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Inequalities in the omission of axillary dissection in sentinel lymph node positive patients in the Netherlands: Innovative hospitals are early adopters of a de-escalating approach

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Abstract

During the last decade completion axillary lymph node dissection (cALND) was gradually omitted in sentinel lymph node positive (SLN+) breast cancer patients. However, adoption varies among hospitals. We analyzed factors associated with the omission of cALND in all Dutch SLN+ patients. As one of the focus hospital-related factors we defined "innovative" as the percentage of gene-expression profile (GEP) deployment within the indicated group of patients per hospital as a proxy for early adoption of innovations. cT1-2N0M0 SLN+ patients treated between 2011 and 2018 were selected from the Netherlands Cancer Registry. Hospitals were defined to be innovative based on their GEP use. Multivariable logistic regression (MLR) was performed to assess the relationship between innovative capacity, patient-, treatment- and hospital-related characteristics and cALND performance. 14 317 patients were included. Treatment in a hospital with high innovative capacity was associated with a lower probability of receiving cALND (OR 0.69, OR 0.46 and OR 0.35 in modestly, fairly and very innovative, respectively). Other factors associated with a lower probability of receiving a cALND were age 70 and 79 years and ≥79 years (ORs 0.59 [95% CI: 0.50-0.68] and 0.21 [95% CI: 0.17-0.26]) and treatment in an academic hospital (OR 0.41 [95% CI: 0.33-0.51]). Factors associated with an increased probability of undergoing cALND were HR−/HER2− tumors (OR 1.46 [95% CI: 1.19-1.80]), macrometastatic lymph node involvement (OR 6.37 [95% CI: 5.70-7.13]) and mastectomy (OR 4.57 [95% CI: 4.09-5.10]). Patients treated in a hospital that early adopted innovations were less likely to receive cALND. Our findings endorse the need for studies on barriers and facilitators of implementing innovations.

Abbreviations: cALND, completion axillary lymph node dissection; GEP, gene-expression profile; HR, hormone receptor; MLR, multivariable logistic regression; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

What's new?

Novel treatment insights and adjusted guidelines have propagated a de-escalating treatment approach in breast cancer. However, little is known about the factors associated with early or late adoption of less aggressive strategies. This nationwide prospective study assesses inequalities in the omission of completion axillary lymph node dissection (cALND) in sentinel lymph node-positive breast cancer patients. Besides known patient and tumor characteristics, treatment in an academic or highly innovative hospital lowers the chance of receiving cALND. The findings call for further research on the implementation of innovation in clinical practice to help reduce national inequalities in breast cancer care.

1 | INTRODUCTION

During the last decade, the treatment spectrum for breast cancer has changed radically. While outcome has improved, attention progressively focused on individualization of treatment and minimization of morbidity.[1-5]

In terms of local treatment, a number of randomized controlled trials (RCTs) catalyzed the shift towards less aggressive axillary surgery in patients with lymph node positive disease. Between 2011 and 2014, the Z0011, IBCSG 23-01 and the AMAROS trial demonstrated that completion axillary lymph-node dissection (cALND) was no longer necessary for all patients with tumor positive sentinel lymph nodes (SLNs).[2-5] Since 2012, both national and international guidelines suggested to consider no further axillary surgery in these patients.[6-8] A decrease in cALND rates among patients with positive SLNs has been observed,[9] however the adoption of the implications of the Z0011 and AMAROS results appeared to vary among hospitals and countries.[9,10]

At the same time gene-expression profiles (GEPs), that had been developed and validated for better outcome prediction,[11-15] were incorporated into clinical practice to contribute to chemotherapy decision-making in hormonal receptor positive (HR+)/HER2-receptor negative (HER2−) disease. RCTs[13,14] commonly led to less chemotherapy use in patients with genomic low-risk breast cancers.[13-17] Since 2012, the Dutch national guideline suggests the use of a GEP in a selection of HR+/HER2− patients.[7] In previous nationwide studies we demonstrated an increased use of GEPs and an overall decrease of chemotherapy use in categories of patients.[16,17] Nevertheless, only a modest proportion of Dutch breast cancer patients who are eligible for GEP use, actually received a GEP.[16]

The common denominator in the implementation of less extensive local therapy and the decreasing use of chemotherapy through the use of GEP is an attitude of surgeons, medical oncologists and multidisciplinary teams to adhere to novel treatment insights and adjusted guidelines that propagate a de-escalating treatment approach. Little is known about factors that are associated with the tendency to adopt early or late to "less is more" strategies.

