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## Quality assurance in breast cancer care and breast implant surgery

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## CHAPTER 6

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.

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## ABSTRACT

**Objectives:** To evaluate patterns of care in axillary surgery for Dutch clinical T1-4N0M0 (cT1-4N0M0) breast cancer patients and to assess the effect of the American College for Surgeons Oncology Group (ACOSOG)-Z0011 and After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial on axillary surgery patterns in Dutch cT1-2N0M0 sentinel node positive breast cancer patients.

**Background:** Since publication of the ACOSOG-Z0011 and AMAROS trial, omitting a completion axillary lymph node dissection (cALND) in sentinel node positive breast cancer patients is proposed in selected patients.

**Methods:** Data were obtained from the nationwide Nationaal Borstkanker Overleg Nederland breast cancer audit. Descriptive analyses were used to demonstrate trends in axillary surgery. Multivariable logistic regression analyses were used to identify factors associated with the omission of cALND in cT1-2N0M0 sentinel node-positive breast cancer patients.

**Results:** Between 2011 and 2015 in cT1-4N0M0 breast cancer patients, the use of sentinel lymph node biopsy as definitive axillary staging increased from 72% to 93%, and (c)ALND as definitive axillary staging decreased from 24% to 6% ( $P < 0.001$ ). The use of cALND decreased from 75% to 17% in cT1-2N0 sentinel node-positive patients ( $P < 0.001$ ). Earlier year of diagnosis, lower age, primary mastectomy, invasive lobular subtype, increasing tumor grade, and treatment in a nonteaching hospital were associated with a lower probability of omitting cALND ( $P < 0.001$ ).

**Conclusions:** This study shows a trend towards less extensive axillary surgery in Dutch cT1-4N0M0 breast cancer patients; illustrated by an overall increase of sentinel lymph node biopsy and decrease in cALND. Despite this trend, particularly noticed in cT1-2N0 sentinel node-positive patients after publication of the ACOSOG-Z0011 and AMAROS trial, variations in patterns of care in axillary surgery are still present.

## INTRODUCTION

Axillary lymph node management in breast cancer patients has changed dramatically during past decades.<sup>1</sup> Previously, performing an axillary lymph node dissection (ALND) was the standard of care for all nonmetastatic breast cancer patients. In the early 90s, sentinel lymph node biopsy (SLNB) was introduced as an accurate and less invasive axillary staging procedure, omitting the need for ALND in cT1-2N0M0 sentinel lymph node-negative breast cancer patients.<sup>2,3</sup> Despite, only small studies investigated accuracy of SLNB in cT3 sentinel lymph node-negative breast cancer patients, SLNB is also widely used in this group of patients.<sup>4,5</sup> In the early years after the introduction of SLNB, a completion ALND (cALND) was indicated in all patients with a positive sentinel lymph node.<sup>6</sup>

The additional value of cALND was first questioned in 2 randomized controlled trials—the American College for Surgeons Oncology Group (ACOSOG)-Z0011 trial and the After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial.<sup>7,8</sup> In the ACOSOG-Z0011 (accrual 1999–2004, published 2011), cT1- 2N0M0 breast cancer patients with 1 to 2 positive sentinel lymph nodes treated with breast-conserving therapy followed by whole breast radiotherapy were randomized between a cALND or no further axillary treatment.<sup>7</sup> Ten years cumulative incidence of ipsilateral axillary recurrences was 0.5% in the ALND group and 1.5% in the SLNB-alone group, with no significant difference in locoregional recurrence-free survival.<sup>9</sup>

The AMAROS trial (accrual 2001–2010, published 2014) evaluated whether regional control was comparable between cALND and axillary radiation therapy in cT1-2N0M0 breast cancer patients with 1 to 2 (and 5% >2) positive sentinel lymph nodes, treated with breast-conserving therapy, including whole breast radiotherapy or mastectomy with or without radiotherapy to the chest wall. There was no significant difference in the 5-year axillary recurrence rate between patients treated with cALND or axillary radiotherapy; 0.43% versus 1.19%. Axillary radiotherapy was associated with significantly less morbidity.<sup>8</sup> The AMAROS results indicated that in case of a positive sentinel node, both cALND and axillary radiotherapy provide excellent and comparable axillary control disease-free and overall survival for patients with cT1-2N0M0 primary breast cancer.

