

Neoadjuvant systemic therapy in breast cancer: use and trends in radiotherapy practice

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ABSTRACT

Background The use of neoadjuvant systemic therapy (NAST) in the treatment of breast cancer is increasing, and the role of adjuvant radiation therapy (RT) in that setting is uncertain. We sought to review and report the use of NAST, its trends over time, and its relationship with the prescribing patterns of locoregional RT in a provincial cancer system.

Methods Patients with stages I–III breast cancer diagnosed during 2007–2012 were identified using a provincial database. Patient, tumour, and treatment characteristics were extracted. Multivariable logistic regression analyses were used to assess associations with the use of NAST. Kaplan–Meier and Cox regression were used for survival analyses.

Results Of the 11,658 patients who met the inclusion criteria, 602 (5%) had received NAST. Use of NAST was more frequent in stage III patients (53%) than in stages I and II patients (2%). In clinically lymph-node positive patients, a pathology assessment was made approximately 50% of the time. Higher clinical tumour stage and increasing clinical nodal stage predicted for increasing use of NAST and of nodal RT after NAST, but pathologic nodal status after NAST was not associated with use of nodal RT. A statistically significant survival difference was observed between patients in the NAST and no-NAST groups, but that significance disappeared in a multivariable Cox regression analysis.

Conclusions This population-based study demonstrated 5% use of NAST for breast cancer. Most patients received nodal RT after NAST, and nodal RT was not associated with pathologic stage after NAST. Findings likely reflect the realities of clinical practice and show that reliance on clinical nodal staging results in outcomes similar to those reported in the literature.

Key Words Breast cancer, neoadjuvant systemic therapies, radiotherapy, nodal irradiation, nodal staging

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INTRODUCTION

Interest in and use of neoadjuvant systemic therapy (NAST) in breast cancer (BCa) has been increasing^{1–3}. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 clinical trial demonstrated that neoadjuvant therapy was not superior to adjuvant chemotherapy for the primary endpoints of disease-free survival or overall survival (OS), but did appear to facilitate more breast-conserving surgery⁴. As a result, although NAST was historically used to enable resection of otherwise unresectable or locally advanced BCa, it is increasingly used for less-advanced tumours to facilitate breast-conserving surgery. Other emerging uses of NAST include the study of novel systemic agents, enabling smaller studies to determine the activity of an agent in a shorter period of time^{5,6}.

The indications for regional radiotherapy (RT) after mastectomy in non-locally-advanced BCa have been based

on nodal status (level I evidence)^{7–11}. As NAST becomes more commonplace, standardization is needed in the delivery of adjuvant locoregional (LR) RT in this context. The lack of evidence in this setting has made such standardization difficult and could affect patient care and LR outcomes.

In the context of adjuvant systemic therapy, the addition of adjuvant LR RT lowers LR relapse rates. It also offers a BCa-free survival benefit in node-positive patients treated with either mastectomy or breast-conserving surgery^{7,8,12,13} and, in some trials, an OS advantage^{9–11}. The decision to offer LR RT has largely been based on the presence or number of positive axillary lymph nodes and tumour size, assessed before chemotherapy^{7,8,10,12,13}.

Although it seems logical to offer LR RT when nodal disease is identified after NAST, whether to offer LR RT when no nodal disease is detected after NAST is unclear, especially if the “clinically involved” nodes were not

pathologically sampled before systemic treatment. Diagnostic imaging—including ultrasonography, magnetic resonance imaging, or combined positron-emission tomography and computed tomography—does not have sufficient specificity or sensitivity to replace pathology assessment^{14,15}. Several recent publications have shown a lower risk of recurrence after pathologic complete response; however, a pathologic complete response after NAST does not entirely eliminate the risk of recurrence^{16–19} [a question that is currently under examination (<https://clinicaltrials.gov/ct2/show/NCT01872975>)]. In the meantime, we sought to review and report on the use of NAST, its trends over time, and its relationship with the prescribing patterns of LR RT in a provincial cancer system.

