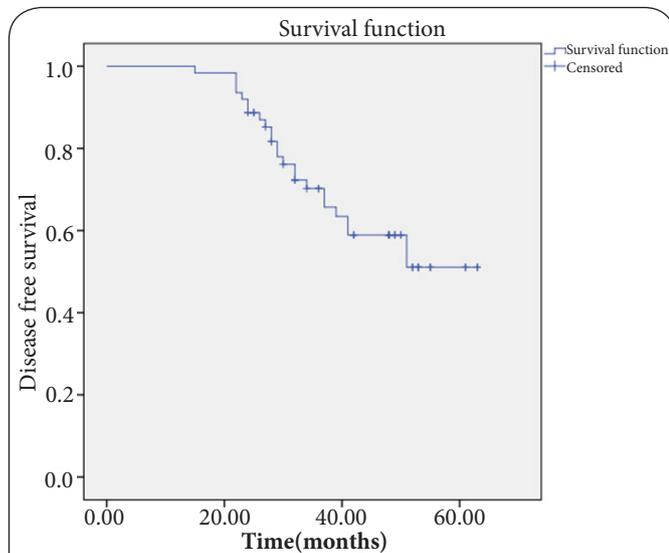

Figure 1. Disease Free survival of 62 patients with LABC receiving post-mastectomy concomitant Docetaxel and radiotherapy.

therapy has been explored in other chemotherapy regimens. Few prospective studies investigated CCRT using anthracycline regimen [23-26]. Fiets et al., [24] showed high rate of high grade skin toxicity, and more cardiac dysfunction, and concluded that this protocol cannot be used in practice. On the other hand, a retrospective study byIsmaili et al., compared 2 adjuvant treatments using CCRT, the first with anthracycline (group A) and the second with CMF (group B). At 5 years, the isolated LRFS was significantly higher in group A compared to group B (98.7% vs 95.3%; P=0.034). In addition, the use of anthracycline regimenswas associated with a higher rate of 5 years EFS (80.4% vs 75.1, P=0.057). The 5 years OS was 83.2% and 79.2% in the anthracycline and CMF groups, respectively (P=0.143) [10]. However, these results may be explained by theeffect of anthracycline regimen and not by the use ofCCRT [26].

In a multicentre randomized trial (Arcoseintrial), CNF (mitoxantrone 12 mg/m², in combination with cyclophosphamide 500 mg/m² and fluorouracil 500 mg/m²) every 21 days for 6 cycles, with RT starting during cycle 1, was compared with sequential CNF and RT. Unfortunately, the concurrent regimen failed to show any benefit in 5-year DFS and OS [27,28]. The 5-year DFS was 80% in both groups; P=0.83, LRFS was 92% in sequential versus 95% inconcurrent; P=0.76, and OS was 90% in sequential versus 91% in concurrent; P=0.76). Nevertheless, concurrent treatment was shown to improve local control in lymph-node-positive patients (the 5-year LRFS was 97% inconcurrent v 91% in sequential; P=0.02).

Similar results were seen in a French multicentre trial comparing concomitant CNF and RT with CEF (cyclophosphamide–epirubicin– 5-fluorouracil) and sequential RT [29]. Unfortunately, mitoxantrone has been associated with high rates of leukemic transformation; it is therefore now rarely used [11].

Taxanes may be a better choice for concurrent therapy than CMF and anthracyclines because of the former's radiation sensitizing properties [30,31]. The advantages of concurrent chemoradiation with taxanes have been well documented in the treatment of other malignancies such as lung [32,33]. However, the published literature regarding the concurrent administration of taxanes and RT in the treatment of breast cancer consists of small trials using varying treatment schedules and doses [34-40] providing no consensus. Paclitaxel was evaluated for concurrent therapy both in the neoadjuvant and adjuvant sittings.

