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Prescribing practices of endocrine therapy for ductal carcinoma *in situ* in British Columbia

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ABSTRACT

Purpose The mainstay of treatment for ductal carcinoma *in situ* (DCIS) involves surgery in the form of mastectomy or lumpectomy. Inconsistency in the use of endocrine therapy (ET) for DCIS is evident worldwide. We sought to assess the variation in ET prescribing for patients with DCIS across a population-based radiotherapy (RT) program and to identify variables that predict its use.

Methods Data from a breast cancer database were obtained for women diagnosed with DCIS in British Columbia from 2009 to 2014. Associations between ET use and patient characteristics were assessed by chi-square test and multilevel multivariate logistic regression. The Kaplan–Meier method, with propensity score matching and Cox regression analysis, was used to assess the effects of ET on overall survival (OS) and relapse-free survival (RFS).

Results For the 2336 DCIS patients included in the study, ET use was 13% in DCIS patients overall, and 17% in patients with estrogen receptor–positive (ER+) tumours treated with breast-conserving surgery and RT. Significant variation in ET use by treatment centre was observed (range: 8%–23%; $p < 0.001$), and prescription of ET by individual oncologists varied in the range 0%–40%. After controlling for confounding factors, age less than 50 years [odds ratio (OR): 1.72; $p = 0.01$], treatment centre, ER+ status (OR: 5.33; $p < 0.001$), and RT use (OR: 1.77; $p < 0.001$) were significant predictors of ET use. No difference in OS or RFS with the use of ET was observed.

Conclusions In this population-based analysis, 13% of patients with DCIS in British Columbia received ET, with variation by treatment centre (8%–23%) and individual oncologist (0%–40%). Age less than 50 years, ER+ status, and RT use were most associated with ET use.

Key Words DCIS, endocrine therapy, British Columbia, treatment variation, prescribing

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INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is a type of pre-invasive breast cancer in which the cancerous cells are confined to the epithelial lining of milk ducts in breast tissue[1]. The widespread use of mammography screening has led to increased detection of DCIS, and DCIS now constitutes 20%–30% of mammography-detected cases of breast carcinoma[2,3]. With modern treatments, the survival rate for women with DCIS is 98% at 5 years after diagnosis and 95% at 28 years[1]. Without treatment, estimates suggest that 25%–30% of DCIS will transform into invasive breast cancer within 5 years[3].

Before the 1990s, the main approach to DCIS was to offer mastectomy. That approach has now been supplanted with increased use of breast-conserving surgery (BCS), involving lumpectomy followed by radiotherapy (RT) to achieve similar outcomes, albeit with a slightly higher risk of recurrence[4,5]. The role of endocrine therapy (ET) in the management of DCIS is controversial. A meta-analysis of two randomized clinical trials investigating the use of tamoxifen in DCIS reported that, compared with placebo, tamoxifen given after lumpectomy (with or without RT) lowered the risk of recurrent ipsilateral and contralateral DCIS, without improvement in all-cause mortality[6]. A subsequent retrospective analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial found that the risk of developing breast cancer was halved when women with estrogen receptor–positive (ER+) tumours received tamoxifen (compared with placebo); no benefit was

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noted for ER-negative tumours[7]. Endocrine therapy (such as tamoxifen) is associated with many side effects, including increased risk for thromboembolic events and uterine cancer, necessitating discussion between physicians and their patients about the risks and benefits of the therapy[5,8].

The use of ET in DCIS by oncologists and treatment centres varies considerably worldwide[3,5,9–11]. That variability suggests inconsistency in the perception by physicians—because of factors relating to the patient, the oncologist, and the tumour—about the applicability of ET in reducing cancer risk[12]. In New Zealand and Australia, ET is rarely prescribed for DCIS: fewer than 19% of patients receive tamoxifen[9]. In North America, prescribing practices vary widely by institution, ranging from approximately 20% to more than 70%[3,11,13,14]. A survey of radiation oncologists in Canada and the United States found a geographic disparity, with recommendations for tamoxifen being highest in the northeastern United States and lowest in Canada (less than in any region of the United States)[3]. The survey also included European physicians, finding that they, compared with North American physicians, were only half as likely to recommend tamoxifen for all cases of DCIS. Possible reasons for the discrepancies in ET use include differences in the understanding of the evidence, institutional practices, weighting of the risks and benefits, and concomitant use of RT[3,5,12].