In the present study, patient-, treatment- and hospital-related factors were analyzed that are associated with the omission of cALND in SLN+ breast cancer patients. Of particular interested was a potential effect of early adoption of innovations within hospitals. In our study we hypothesized that GEP deployment to guide chemotherapy administration in patients who are considered eligible for GEP use was used as a proxy for being innovative, thus early adopt innovations within a multidisciplinary breast care team within a hospital.

2 | METHODS

2.1 | Study design

In this population-based historic cohort study, we used the Netherlands Cancer Registry, which is hosted by the Netherlands Comprehensive Cancer Organization (IKNL). Trained and dedicated data managers register data on patient-, tumor-, hospital- and treatment-related characteristics of all newly diagnosed malignancies following notification by the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA).

2.2 | Study population

All female cT1-2N0M0 staged breast cancer patients were included if diagnosed between 2011 and 2018. Patients who underwent neoadjuvant systemic treatment, patients with a history of breast cancer and patients treated in a foreign hospital were excluded. In addition, patients with an unknown or negative SLN, patients with isolated tumor cells and patients in whom the SLN could not be identified during surgery were also excluded.

2.3 | Outcomes and definitions

The primary outcome of our study was cALND performance in SLN+ patients. In addition to previously described patient and hospital characteristics,[9] the use of the 70-gene signature (GS) to guide adjuvant systemic treatment administration in patients who are considered eligible for GEP use was used as a proxy for early adaption to innovations within hospitals. GEP use was defined as a hospital factor reflected by the percentage of GEPs that were performed in a hospital between 2011 and 2013 in ER+/HER2− Bloom-Richardson grade 1 and >2 cm or grade 2 and >1 cm patients with no or isolated lymph node metastases.

During these years, GEPs were recommended, and therefore mainly deployed, in node negative patients. We used 2011 to 2013 as these were the first years that GEPs entered clinical practice. In this time period, the use of a GEP was associated with a reduction in the administration of adjuvant chemotherapy in node-negative patients,[16] whereas in later years (2013-2016) there were other factors contributing to the decrease in the administration of adjuvant chemotherapy in this category of patients.[17]

The percentage of GEP use in these years was considered to be a proxy indicator of "innovation" of hospitals being early adaptors in the multidisciplinary field of medical oncology.

Based on the proportional use of the 70-GS use in our study, hospitals were categorized into four groups: 0% to 5%, 6% to 10%, 11% to 15% and more than 15% use, reflecting not, modest, fair and very innovative, hospitals, respectively. Hospital volume, which was used as a covariable in the analysis, was defined as the number of new breast cancer incidences per hospital.

2.4 | Statistical analysis

Patient-, tumor-, treatment- and hospital-related characteristics were summarized using descriptive statistics. Missing data were considered to be missing at random. To increase accuracy of the estimates, missing data were corrected by applying multiple imputation statistics using the multiple impute chained equation command in Stata. The imputation was performed 20 times. Estimates and standard errors of all imputed datasets were combined using Rubin's rule.[18] Multivariable logistic regression analysis was performed to assess the relationship between innovative capacity and chance of cALND performance, and to evaluate the influence of patient-, tumor-, treatment- and hospital-related characteristics on this association. Variables included in the multivariable analysis were selected based on clinical foreknowledge and literature. The data was hierarchically structured, therefore a multilevel logistic regression analysis was performed in addition to logistic regression analyses. Hospital of first excision was used as a hierarchical level to account for the dependency of patients within hospitals, thereby providing more accurate estimates than traditional logistic regression analysis.[19] Individual variable effects were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Complete case analysis was performed to assess whether the estimates obtained using imputed datasets were similar to those derived from the original dataset. Statistical tests were two-sided and a *P*-value <.05 was considered to be statistically significant. All statistical analyses were performed in Stata version 17.0 (StataCorp LLC, College Station, Texas).