In the neoadjuvant sitting, two phase i/ii prospective trials, one by Skinner et al.*,* [41] and the second by Kao et al., [42], in 29 and 33 patientswith labc respectively, showed a benefit from concurrent paclitaxel and rt , especially in locoregional control. Skinner et al., concluded that CCRT provides significant pathological response, in up to 33% of patients with locally advanced breast cancer, but with a significant postoperative morbidity rate. With a median follow-up of 43.8 months, Kao et al., reported 4-year actuarial locoregional control, disease-free survival, and overall survival of 83%, 33%, and 56% respectively. In the adjuvant sitting, Chen et al., [43] evaluated Concurrent paclitaxel chemotherapy and radiotherapy in 44 women with

node-positive Stage II and III breast cancer. Radiotherapy was concurrent with the first 2 cycles of adjuvant paclitaxel. The 5-year DFS was 88%, and OSwas 93%. There were nolocal failures [43].

Although docetaxel is highly active against breast cancer and more potent than paclitaxel in promoting tubulin polymerization, it is less well studied as concurrent therapy with radiation in breast cancer. In the neoadjuvant sitting, only a few studies have been published on radiation with concurrent docetaxel in breast cancer [36,44]. Karasawa et al., investigated whether the addition of docetaxel (40 mg/m² biweekly) to radiotherapy enhanced tumor response in patients with advanced or recurrent breast cancer. The rates of CR, PR, SD and PD for all patients were 40%, 37%, 11% and 11%, respectively.CR and PR rates were 9% and 82% for advanced disease patients, 54% and 17% for recurrent patients, Overall survival rates at 1 and 2 years after treatment were 83% and 49%, respectively [44]. Two other phase i/ii Canadian studies of neoadjuvant concurrent radiation with weekly docetaxel (30-35 mg/m²) in patients with locally advanced non-inflammatory breast cancer (otc 1159 and otc 1202) are under way, but have yet to report results [11]. Tapen et al., tested the feasibility of concurrent radiation with weekly docetaxel (30-35 mg/m²) in 33 post-mastectomy patients at high risk of local failure or recurrent disease. Mean TTP was 19.16 months. Five local failures occurred at 13–28 months [45].

In the current study, the 3-year OS and DFS rates were 89.4% and 70.2% respectively. These results are comparable to rates observed in a retrospective analysis done in our University [2]. This analysis assessed different sequential protocols and not concomitant chemotherapy and radiotherapy in LABC. DFS was estimated at 2.5 years, and it was 83.5%, 82.3% and 80% for patient receiving radiation before chemotherapy [group A], sandwich [group B] and after finishing chemotherapy [group C] respectively (p>0.5). In another similar Egyptian retrospective analysis, Abu-Hamar et al., reported 5-year OS and DFS and LRFS rates of 71.8%, 67.6% and 90.9% respectively [46]. A similar 3-year LRFS (93.8%) was found in our patients indicating that no benefit was added from docetaxel as a radiosensitizer.

In our study we did not observe excessive toxicity with concurrent radiation treatment and docetaxel. Five patients (8.1%) had grade 3-4 radiation dermatitis while grade 3-4 radiation pneumonitis developed in 2 patients. Other investigators found some what different results, most likely because of differences in the details of both the chemotherapy agents and doses and radiotherapy. No cases of pneumonitis were reported tohave occurred in a group of 202 patients treated at the Princess Margaret Hospital in Toronto with concurrent radiotherapy and CMF [22]. Five percent of patients (4 of 87 patients) in a report of the "triple M" program of the Royal Marsden Hospital [47] developed symptomatic radiation pneumonitis within 6 weeks of completing radiotherapy. The investigators found that the risk of pneumonitis was correlated with having 3 cm oflung in the tangential radiation field.

A prospective study from William Beaumont Hospital tested RT and concurrent paclitaxel (175 mg/m²) delivered every 21

days. The authors noted that radiation pneumonitis developed in 4 patients (20%), and 13 (65%) had Grade 2 cutaneous toxicity or higher [34]. In a retrospective analysis of the Massachusetts General Hospital experience, Taghian et al., [35] reported a 15% risk of pneumonitis in 21 patients treated with concurrentpaclitaxel and radiation as compared with an institutional incidenceof 1% among women not treated with paclitaxel. Recently, Chen et al., [43] reported thatnone of 44 patients had pneumonitis requiring steroids and acute Grade 3 skin toxicity was developed in only 2 patients.