Compared with studies involving jurisdictions in the United States, studies of the patterns of ET use within Canada are rare. A study of women diagnosed with DCIS from 2000 to 2009 in the province of British Columbia found that 26% were treated with tamoxifen[10]; however, no study has yet investigated variation in tamoxifen use between the various BC Cancer treatment sites nor the factors that might explain the variation and predict tamoxifen use. Moreover, we know of no study that has attempted to quantify ET use at the individual physician level. We therefore sought to assess variation in ET use by radiation oncologists and BC Cancer sites within British Columbia, with the hypothesis that variability in ET use by treatment site would be evident. An understanding of this issue will contribute to the literature about discrepancies in ET use and will further clarify the role of ET in the management of DCIS.

METHODS

Data Abstraction

The study was approved by the University of British Columbia and the BC Cancer Research Ethics Board (no. H16-03443). The BC Cancer Breast Cancer Outcomes Unit identified all women who were diagnosed with DCIS during 2009–2014, who were referred to BC Cancer, and who were B.C. residents at time of diagnosis. All 6 BC Cancer sites were included: Abbotsford Centre, Centre for the North, Fraser Valley Centre, Centre for the Southern Interior, Vancouver Island Centre, and Vancouver Centre. Exclusion criteria included the presence of ipsilateral new breast cancer. Baseline patient, tumour, and treatment characteristics (including RT and ET use) and radiation oncologist and treatment centre information were abstracted from the Breast Cancer Outcomes Unit database. Missing information was updated by reviewing the patient's electronic medical record.

Statistical Analysis

Patient, tumour, and treatment characteristics—age, tumour size, tumour grade, margin status, ER status, BC Cancer site, RT use, and ET use—were analyzed using descriptive statistics. Associations between ET use and patient or tumour characteristics were assessed using the chi-square test. To identify variables that predict for the use of ET, multivariate logistic regression analysis, controlling for confounding factors, was conducted for age category, tumour grade, margin status, tumour size, RT use, ER status, surgery type, and treatment centre. To account for the possible clustering effects of patients within treatment sites, multilevel multivariate logistic regression using a 2-level hierarchical logit model was performed, with the random intercept term varying at the level of treatment site[15,16]. For the survival analysis, patients were followed by their clinic every 6–12 months, and outcomes were measured from the time of diagnosis until September 2016. Events of ipsilateral or contralateral breast tumour recurrence, local or distant metastasis, or development of another tumour were used for a relapse-free survival (RFS) analysis; the overall survival (OS) analysis considered death from any cause. Propensity score matching using the multilevel multivariate logistic regression model was performed before the survival analysis. Subsequently, a Kaplan–Meier analysis, with log-rank test, was performed on the matched data to assess the effects of ET on OS and RFS. Cox regression analysis for ET use, age category, tumour grade, margin status, tumour size, RT use, ER status, and surgery type was also performed to assess survival and hazard ratios. All p values were two-sided, and values less than 0.05 were considered statistically significant. Analyses were conducted using the IBM SPSS Statistics software application (version 24.0: IBM, Armonk, NY, U.S.A.). Multilevel modelling used the generalized linear mixed models function in SPSS.

