Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-020-05589-3

CLINICAL TRIAL

De-escalation of axillary surgery in breast cancer patients treated in the neoadjuvant setting: a Dutch population-based study

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Received: 6 November 2019 / Accepted: 6 March 2020

Abstract

Purpose An overall trend is observed towards de-escalation of axillary surgery in patients with breast cancer. The objective of this study was to evaluate this trend in patients treated with neoadjuvant systemic therapy (NST).

Methods Patients with cT1-4N0-3 breast cancer treated with NST (2006–2016) were selected from the Netherlands Cancer Registry. Patients were classified by clinical node status (cN) and type of axillary surgery. Uni- and multivariable logistic regression analyses were performed to determine the clinicopathological factors associated with performing ALND in cN+ patients.

Results A total of 12,461 patients treated with NST were identified [5830 cN0 patients (46.8%), 6631 cN+ patients (53.2%)]. In cN0 patients, an overall increase in sentinel lymph node biopsy (SLNB) only (not followed by ALND) was seen from 11% in 2006 to 94% in 2016 ($p < 0.001$). SLNB performed post-NST increased from 33 to 62% ($p < 0.001$). In cN+ patients, an overall decrease in ALND was seen from 99% in 2006 to 53% in 2016 ($p < 0.001$). Age (OR 1.01, CI 1.00–1.02), year of diagnosis (OR 0.47, CI 0.44–0.50), HER2-positive disease (OR 0.62, CI 0.52–0.75), clinical tumor stage (T2 vs. T1 OR 1.32, CI 1.06–1.65, T3 vs. T1 OR 2.04, CI 1.58–2.63, T4 vs. T1 OR 6.37, CI 4.26–9.50), and clinical nodal stage (N3 vs. N1 OR 1.65, CI 1.28–2.12) were correlated with performing ALND in cN+ patients.

Conclusions ALND decreased substantially over the past decade in patients treated with NST. Assessment of long-term prognosis of patients in whom ALND is omitted after NST is urgently needed.

Keywords Breast cancer · Node positive · Sentinel lymph node biopsy · Axillary lymph node dissection · Axillary staging · Marked node

Introduction

In breast cancer, systemic therapy is increasingly administered in the neoadjuvant setting [i.e., neoadjuvant systemic therapy (NST)] [1, 2]. One of the advantages of NST is the possibility of downsizing or even downstaging disease, which can occur in breast and/or axilla. In the best-case scenario, patients achieve a pathologic complete response (pCR), meaning that there is no histologic evidence of residual tumor. Downstaging is not only associated with a favorable prognosis but it also enables surgeons to opt for less extensive surgery after NST.

In clinically node-negative (cN0) patients, sentinel lymph node biopsy (SLNB) is widely accepted as primary regional staging procedure. In the case of a positive SLNB with limited tumor burden, it is safe to omit completion axillary lymph node dissection (ALND) in patients treated with lumpectomy in terms of disease-free and overall survival [3–7]. In the AMAROS trial, cT1-2N0 patients with a positive SLNB and treated with lumpectomy or mastectomy were randomly assigned to completion ALND or axillary radiotherapy [8]. The 5-year axillary recurrence rate was comparable in both groups, but measurable lymphedema occurred significantly less frequently in the axillary radiotherapy arm. The results of these trials resulted in decreasing use of ALND, as was proven by several cohort studies over the past years [9–12]. In these studies, patients treated with NST were not included and it is yet unknown if this decrease

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Published online: 16 March 2020

in axillary surgery also affects cN0 patients who were treated with NST.

In clinically node-positive (cN+) patients, axillary staging is an area of controversy. Traditionally, ALND was performed in all patients. However, at least 1 out of 3 cN+ patients treated with NST converts to a pathological node-negative axilla [13]. Since cN+ patients with an axillary pCR are not expected to benefit from ALND, different less invasive methods have been proposed to replace ALND, such as SLNB, MARI (marking the axillary positive lymph node with an iodine seed), and Targeted Axillary Dissection (i.e., a combination of the SLNB and a MARI-like procedure). However, since sufficient data are lacking on the outcome of cN+ patients in whom ALND is omitted after NST, broad implementation of less invasive staging procedures in clinical practice may be hampered.

