

## Clinical Investigation

# Concurrent Neoadjuvant Chemotherapy and Radiation Therapy in Locally Advanced Breast Cancer

Muriel Brackstone, MD, PhD,<sup>\*,†</sup> David Palma, MD, PhD,<sup>\*</sup>  
Alan B. Tuck, MD, PhD,<sup>‡</sup> Leslie Scott, MD,<sup>†</sup> Kylea Potvin, MD,<sup>\*</sup>  
Theodore Vandenberg, MD,<sup>\*</sup> Francisco Perera, MD,<sup>\*</sup>  
David D'Souza, MD,<sup>\*</sup> Donald Taves, MD,<sup>§</sup> Anat Kornecki, MD,<sup>§</sup>  
Giulio Muscedere, MD,<sup>§</sup> and Ann F. Chambers, PhD<sup>\*,‡</sup>

<sup>\*</sup>Department of Oncology, London Regional Cancer Program; Departments of <sup>†</sup>Surgery, and <sup>‡</sup>Pathology, London Health Sciences Centre; and <sup>§</sup>Department of Medical Imaging, St. Joseph's Healthcare Centre, London, Ontario, Canada

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## Summary

This prospective phase 2 trial recruited 32 patients with locally advanced breast cancer to receive neoadjuvant radiosensitizing chemotherapy with concurrent radiation. Patients were matched to a concurrent cohort treated with neoadjuvant chemotherapy, mastectomy, then radiation. Patients showed significantly improved pathologic complete response but no statistically significant difference in survival. A prospective

**Purpose:** To evaluate whether concurrent neoadjuvant radiation added to standard chemotherapy could increase the pathologic complete response (pCR) to treatment for locally advanced breast cancer (LABC).

**Methods and Materials:** This prospective phase 2 trial recruited 32 LABC patients from 2009 to 2011. Patients received neoadjuvant every-3-weekly 5-fluorouracil (500 mg/m<sup>2</sup>), epirubicin (100 mg/m<sup>2</sup>), and cyclophosphamide (500 mg/m<sup>2</sup>) for 3 cycles, followed by weekly docetaxel (35 mg/m<sup>2</sup>) for 9 cycles. Regional radiation (45 Gy/25 plus 5.4 Gy/5) was delivered concurrently with docetaxel, then modified radical mastectomy. Patients were matched post hoc by a blinded statistician to a concurrent cohort treated with neoadjuvant chemotherapy, modified radical mastectomy, and adjuvant regional radiation.

**Results:** Thirty of 32 patients completed treatment. Twenty-seven were successfully matched by propensity score to 81 control patients by age, stage, and molecular subtype. The concurrent chemoradiation produced a significant increase in pCR (14% vs 22%,  $P < .001$ ) but no statistically significant difference in disease-free and overall survival at 3 years (respectively, 69% vs 81%,  $P = .186$ , hazard ratio 0.51; and 74% vs 89%,  $P = .162$ , hazard ratio 0.46). Toxicity included 25% of patients with grade 3 pneumonitis and 25% of patients with dermatitis, and 1 death.

Reprint requests to: Muriel Brackstone, MD, PhD, Department of Oncology, London Regional Cancer Program, 790 Commissioners Rd E, Office A3-931, London, ON N6A 4L6, Canada. Tel: (519) 685-8712; E-mail: [muriel.brackstone@lhsc.on.ca](mailto:muriel.brackstone@lhsc.on.ca)

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randomized trial is warranted using another radiosensitizer to exploit this improved response with reduced toxicity.

**Conclusions:** Concurrent neoadjuvant radiation added to radiosensitizing chemotherapy significantly improved pCR. A prospective randomized clinical trial is warranted to exploit the improved response seen with concurrent therapy but using another radio-sensitizing taxane, to better minimize treatment-related toxicity and determine its impact on overall survival. © 2017 Elsevier Inc. All rights reserved.

## Introduction

Breast cancer is the most common noncutaneous cancer diagnosis for women in Canada, with approximately 24,400 women diagnosed in 2014 and 5000 dying of the disease (1). Although newer treatments have improved overall survival (OS) and progression-free survival for early and metastatic cancer patients, respectively (2), there remains a subgroup of women with locally advanced breast cancer (LABC) who do poorly.