RESULTS

Patient, Tumour, and Treatment Characteristics

Across the province, 2336 DCIS patients were identified at 6 different sites. Table I summarizes patient, tumour, and treatment characteristics. Median age at diagnosis was 59 years (range: 16–93 years). In terms of tumour properties, 66% were ER+, 80% had negative margins, 83% were grade 2 or 3, and 87% were less than 4.0 cm in size. Patients were treated with partial mastectomy (69%), complete mastectomy (29%), RT (53%), and ET (13%). For patients with DCIS who were treated with BCS and RT, the use of ET was 15%; considering only ER+ tumours treated with BCS and RT, ET use rose to 17%. The Vancouver Centre treated the highest proportion of patients (38% overall); the Centre for the North, which was opened midway through the study period, treated the smallest proportion (3%).

Use of ET and Associations with Various Characteristics

Table II demonstrates the associations of patient, tumour, and treatment characteristics with the use of ET. Significant associations were observed for ET use with age ($p = 0.01$), ER status ($p < 0.001$), margin status ($p = 0.003$), and RT use ($p < 0.001$). Wide variation in ET use was observed by treatment centre ($p < 0.001$), ranging from 8% (Abbotsford Centre) to

23% (Centre for the North). Use of ET was lowest in the final 2 years of the study period, but no significant difference in terms of year of diagnosis was found.

TABLE I Patient, tumour, and treatment characteristics

Characteristic	Value
Patient cohort (*n*)	2336
Age category [*n* (%)]	
<50 Years	514 (22)
50–70 Years	1402 (60)
>70 Years	420 (18)
Tumour grade [*n* (%)]	
1	380 (17)
2	917 (41)
3	939 (42)
Margins [*n* (%)]	
Negative	1789 (80)
Close	380 (17)
Positive	67 (3)
Tumour size [*n* (%)]	
<16 mm	1163 (52)
16–40 mm	782 (35)
>40 mm	291 (13)
ER status [*n* (%)]	
Positive	1476 (66)
Negative	291 (13)
Unknown	470 (21)
Surgery [*n* (%)]	
None	45 (2)
Breast-conserving surgery	1543 (69)
Complete mastectomy	648 (29)
Use RT [*n* (%)]	
Yes	1185 (53)
No	1051 (47)
Use endocrine therapy [*n* (%)]	
In all cases (*n*=2336)	291 (13)
ER-positive only (*n*=1546)	247 (16)
BCS and RT only (*n*=1194)	174 (15)
ER-positive with BCS and RT (*n*=1036)	173 (17)
BC Cancer clinic (*n*)	
AC	10
CN	3
FVC	21
CSI	13
VIC	15
VC	38

ER = estrogen receptor; RT = radiation therapy; AC = Abbotsford Centre; CN = Centre for the North; FVC = Fraser Valley Centre; CSI = Sindi Ahluwalia Hawkins Centre for the Southern Interior; VIC = Vancouver Island Centre; VC = Vancouver Centre.

TABLE II Characteristics of patients based on receipt of endocrine therapy (ET)

Characteristic	Patient group		*p* Value
	Overall (*n*)	Received ET (%)	
Age category			
<50 Years	558	17	0.01
50–70 Years	1389	12	
>70 Years	389	10	
Tumour grade			
I	372	12	0.35
II	923	14	
III	944	13	
Margins			
Negative	1854	12	0.003
Close	383	16	
Positive	69	12	
Tumour size			
<16 mm	1176	15	0.84
16–40 mm	790	16	
>40 mm	370	13	
Surgery			
Breast-conserving surgery	1621	13	0.97
Complete mastectomy	678	13	
Estrogen receptor status			
Positive	1291	16	<0.001
Negative	281	1	
Use of radiation therapy			
Yes	1239	18	<0.001
No	1097	11	
BC Cancer clinic			
AC	235	8	<0.001
CN	64	23	
FVC	480	13	
CSI	314	9	
VC	892	16	
VIC	351	9	
Year of diagnosis			
2009	335	14	0.29
2010	313	15	
2011	363	14	
2012	326	14	
2013	355	11	
2014	340	10	

AC = Abbotsford Centre; CN = Centre for the North; FVC = Fraser Valley Centre; CSI = Sindi Ahluwalia Hawkins Centre for the Southern Interior; VIC = Vancouver Island Centre; VC = Vancouver Centre.