With the increased use of NST in both cN0 and cN+ patients, and the de-escalation of axillary surgery in patients treated in the adjuvant setting, it is hypothesized that a trend of de-escalation will also be noticed in patients treated with NST. Therefore, the aim of this study was to evaluate the trends in de-escalation of axillary surgery in cT1-4N0-3 breast cancer patients treated with NST in the Netherlands.

Methods

Data were collected from the Netherlands Cancer Registry (NCR) [14]. The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). Specially trained registration clerks gather data directly form the patient files in all hospitals in the Netherlands. Patients with cT1-4N0-3 breast cancer treated with NST, between 2006 and 2016, were included. Patients with occult breast cancer were also included. For each patient, the following variables were documented: hospital type (academic, teaching, community), age, morphological subtype, receptor status, TNM status prior to and after NST, NST regimens, type of breast, and axillary surgery, axillary pCR, and adjuvant treatment plans. Axillary pCR was defined as the absence of residual axillary disease in all examined lymph nodes independent of the type of axillary surgery. Isolated tumor cells were included in the definition of axillary pCR. Patients were excluded if no lymph nodes were identified during surgery or if the number of positive lymph nodes was unknown. Patients with unknown cN status, distant metastasis, or patients in whom surgery of the breast was not performed were also excluded.

Patients

In the Netherlands, the axilla is generally assessed by means of ultrasound at the time of diagnosis. In the case of suspicious lymph nodes, either fine needle aspiration (FNAC) or core needle biopsy (CNB) is performed to assess the presence of metastasis. A cN0 status was defined as the absence of suspicious lymph nodes on axillary ultrasound or a negative FNAC/CNB (if performed). A cN+ status was defined as the presence of suspicious lymph nodes on axillary ultrasound in combination with pathologically confirmed metastasis by FNAC/CNB. Patients in whom SLNB was performed prior to NAC were always considered as initially cN0 patients.

For cN0 patients, the following subgroups regarding type of axillary surgery were documented: SLNB only (i.e., not followed by completion ALND), SLNB followed by completion ALND, and ALND (not preceded by SLNB). Patients in whom the timing of SLNB was unknown were excluded from analysis. For cN0 patients in whom SLNB was performed prior to NST, data on ypN status were only available when an ALND was performed.

For cN+ patients, the following subgroups were documented: SLNB and/or MARI only (i.e., not followed by completion ALND), SLNB and/or MARI followed by completion ALND, and ALND (not preceded by SLNB and/or MARI). MARI includes any procedure in which the pathologically confirmed positive lymph node was marked prior to NST and selectively removed after NST.

When referred to ypN status, this is always based on pathologic examination of lymph nodes and not on post-NST clinical examination of the axilla.

Statistical analysis

Descriptive statistics were performed to evaluate the trends over time for omission of ALND in the overall population, in cN0 and cN+ patients. In addition, potential differences were explored in the axillary management associated with the type of hospital where patients were treated. Univariable and multivariable logistic regression analyses were performed to determine the clinicopathological factors associated with performing ALND in cN+ patients. Odds ratios (ORs) were presented with 95% confidence intervals (CIs). Two-sided p values of < 0.05 were considered statistically significant. Data analysis was performed using Stata/SE Statistical Software for Windows, version 14.2 (College Station, TX: StataCorp LP).

Results

A total of 15,725 breast tumors treated with NST (10% of all breast tumors) were identified between January 2006 and December 2016 and registered in the NCR. Cases were excluded for the following reasons: distant metastasis ($n = 683$), treated with neoadjuvant radiotherapy ($n = 21$),

unknown cN status ($n=165$), unknown cT status ($n=136$), unknown hospital type ($n=1$), no breast surgery ($n=838$), unknown type of axillary surgery (n = 674), unknown outcome of axillary surgery ($n=193$), and unknown timing of SLNB ($n=553$). Altogether, 12.461 breast tumors were included for the final analysis. See Table 1 for clinicopathologic characteristics. In 7106 of 12,461 (57%) cases, ALND was performed. From 2006 to 2016, an overall decrease in the rate of ALND was observed from 96 to 29% ($p<0.001$).

cN0 patients

Nodal status was negative at the time of diagnosis (cN0) in 5830 cases (46.8%). The proportion of cN0 patients treated with NST increased from 35% in 2006 to 50% in 2016. In total, 4301 (73.8%) underwent SLNB only and 1529 (26.2%) underwent ALND (± preceded by SLNB). From 2006 to 2016, the rate of SLNB only (not followed by ALND) increased from 11 to 94% ($p<0.001$) (see Fig. 1). The rate of ALND decreased in both patient groups with ypN0 and ypN+ status (see Table 2). In the patients in whom SLNB was not followed by ALND, the proportion of patients with positive SLNs increased from 7 to 19%.