Locally advanced breast cancer is most commonly defined as stage IIB (T3N0) and stage IIIA/B/C; clinically these tumors are greater than 5 cm in size and/or extend into the surrounding skin/muscle, with/without matted axillary lymph nodes (N2), internal mammary nodes (N3), or ipsilateral supraclavicular lymph node involvement (3). Locally advanced breast cancer represents 10% to 15% of our population-wide breast cancer cases, and the OS has been estimated at 30% to 42% at 5 years (4), a significant portion of whom will be living with metastatic disease. A subset of women receiving neoadjuvant chemotherapy who achieve a complete pathological response (pCR; no residual disease following neoadjuvant treatment) have an improved 5-year disease-free survival (DFS) rate of 87% (4), with 5-year OS rates of 89% (4) and 90% (5). As such, pCR rates have become the surrogate measure for favorable long-term outcomes in neoadjuvant therapy trials (6, 7), particularly because the efficacy of systemic therapy can only be evaluated with *in vivo* disease. Neoadjuvant chemotherapy has become a standard of care for inoperable LABC and operable LABC for which breast-conserving surgery is being contemplated (8, 9).

Cytotoxic chemotherapy has been shown to have radiosensitizing features in other disease sites, as assessed through improved clinical outcomes with increased locoregional toxicity. The most notable are fluoropyrimidines (10, 11), mitoxantrones (12), taxanes (docetaxel and paclitaxel) (13, 14), and platinum (15) drugs. However, limited published data exist for the use of neoadjuvant chemo/radiotherapy in LABC. The most common reported use of radiation therapy concurrent with radiosensitizing chemotherapy is in metastatic disease, in inoperable or inflammatory breast cancer patients who progress on first-line anthracycline-based chemotherapy (15-18) in which 5-fluorouracil (5-FU) or capecitabine were used as the radiosensitizing agent.

Our hypothesis was that concurrent neoadjuvant radiosensitizing chemotherapy with regional radiation would significantly improve the pCR rate. The rationale for this

approach was to avoid compromising on systemic efficacy for distant relapse with dose reductions, avoiding sandwich techniques that could create dose delays in the chemotherapy delivery, while delivering standard adjuvant doses of regional radiation to provide optimal locoregional control in these high-risk patients.

## Methods and Materials

### Rationale

When this clinical trial began, the only Ontario health care-funded neoadjuvant chemotherapy regimen for breast cancer was AC-T (doxorubicin and cyclophosphamide, followed by paclitaxel). The choice of FEC-D (5-FU 500 mg/m<sup>2</sup>, epirubicin 100 mg/m<sup>2</sup>, and cyclophosphamide 500 mg/m<sup>2</sup> intravenously [IV] every-3-weekly × 3 cycles, then docetaxel 100 mg/m<sup>2</sup> IV weekly × 9 cycles) was based on the superior survival in high-risk patients in the PACS-01 study (19). Furthermore, epirubicin is associated with a lower risk of cardiotoxicity than doxorubicin, which is important when giving concurrent radiation (20, 21). Weekly docetaxel is as effective as docetaxel given every 3 weeks in the metastatic setting (22) but is associated with less toxicity, which should reduce the chances of having to reduce or eliminate cycles of chemotherapy. Therefore, FEC-D was selected.

The weekly docetaxel regimen (35 mg/m<sup>2</sup>) was selected to provide constant radiosensitizing during chemotherapy (22, 23). Special permission was obtained from Cancer Care Ontario to have this regimen funded through the Ministry of Health for this trial only. Standard regional intensity modulated radiation therapy (IMRT) (45 Gy/25 fractions ± 5.4 Gy/3 fractions or 9 Gy/5 fractions boost for gross residual disease) was selected to provide optimal regional therapy for these patients at high risk of relapse. Permission was obtained from Health Canada for use of these regimens concurrently in the neoadjuvant setting. This study was approved by Western University's Health Subjects Research Ethics Board and conforms to the precepts established by the Helsinki Declaration.

### Patient description

Thirty-two patients presenting to the London Regional Cancer Program with noninflammatory LABC participated in this single-arm prospective phase 2 clinical trial from 2009 to 2011. Patients were eligible if they had biopsy-

proven LABC (any T3 or T4 tumor stage or any N2 or N3 nodal stage by American Joint Committee on Cancer [24] staging). Patients were all female, at least 18 years of age, and able to give informed consent, with a negative serum pregnancy test, no prior history of invasive cancer, and adequate renal, hepatic, pulmonary, and cardiac function. Patients were staged using physical examination, computed tomography of the chest/abdomen/pelvis, and bone scan to rule out metastases. Serial methoxyisobutylisonitrile (MIBI) single photon emission computed tomography/computed tomography imaging was used at 3 time points as an exploratory imaging substudy and is therefore not described in this study.