As depicted in Figure 1, variability in ET use was evident by individual radiation oncologist within each centre, ranging from 0% to 40%. Certain centres demonstrated consistently higher individual use rates. For example, the lowest individual rate at Vancouver Centre (13%) was greater than the highest individual rate at the Centre for the Southern Interior (11%), and similar to the highest individual rate at the Abbotsford Centre (14%). Only 2 radiation oncologists from the Centre for the North had recorded rates, with one prescribing ET in 33% of cases, and the other, in 0%. Intrasite variability was highest at the Vancouver Island Centre (0%–40%) and lowest at the Centre for the Southern Interior (0%–11%).

Table III presents the multivariate logistic regression analysis predicting the use of ET. After controlling for confounding factors, the strongest predictor was ER+ status [odds ratio (OR): 15.25; 95% confidence interval (CI): 5.58 to 41.67; $p < 0.001$]. Patients less than 50 years of age were more likely to receive ET (OR: 1.70; 95% CI: 1.13 to 2.54; $p = 0.01$), as were those receiving RT (OR: 1.60; 95% CI: 1.28 to 2.06; $p < 0.001$). The use of ET was significantly associated with treatment centre on single-level analysis: based on Vancouver Centre (the largest centre) as a reference, the Vancouver Island Centre (OR: 0.45; 95% CI: 0.30 to 0.69), the Centre for the Southern Interior (OR: 0.46; 95% CI: 0.30 to 0.71), and the Abbotsford Centre (OR: 0.41; 95% CI: 0.25 to 0.70) were all less likely to be associated with ET use (all $p < 0.001$). On multilevel analysis, with the possible effects of patient clustering by treatment site controlled, the same pattern was maintained; and ER+ status, age less than 50 years, and RT use remained significant predictors of ET use.

Impact of ET on OS and RFS

Kaplan–Meier analysis using propensity score matching revealed no significant difference in OS ($p = 0.46$) and RFS ($p = 0.22$) between patients receiving and not receiving ET. The 5-year RFS and OS were, respectively, 97.6% and 96.6%, and 98.1% and 97.6%, in those two groups. Cox regression analysis also showed no significant effect of ET on RFS (hazard ratio: 0.78; 95% CI: 0.33 to 2.57; $p = 0.69$) or on OS (hazard ratio: 0.90; 95% CI: 0.29 to 3.42; $p = 0.75$). When limiting the Kaplan–Meier analysis to patients with ER+ tumours treated with BCS and RT (per NSABP B-24 and subsequent re-analysis studies), no significant difference remained in OS ($p = 0.34$) and RFS ($p = 0.11$).

DISCUSSION

In this population-based analysis of ET use for DCIS patients in British Columbia, we found that oncologists prescribed ET for 13% of all patients with DCIS, for 15% of DCIS patients treated with BCS and RT, and for 17% of patients with ER+ tumours treated with BCS and RT. We found significant variation in ET use by treatment centre (range: 8%–23%) and by individual prescriber (range: 0%–40%), suggesting widespread inconsistency in ET use at the various BC Cancer sites in the province. Additionally, after controlling for confounding variables, we discovered certain patient and treatment characteristics that predicted for the use of ET: age less than 50 years, ER+ tumour, and concurrent RT use.