SLNB was performed prior to compared with after NST in 3401 (65%) and 1815 (35%) cases, respectively. Over time, SLNB was increasingly performed after NST (33% in 2006 vs. 62% in 2016, $p<0.001$). The overall rate of completion ALND was 23.4% when SLNB was performed prior to NST and 6.7% when SLNB was performed after NST ($p<0.001$). For SLNB performed prior to NST, the rate of completion ALND decreased from 58 to 12%; for SLNB performed after NST the rate of completion ALND decreased from 46 to 2% (see Fig. 1).

Overall, 4288 of 5830 cN0 patients (74%) were treated with adjuvant radiotherapy (80% in 2006 and 68% in 2016). Data on radiotherapy fields were unknown for the majority

Table 1 Clinicopathologic characteristics of all cT1-4N0-3 breast cancer patients treated with NST between 2006 and 2016 ($n=12.461$)

Characteristics	*n* (%)
Year of diagnosis	
2006—2009	2286 (18.4)
2010—2013	4712 (37.8)
2014—2016	5463 (43.8)
Age in years, median (range)	50 (range 18–87)
Histologic subtype	
Ductal	9832 (79)
Lobular	1256 (10)
Adenocarcinoma NOS	550 (4.4)
Mixed ductal and lobular	307 (2.5)
Other	516 (4.1)
Receptor status	
HR−/HER2−	1751 (16.3)
HR−/HER2+	987 (9.2)
HR+/HER2+	1756 (16.4)
HR+/HER2−	6243 (58.2)
HR and/or HER2 status	1724 (13.8)
Unknown	
TNM status	
T0—1—2—3—4	14 (0.1)–1647 (13.2)–6595 (53)–2696 (21.6)–1509 (12.1)
N0—1—2—3	5830 (47)–5610 (45)–258 (2)–760 (8)
M0—X	12,351 (99)–110 (1)
Lumpectomy	5087 (41)
Mastectomy	7374 (59)
Neoadjuvant systemic regimen	
Chemotherapy only	9382 (75)
Chemotherapy with HER2 therapy	2732 (22)
Chemotherapy with endocrine therapy	286 (2)
Chemotherapy with HER2 and endocrine therapy	61 (1)

NOS not otherwise specified, *HR* hormone receptor, *NST* neoadjuvant systemic therapy