On the other hand, a retrospective analysis from the University of Washington evaluated 44 women who received RT concurrent with either paclitaxel or docetaxel chemotherapy. There were no reports of pneumonitisal though a 20% rate of Grade 3 acute skin toxicity was seen. However, this group was more heterogeneous in treatment schema [36]. Hanna et al., [34] reported a higher-than-expected rate of radiation-induced pulmonary toxicity. They noted an increased rate of toxicity among those treatedwith MRM, which may be related to RT dose/field size. In the study conducted by Tapen et al., [45], all patients had radiation dermatitis. Four patients (8%) had grade 3 desquamation; none had grade 4 or 5. Chest wall/axillary or arm pain occurred in eleven patients. Grade 1-2 or grade 3 hematologic toxicity occurred in six and two patients respectively. Grade 1 neuropathy in three patients. Grade 1-2 nausea/vomiting occurred in eight patients. Grade 1-2 diarrhea occurred in three patients [45].

In accordance to the previous studies [22,34-36,43-46], late toxicity was unusual in the current trial. Skin pigmentation and telangectasia were recorded in 8.1%, and 3.2% of the study patients respectively. Each of radiation pneumonitis, and esophagitis were recorded in 3.2% of the study patients. There were no cases of subcutaneous fibrosis, brachial plexopathy or rib fracture.

We acknowledge some of the limitations of the current study. First, the sample size was too small to meaningfully stratify the patients' outcome by the risk factors. Second, the follow up period was relatively short and longer period is needed to confirm our results.

Conclusion

Our study showed that concurrent docetaxel and radiotherapy is an acceptable adjuvant regimen for patients with LABC. Although it does not apparently improve local control and/or survival, it shortened total treatment time, and was well tolerated without significant pulmonary toxicity. Longer follow up and larger randomized controlled clinical trials are needed to determine whether this regimen is superior to sequential regimens and to confirm the validity of such a strategy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors shared in research design and conduction and analysis of data. The main author (AlGizawy SM) wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

References

1. Burstein HJ, Harris JR and Morrow M. **MALIGNANT TUMORS OF THE BREAST in DeVita, Hellman, and Rosenberg's Principles &Practice of Oncology**. *Wolters Kluwer; Lippincott Williams &Wilkins*. 2011; 1438.

2. Abbas H, Elyamany A, Salem M, Salem A, Binziad S and Gamal B. **The optimal sequence of radiotherapy and chemotherapy in adjuvant treatment of breast cancer**. *Int Arch Med*. 2011; **4**:35. | Article | PubMed Abstract | PubMed FullText

3. Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, van der Geest LG, Janssen-Heijnen ML, Dekkers OM, van de Velde CJ and Westendorp RG. **Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients**. *Breast Cancer Res Treat*. 2010; **124**:801-7. | Article | PubMed

4. Buchholz TA and Haffty BG. **Breast Cancer: Locally Advanced and Recurrent Disease, Postmastectomy Radiation, and Systemic Therapies in: Perez and Brady's Principles and Practice of Radiation Oncology**. *Lippincott Williams & Wilkins, Philadelphia*. 2008; 1307.

5. Piroth MD, Pinkawa M, Gagel B, Stanzel S, Asadpour B and Eble MJ. **Sequencing chemotherapy and radiotherapy in locoregional advanced breast cancer patients after mastectomy - a retrospective analysis**. *BMC Cancer*. 2008; **8**:114. | Article | PubMed Abstract | PubMed FullText

6. Hartsell WF, Recine DC, Griem KL and Murthy AK. **Delaying the initiation of intact breast irradiation for patients with lymph node positive breast cancer increases the risk of local recurrence**. *Cancer*. 1995; **76**:2497-503. | PubMed

7. Buchholz TA, Austin-Seymour MM, Moe RE, Ellis GK, Livingston RB, Pelton JG and Griffin TW. **Effect of delay in radiation in the combined modality treatment of breast cancer**. *Int J Radiat Oncol Biol Phys*. 1993; **26**:23-35. | Article | PubMed