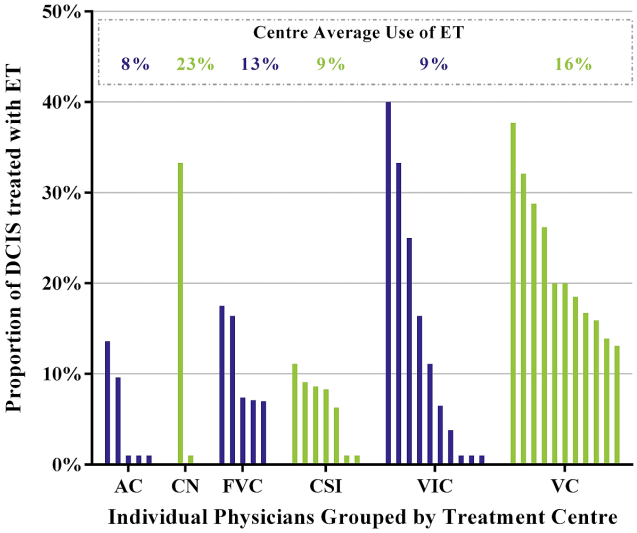

FIGURE 1 Prescription of endocrine therapy (ET) by individual radiation oncologist, grouped by cancer treatment centre. DCIS = ductal carcinoma *in situ*; AC = Abbotsford Centre; CN = Centre for the North; FVC = Fraser Valley Centre; CSI = Sindi Ahluwalia Hawkins Centre for the Southern Interior; VIC = Vancouver Island Centre; VC = Vancouver Centre.

Our data contribute to the literature regarding the large variation in ET use for DCIS worldwide. Notably, our report of 13% ET use overall falls at the lower end of the range revealed by earlier studies in other jurisdictions. A study of patients with DCIS diagnosed during 2002–2005 in a California program found an ET use rate of 47%[5], and a study of 2090 patients diagnosed in North Carolina during 2006–2010 found a rate of 37%[16]. Our rate is more comparable to the 19% reported in an Australia and New Zealand study[9]. Our study supports the findings of Ceilley *et al.*[3], who demonstrated that oncologists in the United States were far more likely than their Canadian counterparts to recommend the use of ET.

An earlier study in British Columbia by Lo *et al.*[13], which included DCIS patients treated with BCS and RT during the period 2000–2009, yielded an ET use rate of 26%. Comparatively, our study (analyzing 2009–2014 data) yields an ET use rate of 15% in patients treated only with BCS and RT. Interestingly, the former analysis showed a decline in ET use during the study period, with a peak of almost 50% in 2001 (after publication of the NSABP B-24 trial), followed by a drop to less than 20% by 2009. Our data suggest that the downward trend of ET use continued after 2009, given that the overall use of ET for patients with DCIS dropped to 10% by 2014 from 14% in 2009 (Table II). Reasons for that possible trend are unknown, but perhaps attitudes or understanding on the part of physicians about ET have changed in the decades since the publication of the NSABP B-24 trial.

The evident variation in ET use could be explained by several factors. At Vancouver Centre, which is the largest BC Cancer site, the average rate of ET use was the highest (other than at the new and small Centre for the North) at 16%, and no oncologist prescribed ET in 0% of cases, a finding that did not hold true for the other sites. That observation

TABLE III Multilevel multivariate logistic regression analysis for the use of endocrine therapy

Characteristic	Single-level multivariate analysis			Multi-level multivariate analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age category						
>70 Years		(Reference)			(Reference)	
50–70 Years	1.24	0.85 to 1.8	0.26	1.32	0.97 to 1.85	0.09
<50 Years	1.70	1.13 to 2.54	0.01	1.72	1.14 to 2.56	0.01
Tumour grade						
1		(Reference)			(Reference)	
2	1.01	0.46 to 2.20	0.99	1.15	0.80 to 1.70	0.42
3	1.03	0.59 to 2.02	0.90	1.23	0.84 to 1.62	0.20
Margin status						
Negative		(Reference)			(Reference)	
Close	1.45	0.761 to 2.76	0.26	1.29	0.94 to 1.75	0.11
Positive	1.34	0.40 to 4.55	0.64	0.82	0.39 to 1.74	0.60
Tumour size						
<16 mm		(Reference)			(Reference)	
16–40 mm	0.95	0.34 to 2.66	0.93	1.17	0.80 to 1.70	0.42
>40 mm	1.06	0.36 to 3.11	0.91	1.25	0.85 to 1.63	0.34
Use of radiation therapy						
No		(Reference)			(Reference)	
Yes	1.60	1.28 to 2.06	<0.001	1.77	1.26 to 2.47	<0.001
Estrogen receptor status						
Negative		(Reference)			(Reference)	
Positive	15.25	5.58 to 41.67	<0.001	5.33	2.82 to 10.08	<0.001
Surgery						
Partial mastectomy		(Reference)			(Reference)	
Complete mastectomy	1.07	0.77 to 1.37	0.86	1.11	0.71 to 1.31	0.44
BC Cancer Agency clinic						
VC		(Reference)				
VIC	0.45	0.30 to 0.69	<0.001			
FVC	0.73	0.53 to 1.02	0.06			
CSI	0.46	0.30 to 0.71	<0.001			
CN	1.56	0.84 to 2.89	0.16			
AC	0.41	0.25 to 0.70	<0.001			