METHODS

Data Source and Extraction

The BC Cancer Agency (BCCA) is the sole provider of RT in British Columbia. Patients with nonmetastatic bca diagnosed between July 2012 and June 2012 were identified through the Breast Cancer Outcomes Unit database, which prospectively records tumour, stage, treatment, and outcome data. The proportion of patients who received NAST as part of their initial therapy was determined. Prognostic and treatment factors were extracted from the Breast Cancer Outcomes Unit database, and the patient's electronic medical chart was reviewed to determine additional information, including the method of lymph node assessment before NAST.

Statistical Analysis

Patient characteristics are presented as descriptive statistics, and the chi-square and Fisher exact tests were used to assess associations with the use of NAST, treatment facility, and year of treatment. Multivariable logistic regression analyses were used to assess the associations between variables and the subsequent use of NAST. All *p* values were 2-sided, and values less than 0.05 were considered statistically significant. Kaplan–Meier analysis was used to estimate os, locoregional relapse-free survival (LRRFS), and distant metastasis-free survival (DMFS), with os being calculated from the date of diagnosis to date of death, LRRFS being calculated from the date of diagnosis to time to relapse in breast or regional lymph nodes as a first event, and DMFS being calculated from the date of diagnosis to the date of first metastatic event. Cox regression analysis was used to analyze the effect of risk factors on os, LRRFS, and DMFS. The analyses were conducted using the SPSS software application (version 14.0: SPSS, Chicago, IL, U.S.A.). The study was approved by the BCCA–University of British Columbia research ethics board.

RESULTS

Overall Demographics

During the study period, 11,658 patients were diagnosed and referred to the BCCA with nonmetastatic bca. Of those patients, 602 (5%) received NAST, 330 of whom (55%) were clinical stage III and 272 of whom (45%) were stages I–II. The NAST consisted mainly of chemotherapy (92%) as opposed to endocrine therapy. Table 1 summarizes

TABLE 1 Patient, tumour, and treatment characteristics

Characteristic	Received neoadjuvant systemic therapy		<i>p</i> Value
	No	Yes	
Patients (<i>n</i>)	11,056	602	
Median age (years)	61	53	<0.001
Menopausal status [<i>n</i> (%)]			
Premenopausal	2947 (27)	294 (49)	<0.001
Postmenopausal	8070 (73)	301 (50)	
Pregnant	7 (<1)	1 (<1)	
Unknown	32 (<1)	6 (1)	
Receptor status [<i>n</i> (%)]			
ER-positive	9509 (86)	434 (72)	<0.001
HER2-positive	1606 (15)	198 (33)	<0.001
Clinical tumour stage [<i>n</i> (%)]			
T1	6911 (63)	50 (8)	<0.001
T2	3142 (28)	159 (26)	
T3	273 (2)	174 (29)	
T4	161 (1)	203 (34)	
Unknown	569 (5)	16 (3)	
Clinical nodal status [<i>n</i> (%)]			
N0	9909 (90)	234 (39)	<0.001
N1	1044 (9)	270 (45)	
N2	69 (<1)	70 (12)	
N3	34 (<1)	28 (5)	
Tumour grade [<i>n</i> (%)]			
1	2612 (24)	35 (6)	<0.001
2	4606 (42)	205 (34)	
3	3708 (34)	311 (52)	
Unknown	130 (1)	51 (8)	
Overall stage [<i>n</i> (%)]			
I–II	10766 (97)	272 (45)	<0.001
III	290 (3)	330 (55)	
Primary surgery [<i>n</i> (%)]			
Breast-conserving surgery	6376 (58)	50 (8)	<0.001
Mastectomy	4413 (40)	543 (90)	
None	267 (2)	9 (1)	
Nodal surgery [<i>n</i> (%)]			
SLNB	5487 (50)	51 (8)	<0.001
ALND	2852 (26)	462 (77)	
SLNB+ALND	2211 (20)	72 (12)	
None	506 (5)	17 (3)	
Nodal irradiation [<i>n</i> (%)]	2863 (26)	510 (85)	<0.001
Type of neoadjuvant systemic therapy [<i>n</i> (%)]			
Chemotherapy	NA	540 (90)	—
Endocrine therapy	NA	48 (8)	
Other	NA	2 (<1)	
Missing	NA	12 (2)	

ER = estrogen receptor; HER2 = human epidermal growth factor receptor; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; NA = not applicable.