8. Recht A, Come SE, Gelman RS, Goldstein M, Tishler S, Gore SM, Abner AL, Vicini FA, Silver B, Connolly JL and et al. **Integration of conservative surgery, radiotherapy, and chemotherapy for the treatment of early-stage, node-positive breast cancer: sequencing, timing, and outcome**. *J Clin Oncol*. 1991; **9**:1662-7. | Article | PubMed

9. Huang J, Barbera L, Brouwers M, Browman G and Mackillop WJ. **Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review**. *J Clin Oncol*. 2003; **21**:555-63. | Article | PubMed

10. Ismaili N, Elmajjaoui S, Lalya I, Boulaamane L, Belbaraka R, Abahssain H, Aassab R, Benjaafar N, El Guddari Bel K, El Mesbahi O, Sbitti Y, Ismaili M and Errihani H. **Anthracycline and concurrent radiotherapy as adjuvant treatment of operable breast cancer: a retrospective cohort study in a single institution**. *BMC Res Notes*. 2010; **3**:247. | Article | PubMed Abstract | PubMed FullText

11. Mandilaras V, Bouganim N, Spayne J, Dent R, Arnaout A, Boileau JF, Brackstone M, Meterissian S and Clemons M. **Concurrent chemoradiotherapy for locally advanced breast cancer-time for a new paradigm?** *Curr Oncol*. 2015; **22**:25-32. | Article | PubMed Abstract | PubMed FullText

12. Manfredi JJ, Parness J and Horwitz SB. **Taxol binds to cellular microtubules**. *J Cell Biol*. 1982; **94**:688-96. | Article | PubMed Abstract | PubMed FullText

13. Parness J and Horwitz SB. **Taxol binds to polymerized tubulin in vitro**. *J Cell Biol*. 1981; **91**:479-87. | Article | PubMed Abstract | PubMed FullText

14. Gueritte-Voegelein F, Guenard D, Lavelle F, Le Goff MT, Mangatal L and Potier P. **Relationships between the structure of taxol analogues and their antimitotic activity**. *J Med Chem*. 1991; **34**:992-8. | PubMed

15. Schiff PB and Horwitz SB. **Taxol stabilizes microtubules in mouse fibroblast cells**. *Proc Natl Acad Sci U S A*. 1980; **77**:1561-5. | PubMed Abstract | PubMed FullText

16. Kim E.S and Khuri F.R. **Docetaxel and radiation as combined-modality therapy**. *Oncology (Williston Park)*. 2002; **16**:97-105.

17. Roche H, Fumoleau P, Spielmann M, Canon JL, Delozier T, Serin D, Symann M, Kerbrat P, Soulie P, Eichler F, Viens P, Monnier A, Vindevoghel A, Campone M, Goudier MJ, Bonneterre J, Ferrero JM, Martin AL, Geneve J and Asselain B. **Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial**. *J Clin Oncol*. 2006; **24**:5664-71. | Article | PubMed

18. Kouloulias VE, Dardoufas CE, Kouvaris JR, Gennatas CS, Polyzos AK, Gogas HJ, Sandilos PH, Uzunoglu NK, Malas EG and Vlahos LJ. **Liposomal doxorubicin in conjunction with reirradiation and local hyperthermia treatment in recurrent breast cancer: a phase I/II trial**. *Clin Cancer Res*. 2002; **8**:374-82. | Article | PubMed

19. Arcangeli G, Pinnaro P, Rambone R, Giannarelli D and Benassi M. **A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer**. *Int J Radiat Oncol Biol Phys*. 2006; **64**:161-7. | Article | PubMed

20. Bellon JR, Shulman LN, Come SE, Li X, Gelman RS, Silver BJ, Harris JR and Recht A. **A prospective study of concurrent cyclophosphamide/methotrexate/5-fluorouracil and reduced-dose radiotherapy in patients with early-stage breast carcinoma**. *Cancer*. 2004; **100**:1358-64. | Article | PubMed