3 | RESULTS

3.1 | Study population

Between 2011 and 2018, 84 765 female patients underwent surgery for cT1-2N0 invasive breast cancer in the Netherlands. Patients who underwent neo-adjuvant systemic therapy (n = 7400), had a prior history of breast cancer (n = 8008), did not receive SLN biopsy (SLNB) (n = 1978) or were treated in a foreign hospital (n = 43) were excluded for the current study, leaving 67 336 patients in whom a SLNB was performed. Of these patients, 47 555 had a negative SLN result, 746 had an unknown SLNB result, in 968 patients the SLN could not be identified during surgery and 3750 patients had only isolated tumor cells and were therefore excluded in the current study (79% of all patients in whom SLNB was performed). Our study population comprised the remaining 21% (n = 14 317) of patients who were diagnosed with nodal micrometastasis or macrometastasis according to SLN (Figure 1).

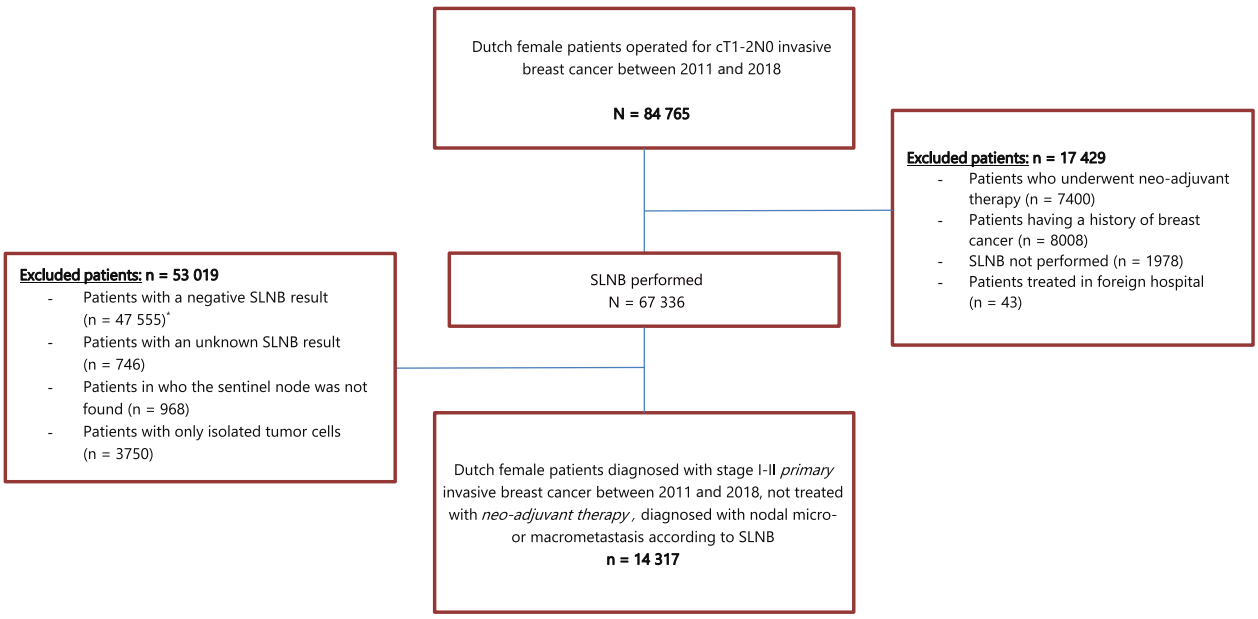

FIGURE 1 Flowchart of included patients. *The hospital factor reflecting the percentage of gene-expression profile use within a hospital as a proxy for innovation was constructed within this subset of node-negative breast cancer patients

TABLE 1 Baseline characteristics of all included patients diagnosed with nodal micrometastasis or macrometastasis according to a sentinel lymph node biopsy (n = 14 317)