additional patient, tumour, and treatment characteristics, demonstrating a marked difference between patients who did and did not receive NAST. As expected, patients in the NAST cohort had more advanced disease: 63% compared with 5% in the no-NAST cohort had cT3 or cT4 disease ($p < 0.001$), and 61% compared with just 10% in the no-NAST cohort had clinically node-positive disease ($p < 0.001$). Stage III BCa was more common in the NAST cohort than in the no-NAST cohort (55% vs. 3%, $p < 0.001$). The patients who received NAST received more aggressive surgery: 90% compared with 40% in the no-NAST cohort underwent mastectomy, and 77% compared with 26% in the no-NAST cohort underwent axillary lymph node dissection ($p < 0.001$). Compared with patients having stages I–II disease, patients with stage III BCa were significantly more likely to receive NAST (53% vs. 2%, $p < 0.001$).

Temporal Trends in NAST Use

Table II shows that use of NAST did not increase during the study period; it remained at 5%–6% per year ($p = 0.13$). A statistically significant increase in the use of NAST to 3% from 2% ($p < 0.001$) was seen in all stage I–II patients and corresponds to a 50% relative increase in patients treated with NAST to 51% in 2012 from 37% in 2007 ($p = 0.003$). We observed no statistical difference in the proportion of stage III patients treated with NAST during the study period ($p = 0.3$). On multivariable regression analysis (Table III), year of treatment was not significantly associated with the use of NAST.

Assessment of Lymph Node Status Before NAST

Table IV shows that, before NAST, clinical exam was the most frequent method of assessing lymph node status and only a small number of patients underwent pathology assessment. In clinically lymph node–positive patients, a pathology assessment based on a fine-needle aspiration or core biopsy was performed roughly 50% of the time (47%, 42%, and 50% for cN1, cN2, and cN3 respectively). In clinically node-negative patients, 4% underwent sentinel lymph node biopsy (SLNB) before NAST. Axillary staging by methods other than clinical exam alone increased during the study period to 45% in 2010–2012 from 30% in 2007–2009 ($p < 0.001$, Table V).

Use of Nodal Irradiation

Compared with the no-NAST patients, patients treated with NAST were more likely to receive nodal irradiation (85% vs. 27%, $p < 0.001$, Table I). The use of nodal RT differed between the patients with lower-stage (I–II) and higher-stage (III) disease (80% vs. 89% respectively, $p = 0.002$). A statistically significant association of increasing use of nodal RT with increase in clinical nodal stage was evident: 78%, 89%, 90%, and 94% for cN0, cN1, cN2, and cN3 respectively ($p = 0.002$). Pathologic nodal status after chemotherapy (yp stage) was not associated with subsequent delivery of nodal RT ($p = 0.80$, Table VI).

Multivariable Analysis

To find associations with the use of NAST, a multivariable regression analysis controlling for age, stage, year, BCa

TABLE II Use of neoadjuvant systemic therapy, 2007–2012

Year	Pts (n)	Proportion of patients who received neoadjuvant systemic therapy [n/N (%)]					
		Overall (n=11,648 ^a)	p Value	Stage I–II (n=11,028 ^a)	p Value	Stage III (n=620)	p Value
2007 (partial)	634	35 (6)	0.13	13/603 (2)	<0.001	22/31 (71)	0.30
2008	2128	96 (5)		31/1995 (2)		65/133 (49)	
2009	2208	101 (5)		36/2093 (2)		65/115 (56)	
2010	2385	139 (6)		69/2257 (3)		70/128 (55)	
2011	2528	147 (6)		80/2397 (3)		67/131 (51)	
2012 (partial)	1765	84 (5)		43/1683 (3)		41/82 (50)	

^a Data missing for 10 patients.
Pts = patients.