21. Livi L, Saieva C, Borghesi S, Paoletti L, Meattini I, Rampini A, Petrucci A, Scoccianti S, Paiar F, Cataliotti L, Leonulli BG, Bianchi S and Biti GP. **Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for early breast carcinoma**. *Int J Radiat Oncol Biol Phys*. 2008; **71**:705-9. | Article | PubMed

22. Isaac N, Panzarella T, Lau A, Mayers C, Kirkbride P, Tannock IF and Vallis KA. **Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for breast carcinoma: a well tolerated adjuvant regimen**. *Cancer*. 2002; **95**:696-703. | Article | PubMed

23. van der Wall E, Schaake-Koning CC, van Zandwijk N, Baars JW, Schornagel JH, Richel DJ, Rutgers EJ, Borger JH, Beijnen JH and Rodenhuis S. **The toxicity of radiotherapy following high-dose chemotherapy with peripheral blood stem cell support in high-risk breast cancer: a preliminary analysis**. *Eur J Cancer*. 1996; **32A**:1490-7. | Article | PubMed

24. Fiets WE, van Helvoirt RP, Nortier JW, van der Tweel I and Struikmans H. **Acute toxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer patients. a prospective, comparative, non-randomised study**. *Eur J Cancer*. 2003; **39**:1081-8. | Article | PubMed

25. Clements IP, Davis BJ and Wiseman GA. **Systolic and diastolic cardiac dysfunction early after the initiation of doxorubicin therapy: significance of gender and concurrent mediastinal radiation**. *Nucl Med Commun*. 2002; **23**:521-7. | Article | PubMed

26. Bedard PL, Di Leo A and Piccart-Gebhart MJ. **Taxanes: optimizing adjuvant chemotherapy for early-stage breast cancer**. *Nat Rev Clin Oncol*. 2010; **7**:22-36. | Article | PubMed

27. Toledano A, Garaud P, Serin D, Fourquet A, Bosset JF, Breteau N, Body G, Azria D, Le Floch O and Calais G. **Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study**. *Int J Radiat Oncol Biol Phys*. 2006; **65**:324-32. | Article | PubMed

28. Toledano A, Azria D, Garaud P, Fourquet A, Serin D, Bosset JF, Miny-Buffet J, Favre A, Le Floch O and Calais G. **Phase III trial of concurrent or sequential adjuvant chemoradiotherapy after conservative surgery for early-stage breast cancer: final results of the ARCOSEIN trial**. *J Clin Oncol*. 2007; **25**:405-10. | Article | PubMed

29. Rouesse J, de la Lande B and Bertheault–Cvitkovic F et al. **On behalf of the Centre René Huguenin Breast Cancer Group. A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in operable node-positive breast cancer: final results**. *Int J RadiatOncolBiolPhys*. 2006; **64**:1072–80.

30. Hall EJ and Giaccia AJ. **Radiobiology for the Radiologist. *6th ed***. Philadelphia: Lippincott Williams & Wilkins. 2006.

31. Tishler RB, Geard CR, Hall EJ and Schiff PB. **Taxol sensitizes human astrocytoma cells to radiation**. *Cancer Res*. 1992; **52**:3495-7. | Article | PubMed

32. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J and Curran WJ, Jr. **Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol**. *J Clin Oncol*. 2005; **23**:5883-91. | Article | PubMed

33. Vokes EE, Herndon JE, 2nd, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, Atkins JN, Watson DM, Akerley W and Green MR. **Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B**. *J Clin Oncol*. 2007; **25**:1698-704. | Article | PubMed

34. Hanna YM, Baglan KL, Stromberg JS, Vicini FA and D AD. **Acute and subacute toxicity associated with concurrent adjuvant radiation therapy and paclitaxel in primary breast cancer therapy**. *Breast J*. 2002; **8**:149-53. | PubMed

35. Taghian AG, Assaad SI, Niemierko A, Kuter I, Younger J, Schoenthaler R, Roche M and Powell SN. **Risk of pneumonitis in breast cancer patients treated with radiation therapy and combination chemotherapy with paclitaxel**. *J Natl Cancer Inst*. 2001; **93**:1806-11. | PubMed