	No cALND (n = 10 302)		cALND (n = 4015)	
Characteristics	**N**	**%**	**N**	**%**
Year of diagnosis				
2011	588	5.7%	1415	35.2%
2012	1042	10.1%	931	23.2%
2013	1253	12.2%	604	15.0%
2014	1411	13.7%	396	9.9%
2015	1449	14.1%	237	5.9%
2016	1556	15.1%	178	4.4%
2017	1555	15.1%	146	3.6%
2018	1448	14.1%	108	2.7%
Age group				
<40 years	348	3.4%	227	5.7%
40-49 years	1664	16.2%	879	21.9%
50-59 years	2859	27.8%	1154	28.7%
60-69 years	2809	27.3%	1049	26.1%
70-79 years	1838	17.8%	542	13.5%
>79 years	784	7.6%	164	4.1%
Socioeconomic status				
Low	3372	32.7%	1506	37.5%
Medium	2434	23.6%	956	23.8%
High	3471	33.7%	1190	29.6%
Unknown	1025	9.9%	363	9.0%
Histological tumor type				
Ductal	8465	82.2%	3212	80.0%
Lobular	1248	12.1%	588	14.6%
Mixed	390	3.8%	137	3.4%
Other	199	1.9%	78	1.9%
Differentiation grade				
Grade I	2460	23.9%	793	19.8%
Grade II	5456	53.0%	2005	49.9%
Grade III	2251	21.9%	1132	28.2%
Unknown	135	1.3%	85	2.1%
Clinical tumor size				
cT1 not further specified	54	0.5%	25	0.6%
cT1a	114	1.1%	38	1.0%
cT1b	1476	14.3%	447	11.1%
cT1c	5098	49.5%	1726	43.0%
cT2	3560	34.6%	1779	44.3%
Multifocality				
No	8499	82.5%	3126	77.9%
Yes	1780	17.3%	880	21.9%
Unknown	23	0.2%	9	0.2%
Breast cancer subtype				
HR+/HER2−	8766	85.1%	3206	79.9%
HR+/HER2+	682	6.6%	344	8.6%

(Continues)

TABLE 1 (Continued)

Characteristics	No cALND (n = 10 302)		cALND (n = 4015)	
	N	%	N	%
HR−/HER2+	208	2.0%	125	3.1%
HR−/HER2−	465	4.5%	300	7.5%
Unknown	181	1.8%	40	1.0%
Treatment characteristics				
Type of surgery				
Breast-conserving surgery	6926	67.2%	1663	41.4%
Mastectomy	3376	32.8%	2352	58.6%
Result of SLNB				
Micrometastasis	4710	45.7%	678	16.9%
Macrometastasis	5592	54.3%	3337	83.1%
Radiation therapy				
No	1475	14.3%	1673	41.7%
Yes	8827	85.7%	2342	58.3%
Hormonal therapy				
No	1700	16.5%	656	16.3%
Yes	8602	83.5%	3359	83.7%
Chemotherapy				
No	5691	55.2%	1227	30.6%
Yes	4611	44.8%	2788	69.4%
Hospital characteristics				
Hospital volume				
<150 resections per year	3484	33.8%	1526	38.0%
150-300 resections per year	6144	59.6%	2314	57.6%
>300 resections per year	674	6.5%	175	4.4%
Hospital type				
General nonteaching	2443	23.7%	1072	26.7%
Teaching hospital	7172	69.6%	2745	68.4%
Academic hospital	687	6.7%	198	4.9%
Hospital innovative capacity				
Not innovative (0%-5% GEP use)	2638	25.6%	1395	34.7%
Moderately innovative (6%-10% GEP use)	3384	32.8%	1440	35.9%
Fairly innovative (11%-15% GEP use)	2092	20.3%	626	15.6%
Very innovative (>15% GEP use)	2188	21.2%	554	13.8%

Abbreviations: c, clinical; GEP, gene expression profile; HER2, human epidermal growth factor receptor 2; HR, hormonal receptor; mi, micrometastasis; NOS, not otherwise specified; p, pathological; SLNB, sentinel lymph node biopsy.

3.2 | Baseline characteristics

Overall, 28.0% (n = 4015) of the patients in our study cohort received a cALND and we observed a clear downward trend in the use of cALND over time: 71% vs 7% of patients underwent cALND in 2011 vs 2018, respectively (Table 1). Patients in whom cALND was omitted were treated in more recent years and suffered of less aggressive (HR+/HER2−) tumors of smaller size and grade, as compared to patients who underwent cALND. Furthermore, patients who did not receive cALND more frequently underwent breast-conserving surgery (67% vs 41%) and radiation therapy (86% vs 58%), as compared to patients in whom cALND was performed. Adjuvant chemotherapy was administered in 69% vs 45% of patients who did, and did not, receive cALND, respectively (Table 1).