## Treatment regimen

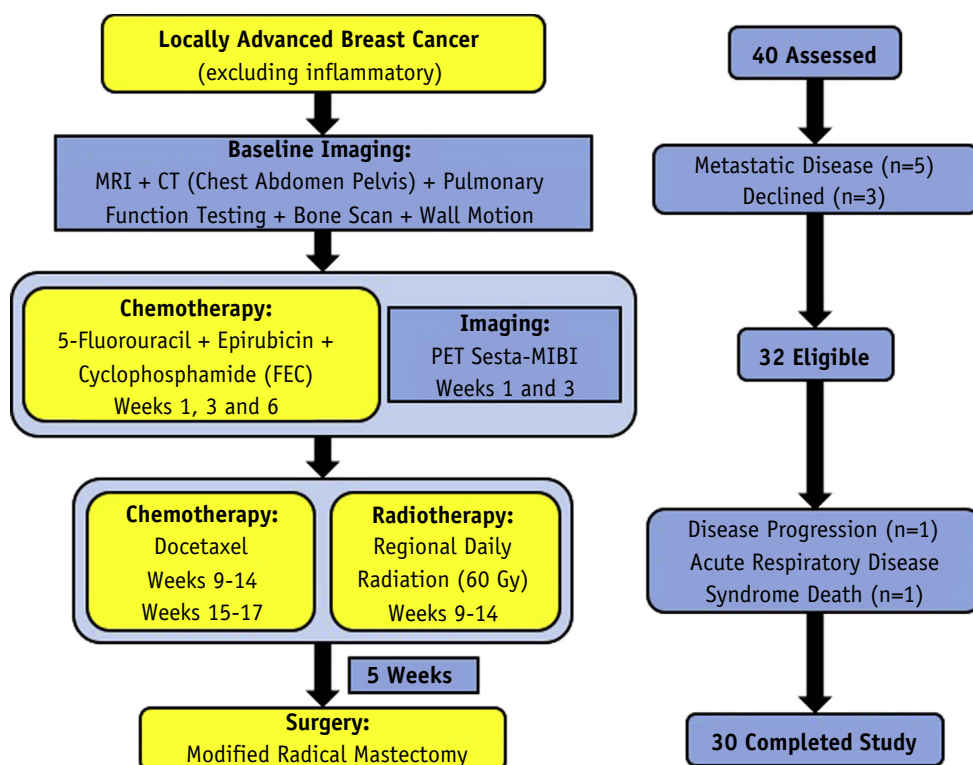
Patients were treated with 3 cycles of FEC every-3-weekly, followed by docetaxel weekly  $\times$  9 weeks (Fig. 1).

On the evening before docetaxel chemotherapy, dexamethasone (8 mg oral) was taken by each patient. Concurrent radiation therapy was started during the first day of docetaxel. Radiation therapy consisted of external beam IMRT for a dose of 45 Gy in 25 fractions. A reduced-volume boost of 5.4 Gy in 3 fractions to 9 Gy in 5 fractions was given to residual gross disease in the breast and/or regional lymph nodes. Treatment planning was performed on the Philips Pinnacle workstation (Philips, Amsterdam, The Netherlands), and treatment was delivered on

megavoltage machines using 6-MV energy or greater. Chemoradiation was followed by modified radical mastectomy (with level 1 and 2 axillary node dissection) 5 weeks after chemotherapy, allowing 8 weeks of radiation recovery preoperatively. Patients were not offered breast-conserving surgery because modified radical mastectomy was considered the standard of care at our institution at the time of this study, which was aimed at patients with tumors that were large and inoperable or operable by mastectomy.

Adverse events and toxicity grading were assessed by the patient's treating oncologist as per the National Cancer Institute (25). Patient tolerability was assessed every 3 patients, and any toxicity grade  $\geq$ 4 or treatment delays were reviewed by an independent data safety monitoring committee (IDSMC). Mid-study the protocol was modified to require normal pulmonary function tests and nonsmoker status after the first 3 patients with pneumonitis were reviewed by the IDSMC.

Women with HER2-positive disease received 1 year of trastuzumab, initiated concurrently with docetaxel, given the absence of cardiotoxicity even when administered concurrently with radiation or taxanes (26, 27). Cardiotoxicity was monitored using a wall motion study performed every 3 months while on therapy. Dose modification was made as per international and institutional guidelines for trastuzumab-associated cardiac dysfunction (28). Women with estrogen receptor (ER)-positive disease received postoperative endocrine therapy according to their menopausal status.