TABLE III Lymph node assessment before neoadjuvant systemic therapy

Assessment type	Pts (n)	Clinical nodal status [n (%)] ^a				p Value
		N0 (n=228)	N1 (n=267)	N2 (n=69)	N3 (n=26)	
SLNB	10	10 (4)	0	0	0	<0.001
Ultrasonography	23	10 (4)	10 (4)	2 (3)	1 (4)	
Clinical only	357	180 (79)	129 (48)	37 (54)	11 (42)	
FNA or core biopsy	200	28 (12)	128 (48)	30 (43)	14 (54)	

^a Data missing for 12 patients.
Pts = patients; SLNB = sentinel lymph node biopsy; FNA = fine-needle aspiration.

facility, tumour characteristics, and use of non-systemic treatment was performed. Increasing age was significantly associated with decreasing use of NAST (odds ratio: 0.95 per year; 95% CI: 0.93 to 0.96; $p \leq 0.001$). Increased use of NAST was associated with increasing clinical tumour and clinical

TABLE IV Multivariable logistic regression analysis

Characteristic	Receipt of neoadjuvant systemic therapy		
	OR ^a	95% CI	p Value
Age of patient (continuous)	0.95	0.93 to 0.96	<0.001
Menopausal status			
Postmenopausal	Reference		
Premenopausal	0.76	0.53 to 1.1	0.15
Pregnant	0.22	0.02 to 2.5	0.22
BCCA centre			
1	Reference		
2	0.22	0.14 to 0.33	<0.001
3	0.55	0.39 to 0.78	0.001
4	0.87	0.61 to 1.24	0.44
5	0.60	0.39 to 0.94	0.03
6	1.83	0.24 to 13.87	0.56
Year of treatment			
2012	Reference		
2011	1.54	0.82 to 2.88	0.18
2010	0.8	0.51 to 1.26	0.34
2009	1.04	0.67 to 1.6	0.88
2008	1.34	0.88 to 2.03	0.17
2007	1.29	0.86 to 1.94	0.22
Clinical primary tumour stage			
T1	Reference		
T2	4.88	3.32 to 7.17	<0.001
T3	48.6	31.9 to 73.87	<0.001
T4	225.58	140.44 to 362.31	<0.001
Clinical nodal stage			
N0	Reference		
N1	3.84	2.94 to 5.0	<0.001
N2	14.0	8.14 to 24.17	<0.001
N3	12.69	5.58 to 28.82	<0.001
Tumour grade			
Low (1, 2)	Reference		
High (3)	0.95	0.72 to 1.25	0.71
ER status			
Positive	Reference		
Negative	1.19	0.87 to 1.62	0.28
HER2 status			
Negative	Reference		
Positive	1.84	1.39 to 2.44	<0.001

^a A result >1 favours neoadjuvant systemic therapy. BCCA = BC Cancer Agency; ER = estrogen receptor; HER2 = human epidermal growth factor receptor.

nodal stage and with HER2-positive disease (1.84; 95% CI: 1.4 to 2.4; $p < 0.001$; Table III).

When a multivariable regression analysis was performed to look at the use of nodal RT in the NAST group, clinical T2 [hazard ratio (HR): 6.46; 95% CI: 1.21 to 34.54; $p = 0.029$], T3 (HR: 9.52; 95% CI: 1.44 to 62.84; $p = 0.019$), and T4 disease (HR: 16.9; 95% CI: 2.27 to 126.0; $p = 0.006$), and high grade (HR: 7.4; 95% CI: 1.9 to 28.88; $p = 0.004$) were predictive of the use of nodal RT. Increasing age (HR: 0.91; 95% CI: 0.85 to 0.98; $p = 0.01$), estrogen receptor negativity (HR: 0.23; 95% CI: 0.06 to 0.89; $p = 0.03$), undergoing SLNB (HR: 0.22; 95% CI: 0.6 to 0.89; $p = 0.03$), having breast-conserving surgery (HR: 0.12; 95% CI: 0.03 to 0.5; $p = 0.004$), and being treated at centre 2 (HR: 0.11; 95% CI: 0.02 to 0.64; $p = 0.014$) were found to be predictive of less nodal RT. The remaining variables, including clinical nodal status, pathologic T or N status, lymphovascular space invasion, HER2 status, and year of treatment were not significant (data not shown).

Survival and Control Analysis

Patients in the NAST and no-NAST groups showed statistically significant differences in 5-year OS, LRRFS, and DMFS

TABLE V Method of axillary nodal staging for patients receiving neoadjuvant systemic therapy^a

Study period	Pts (n)	Assessment method [n (%)]		p Value
		Clinical only (n=357)	Others (n=233)	
2007–2009	228	160 (70)	68 (30)	<0.001
2010–2012	362	197 (54)	165 (46)	

^a Data missing for 12 patients.

