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Original article

Four cycles of docetaxel and cyclophosphamide as adjuvant chemotherapy in node negative breast cancer: A real-world study

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ABSTRACT

Introduction: The optimal number of cycles of adjuvant docetaxel and cyclophosphamide (DC) in patients with node negative breast cancer is not known. We aimed to analyse the survival outcomes of patients with node negative and human epidermal growth factor receptor (HER2)-negative breast cancer treated with four cycles of DC.

Methods: Patients with node negative and HER2-negative breast cancer treated with four cycles of DC after surgery in a large Canadian province from 2008 to 2012 were identified. We analysed the 4-year and 9-year invasive disease free survival (iDFS) and overall survival (OS). Cox regression models were constructed to examine the associations of clinical characteristics with survival outcomes.

Results: A total of 657 patients were eligible for the current analysis. The median age was 53 years and 71.2% of patients had hormone receptor-positive breast cancer. Approximately three-fourths of patients had grade III tumours. At a median follow-up of nine years, the 4-year iDFS and OS were 91.0% and 95.5% and the corresponding 9-year rates were 80.5% and 88.0%, respectively. On multivariable Cox regression analysis, grade III tumour predicted worse iDFS (hazard ratio [HR], 2.15; 95% confidence interval [CI], 1.09–4.21; P = 0.026) and OS (HR, 3.15; 95% CI, 1.18–8.45; P = 0.022).

Conclusions: Adjuvant chemotherapy with four cycles of DC in a select population of node negative breast cancer was associated with encouraging long-term survival. In the absence of a randomized comparison between four and six cycles of DC, this study presents real-world evidence to consider four cycles of DC as a reasonable option.

1. Introduction

Breast cancer is the most common cancer in females, accounting for around 2.1 million new diagnoses and over 0.6 million deaths annually across the globe [1]. While the stage distribution at diagnosis varies widely across different demographic regions and different ethnicities in the same region, around 60–70% of patients in North America present with axillary lymph node negative disease [2,3]. Likewise, approximately 75–85% of patients have hormone receptor-positive breast cancer, while human epidermal growth factor receptor-2 (HER2) positive and triple negative tumours account for 15–20% and 10–15%, respectively [4].

The multidisciplinary treatment of patients with node negative breast cancer includes surgery, radiation therapy and systemic therapy (chemotherapy, targeted therapy and hormonal agents) [5]. Adjuvant chemotherapy for node negative, HER2-negative breast cancer has evolved over decades from non-anthracycline, non-taxane, alkylator-based regimens, to anthracycline-based regimens, and finally to sequential administration of anthracyclines and taxanes [6–11]. However, long-term serious adverse events associated with anthracyclines, including irreversible cardiotoxicity, myelodysplastic syndromes and therapy-related leukemias, have led researchers to question the benefit-risk ratio of anthracycline-based chemotherapy regimens, especially in those lacking axillary lymph node involvement [12]. As a result, trials evaluating anthracycline-free, taxane-based chemotherapy regimens, including docetaxel and cyclophosphamide (DC), have been conducted [13,14].

The US Oncology (USON) 9735 trial compared four cycles of

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Abbreviations

DC	Docetaxel and Cyclophosphamide
HER2	Human Epidermal growth factor Receptor-2
iDFS	Invasive Disease Free Survival
OS	Overall Survival
HR	Hazard Ratio
CI	Confidence Interval
AT	Anthracycline and Taxane
USON	United States Oncology
AC	Doxorubicin and Cyclophosphamide
ABC	Anthracycline in early Breast Cancer
AHS	Alberta Health Services
BDM	Breast Data Mart
ACR	Alberta Cancer Registry
DAD	Discharge Abstract Database
NACRS	National Ambulatory Care Reporting System
ER	Estrogen Receptor
PR	Progesterone Receptor
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
AJCC	American Joint Committee on Cancer
MBR	Modified Bloom Richardson
BMI	Body Mass Index
CCI	Charlson's Comorbidity Index
G-CSF	Granulocyte-Colony Stimulating Factor
WHO	World Health Organization