Patients were treated in 79 individual hospitals and the number of treated patients ranged from 2 to 281 per hospital for this cohort. Sixty-nine hospitals (87%) deployed a GEP during the study period. The percentage of patients within the indicated area who received a GEP ranged from 0% to 43.8% within hospitals. Twenty-one percent

TABLE 2 Multivariable logistic regression analyses to assess factors associated with receiving completion axillary lymph node dissection (cALND)

	Odds ratio	Lower 95% limit	Upper 95% limit	*P*-value
Hospital innovative capacity				
Not innovative	*Reference*			
Moderately innovative	0.69	0.62	0.78	**<.001**
Fairly innovative	0.46	0.39	0.53	**<.001**
Very innovative	0.35	0.30	0.40	**<.001**
Year of diagnosis[a]	0.52	0.51	0.54	**<.001**
Age group				
<40 years	1.21	0.95	1.55	.115
40-49 years	1.10	0.96	1.26	.176
50-59 years	*Reference*			
60-69 years	0.90	0.80	1.02	.114
70-79 years	0.59	0.50	0.68	**<.001**
>79 years	0.21	0.17	0.26	**<.001**
Socioeconomic status				
Low	*Reference*			
Medium	0.88	0.77	0.99	**.039**
High	0.76	0.68	0.86	**<.001**
Histological tumor type				
Ductal	*Reference*			
Lobular	0.99	0.86	1.15	.942
Mixed	0.73	0.57	0.95	**.018**
Other	0.96	0.68	1.36	.822
Differentiation grade				
Grade I	*Reference*			
Grade II	1.04	0.92	1.17	.576
Grade III	1.14	0.99	1.33	.076
Clinical tumor size				
T1	*Reference*			
T2	1.06	0.96	1.18	.238
Multifocality				
No	*Reference*			
Yes	0.99	0.87	1.12	.875
Breast cancer subtype				
HR+/HER2−	*Reference*			
HR+/HER2+	0.93	0.77	1.11	.397
HR−/HER2+	0.92	0.68	1.23	.558
HR−/HER2−	1.46	1.19	1.80	**<.001**
Type of surgery				
Breast-conserving surgery	*Reference*			
Mastectomy	4.57	4.09	5.10	**<.001**
SLNB result				
Micrometastasis				
Macrometastasis	6.37	5.70	7.13	**<.001**
Hospital volume				
<150 resections per year	*Reference*			
150-300 resections per year	0.94	0.83	1.07	.335
>300 resections per year	0.90	0.70	1.15	.391

(Continues)

TABLE 2 (Continued)

	Odds ratio	Lower 95% limit	Upper 95% limit	*P*-value
Hospital type				
General non-teaching	*Reference*			
Teaching hospital	1.05	0.92	1.20	.442
Academic hospital	0.41	0.33	0.51	**<.001**

[a]2011 served as reference year, the OR represents the OR per year increase.

of patients in whom cALND was omitted were treated in a hospital in which GEPs were frequently used (>15%) as compared to 14% of patients who did receive a cALND (Table 1).

3.3 | Multivariable (multilevel) logistic regression analysis

Multivariable logistic regression analyses revealed that treatment in a hospital with high innovative capacity was associated with a significant lower probability of receiving a cALND (OR 0.69, OR 0.46 and OR 0.35 in hospitals with 6% to 10%, 11% to 15% and more than 15% GEP use, respectively, compared to hospitals with <5% GEP use). Other factors that were significantly associated with a lower probability of cALND were year of diagnosis (OR 0.52 [95% CI: 0.51-0.54]), age 70 to 79 and ≥79 years (ORs 0.59 [95% CI: 0.50-0.68] and 0.21 [95% CI: 0.17-0.26], compared to age 50-59 years) medium and high socioeconomic status (SES) (OR 0.88 [95% CI: 0.77-0.99] and 0.68 [95% CI: 0.68-0.86], compared to low SES), mixed tumor histology (OR 0.73 [95% CI: 0.57-0.95], compared to ductal histology) and treatment in an academic hospital (OR 0.41 [95% CI: 0.33-0.51], compared to general nonteaching hospitals) (Table 2). Factors associated with an increased probability of undergoing a cALND were HR−/HER2− tumors (OR 1.46 [95% CI: 1.19-1.80], compared to HR+/HER2−), macrometastasis according to SLN (OR 6.37 [95% CI: 5.70-7.13], compared to micrometastasis) and treatment with mastectomy (OR 4.57 [95% CI: 4.09-5.10], compared to breast-conserving surgery). Hospital volume was not associated with the risk of cALND (Table 2). Multilevel logistic regression analyses, in which the dependency of patients within hospitals was accounted for, showed similar results except for SES. The latter was not significantly associated with a lower risk of receiving cALND anymore. In addition, grade was not significant in the conventional logistic regression model, but it was significant in the multilevel model. However, the OR estimates were similar for the two models (Table 3).