TABLE VI Nodal irradiation in patients receiving neoadjuvant systemic therapy by stage and nodal status

Variable	Pts (n)	Received nodal radiotherapy [n (%)]	p Value
Stage			
I–II	272	217 (80)	0.002
III	330	298 (90)	
Nodal status			
Clinical			
N0	234	182 (78)	0.002
N1	270	239 (89)	
N2	70	63 (90)	
N3	28	26 (93)	
Pathologic			
ypN0	264	220 (83)	0.80
ypN1	176	151 (86)	
ypN2	93	82 (88)	
ypN3	29	24 (83)	
ypNX	40	33 (83)	

estimates: OS, 74% (95% CI: 71% to 78%) and 89% (95% CI: 88% to 90%) respectively, $p < 0.001$; LRRFS, 94% (95% CI: 92% to 96%) and 97% (95% CI: 97% to 97%), $p < 0.001$; and DMFS, 73% (95% CI: 70% to 77%) and 92% (95% CI: 91% to 92%), $p < 0.001$ (Figure 1). When Cox regression incorporating age, stage, histologic features, and treatment was applied, the HR between the NAST and no-NAST groups did not reach significance (OS HR: 1.15; 95% CI: 0.93 to 1.42; $p = 0.21$; LRRFS HR: 0.92; 95% CI: 0.61 to 1.4; $p = 0.71$; DMFS HR: 0.95; 95% CI: 0.76 to 1.18; $p = 0.62$).

In stage III patients, no significant difference for the LRRFS at 5 years [90% (95% CI: 86% to 93%) vs. 87% (95% CI: 82% to 91%), $p = 0.31$] or for the DMFS [64% (95% CI: 58% to 69%) vs. 61% (95% CI: 55% to 67%), $p = 0.35$] was found between the NAST and the no-NAST groups [Figure 2(B,C)]. A difference in OS at 5 years was seen between the groups: 65% (95% CI: 60% to 70%) in the NAST group compared with 55% (95% CI: 49% to 61%) in the no-NAST group, $p = 0.001$ [Figure 2(A)], although the difference was nonsignificant on multivariable Cox regression analysis when controlling for patient, tumour, and treatment factors (HR: 1.01; 95% CI: 0.79 to 1.47; $p = 0.64$).

DISCUSSION

This multicentre population-based study found a 5% rate of NAST use for nonmetastatic BCa between 2007 and 2012, while the use of NAST in stages I–II patients increased statistically significantly during the study period. Nodal assessment before NAST rarely included imaging or pathology confirmation of involvement. Delivery of RT included nodal regions in most cases, regardless of the pathologic nodal stage after NAST.

The incidence of NAST in British Columbia is similar to that in other reports, including the reported 3.8% use of NAST in 4 large U.S. treatment centres²⁰ and the 8.5% use in another Canadian province²¹. Use of NAST was quite a bit lower than in another American study, which reported a NAST rate of 17.4%²². All of those studies demonstrated variability by stage, centre²⁰, surgeon²¹, and geographic region²², as in our cohort, for whom use of NAST varied by cancer centre—a finding showing that, despite widely published guidelines^{23,24}, potential biases based on region and training can affect patient care.

We had hypothesized that use of NAST would increase during the study period, as reported by others^{21,22}; however, in our cohort, use of NAST was relatively stable. The difference might be explained by our shorter time period (5 years compared with the 8 years used by Mougalian *et al.*²²) or by significant increases in NAST use after 2012 (the period used by Graham *et al.*²¹). Notably, use of NAST increased for early-stage disease (I–II), but stayed stable for stage III disease. Given that observation, it is possible that the increase in NAST use for early-stage patients was not enough to cause a statistically significant change in the overall use of NAST, resulting in stable NAST use over the period studied.