doxorubicin and cyclophosphamide (AC) with four cycles of DC in patients with resected stage I to III breast cancer [13]. Disease free survival (DFS) at a median follow-up of 5.5 years, and subsequently overall survival (OS) after 7-years follow-up, were superior with four cycles of DC [13,15]. Although the control arm represented one of the standard adjuvant chemotherapy regimens at the time, sequential/concurrent anthracycline-taxane (AT) regimens became widely adopted because of improved survival outcomes seen across multiple studies [16]. Subsequently, three clinical trials, collectively referred as anthracyclines in early breast cancer (ABC), compared six cycles of DC with several AT regimens (two of three trials had concurrent taxane- and anthracycline-based chemotherapy, while the third trial allowed either concurrent or sequential regimens) [14]. In an interim analysis at a median follow-up of 3.3 years, six cycles of DC did not meet the prespecified threshold for non-inferiority and the 4-years invasive DFS (iDFS) of AT was significantly different (90.7% vs. 88.2%, $P = 0.04$). However, an exploratory analysis demonstrated that the benefit of AT was driven by patients with triple negative breast cancer and those with regional lymph node involvement, while survival outcomes were similar in hormone receptor-positive and node negative subgroups [14]. Another clinical trial, West German Study PlanB, evaluated the non-inferiority of six cycles of DC with four cycles each of sequential epirubicin/cyclophosphamide and docetaxel [17]. At a median follow-up of five years, the 5-year DFS and OS were non-inferior in the DC arm across all subgroups.

While several guidelines have included DC as an acceptable regimen for adjuvant chemotherapy in patients with HER2 negative node-negative breast cancer [18–21], the optimal number of cycles continues to be a subject of debate. In Alberta, a large province in Canada with a population of over four million residents, four cycles of DC has been used as a standard chemotherapy regimen in node negative breast cancer. The aim of this study was to determine the survival outcomes (iDFS and OS) of patients with node negative, HER2 negative breast cancer treated with four cycle of adjuvant DC and further, to explore associations of clinical characteristics with survival outcomes.

2. Methods

2.1. Study cohort

Patients were retrieved from the Alberta Health Services (AHS) Cancer Control Breast Data Mart (BDM). The BDM is a data repository of all breast cancer patients diagnosed from January 1, 2004 onwards in Alberta and includes information on patient demographics, tumour characteristics, surgical intervention, Cancer Control Alberta clinic visits, systemic therapies administered, and vital status. The information is prospectively collected from various sources including the Alberta Cancer Registry (ACR), the Cancer Centre Electronic Medical Record (ARIA MO), the Discharge Abstract Database (DAD), and the National Ambulatory Care Reporting System (NACRS).

We included patients diagnosed with HER2-negative, axillary lymph node negative breast cancer diagnosed January 1, 2008 through December 31, 2012, who were prescribed four cycles of adjuvant DC chemotherapy. As in the ABC group of trials [14], for patients with estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive breast cancer, the tumour was pT1c and grade III, or pT2-pT3 with any grade. Patients who were switched to an anthracycline-based regimen after starting DC or who received four cycles of DC for resected locoregional recurrence were excluded.

The conduct and results of our study are reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [22]. Ethics were institutionally approved under the Alberta Research Ethics Community Consensus Initiative [23].

2.2. Clinical variables

The following variables were extracted from the BDM: patient age at diagnosis, gender, first surgical date, use of adjuvant radiotherapy, tumour characteristics (American Joint Committee on Cancer [AJCC] 7th edition stage, histological subtype, modified Bloom-Richardson (MBR) grade, lymphovascular invasion, and status of ER-receptor, PR-receptor and HER2), vital status, date and cause of death if deceased, and date of last contact with AHS or Cancer Control if not deceased. Review of ARIA-MO was completed to obtain: co-morbidities, body mass index (BMI), type of surgery, date of first cycle of DC, number of cycles of DC completed, use of prophylactic granulocyte-colony stimulating factor (G-CSF) and/or antibiotics, and recurrence or new primary cancer diagnosis (date and type). The Charlson comorbidity index (CCI) score was computed from the data on comorbidities [24]. The BMI was categorized according to the World Health Organization (WHO) classification as underweight, normal, overweight and obese [25].