Multilevel and logistic regression analyses performed on complete cases only yielded similar results (Tables S1 and S2).

4 | DISCUSSION

Between 2011 and 2018, 28% of the Dutch breast cancer patients who suffered from cT1-2 breast cancer received an cALND, after SLN revealed nodal metastases. Besides known patient- and tumor characteristics, undergoing a cALND was associated with several hospital factors in the current study. Patients who were treated in a hospital with high innovative capacity, based on frequent GEP use in routine breast cancer care or in an academic hospital, had a lower probability of receiving a cALND. Our findings suggest that early adoption to new innovations within a multidisciplinary breast cancer team results in a more reticent attitude toward axillary treatment.

As a result of the Z0011 and the AMAROS study, the Dutch national guidelines of 2012 first suggested to consider no further axillary surgery or to propose axillary radiotherapy as an alternative in some cases, in cT1-2 patients with a positive SLN.[20] The effect of this guideline change was clear: as reported in our study, in 2011 71% of cT1-2N1 patients received a cALND compared to 44% of patients in 2012. Over time this percentage further decreased to only 7% of patients receiving a cALND in 2018, illustrating a slow but almost full adaption of this de-escalating approach in Dutch clinical practice.

In the current study, several factors were associated with the risk of receiving cALND. Older age was associated with a lower risk of receiving a cALND, whereas a more aggressive tumor subtype (HR−/HER2−) increased the risk of receiving cALND. Ong et al reported similar results in a nationwide cohort of patients eligible for the Z0011 (cT1-2N0) criteria in the United States treated between 2009 and 2014.[21] These results suggest that physician-driven risk stratification may drive the extent of axillary surgery, resulting in higher rates of cALND in younger patients or patients with aggressive tumor biology. This is despite the fact that several studies have shown that more extensive axillary therapy may not always be warranted in these patients and is associated with higher morbidity rates as compared to radiotherapy.[22,23]

Patients treated in a hospital with high innovative capacity (ie, early adopters of GEP use), had a lower risk of receiving cALND. This finding suggests that in hospitals in which multidisciplinary teams tend to individualize systemic treatment by using GEPs, those teams are also more inclined to de-escalate axillary surgery. In line with this finding is a study conducted by Morrow et al that showed that surgeons with less acceptance of the "no ink on tumor" as a definition of a negative margin, where also less likely to implement the results of the Z0011 trial.[24] While the latter data indicates that variation exists in the acceptance of a more limited surgical approach among breast cancer surgeons, the present study suggests that innovative propensity is an asset of a multidisciplinary team or hospital and underscores the need for ongoing education of surgeons and multidisciplinary teams in order to improve acceptance.

TABLE 3 Multivariable multilevel logistic regression to assess factors associated with receiving completion axillary lymph node dissection (cALND)

	Odds ratio	Lower 95% limit	Upper 95% limit	*P*-value
Hospital innovative capacity				
Not innovative	*Reference*			
Moderately innovative	0.49	0.26	0.92	**.025**
Fairly innovative	0.43	0.21	0.88	**.020**
Very innovative	0.27	0.12	0.60	**.001**
Year of diagnosis[a]	0.47	0.46	0.49	**<.001**
Age group				
<40 years	1.29	0.99	1.67	.055
40-49 years	1.11	0.95	1.29	.179
50-59 years	*Reference*			
60-69 years	0.88	0.77	1.01	.071
70-79 years	0.57	0.48	0.67	**<.001**
>79 years	0.16	0.13	0.21	**<.001**
Socioeconomic status				
Low	*Reference*			
Medium	0.95	0.83	1.09	.448
High	0.99	0.78	1.01	.069
Histological tumor type				
Ductal	*Reference*			
Lobular	1.03	0.88	1.20	.759
Mixed	0.88	0.66	1.16	.367
Other	0.90	0.62	1.31	.575
Differentiation grade				
Grade I	*Reference*			
Grade II	1.00	0.88	1.15	.958
Grade III	1.22	1.04	1.44	**.016**
Clinical tumor size				
cT1	*Reference*			
cT2	1.09	0.98	1.22	.133
Multifocality				
No	*Reference*			
Yes	1.09	0.95	1.25	.215
Breast cancer subtype				
HR+/HER2−	*Reference*			
HR+/HER2+	0.93	0.77	1.13	.455
HR−/HER2+	0.87	0.63	1.19	.376
HR−/HER2−	1.41	1.12	1.76	**.003**
Type of surgery				
Breast-conserving surgery	*Reference*			
Mastectomy	4.80	4.26	5.43	**<.001**
SLNB result				
Micrometastasis	*Reference*			
Macrometastasis	8.52	7.52	9.65	**<.001**
Hospital volume				
<150 resections per year	*Reference*			