OR = odds ratio; CI = confidence interval; VC = Vancouver Centre; VIC = Vancouver Island Centre; FVC = Fraser Valley Centre; CSI = Sindi Ahluwalia Hawkins Centre for the Southern Interior; CN = Centre for the North; AC = Abbotsford Centre.

might reflect differences in culture or training at each of the sites, given that factors such as area of training, presence of guidelines, and physician knowledge have been suggested to affect an oncologist's decision to offer ET[3,5,12]. Patient receptiveness is also a key issue, with factors such as demographics, language abilities, strength of recommendation, and degree of knowledge all affecting the likelihood of the patient accepting treatment[5,17]. Unfortunately, variables reflecting patient and physician beliefs or demographics were not tested in the present study.

Our results agree with those from earlier publications, indicating that younger age, an ER+ tumour, and concurrent RT use are associated with ET use[7,11,13,18]. In the original NSABP B-24 trial, tamoxifen was shown to benefit patients receiving BCS and RT, reducing both ipsilateral and contralateral recurrence, and so it appears that oncologists following the trial protocol were likely to prescribe tamoxifen[5,17,18,19]. The link to the ER+ status of the tumour is unsurprising, given that a reanalysis of the NSABP B-24 data revealed that the benefit of ET was limited to patients with ER+ DCIS[7]. Surprisingly, however, we found no effect of ET on the 5-year OS or RFS, either for DCIS patients overall or for those with ER+ disease treated with BCS and RT. That observation contradicts the findings in earlier studies, but could be partly attributable to the observational nature of our study (for which we attempted to compensate with

multivariate analysis and matching), to the relatively small population of patients receiving ET, and to the short follow-up[13,20].

Our study should be interpreted in context of its strengths and limitations. Because this observational retrospective study did not capture physician or patient opinions about ET use, we were not able to explore how those factors might have influenced the variation in ET use by jurisdictions. Moreover, although we controlled for many factors in the multivariate analysis and used propensity score matching for the survival analysis, other confounding factors might not have been identified and controlled for or might have been unbalanced in the ET and non-ET groups because of a lack of randomization (an inherent bias of retrospective studies)[13]. As mentioned earlier, such factors might have contributed to our inability to detect a survival benefit associated with ET use. Finally, our study focused on tamoxifen and, because of insufficient data for our study population, did not explore the use of aromatase inhibitors.

CONCLUSIONS

Overall, our initial hypothesis was satisfied. The data show variation in ET use for DCIS at the various BC Cancer treatment centres (range: 8%–23%) and by individual oncologists (range: 0%–40%). That variation might be a consequence of a lack of clear guidelines for ET use, possibly resulting in various patient and physician factors affecting determination of the need for ET. As expected, ER+ status, RT use, and younger age predicted for ET use. Survival (OS and RFS) was not significantly different between patients receiving and not receiving ET.

Future studies should seek to characterize the effect on ET use of physician-specific variables (such as length and location of training, age, sex) and treatment site characteristics. If uniform quality care is to be delivered throughout our population-based program, standardized guidelines are needed.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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