2.3. Outcome measures

The end-points for this study included invasive disease free survival (iDFS) and overall survival (OS). We defined iDFS as time from diagnosis of breast cancer to local, regional or distant recurrence, invasive contralateral breast cancer, second primary cancer

(except non-melanoma skin cancer and in-situ cancer), or death due to any cause. The OS was defined as time from diagnosis to death as a result of any cause. The ABC group of trials, the Plan B and the TAILORx studies reported the survival rates at 4, 5 and 9 years, respectively [14,17,26]. We, therefore, estimated iDFS and OS rates at multiple time-points to assess the outcomes in our population to have reference comparisons.

2.4. Statistical analysis

Descriptive statistics were used to analyse baseline clinical and treatment characteristics. Kaplan–Meier methods were used to determine iDFS and OS and then log rank tests were used to describe differences between hormone receptor-positive and triple negative breast cancer. Multivariable Cox proportional hazards models were constructed to examine the associations between clinical characteristics and survival outcomes. We included age categories (<50/50–59/> = 60 years), hormone receptor status (ER and/or PR positive vs triple negative breast cancer), lymphovascular invasion, grade (I/II vs III), AJCC stage (I/II), CCI score (0/1/>1), BMI (normal and underweight, overweight, obese). The prognostic impact of these clinical-pathologic characteristics has been reported in prior studies [27–30]. Due to low number of patients with BMI <18.5 and grade I tumours, normal and underweight, and grade I/II tumours were categorized together, respectively. All statistical tests used in this study were two-sided and the significance level was defined *a priori* as <0.05. The analyses were performed using Stata statistical software (StataCorp. 2013. Release 13. College Station, TX).

3. Results

3.1. Patient characteristics

We identified a total of 715 patients with node negative breast cancer who were planned for non-anthracycline based adjuvant chemotherapy with DC. Of these, 58 patients were excluded due to HER2-positive disease and concomitant administration of trastuzumab (32.8%), locoregional recurrent cancer prior to administration of DC (25.9%), and subsequent switch to anthracycline-based adjuvant chemotherapy (19.0%) (Fig. 1). In the final cohort of 657 patients, the median age at diagnosis was 53 years (interquartile range, 26–73 years) and approximately one-fourth of the patients were older than 60 years. While 99.7% of patients were women, two patients were men (0.3%).

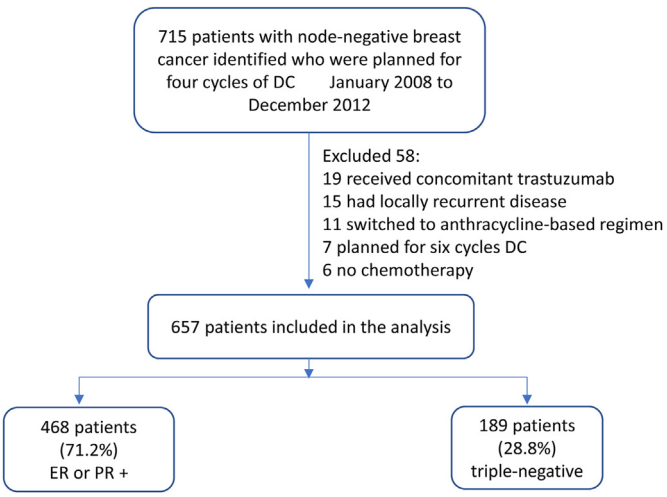

Fig. 1. Patient selection for the study.

Breast conserving surgeries were performed in 59.2% patients and mastectomies in 40.8%. While more than half of the patients (58.6%) had a tumour size of great than 2 cm to 5 cm, around one-third had a tumour 2 cm or smaller. The most common histological subtype was invasive ductal cancer (76.4%) while lobular and mixed histologies were reported in 6.2% and 14.6% patients, respectively. There were 468 patients (71.2%) with hormone receptor-positive tumours and 189 (28.8%) had triple negative disease. While three-fourths of the patients had MBR grade III tumours, those with grade I and II breast cancer accounted for 4.0% and 21.2%, respectively. Lymphovascular invasion was present in 18.9% of tumours, although data was not available for one-third of histopathology specimens. Post-operative radiotherapy was administered in 60.4% of the patients.