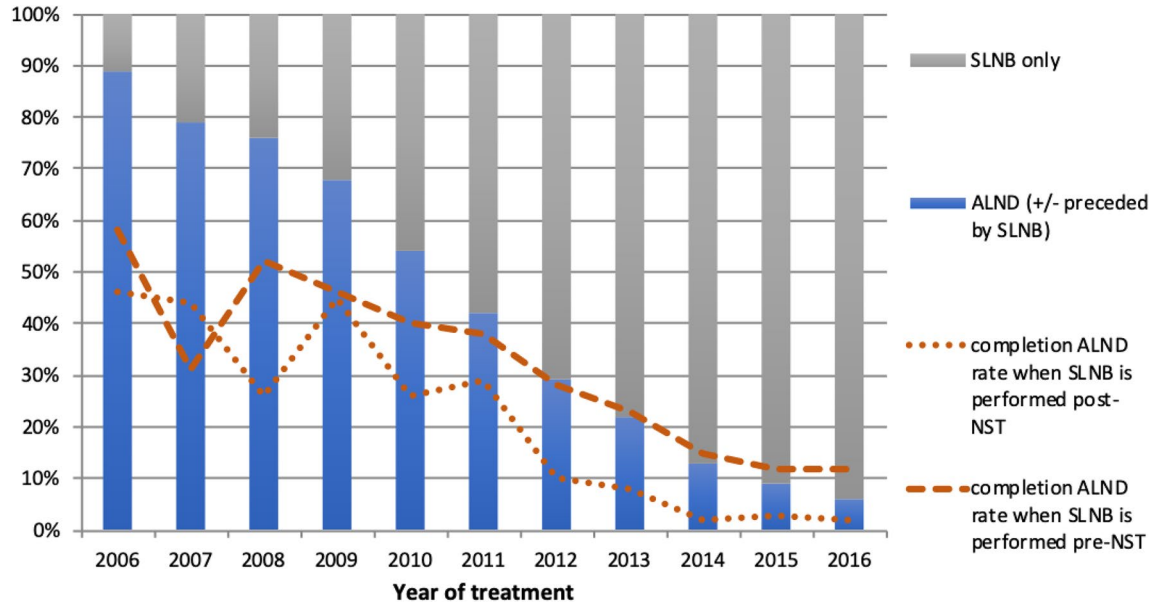

Fig. 1 Course over time for axillary staging in cN0 patients treated with NST. *cALND* completion ALND

of cN0 patients until 2010. From 2011 until 2016, data on radiotherapy fields were known for 91.7% (3244/3539) of cN0 patients treated with adjuvant radiotherapy, ranging from 84 to 95.8% dependent on the year of diagnosis. Adjuvant radiotherapy included *regional* radiotherapy in 36% (122/339) of cN0 patients treated with radiotherapy in 2011 and in 26% (100/381) of cN0 patients treated with radiotherapy in 2016. Out of the 3244 cN0 patients treated from 2011 until 2016 with known radiotherapy fields, 72% of patients with an ypN+ status received regional radiotherapy compared to 6% of patients with an ypN0 status ($p < 0.001$).

cN+ patients

Nodal status was positive at the time of diagnosis (cN+) in 6631 patients (53.2%). In total, 1054 (16%) underwent SLNB and/or MARI only and 5577 cN+ patients (84%) underwent ALND (± preceded by SLNB and/or MARI). From 2006 to 2016, the rate of SLNB and/or MARI only increased from 1 to 46% and the rate of (completion) ALND decreased from 99 to 54% ($p < 0.001$) (see Fig. 2). Over this period, the rate of ALND decreased from 98% (55/56) to 42% (48/115) in cN+ ypN0 patients and from 100 to 56% (296/526) in cN+ ypN+ patients (see Table 2). In 2016, 372 cN+ patients (58%) underwent staging by SLNB and/or MARI: in 294 patients (79%), this was not followed by ALND.

In multivariable logistic regression analysis, the following variables were associated with significantly decreased odds ratios for ALND: year of diagnosis (OR 0.47, CI 0.44–0.50) and HER2-positive disease (OR 0.62, CI 0.52–0.75). The following variables were associated with significantly increased odds ratios for ALND: age (OR 1.01, CI 1.00–1.02), clinical tumor stage (T2 vs. T1 OR 1.32, CI 1.06–1.65, T3 vs. T1 OR 2.04, CI 1.58–2.63, T4 vs. T1 OR 6.37, CI 4.26–9.50), and clinical nodal stage (N3 vs. N1 OR 1.65, CI 1.28–2.12) (see Table 3).

Overall, 5.824 out of 6631 cN+ patients (88%) were treated with adjuvant radiotherapy. Data on radiotherapy fields were unknown for the majority of cN+ patients until 2010. From 2011 until 2016, data on radiotherapy fields were known for 91.9% (3671/3996) of cN+ patients treated with adjuvant radiotherapy, ranging from 83.6% to 97% dependent on the year of diagnosis. Adjuvant radiotherapy included *regional* radiotherapy in 67.8% (318/469) of cN+ patients treated with radiotherapy in 2011 and in 80% (368/458) of cN+ patients treated with radiotherapy in 2016. Out of the 3671 cN+ patients treated from 2011 until 2016 with known radiotherapy fields, 2251/2955 (76%) of patients with an ypN+ status received regional radiotherapy compared to 424/716 (59%) of patients with an ypN0 status ($p < 0.001$). In 2955 cN + ypN + patients, 73% received regional radiotherapy when ALND was performed compared to 85% when ALND was not performed. In 716 cN + ypN0 patients, 57% received regional radiotherapy when ALND was performed compared to 62.5% when ALND was not performed).