Since the publication of the NSABP B-18 trial⁴, a growing number of reports have described the use of NAST to allow for breast conservation and improved cosmetic outcomes^{3,5,19,25}. In the research community, interest is also growing in the use of NAST as a way to evaluate *in vivo*

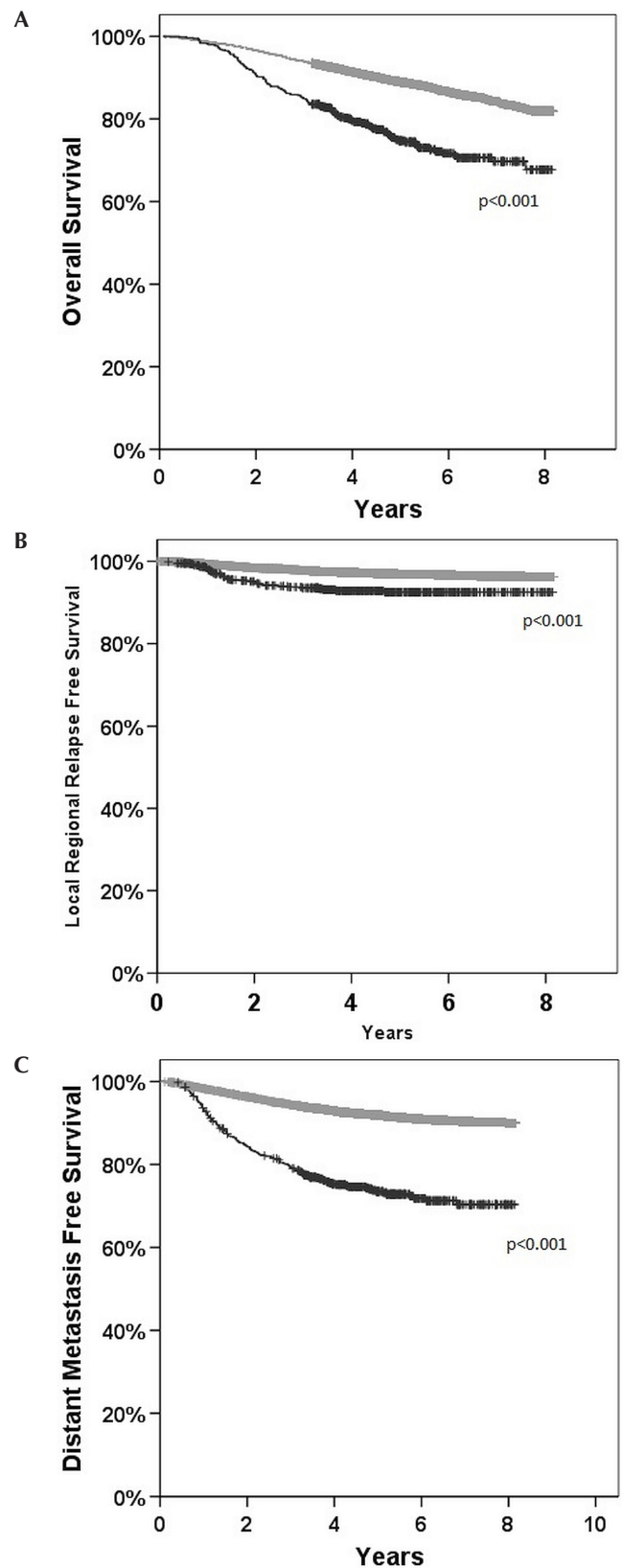


FIGURE 1 Kaplan–Meier survival estimates for (A) overall survival, (B) locoregional relapse-free survival, and (C) distant metastasis-free survival, comparing all patients treated with (dark grey) and without (light grey) neoadjuvant systemic therapy.