We compared the clinical and pathological characteristics of patients with hormone receptor-positive tumours and those with triple negative breast cancer. The age at diagnosis was similar in both groups (52 vs 54 years, P = 0.116). While triple negative breast cancers were more likely to be grade III (92.6% vs 67.7%, P < 0.001), hormone receptor-positive tumours were more likely to be AJCC stage II (69.0% vs 43.4%, P < 0.001) and have lymphovascular invasion (32.8% vs 17.5%, P = 0.002). Thus, the selected population represented higher risk hormone receptor-positive tumours and lower risk triple negative breast cancer.

With regards to comorbid medical conditions, 14.6% and 8.5% of the patients had a CCI score of one and more than one, respectively. Of note, one-third of patients were overweight and a similar proportion were obese (Table 1).

3.2. Treatment details

Overall, 95.6% of the patients completed the planned adjuvant chemotherapy with four cycles of DC. Twenty-nine patients (4.4%) discontinued chemotherapy after receiving one (1.2%), two (1.7%) or three (1.5%) cycles, respectively. In terms of prophylaxis for febrile neutropenia, oral ciprofloxacin was administered in 54.3% patients, 10.5% received prophylactic growth factor support, and 4.3% received both (Supplementary Table 1).

3.3. Survival outcomes

At a median follow-up of nine years, 125 patients developed an iDFS event, which included 70 distant metastases and 29 new primary cancers (Table 2). The 4-year, 5-year and 9-year iDFS rates were 91.0%, 88.4% and 80.5%, respectively. Likewise, there were 79 deaths, of which 55 were related to breast cancer. The 4-year, 5-year and 9-year OS rates were 95.5%, 92.9% and 88.0%, respectively.

Common sites of distant metastases included bone (25.7%), lung (24.3%) and liver (11.4%). Common new primary cancer sites included ovary and fallopian tube (24.1%), endometrium (17.2%) and colorectum (10.3%).

3.4. Survival outcomes by hormone receptor status

We compared the iDFS and OS rates between patients with hormone receptor-positive tumours and triple negative breast cancer. The 4-year iDFS rates were 91.3% in hormone receptor-positive breast cancer patients compared with 90.3% in those with triple negative breast cancer. The corresponding 9-year iDFS rates were 80.7% and 80.0%, respectively (Fig. 2A). The observed hazard ratio (HR) was 0.98 (95% confidence interval [CI], 0.66–1.45; P = 0.913).

Likewise, the 4-year OS rates were 96.1% and 94.2%, and 9-year

Table 1
Baseline characteristics (n = 657).

Age	
Median	53
Interquartile range	26–73
Age group	
<50	245 (37.3%)
50–59	242 (36.8%)
≥60	170 (25.9%)
Sex	
Male	2 (0.3%)
Female	655 (99.7%)
Year of diagnosis	
2007–2009	218 (33.2%)
2010–2012	439 (66.8%)
Histological type	
Ductal	502 (76.4%)
Lobular	41 (6.2%)
Mixed	96 (14.6%)
Other	18 (2.7%)
Surgery	
BCS	388 (59.2%)
Mastectomy	267 (40.8%)
Tumour stage (AJCC 7th Edition)	
T1a	2 (0.3%)
T1b	17 (2.6%)
T1c	233 (35.5%)
T2	385 (58.6%)
T3	20 (3.0%)
Hormonal status	
ER + or PR+	468 (71.2%)
ER-/PR-	189 (28.8%)
Grade	
I	26 (4.0%)
II	139 (21.2%)
III	492 (74.9%)
Lymphovascular invasion	
No	310 (47.2%)
Yes	124 (18.9%)
Unknown	223 (33.9%)
Stage	
I	252 (38.4%)
II	404 (61.5%)
Unknown	1 (0.2%)
Radiotherapy	
No	260 (39.6%)
Yes	397 (60.4%)
CCI score	
0	505 (76.9%)
1	96 (14.6%)
>1	56 (8.5%)
BMI	
<18.5	11 (1.7%)
18.5–24.9	195 (29.7%)
25–29.9	222 (33.8%)
≥30	229 (34.9%)

AJCC: American Joint Committee on Cancer; ER: Estrogen Receptor; PR: Progesterone Receptor; CCI: Charlson Comorbidity Index; BMI: Body Mass Index.