**Fig. 1.** Schema for the locally advanced breast cancer clinical trial. *Abbreviations:* CT = computed tomography; MIBI = methoxyisobutylisonitrile; MRI = magnetic resonance imaging; PET = positron emission tomography.

## Assessment of pathologic response

Pathological response was subcategorized as follows (29): pCR: pathologic complete response (no residual invasive disease in the breast or axilla); pSPR: pathologic significant partial response (<10 microscopic foci of tumor within breast); pPR: pathologic partial response (<30% of original tumor remaining); SD: stable disease (30%-80% of original tumor remaining); NR: no response (81%-120% of original tumor remaining). This classification was used to identify pCR versus non-pCR (which comprised partial responders because nonresponders were taken off study in favor of second-line therapies).

Molecular subtype was categorized using tumor phenotype as a surrogate for genotypic classification, as follows: luminal A: ER and/or progesterone receptor (PR) positive, epidermal growth factor receptor ErbB2 (HER2) negative, not high grade; luminal B: ER and/or PR positive, high grade only (HER2 positive or negative); HER2+: ER and PR negative, HER2 positive; basal: ER and PR negative, HER2 negative.

The proliferation marker Ki67 is not measured at our institution.

## Statistical analysis

This study was designed to accrue 52 patients, on the basis of a sample size calculation powered to detect a doubling of pCR rate (26%-52%) from published clinical trials of neoadjuvant chemotherapy (9), but the study closed prematurely after a treatment-related death and high rates of radiation pneumonitis, with 32 patients accrued, at the recommendation of the IDSMC. The treatment cohort (n=30) was compared with a concurrent control cohort of LABC patients off-study treated at the same institution by other surgeons, who received neoadjuvant chemotherapy (FEC-D or AC-T), modified radical mastectomy, and equivalent locoregional radiation delivered in the adjuvant setting (50 Gy/25 fractions using IMRT; patients were matched by a blinded statistician 1:N by stage, age, and molecular subtype using greedy matching by propensity score  $\pm$  0.1 to minimize selection bias). Student *t* test was used to compare age and tumor size, whereas  $\chi^2$  analysis was used to compare nodal status and luminal subtype between groups. Cox regression analysis was used with a robust sandwich estimator for paired comparison of pCR rates between the concurrent chemoradiation cohort and the control cohort. Kaplan-Meier estimates were generated for disease-free and OS for matched patients (n=108) stratified by treatment group. Cox proportional hazards analysis was used to compare disease-free and OS, adjusted for matched design (n=108). SAS 9.4 (SAS Institute, Cary NC) was used for statistical analyses, using 2-sided testing with a significance of .05.

## Results

Of the 32 patients accrued to the study, 1 progressed during the FEC portion of the treatment and was taken off study in

favor of second-line chemotherapy. Another patient with inoperable bilateral LABC received bilateral regional radiation therapy during the docetaxel/radiation portion of the study and developed pneumonitis-induced acute respiratory distress syndrome after completion of radiation. This patient did not receive surgery and died shortly thereafter. The study was prematurely terminated after this event because of concerns around that time of high rates of pneumonitis seen with taxotere both on and off this study. Of the 30 patients who completed neoadjuvant therapy and surgery, 27 were matched to 81 concurrent control patients, because statistical power was optimized with a 1:3 matching.

No statistically significant difference in patient age, pretreatment tumor size, pretreatment nodal status, or molecular subtype was found using Student *t* test for age and tumor size and  $\chi^2$  analysis for nodal status and molecular subtype (Table 1).

A statistically significant difference in post-chemotherapy tumor size was seen (mean residual tumor size in the concurrent chemoradiation cohort was 13 mm, vs 31 mm in the control cohort,  $P<.001$ ) (Table 2).

The pCR rate was higher in the concurrent chemoradiation cohort (22.6% vs 14.9% in the control cohort,  $P=.019$ ) (Table 2). The number of patients in each molecular subtype group was too small to permit statistical comparisons of pCR rates by molecular subtype. None of

**Table 1** Patient demographics comparing neoadjuvant concurrent chemotherapy and radiation therapy in LABC study patients with a concurrent matched control cohort

Variable	LABC		P
	chemotherapy matched cohort (3:1) (n=81)	Chemoradiation LABC study* (n=27)	
Mean age at registration (y)	51.2	49.3	.58
Baseline mean tumor size (mm), pretreatment (baseline ultrasound)	42.0	43.2	.84
Baseline clinical node (%)			.29
N0	10.1	28.1	
N1-N3c	65.9	68.8	
NX	24.0	3.1	
Luminal subgroup, n (%)			.99
Luminal A	29 (34.9)	9 (33.3)	
Luminal B	33 (39.8)	10 (37.0)	
HER2+	8 (9.6)	3 (11.1)	
Basal	13 (15.7)	5 (18.5)	

Abbreviation: LABC = locally advanced breast cancer.