(Continues)

TABLE 3 (Continued)

	Odds ratio	Lower 95% limit	Upper 95% limit	*P*-value
150-300 resections per year	0.77	0.59	1.02	.070
>300 resections per year	0.68	0.45	1.04	.072
Hospital type				
General non-teaching	*Reference*			
Teaching hospital	1.00	0.57	1.76	.993
Academic hospital	0.34	0.14	0.83	**.017**

```
------------------------------------------------------------------------------
 Random-effects parameters |  Estimate   Std. err.     [95% conf. interval]
---------------------------+--------------------------------------------------
zkhexc: Identity           |
                sd(_cons) |  1.082849   .0975049     .9076568    1.291856
------------------------------------------------------------------------------
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Note: Hospital of first excision was used as hierarchical level to account for the dependency of patients within hospitals.
[a]2011 served as reference year, the OR represents the OR per year increase.

Our findings also show that patients treated in an academic hospital had a lower risk of receiving cALND. Ong et al also reported a lower incidence of cALND in patients treated in academic centers as compared to patients treated in community cancer centers. Prior literature already suggested that although individual doctors may adapt novel clinical trial insights, as a whole, academic centers preceded community hospitals in evidence-based practice change.[25,26] This could partially be explained by higher participation rates of academic hospitals in clinical trials in which innovations are implemented in clinical practice. The fact that hospitals in which GEPs were applied more often—and thus de-escalate systemic treatment—were also more inclined to limit axillary treatment, further endorse the finding that hospitals with an innovative propensity are more likely to make evidence-based practice change in other parts of breast cancer treatment.

In the current study, with robust nationwide data, factors were revealed which are associated with the probability of receiving cALND in SLN+ breast cancer patients. We are the first to assess the association between omission of cALND (which can be interpreted as a proxy for de-escalating local breast cancer treatment) and a hospitals innovative capacity (defined as GEP use). It should be noted that both GEP use as omission of cALND could be mediated by a high innovative capacity of multidisciplinary teams. Furthermore, it is important to note that the time period for early adoption of GEP use is arbitrarily chosen and based on previous data on GEP use and chemotherapy administration in the Netherlands.[16,17] After closure of patient accrual for the MINDACT study in 2011, GEPs first entered clinical practice. In a previous nationwide study conducted between 2011 and 2013 evaluating the impact of GEP use on the administration of adjuvant chemotherapy, we observed that the use of a GEP was accompanied by a decrease in chemotherapy administration mainly in node-negative patients.[16] However, in the years thereafter (2013-2016), this association was no longer observed. In the latter years, a further decline in chemotherapy administration was observed in all node negative patients and this trend was irrespective of GEP use.[17] We therefore decided to focus only on the years 2011 to 2013, since in this period the use of GEPs had the major clinical implication of withholding chemotherapy. However, a possibility of bias resulting from this approach cannot be ruled out. Therefore, our study should mainly be interpreted as hypothesis-generating material on adaption of innovation, rather than assessing causality between cALND and the use of GEPs.

In conclusion, a downward trend was observed in the use of cALND in Dutch SLN+ breast cancer patients between 2011 and 2018. Patients treated in hospitals with innovative capacity, based on the use of GEPs in clinical practice, had a lower probability of receiving cALND. This suggests that hospitals that early adopt innovations to de-escalate systemic treatment are also more likely to de-escalate axillary treatment. The latter observation is not only of importance for involved patients, as de-escalation is often accompanied by less morbidity, but also affects our health care system since costs are rising and adapting to innovation to de-escalate treatment plays a key role in keeping our health care system viable. Therefore, our findings endorse the need for studies on barriers and facilitators of implementing innovations to increase the nationwide uptake of innovation, ultimately to reduce interinstitutional inequality in breast cancer care.