Trends by hospital type

Overall, 823 (6.6%), 6457 (51.8%), and 5181 (41.6%) patients were treated in academic hospitals, teaching hospitals, and community hospitals, respectively. From 2006 to 2016, an overall decrease in ALND was observed from

Table 2 Overview of decrease in ALND rates for subgroups based on ypN status for both cN0 and cN+patients (all patients of the cohort were included in this analysis)

Year of diagnosis	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
cN0 patients, *n*	164	138	191	185	303	523	610	831	943	1280	662
ALND rate in:											
ypN0, % (absolute numbers)	78.3 (65/83)	69.7 (62/89)	63.2 (67/106)	44.2 (42/95)	31.9 (59/185)	13.1 (37/282)	6.1 (22/359)	3.8 (20/520)	3 (19/626)	2.4 (22/927)	1.2 (6/512)
ypN+, % (absolute numbers)	100 (81/81)	95.9 (47/49)	91.8 (78/85)	92.2 (83/90)	88.1 (104/118)	75.9 (183/241)	61.8 (155/251)	50.5 (157/311)	31.2 (99/317)	24.6 (87/353)	22.7 (34/150)
Year of diagnosis	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
cN+patients, *n*	302	363	456	487	487	606	608	744	806	1120	652
ALND rate in:											
ypN0, % (absolute numbers)	98.2 (55/56)	98.8 (85/86)	100 (103/103)	100 (82/82)	93.6 (102/109	92.1 (116/126	94 (125/133)	80 (133/166)	65.9 (116/176)	45.2 (109/241)	41.9 (49/117)
ypN+, % (absolute numbers)	99.6 (245/246)	99.6 (276/277)	100 (353/353)	99.8 (404/405)	100 (378/378)	97.9 (470/480)	97.3 (462/475)	93.6 (541/578)	84.9 (535/630)	61.7 (542/879)	55.5 (297/535)

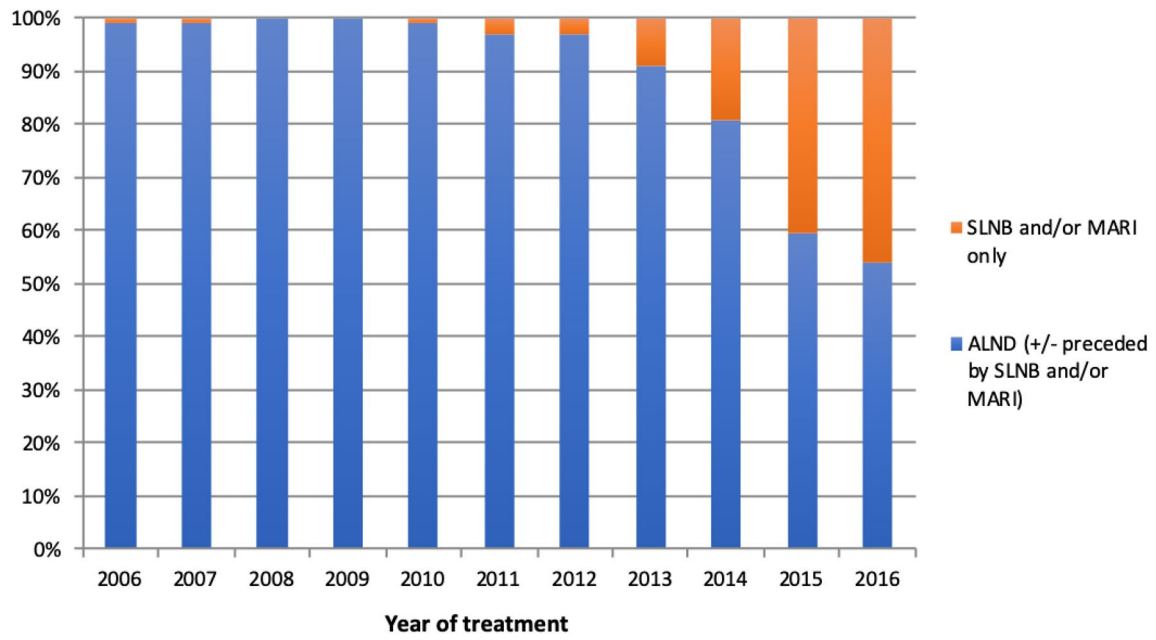

Fig. 2 Course over time for axillary staging in cN+ patients treated with NST

Table 3 Univariable and multivariable analysis for performing ALND in cT1-4N+ patients treated with NST