\* The LABC chemoradiation cohort sample size = 32; 1 patient excluded because of disease progression before receiving radiation, therefore changed protocol; 1 patient excluded because of death during treatment; 3 patients could not be matched, therefore not included in matched analyses.



the concurrent chemoradiation cohort patients who achieved pCR have had a recurrence, whereas 36% of patients who did not achieve pCR recurred and died of their disease within 36 months of treatment.

There was no statistically significant difference in DFS or OS between the treatment groups at 36 months, with a DFS for the concurrent chemoradiation cohort of 81%, versus 69% for the control cohort (Fig. 2).

The hazard ratio (HR) for DFS in the concurrent chemoradiation cohort was 0.51 (95% confidence interval 0.18-1.39;  $P=.186$ ). Similarly, OS was not statistically significantly different between the concurrent chemoradiation cohort (89%) and the matched control cohort (74%) (Fig. 3).

The HR for OS was 0.46 in favor of the concurrent chemoradiation cohort (95% confidence interval 0.16-1.36;  $P=.162$ ).

There was a 25% rate of grade 3 dermatitis and a 25% rate of grade  $\geq 3$  pneumonitis, which includes 1 death from acute respiratory distress syndrome. The list of toxicities seen in the chemoradiation is outlined in Table 3. The toxicity profile of the control cohort was not collected prospectively and is therefore not available for comparison.

**Table 2** Clinical response to neoadjuvant therapy (primary chemotherapy for LABC chemotherapy matched cohort vs concurrent chemotherapy with radiation therapy for LABC study patients)

Variable	LABC chemotherapy matched cohort (3:1) (n=81)	Chemoradiation LABC study* (n=27)	P
Mean tumor size (mm), posttreatment (pathology)	31.1	13.2 <sup>†</sup>	.001
Lymph nodes positive (%) after treatment	60.9	53.3	‡
Luminal subgroup with pCR (%)			
Luminal A	6.0	0	
Luminal B	13.9	27.3	
HER2+	30.3	66.7	
Basal	18.0	40.0	
Total with pCR (%)	14.9	22.6 <sup>§</sup>	.019

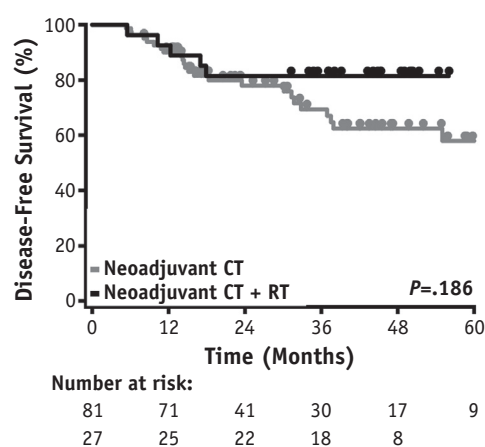
Abbreviation: pCR = pathologic complete response. Other abbreviation as in Table 1.

\* The LABC chemoradiation cohort sample size = 32; 1 patient excluded because of disease progression before receiving radiation, therefore changed protocol; 1 patient excluded because of death during treatment; 3 patients could not be matched, therefore not included in matched analyses.

<sup>†</sup>  $P<.05$ .

<sup>‡</sup> Posttreatment nodal status was not statistically compared. A difference would be expected from the axillary radiation in the LABC chemoradiation cohort, whereas the control group had not yet received axillary radiation.

<sup>§</sup> Excluded 1 patient who did not complete chemotherapy or have surgery.

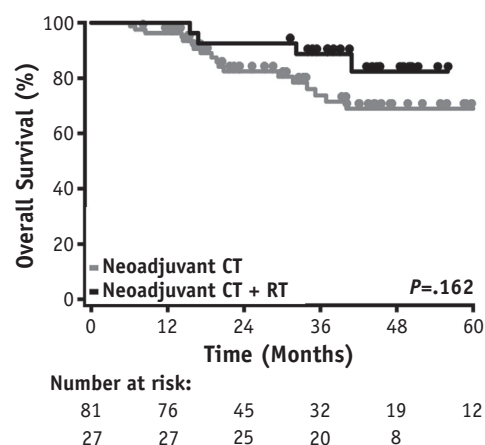


**Fig. 2.** Disease-free survival comparing the concurrent chemoradiation cohort with the matched chemotherapy control cohort. Abbreviations: CT = chemotherapy; RT = radiation therapy.