The first presentation of results of the ACOSOG-Z0011 in 2011 generated great debate under physicians. Some argued that the results should be considered unreliable since patients' accrual was discontinued before the foreseen number of patients was included. In addition, questions were raised regarding the selection of a favorable subgroup of patients; not all patients were treated with whole-breast radiotherapy as planned and lack of consistent documentation of radiation fields.<sup>10-14</sup> The safety of omitting cALND in sentinel node-positive breast cancer patients was questioned and resulted in hesitations to implement axillary lymph node-conserving treatment. This is illustrated by the 2012 Dutch Breast Cancer Guideline, merely suggesting omission of cALND in cT1-2N0M0 breast cancer patients with a maximum of 2 positive sentinel nodes treated with breast-conserving treatment and adjuvant systemic therapy. Based on previous literature and preliminary experience with the AMAROS trial, this guideline also suggested that axillary irradiation could serve as an alternative to cALND in sentinel node-positive patients for whom treatment of the axillary was considered necessary.<sup>15</sup>

The first aim of this study was to demonstrate patterns of care in axillary surgery for all Dutch cT1-4N0M0 breast cancer patients diagnosed between 2011 and 2015. The second aim was to evaluate the effects of the ACOSOG Z0011 and AMAROS trials in Dutch daily clinical practice. Furthermore, this study identified patient, tumor, and hospital-related factors associated with axillary surgery in cT1-2N0M0 sentinel node-positive breast cancer patients.

## METHODS

Data were obtained from the Dutch Nationaal Borstkanker Overleg Nederland Breast Cancer Audit (NBCA). The NBCA is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of patients who are surgically treated for breast cancer in the Netherlands since 2011. It is facilitated by the Comprehensive Cancer Center Netherlands (IKNL) and the Dutch Institute for Clinical Auditing (DICA). Data are registered directly by the hospital itself or by IKNL data managers. The quality of the Dutch Cancer registry is high and data completeness is estimated to be at least 95%.<sup>16</sup>

### *Patients and Hospitals*

The current study sample consisted of Dutch patients diagnosed with cT1-4N0M0 invasive breast cancer between January 2011 and October 2015. Patients with the following criteria were excluded: <18 years of age, those who received neoadjuvant systemic therapy, had any prior surgery of the breast or those of whom information on the axillary surgery was indistinct. Data from 85 different Dutch hospitals (9 academic, 38 teaching, and 38 general nonteaching hospitals) were included. Not every hospital is represented in each year due to mergers or acquisitions, resulting in 82 entities in 2011 versus 71 entities in 2015.

### *Construction of Variables*

Hospitals were divided into groups according to their teaching status (general nonteaching, teaching, academic) and surgical hospital volume. Teaching and academic hospitals both provide in-house surgical training to residents, with distinction that academic hospitals are directly connected with a medical faculty of a university. Specialized oncologic hospitals were classified as academic hospitals. Hospital volume was defined as the number of patients who underwent breast cancer surgery per year. Hospitals were divided into low volume (<150 resections), middle volume (150–300 resections), and high volume (>300 resections) on average per year. The cut-off points chosen were based on those reported in a publication of Eusoma, the European Society of Breast Cancer Specialist,<sup>17</sup> and those reported in an article from Greenup et al.<sup>18</sup> A positive sentinel node included micrometastases and macrometastases; isolated tumor cells were considered as sentinel node-negative.

Since the NBCA did not register the radiation fields, we could not describe whether or not a patient received radiotherapy on the breast (partial or whole) and/or axilla and/or other regions. Furthermore, we did not have access to information on adjuvant hormonal therapy in all patients.

### ***Statistical Analyses***

Descriptive analyses were used to report on the trends in axillary surgery for all cT1-4N0M0 breast cancer patients. The outcome of interest was the definitive surgical axillary treatment and was divided into 4 groups: no surgical nodal staging; SLNB-negative; SLNB-positive, no cALND; (c)ALND. The fourth group consisted of patients who were treated with SLNB followed by cALND, and of patients treated with ALND directly.

Univariable and multivariable logistic regression analyses were used to determine the probability to omit a cALND in selected cT1-2N0M0 sentinel node-positive breast cancer patients. A P value of <0.05 was considered statistically significant. Data analysis was performed using SPSS version 24 (SPSS Inc, Chicago, IL).