Table 2
Type of relapse.

Type of relapse	Number	Percent
Ipsilateral breast only	5	4
Ipsilateral axillary nodes only	8	6.4
Ipsilateral breast and axillary nodes	2	1.6
Ipsilateral chest wall only	1	0.8
Ipsilateral chest wall and axillary nodes	1	0.8
Contralateral breast ± nodes	9	7.2
Metastatic only	55	44
Local-regional and metastatic	15	12
New primary cancer	29	23.2
	125	100

OS rates were 89.4% and 84.6% in patients with hormone receptor-positive and triple negative breast cancer, respectively (Fig. 2B). The observed HR was 1.28 (95% CI, 0.80–2.03; P = 0.304).

3.5. Associations of clinical characteristics with survival outcomes

We constructed multivariable Cox proportional hazards models to determine the associations of clinical characteristics with iDFS and OS. Presence of lymphovascular invasion (HR, 2.17; 95% CI, 1.36–3.45; P = 0.001) and grade III tumour (HR, 2.15; 95% CI, 1.09–4.21; P = 0.026) predicted worse iDFS (Fig. 2C). Similarly, grade III tumour (HR, 3.15; 95% CI, 1.18–8.45; P = 0.022) was significantly associated with worse OS while a trend was observed for lymphovascular invasion (HR, 1.79; 95% CI, 0.97–3.32; P = 0.063) (Fig. 2D). However, age category, hormone receptor status, stage, BMI and CCI score were not related to iDFS (Table 3).

4. Discussion

In this real-world study of patients with node negative breast cancer treated with four cycles of DC chemotherapy, the 9-year iDFS and OS rates were 80.5% and 88.0%, respectively. Higher grade tumours and those with lymphovascular invasion were associated with worse survival. Of note, there was no significant difference in survival outcomes of patients with hormone receptor-positive and triple negative breast cancer.

In the ABC group of trials, the 4-year iDFS rate was 88.2% in patients who received six cycles of DC [14]. Sixty percent of patients included in their pooled analysis were node positive. However, their subgroup analyses for node negative patients demonstrated 4-year iDFS rate of 87.0% for those with triple negative disease and 94.2% for those with hormone receptor-positive breast cancer. The corresponding 4-year iDFS rates in our patients were reassuringly similar at 90.4% and 91.3%, respectively. While the age distribution and proportion of patients with triple-negative breast cancer in our study are quite similar to those of the ABC trials, approximately three-fourths of our patients had MBR grade III tumours as compared with their 51%. Further, the median follow-up of the combined ABC trials was 3.3 years and 9.0 years in our study.

In contrast to the ABC trials, more patients enrolled in the PlanB trial were node negative. Further, there was an interim protocol amendment to exclude patients with hormone receptor positive breast cancer with pathological involvement of 0–3 lymph node, who had a recurrence score of 11 or lower on OncotypeDX testing. PlanB did not report on survival outcomes by nodal status but we can make some broad comparisons with our study results. In PlanB, amongst patients who received six cycles of DC, 5-year DFS and OS rates were 89.9% and 94.7% [17]. The corresponding rates in our study were again, reassuringly similar at 88.4% and 92.9%, respectively. Despite inclusion of node positive patients, the population in PlanB had otherwise more favourable clinical risk as exemplified by 57.5% patients with pT1 tumour and only 18.6% patients with triple-negative breast cancer. In our study, 38.4% had pT1 tumour, while 28.8% were triple-negative. Moreover, there were 42.1% grade III tumours in the PlanB study as compared to 74.9% in our patients. In the absence of a direct randomized comparison of four vs six cycles of DC in patients with node-negative HER2 negative breast cancer, the results of our real-world study support comparable outcomes with four cycles of DC in this population.

Reports on longer term follow-up of ABC trial and PlanB patients have not been presented or published and hence we have also reflected on results from TAILORx where just over half of participants treated with chemotherapy were prescribed DC for at least four cycles. For our patients with hormone receptor-positive breast cancer, 9-year iDFS and OS rates were 80.7% and 89.4%, respectively.