## Discussion

This study suggests that the addition of neoadjuvant radiation to anthracycline and taxane-based chemotherapy significantly improved the pCR rate in LABC patients; however, the 15% difference in DFS and OS at 3 years was not statistically significant when compared with a propensity-matched control group.

Since this trial began, other trials using concurrent neoadjuvant chemoradiation for breast cancer have been published. Follow-up data from Formenti et al (13) were published (30), demonstrating a combined pCR and pPR rate of 34%, resulting in a significant association with better DFS and OS for patients achieving a pCR (HR 0.35 for recurrence and HR 4.27 for OS,  $P<.01$ ) when compared with nonresponders within the same treatment cohort. In that study only taxane was given neoadjuvantly, with the



**Fig. 3.** Overall survival in the concurrent chemoradiation cohort compared with the matched chemotherapy control cohort. Abbreviations: CT = chemotherapy; RT = radiation therapy.

**Table 3** Toxicity profile of LABC patients treated with concurrent neoadjuvant chemotherapy and locoregional radiation

Toxicity	No. (%) patients*
Dermatitis, grade 3	8 (25)
Pneumonitis	
Grade 3	7 (22)
Grade 5	1 (3)
Postoperative seroma, grade 2	1 (3)
Wound infection	0 (0)
Febrile neutropenia	0 (0)

\* Number of patients with grade  $\geq 2$  toxicity out of chemoradiation cohort (n=31), including the patient with acute respiratory distress syndrome. Included in the list are toxicities seen by patients within this study and toxicities expected from this cohort.

remainder of the chemotherapy being given adjuvantly. It did not compare concurrent versus sequential chemotherapy and radiation, as this trial does.

Trials of neoadjuvant chemoradiotherapy evaluating regimens without taxane have since been published (31-34), most using 5-FU as the radiosensitizing agent, demonstrating feasibility and reasonable toxicity, with pCR rates of 10% to 29% and an OS of 84%. These were mostly retrospective studies in highly selected patients.

Other trials evaluated neoadjuvant concurrent chemoradiotherapy as a rescue for LABC patients who progressed on first-line neoadjuvant chemotherapy, using 5-FU as the radiosensitizer (35, 36), with reasonable pCR rates and resultant operability. Long-term outcomes were not reported.

Ours is the first clinical trial evaluating concurrent neoadjuvant chemoradiation with a taxane as part of a modern chemotherapy regimen (FEC-D), delivered with locoregional radiation in LABC patients. Our findings support those of the Formenti group (30), whereby pCR rates increased with concurrent delivery of radiation and taxane chemotherapy.

This regimen had high rates (25%) of grade 3 dermatitis (moist desquamation of chest wall skin), which may be clinically acceptable, though the 25% rate of grade  $\geq 3$  pneumonitis was concerning. Patients presenting with clinical pneumonitis had the diagnosis confirmed on computed tomography scan and were treated with a tapering regimen of corticosteroids. One patient suffered acute respiratory distress syndrome shortly after completion of chemotherapy with bilateral regional radiation and died. None of the 30 patients proceeding to surgery required a delay in surgery due to pneumonitis. The pneumonitis experienced by the patients in this study behaved clinically like acute interstitial pneumonitis and not radiation pneumonitis, in that the symptoms resolved acutely and did not lead to long-term impairment; however, the radiation likely exacerbated its presentation (37).

Capillary leak and interstitial pneumonitis from taxane chemotherapy is well known, and pretreatment with 8 mg of dexamethasone (used here) is thought to reduce this risk. The typical rate of pneumonitis (1%-5% for every-3-

weekly docetaxel) (38) increases when administered weekly, reportedly to 27% (comparable to our study) (39). Rates of pneumonitis are also elevated in patients with pre-existing lung disease (40). However, with the weekly regimen no patients suffered other toxicities commonly associated with docetaxel, such as febrile neutropenia or peripheral neuropathy. No patients developed postoperative wound infections or dehiscence, although 1 patient had a protracted seroma requiring multiple aspirations.