AUTHOR CONTRIBUTIONS

Julia E. C. van Steenhoven: Conceptualization, writing original draft. **Marissa C. van Maaren:** Methodology, formal analysis, review and editing. **Eline E. F. Verreck:** Writing review and editing. **Robert J. Schipper:** Conceptualization, writing review and editing. **Grard A. P. Nieuwenhuijzen:** Writing review and editing. **Anne Kuijer:** Conceptualization, formal analysis, writing original draft and methodology. **Sabine Siesling:** Conceptualization, writing review and editing. **Thijs van Dalen:** Conceptualization, writing review and editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

Our study has been approved by the privacy committee of the Netherlands Cancer Registry (request number K18.149).

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REFERENCES

1. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362(6):513-520.
2. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569-575.
3. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA*. 2017;318:918-926.
4. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised con- trolled trial. *Lancet Oncol*. 2013;14:297-305.
5. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303-1310.
6. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Breast Cancer (ver 2.2017)*. NCCN. 2017.
7. Kwaliteitsinstituut voor de Gezondheidszorg CbO VvIK. Landelijke Richtlijn Mammacarcinoom; 2012.
8. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32:1365-1383.
9. Poodt IGM, Spronk PER, Vugts G, et al. Trends on axillary surgery in nondistant metastatic breast cancer patients treated between 2011 and 2015: a Dutch population-based study in the ACOSOG-Z0011 and AMAROS era. *Ann Surg*. 2018;268(6):1084-1090.
10. Gondos A, Jansen L, Heil J, et al. Time trends in axilla management among early breast cancer patients: persisting major variation in clinical practice across European centers. *Acta Oncol*. 2016;55(6):712-719.
11. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 2002;347(25):1999-2009.
12. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifentreated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817-2826.
13. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70- gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375:717-729.
14. Sparano JA, Gray RJ, Della F, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121.
15. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res*. 2011;17(18):6012-6020.
16. Kuijer A, van Bommel ACM, Drukker CA, et al. Using a gene expression signature when controversy exists regarding the indication for adjuvant systemic treatment reduces the proportion of patients receiving adjuvant chemotherapy: a nationwide study. *Genet Med*. 2016;18(7):769-775.
17. Van Steenhoven JEC, Kuijer A, Schreuder K, et al. The changing role of gene-expression profiling in the era of de-escalating adjuvant chemotherapy in early-stage breast cancer. *Ann Surg Oncol*. 2019 Oct;26(11):3495-3501.
18. White I, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.
19. Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently? *Am Heart J*. 2003;145(1):27-35.
20. Kwaliteitsinstituut Voor De Gezondheidszorg CBO VvIK. *Risicoprofilering*. Richtlijn Mammacarcinoom; 2012.
21. Ong C, Thomas SM, Blitzblau RC, et al. Patient age and tumor subtype predict the extend of axillary surgery among breast cancer patients eligible for the American college of surgeons oncology group trial Z0011. *Ann Surg Oncol*. 2017;24(12):3559-3566.
22. Chung A, Gangi A, Mirocha J, Giuliano A. Applicability of the ACOSOG Z0011 criteria in women with high-risk node-positive breast cancer undergoing breast conserving surgery. *Ann Surg Oncol*. 2015;22:1128-1132.
23. Dengel LT, Van Zee KJ, King TA, et al. Axillary dissection can be avoided in the majority of clinically node-negative patients undergoing breast-conserving therapy. *Ann Surg Oncol*. 2014;21:22-27.
24. Morrow M, Jagsi R, McLeod MC, Shumway D, Katz SJ. Surgeon attitudes toward the omission of axillary dissection in early breast cancer. *JAMA Oncol*. 2018;4:1511-1516.
25. Mamtani A, Patil S, Van Zee KJ, et al. Age and receptor status do not indicate the need for axillary dissection in patients with sentinel lymph node metastases. *Ann Surg Oncol*. 2016;23:3481-3486.
26. Mohiuddin JJ, Deal AM, Carey LA, et al. Neoadjuvant systemic therapy use for younger patients with breast cancer treated in different types of cancer centers across the United States. *J Am Coll Surg*. 2016;223(5):717-728.e4.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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