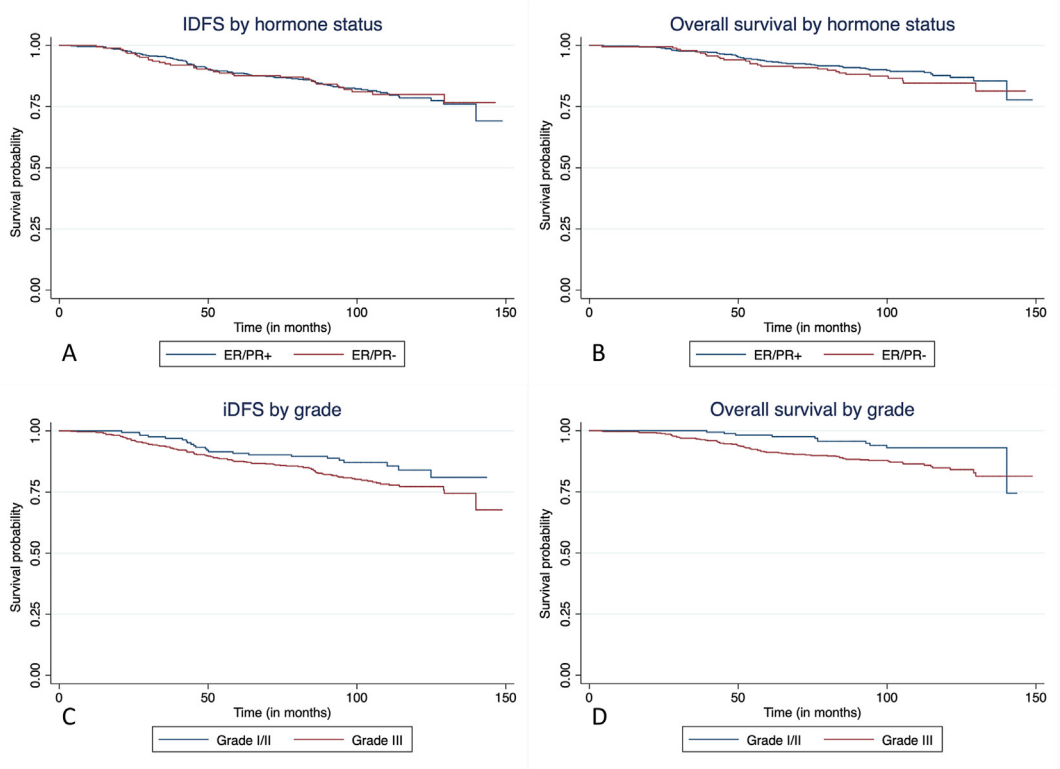

Fig. 2. Invasive disease free survival (iDFS) and overall survival (OS) of patients with breast cancer by hormone receptor status (A and B) and grade (C and D).

These rates are somewhat lower than 84.3% and 93.8% reported in patients with intermediate recurrence score who received chemoendocrine treatment in the TAILORx trial. On the other hand, our patients fared better compared to TAILORx patients with high recurrence score who received chemoendocrine treatment with respect to 9-year iDFS at 75.7% with OS similar at 89.3% [26]. Publicly funded gene expression profile testing was not available in our jurisdiction until 2014 but high-risk classic pathology characteristics were common as exemplified by 74.9% patients with grade III tumours.

Table 3
Multivariable Cox regression model for invasive disease free survival and overall survival.