One main limitation of this study was its sample size, which limits the strength of any conclusion. Additionally, as a matched-cohort phase 2 trial, there was no randomization to a control arm to correct for unanticipated bias, and a matched design to a control cohort may have inadvertently introduced selection bias. A randomized design was not selected for this trial given the small population of patients with nonmetastatic locally advanced breast cancer seen in each institution and the prohibitive cost associated with a multi-centered randomized trial at the time of this study, as well as the lack of clinical equipoise between concurrent versus sequential therapy. To minimize bias with the matched cohort design, a blinded statistician performed the matching to our patient population database by all variables thought to affect the outcomes of interest, using propensity score (41). Generally, propensity score-matched studies are ranked by level of evidence to typically fall below randomized trials but to be superior to traditional matching and observational or review studies. This method is well established in the literature (42, 43). Matched patients were selected from patients treated in the same time period as the study patients, to create a concurrent control cohort and avoid historical bias from unequal follow-up duration. Nevertheless, unanticipated confounders could have influenced our results.

The 15% difference in DFS and OS at 3 years was not statistically significant. We cannot know the impact that premature termination of the study had on its findings.

## Conclusion

The use of concurrent neoadjuvant chemoradiotherapy in LABC significantly improved the pCR rate. Use of docetaxel seems to be associated with a high rate of pneumonitis, therefore a future large, multi-center trial should be undertaken in which the radiosensitizing benefit of taxanes can be exploited, using for example paclitaxel (30) concurrently with locoregional radiation as part of a full neoadjuvant chemotherapy regimen.

## Key Message/Synopsis

Neoadjuvant radiosensitizing chemotherapy with concurrent radiation in locally advanced breast cancer significantly improved pathologic complete response but did not show a statistically significant difference in overall survival at 3 years in this phase 2 trial.