36. Bellon JR, Lindsley KL, Ellis GK, Gralow JR, Livingston RB and Austin Seymour MM. **Concurrent radiation therapy and paclitaxel or docetaxel chemotherapy in high-risk breast cancer**. *Int J Radiat Oncol Biol Phys*. 2000; **48**:393-7. | Article | PubMed

37. Formenti SC, Volm M, Skinner KA, Spicer D, Cohen D, Perez E, Bettini AC, Groshen S, Gee C, Florentine B, Press M, Danenberg P and Muggia F. **Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a phase I/II trial**. *J Clin Oncol*. 2003; **21**:864-70. | Article | PubMed

38. Chakravarthy AB, Kelley MC, McLaren B, Truica CI, Billheimer D, Mayer IA, Grau AM, Johnson DH, Simpson JF, Beauchamp RD, Jones C and Pietenpol JA. **Neoadjuvant concurrent paclitaxel and radiation in stage II/III breast cancer**. *Clin Cancer Res*. 2006; **12**:1570-6. | Article | PubMed

39. Ellerbroek N, Martino S, Mautner B, Tao ML, Rose C and Botnick L. **Breast-conserving therapy with adjuvant paclitaxel and radiation therapy: feasibility of concurrent treatment**. *Breast J*. 2003; **9**:74-8. | PubMed

40. Karasawa K, Katsui K, Seki K, Kohno M, Hanyu N, Nasu S, Muramatsu H, Maebayashi K, Mitsuhashi N, Haga S, Kimura T and Takahashi I. **Radiotherapy with concurrent docetaxel for advanced and recurrent breast cancer**. *Breast Cancer*. 2003; **10**:268-74. | PubMed

41. Skinner KA, Silberman H, Florentine B, Lomis TJ, Corso F, Spicer D and Formenti SC. **Preoperative paclitaxel and radiotherapy for locally advanced breast cancer: surgical aspects**. *Ann Surg Oncol*. 2000; **7**:145-9. | PubMed

42. Kao J, Conzen SD, Jaskowiak NT, Song DH, Recant W, Singh R, Masters GA, Fleming GF and Heimann R. **Concomitant radiation therapy and paclitaxel for unresectable locally advanced breast cancer: results from two consecutive phase I/II trials**. *Int J Radiat Oncol Biol Phys*. 2005; **61**:1045-53. | Article | PubMed

43. Chen WC, Kim J, Kim E, Silverman P, Overmoyer B, Cooper BW, Anthony S, Shenk R, Leeming R, Hanks SH and Lyons JA. **A phase II study of radiotherapy and concurrent paclitaxel chemotherapy in breast-conserving treatment for node-positive breast cancer**. *Int J Radiat Oncol Biol Phys*. 2012; **82**:14-20. | Article | PubMed

44. Karasawa K, Katsui K, Seki K, Kohno M, Hanyu N, Nasu S, Muramatsu H, Maebayashi K, Mitsuhashi N, Haga S, Kimura T and Takahashi I. **Radiotherapy with concurrent docetaxel for advanced and recurrent breast**

cancer. *Breast Cancer*. 2003; **10**:268-74. | PubMed

45. Tapen E, Halberg F.E, Champion L.A, Davis CRAB, Dutton S.C and Rosenthal S.A. **Treatment of locally recurrent or high-risk carcinoma of the breast with radiation therapy and weekly docetaxel given as a radiosensitizer**. *Journal of Clinical Oncology, 2008 ASCO Annual Meeting Proceedings (Post-Meeting Edition)*. 2008; **26**:11538. | Article

46. Abu-Hamar Ael H, Barakat AF, Elgantiry M and Nasef HH. **Sequence of radiation therapy and chemotherapy as adjuvant treatment in breast cancer**. *J Egypt Natl Canc Inst*. 2010; **22**:95-104. | Pdf | PubMed

47. Fernando IN, Powles TJ, Ashley S, Grafton D, Harmer CL and Ford HT. **An acute toxicity study on the effects of synchronous chemotherapy and radiotherapy in early stage breast cancer after conservative surgery**. *Clin Oncol (R Coll Radiol)*. 1996; **8**:234-8. | Article | PubMed