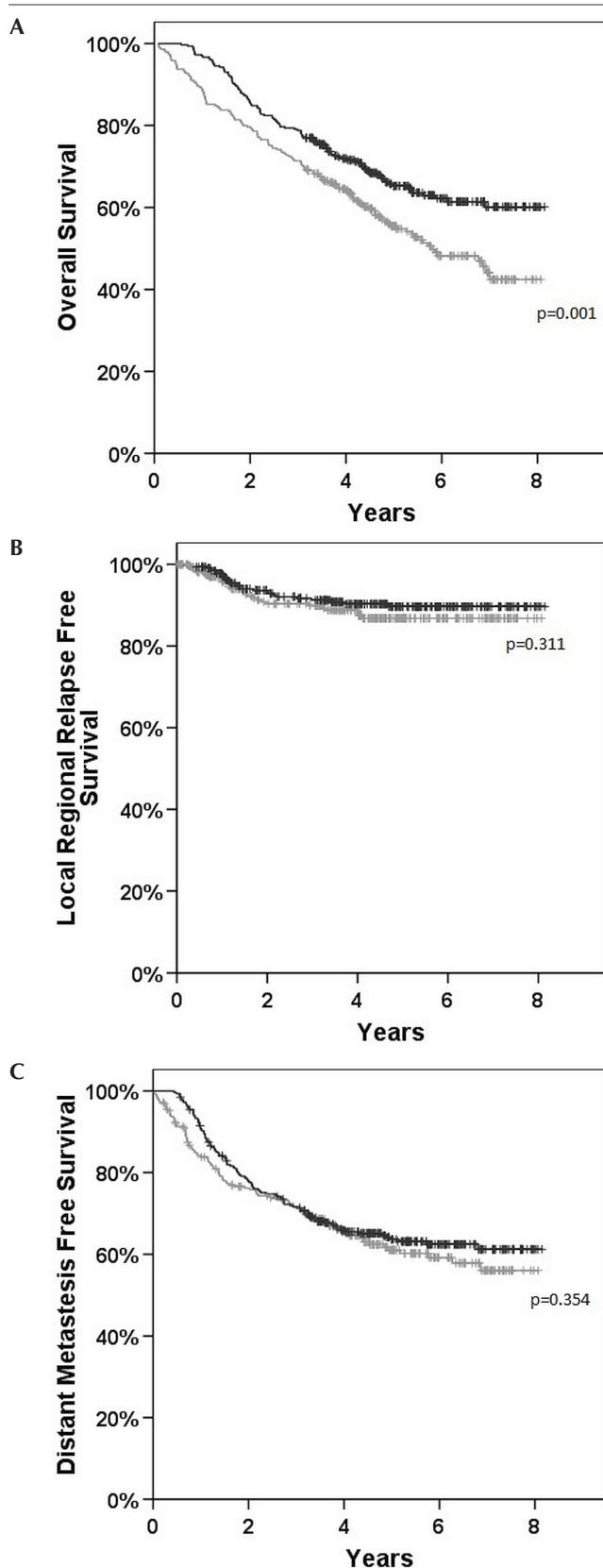


FIGURE 2 Kaplan–Meier survival estimates for (A) overall survival, (B) locoregional relapse-free survival, and (C) distant metastasis-free survival, comparing only stage III patients treated with (dark grey) and without (light grey) neoadjuvant systemic therapy.

tumour response to chemotherapy and to assess systemic agents that are active against bca^{26,a}. Given the expanded potential indications for NAST, education of oncologists in its possible uses are needed to ensure that all eligible patients are considered for NAST, while at the same time ensuring that the effects of NAST on other treatment modalities are also considered.

Multiple institutions have proposed approaches to axillary staging and the use of SLNB^{3,14,23,27}. In our population-based cohort, no consistent approach to axillary staging was observed. Clinical examination alone was the most frequent method; however, the use of methods other than clinical exam increased. The rate of clinical assessment alone that we observed is not dissimilar to the 45% rate reported by Kilbride *et al.*²⁷, despite a standardized nodal staging guideline being in place at their centre. When pathology assessment was performed before NAST in our cohort, the most common method was fine-needle aspiration or core-needle biopsy. The accuracy of those methods has been investigated, and in clinically suspicious lymph nodes, the sensitivity falls into the 60%–70% range, with the specificity approaching 100%^{14,15,27}.