	Number of cases with ALND (%)	Univariable analysis		Multivariable analysis ($n=6442$)	
		OR (95% CI)	p value	OR (95% CI)	p value
Year of diagnosis	300/302 (99.3%) in 2006 to 346/652 (53.1%) in 2016	0.48 (0.45–0.50)	$p<0.001$	0.47 (0.45–0.50)	$p<0.001$
Age (per year)		1.01 (0.99–1.01)	$p=0.051$	1.01 (1.00–1.02)	$p=0.037$
Clinical tumor status					
T1	635/845 (75.1%)	Reference		Reference	
T2	2411/2996 (80.5%)	1.36 (1.14–1.63)	$p=0.001$	1.32 (1.06–1.63)	$p=0.013$
T3	1391/1611 (86.3%)	2.09 (1.69–2.58)	$p<0.001$	2.00 (1.56–2.58)	$p<0.001$
T4	1127/1166 (96.7%)	9.56 (6.70–13.63)	$p<0.001$	6.49 (4.36–9.66)	$p<0.001$
Clinical node status					
N1	4697/5582 (84.1%)	Reference		Reference	
N2	220/257 (85.6%)	1.12 (0.79–1.60)	$p=0.531$	1.31 (0.87–1.96)	$p=0.197$
N3	658/759 (86.7%)	1.23 (0.93–1.53)	$p=0.070$	1.66 (1.29–2.14)	$p<0.001$
ER positive		0.97 (0.84–1.12)	$p=0.703$		
No	1831/2157 (84.9%)				
Yes	3599/4258 (84.5%)				
HER2 positive		0.83 (0.72–0.96)	$p=0.013$	0.62 (0.52–0.73)	$p<0.001$
No	3920/4604 (85.1%)				
Yes	1532/1851 (82.7%)				

OR odds ratio, *CI* confidence interval

97 to 38% in academic hospitals ($p<0.001$), from 94 to 27% in teaching hospitals ($p<0.001$) and from 97 to 32% in community hospitals ($p<0.001$). In 2016, staging was performed by means of SLNB and/or MARI in 53% (16/30) of cN+ patients in academic hospitals, 61% (216/354) in teaching hospitals, and 52% (140/268) in community hospitals ($p=0.083$). In these patients, SLNB and/or MARI was not followed by ALND in 75% (12/16), 75% (161/216), and 86% (121/140), respectively ($p=0.025$). In 2016, the overall axillary pCR rate in cN+ patients was 17.9%.

Discussion

This large Dutch population-based cohort study showed that axillary surgery has changed considerably in daily practice over the past decade in cT1-4N0-3 breast cancer patients treated with NST. In cN0 patients, a substantial decrease in ALND and increase in SLNB only was observed, with SLNB being increasingly performed after NST. Additionally, this study revealed that ALND has increasingly been omitted after NST in cN+ patients.

In patients who undergo adjuvant systemic therapy, indications for omitting ALND in cN0 patients have extended over the years from patients with negative SLNS(s) to patients with positive SLN(s) [15]. Even 10-year survival outcomes from the ACOSOG Z0011 and IBCSG 23-01 trials corroborated non-inferiority of SLNB alone compared to ALND for patients with limited positive SLN(s) [4, 16]. Abandoning completion ALND in cN0 patients with positive SLN(s) treated with adjuvant systemic therapy is already ongoing for years, even prior to the publication of the abovementioned trials [17–20]. Ever since the publication of these trial results, implementation of SLNB only in this population is expanding [11, 21]. The current study shows that abandoning completion ALND in cN0 patients with positive SLN(s) is also taking place in patients treated with NST, even though results of the previous trials only apply to patients treated with *adjuvant* systemic therapy. Over the past decade, SLNB was increasingly performed after NST rather than prior to NST. Several previous studies demonstrated that performing SLNB after NST is associated with lower rates of a positive SLNB [22–24]. Thus, ALND can be omitted more often when SLNB is performed after NST. Hence, the change in timing of SLNB found in this study contributed to the decreasing use of ALND.