	Invasive disease free survival			Overall survival		
Variable	Hazard ratio	95% confidence interval	P-value	Hazard ratio	95% confidence interval	P-value
Age category						
<50	Ref					
50–59	1.26	0.74–2.14	0.401	1.73	0.82–3.68	0.153
≥ 60	1.13	0.61–2.07	0.700	1.82	0.83–4.00	0.136
Hormone status						
ER/PR+	Ref					
TNBC	1.23	0.72–2.09	0.442	1.29	0.66–2.50	0.458
LVI						
No	Ref					
Yes	2.17	1.36–3.45	0.001	1.79	0.97–3.32	0.063
Grade						
I/II	Ref					
III	2.15	1.09–4.21	0.026	3.15	1.18–8.45	0.022
Stage						
I	Ref					
II	1.48	0.90–2.43	0.122	1.72	0.90–3.27	0.099
CCI score						
0	Ref					
1	0.57	0.27–1.21	0.141	1.07	0.48–2.39	0.871
1+	0.8	0.33–1.97	0.623	0.91	0.30–2.77	0.865
BMI						
Normal	Ref					
Overweight	0.97	0.54–1.71	0.904	0.99	0.46–2.14	0.989
Obese	1.03	0.58–1.84	0.907	1.02	0.47–2.22	0.952

ER: Estrogen Receptor; PR: Progesterone Receptor; TNBC: Triple Negative Breast Cancer; LVI: Lymphovascular invasion; CCI: Charlson Comorbidity Index; BMI: Body Mass Index.

Histological grade was the only tumour characteristic significantly associated with iDFS and OS in our study. Although subject to inter-pathologist variability in assessment, MBR grade has been extensively validated as a clinical prognostic marker in patients with node negative breast cancer [31–33]. In resource constrained settings, where genomic testing is not available and not publicly funded, the MBR grade is used extensively as one of the clinical markers to guide the role of adjuvant chemotherapy in hormone-receptor-positive node negative breast cancer [34,35]. Likewise, lymphovascular invasion was significantly associated with worse iDFS and a trend was observed with OS. Existing literature suggests a prognostic value of lymphovascular invasion in node-negative breast cancer [36–38]. Of note, we did not find a significant difference in iDFS and OS of patients with hormone receptor-positive breast cancer and triple negative breast cancer, although, this finding should be interpreted with caution. Our patients with hormone receptor-positive breast cancer were selected to receive adjuvant DC chemotherapy based on the known clinical and pathologic factors associated with worse prognosis, including grade and lymphovascular invasion, in addition to consideration of younger age and larger tumour size. Further, patients with triple-negative breast cancer treated with sequential or concurrent anthracycline and taxane chemotherapy were not included in this study. Amongst triple negative patients, those prescribed DC may have been clinically lower risk. Further, the subgroups of patients with hormone receptor-positive and triple negative breast cancer were neither randomized, nor numerically balanced.

Seven patients developed a subsequent ovarian or fallopian tube cancer on follow-up. Although we did not have access to family history and genetic information on our patients, this finding raises concern for deleterious germline BRCA1 or BRCA2 mutations and potential missed opportunities for timely genetic testing and risk-reducing procedures. At least two of these patients would have met genetic testing criteria in the era considered based on age $</ = 50$ and diagnosis of triple negative breast cancer. Further, at least four of these patients would have met current criteria based on age $</ = 65$ and diagnosis of triple negative breast cancer, validating a change in our guidelines.

This study was limited by its retrospective design. The decision of offering non-anthracycine based adjuvant chemotherapy was based on the provincial guidelines and discussion of the treating oncologists with patients. Moreover, genomic risk tools like the OncotypeDX and the Prosigna assay were not funded during 2008–2012 and some of the patients classified as clinical high risk may have actually been genomic low-risk of recurrence. Further, lymphovascular invasion, which was associated with survival outcomes, was not known in two-thirds of the patients. Information on menopausal status of our patients was not collected in this study. Lastly, other factors that could potentially affect the survival outcomes but were not assessed include chemotherapy dose-reduction and delays along with uptake, type and persistence with hormone therapy. The major strengths of this study include a homogeneous population of patients with node-negative breast cancer and a long median follow-up of nine years.

5. Conclusions

In conclusion, the long-term survival outcomes of patients with node negative breast cancer treated with four cycles of DC in the adjuvant setting are encouraging, even in those with triple negative breast cancer. In the absence of randomized data comparing four versus six cycles of DC, the results of our real-world study suggest that it may be reasonable to consider either of the regimens after a detailed discussion with patients. Moreover, four cycles of DC may have a particular role in publicly funded and resource constrained settings.

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Data statement

The data can be shared with the journal for review, if needed.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.08.002.

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