In our cohort, use of SLNB before NAST was low (only 4% for cN0). The clinically negative axilla poses a challenge in terms of adequate assessment and potentially makes the decision about future nodal RT difficult. A concern with upfront SLNB is delay in the start of systemic treatment. Kilbride *et al.*²⁷ reported that, even with SLNB, only 4 weeks elapsed between initial diagnosis and the start of systemic treatment, but whether that timeline is achievable at all centres without directed resources for the purpose is unclear. Some physicians advocate for the use of SLNB only after completion of NAST, but the accuracy of SLNB in that setting is not conclusive. Data from a retrospective analysis²⁸ and a meta-analysis²⁹ showed that results from SLNB after NAST seem similar to those obtained upfront. However, a large randomized trial investigating SLNB in the NAST setting has cast doubt on the reliability of that observation, concluding that the false-negative rate is greater than 10% and that results should be interpreted with caution³⁰. The best use of SLNB in the NAST setting has yet to be determined.

Compared with reports emerging from randomized controlled trials^{30–32}, the non-uniform approach to axillary staging seen in our cohort likely reflects the reality of clinical practice and the balance between requesting staging investigations and initiating treatment in a timely fashion. With emerging data suggesting that a pathology assessment of response in lymph nodes might inform the need for nodal irradiation^{16,33}, the importance of adequate initial nodal staging is increasing. At a minimum, fine-needle aspiration should be attempted before NAST [adequate for eligibility to enrol in NSABP B-51/Radiation Therapy Oncology Group 1304 (NRG 9353)²⁰ and recommended by the U.S. National Comprehensive Cancer Network²³].

The use of LR RT after NAST was high (86%), more frequent in stage III patients, and increased in frequency with increasing clinical nodal stage. Pathologic nodal stage was

^a Also see NCT02413320 and NCT02413320 at <https://ClinicalTrials.gov>.

not associated with the use of nodal RT after NAST, which might be attributable to the uncertainty of omitting nodal RT in that setting. Recent randomized trials in the adjuvant setting^{12,13} have shown that patients with 1–3 positive nodes benefit from nodal irradiation, with improved local control and improved distant disease-free survival. However, a meta-analysis and subgroup analysis of the NSABP B-18 and B-27 trials indicate that patients with a pathologic complete response in the axilla have a low risk of LR relapse^{16,33}. That observation has led to the current NSABP B-51/Radiation Therapy Oncology Group 1304 (NRG 9353)²⁰ trial addressing the question of whether nodal RT can be omitted after nodal pathologic complete response with NAST. Until those results are available (in 2025 or beyond), uncertainty will remain about whether post-NAST nodal status can be used to exclude the benefit of regional RT for pathologically positive nodes.

In the present study, 5-year OS, LRRFS, and DMFS were not, on multivariable analysis, different for the stage III patients in the NAST and no-NAST cohorts. That finding was expected, based on the randomized trial data^{4,34}, and it continues to support the understanding that the timing of chemotherapy does not seem to influence survival outcomes.

The results of our study should be interpreted within the context of its strengths and limitations. Given the retrospective nature of the study, we were not fully able to explore physician rationale for prescribing or not prescribing LR RT. Additionally, the study examined an era during which NAST was not commonly used to enable breast-conserving surgery. Before NAST, too few patients underwent pathologic axillary staging, and that non-uniform pre-NAST axillary staging limits our ability to comment on the effect of NAST treatment response, subsequent irradiation, and outcomes. Since 2012, the use of NAST might have continued to increase; our report might therefore not reflect the most current rates of NAST use. However, no level 1 evidence to support a change in use of RT in the setting of NAST has been published, and therefore the pattern of RT practice observed here is likely still to be representative of current practice. Additionally, our study undertook a large population-based analysis in a jurisdiction with universal health coverage and a single provider of RT services, thus limiting referral and selection bias. It therefore describes the observed prescription pattern of LR RT for BCa after NAST for all patients referred to the BCCA during the study period.

CONCLUSIONS

Our population-based study found a 5% use of NAST for BCa, with a statistically significant increase in its use in early-stage disease during the study period. Most patients received LR RT after NAST, even in the context of clinical stage I and II cancers, independent of pathologic stage after NAST. Our study likely reflects the current realities of clinical practice and shows that reliance on clinical staging of the axilla results in survival outcomes similar to those reported in the literature. Hopefully, future research will provide further guidance about which patients can avoid LR RT after NAST and clarity about the most robust method of axillary staging before NAST.

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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 the following interests: TAK received fellowship funding from CARO while this work was being done. RO has received funding from Varian, but not in relation to the present work. The other co-authors have no conflicts of interest to disclose.

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