The results presented here prove that clinicians are willing to adopt a SLNB-only strategy in the neoadjuvant setting as well, even though such a strategy is not evidence-based. Whether SLNB alone instead of the routine use of ALND in patients with limited positive SLN(s) treated in the *neoadjuvant* rather than adjuvant setting provides similar results in terms of overall survival is yet unknown. One should bear in mind that in contrast to the adjuvant setting, positive SLN(s) in the neoadjuvant setting indicates therapy-resistant disease and may represent a different tumor biology. Since long-term follow-up of cN0 patients with positive SLNs that did not undergo completion ALND in the neoadjuvant setting is lacking, it is too early to tell whether it is safe to consider and treat these groups similarly. Furthermore, it is unknown to what extent ALND has been replaced by regional radiotherapy in these patients.

Regarding cN+ patients treated with NST, several less invasive procedures have been proposed over the past years in an attempt to prevent unnecessary ALND in patients who achieve axillary pCR: SLNB, excision of a pre-treatment marked positive lymph node (like MARI) or a combination of these two procedures (like Targeted Axillary Dissection and RISAS) [13, 25–27]. Despite limited evidence for the safety of replacing ALND by these procedures, implementation of such strategies is occurring worldwide [28]. The results of the current study confirm this trend: from 2013 (prior to publications on accuracy of MARI and TAD), rates of SLNB and/or MARI for axillary staging after NST started increasing up to 58% in 2016. The increase in rates of SLNB and/or MARI in cN+ patients was present in all three types of hospitals. Although SLNB and/or MARI is offered more and more to cN+ patients in order to omit ALND in case of axillary pCR, 42% of patients with an axillary pCR still underwent (completion) ALND in 2016. This indicates that selecting the right patient for the appropriate procedure is challenging. At the same time, completion ALND may have been performed as part of validating studies. In some institutions, ALND is performed in all cN+ patients, irrespective of response to NST, which may also in part explain this finding. Again, it is unknown to what extent ALND has been replaced by regional radiotherapy.

Notably, the decrease in ALND rates in cN+ patients treated with NST is also present in patients who do not achieve an axillary pCR. In 2016, 44% of the cN+ patients with post-NST residual axillary disease did not undergo completion ALND. Multiple studies reported improved survival for patients with a complete response (ypT0/ypN0) to NST compared to patients without a complete response [29, 30]. These results indicate the necessity of treatment escalation rather than de-escalation in patients without axillary pCR to improve prognosis, especially in certain subtypes (such as triple negative breast cancer) [31]. Whether current practices of omitting ALND in cN+ patients without axillary pCR will negatively impact prognosis is yet unknown. In the Alliance 11,202 trial, prognosis of cN+ patients with positive SLN(s) after NST is compared between those treated with completion ALND and those treated with axillary radiotherapy [32].

Although the current study describes a large cohort of patients, several limitations have to be taken into account. Regarding adjuvant treatment plans, sufficient data on radiotherapy fields were not available for the whole cohort. It is expected that simultaneously with the decreasing rates of ALND, rates of regional radiotherapy increase. This study did suggest such a trend in cN+ patients, but further research is needed for a thorough assessment of (regional) radiotherapy administration in patients treated with NST. Furthermore, the impact of omitting ALND on prognosis in terms of overall and disease-free survival could not be assessed since data on recurrences are not (yet) available for this cohort.

To conclude, axillary surgical staging changed significantly with a major decrease in ALND rates in breast cancer

patients treated with NST over the past decade. However, selecting the right patients for whom omitting ALND is oncologic safe appears challenging, especially in pre-treatment cN+ patients and patients with residual axillary disease. Studies assessing long-term prognosis of such patients in whom ALND is omitted are urgently needed.

Acknowledgements The authors thank the registration clerks and the staff for gathering the data for the NCR and L. de Munck and S.J. Hogewoning for assistance with statistical analysis. JM Simons received salary from the Dutch Cancer Society (KWF Kankerbestrijding).

Funding This study did not receive funding.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent We received all patient data in this study anonymously (without patient identifiers) from the Netherlands Cancer Registry (NCR). According to the Dutch law, all cancer patients are included in the NCR as maintained by the Netherlands Comprehensive Cancer Organisation (IKNL), unless the patient has objected to be registered. Therefore, informed consent was not applicable for this study.

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