## References

- Canadian Cancer Society. Breast cancer statistics. Available at: [www.cancer.ca/en/cancer-information/cancer-type/breast/statistics/?region=bc](http://www.cancer.ca/en/cancer-information/cancer-type/breast/statistics/?region=bc); 2014. Accessed November 11, 2016.
- American Cancer Society. Breast cancer survival by stage. Available at: [www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage](http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage); 2014. Accessed November 11, 2016.
- National Institute of Health. Breast cancer treatment (PDQ)-health professional version. Available at: [www.cancer.gov/types/breast/hp/breast-treatment-pdq](http://www.cancer.gov/types/breast/hp/breast-treatment-pdq); 2014. Accessed November 11, 2016.
- Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 1999;17:460-469.
- Formenti SC, Dunnington G, Uzieli B, et al. Original p53 status predicts for pathological response in locally advanced breast cancer patients treated preoperatively with continuous infusion 5-fluorouracil and radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;39:1059-1068.
- Untch M, von Minckwitz G. Recent advances in systemic therapy: Advances in neoadjuvant (primary) systemic therapy with cytotoxic agents. *Breast Cancer Res* 2009;11:203.
- Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. *Lancet* 2014;384:164-172.
- Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16:2672-2685.
- Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008;26:778-785.
- Lerouge D, Touboul E, Lefranc JP, et al. Combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer: Updated results in a series of 120 patients. *Int J Radiat Oncol Biol Phys* 2004;59:1062-1073.
- Shanta V, Swaminathan R, Rama R, et al. Retrospective analysis of locally advanced noninflammatory breast cancer from Chennai, South India, 1990-1999. *Int J Radiat Oncol Biol Phys* 2008;70:51-58.
- Rouesse J, de la Lande B, Bertheault-Cvitkovic F, et al. 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 Radiat Oncol Biol Phys* 2006;64:1072-1080.
- Formenti SC, Volm M, Skinner KA, et al. 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;21:864-870.
- Chakravarthy AB, Kelley MC, McLaren B, et al. Neoadjuvant concurrent paclitaxel and radiation in stage II/III breast cancer. *Clin Cancer Res* 2006;12:1570-1576.
- Genet D, Lejeune C, Bonnier P, et al. Concomitant intensive chemoradiotherapy induction in non-metastatic inflammatory breast cancer: Long-term follow-up. *Br J Cancer* 2007;97:883-887.
- Ren H, Wang Qi, Yaoxiang Y, et al. Preoperative chemoradiotherapy for inflammatory breast cancer. *Chin J Clin Oncol* 2006;3:130-133.
- Gauj MF, Amorim G, Arcuri RA, et al. A phase II study of second-line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline-resistant locally advanced breast cancer. *Am J Clin Oncol* 2007;30:78-81.
- Touboul E, Lefranc JP, Blondon J, et al. Primary chemotherapy and preoperative irradiation for patients with stage II larger than 3 cm or locally advanced non-inflammatory breast cancer. *Radiat Oncol* 1997;42:219-229.
- Amat S, Bougnoux P, Penault-Llorca F, et al. Neoadjuvant docetaxel for operable breast cancer induces a high pathological response and breast-conservation rate. *Br J Cancer* 2003;88:1339-1345.
- Ryberg M, Nielsen D, Skovsgaard T, et al. Epirubicin cardiotoxicity: An analysis of 469 patients with metastatic breast cancer. *J Clin Oncol* 1998;16:3502-3508.
- Kaklamani VG, Gradishar WJ. Epirubicin versus doxorubicin: Which is the anthracycline of choice for the treatment of breast cancer? *Clin Breast Cancer* 2003;4:S26-S33.
- Rivera E, Mejia JA, Arun BK, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008;112:1455-1461.
- Taberero J, Climent MA, Lluch A, et al. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol* 2004;15:1358-1365.
- Edge SB, Byrd DR, Compton CC, et al. editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
- National Cancer Institute. NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/ctcae3.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf); 2014. Accessed November 11, 2016.
- Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008;26:1231-1238.
- Rastogi P. Five-year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)-paclitaxel compared to AC-T with trastuzumab. *Proc Am Soc Clin Oncol* 2007;25:6s.
- Mackey JR, Clemons M, Cote MA, et al. Cardiac management during adjuvant trastuzumab therapy: Recommendations of the Canadian Trastuzumab Working Group. *Curr Oncol* 2008;15:24-35.
- Honkoop AH, van Diest PJ, de Jong JS, et al. Prognostic role of clinical, pathological and biological characteristics in patients with locally advanced breast cancer. *Br J Cancer* 1998;77:621-626.
- Adams S, Chakravarthy AB, Donach M, et al. Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: Pathologic response correlates with five-year overall survival. *Breast Cancer Res Treat* 2010;124:723-732.
- Bollet MA, Belin L, Reyat F, et al. Preoperative radio-chemotherapy in early breast cancer patients: Long-term results of a phase II trial. *Radiat Oncol* 2012;102:82-88.
- Alvarado-Miranda A, Arrieta O, Gamboa-Vignolle C, et al. Concurrent chemo-radiotherapy following neoadjuvant chemotherapy in locally advanced breast cancer. *Radiat Oncol* 2009;4:24.
- Fisher CS, Ma CX, Gillanders WE, et al. Neoadjuvant chemotherapy is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative breast cancer only after complete pathologic response. *Ann Surg Oncol* 2012;19:253-258.
- Nardone L, Valentini V, Marino L, et al. A feasibility study of neoadjuvant low-dose fractionated radiotherapy with two different concurrent anthracycline-docetaxel schedules in stage IIA/B-IIIa breast cancer. *Tumori* 2012;98:79-85.
- Bourgier C, Ghorbel I, Heymann S, et al. Effect of preoperative rescue concomitant FUN/XUN-based chemo-radiotherapy for neoadjuvant chemotherapy-refractory breast cancer. *Radiat Oncol* 2012;103:151-154.
- Karasawa K, Matsumoto F, Ito S, et al. Hyperfractionated radiotherapy with concurrent docetaxel for advanced head and neck cancer: A phase II study. *Anticancer Res* 2012;32:4013-4018.
- Chow TL, Louie AV, Palma DA, et al. Radiation-induced lung injury after concurrent neoadjuvant chemoradiotherapy for locally advanced breast cancer. *Acta Oncol* 2014;53:697-701.

38. King TE, Jett JR. Taxane-induced pulmonary toxicity. Available at: [www.uptodate.com/contents/taxane-induced-pulmonary-toxicity](http://www.uptodate.com/contents/taxane-induced-pulmonary-toxicity); 2014. Accessed November 11, 2016.
39. Chen YM, Shih JF, Perng RP, et al. A randomized trial of different docetaxel schedules in non-small cell lung cancer patients who failed previous platinum-based chemotherapy. *Chest* 2006;129:1031-1038.
40. Tamiya A, Naito T, Miura S, et al. Interstitial lung disease associated with docetaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* 2012;32:1103-1106.
41. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
42. Smith GD, Pickles T, Crook J, et al. Brachytherapy improves biochemical failure-free survival in low- and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: A propensity score-matched analysis. *Int J Radiat Oncol Biol Phys* 2015;91:505-516.
43. Rodrigues G, Oberije C, Senan S, et al. Is intermediate radiation dose escalation with concurrent chemotherapy for stage III non-small-cell lung cancer beneficial? A multi-institutional propensity score matched analysis. *Int J Radiat Oncol Biol Phys* 2015; 91:133-139.