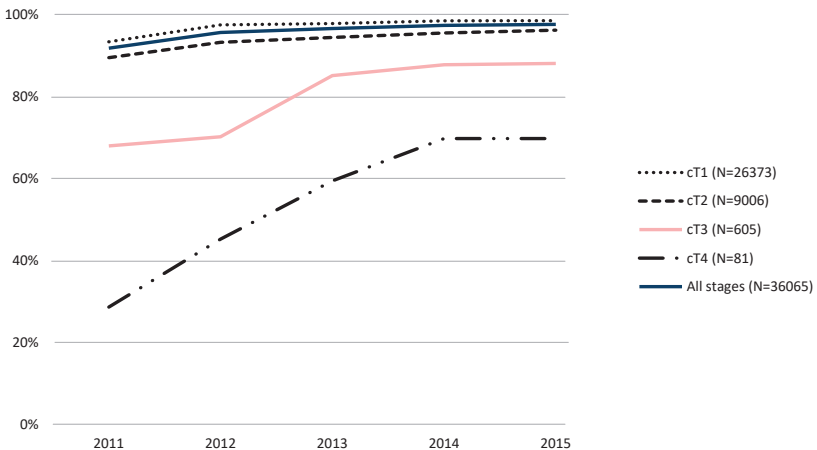
## RESULTS

### Patients

In all, 44,902 patients were diagnosed with cT1-4N0M0 invasive breast cancer between January 2011 and October 2015, and registered in the NBCA. Exclusion of patients <18 years of age (n=14), those who received neoadjuvant systemic therapy (n=3333), had any prior surgery of the breast (n=4014), or those of whom information on the axillary surgery was indistinct (n=21), resulted in a study population of 37,520 patients (see flowchart of exclusion criteria, supplement). Median age was 63 years (19-98); 5335 patients (12%) were older than 75 years. Most of the patients were diagnosed with a cT1 tumor (72%, n=27,066), whereas 26% of the patients were diagnosed with a cT2 tumor (n=9575), 2% with a cT3 tumor (n=743), and 0.4% with a cT4 tumor (n=136) (see **supplemental Table A**, which demonstrates the clinical-pathological and hospital characteristics of all cT1-4N0M0 patients [n= 37,520] and percentages of an ALND).

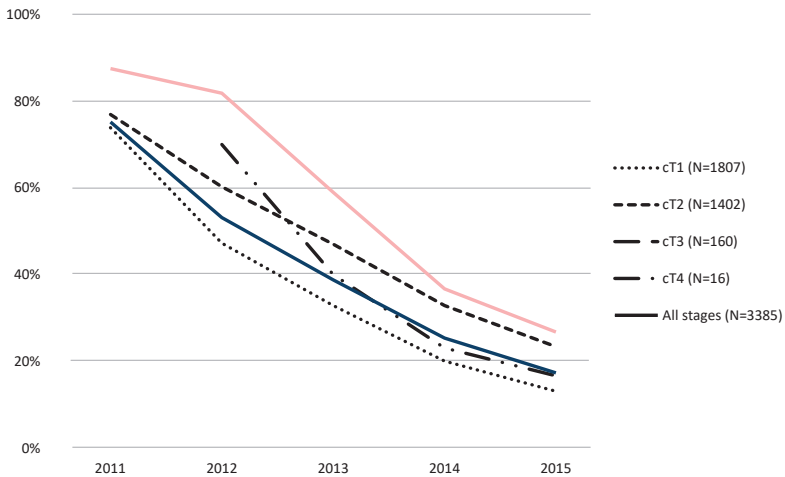
### Trends in Axillary Surgery in cT1-4N0M0 Breast Cancer Patients

In 2011, 92% of all cT1-4N0M0 breast cancer patients were staged using SLNB, increasing to 98% in 2015. According to the tumor stage the use of SLNB increased from 93% to 98% in cT1 tumors, from 92% to 98% in cT2 tumors, from 68% to 88% in cT3 tumors, and from 29% to 70% in cT4 tumors (**Fig. 1**).



**Figure 1.** Trend in percentages of sentinel lymph node biopsy (SLNB) in cT1-4N0M0 breast cancer patients in the Netherlands from 2011 to 2015 according to clinical tumor (cT) stage.

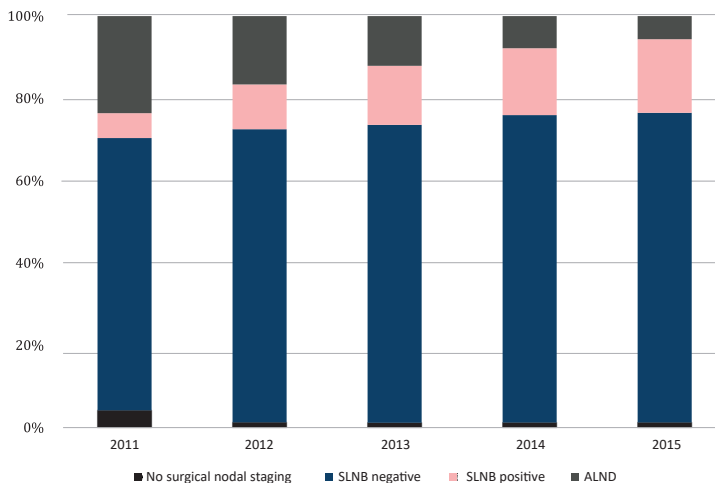
In case of a positive SLNB within the group of cT1-4N0M0 breast cancer patients (n=8539), the use of a cALND decreased between 2011 and 2015. As shown in Fig. 2, this decline was noticed in all clinical tumor stages of disease: from 74% to 13% for cT1 (n=5159) tumors and 77% to 23% for cT2 tumors (n=3032). Of note, also in cT3 and cT4 tumors, a decreasing trend was observed in the use of a cALND: from 88% to 27% in cT3 tumors (n=307) and from 50% to 17% in cT4 tumors (n=41), respectively.



**Figure 2.** Trend in percentages of complementary axillary lymph node dissection (cALND) in cT1-4N0M0 sentinel node positive breast cancer patients in the Netherlands from 2011 to 2015 according to clinical tumor (cT) stage.

**Figure 3** shows the percentage of patients according to their definitive axillary staging in the period 2011 to 2015. Hence, these are percentages of the complete group of patients diagnosed with cT1-4N0M0 invasive breast cancer (n=37,520) divided into the following groups: no axillary staging (n=954), SLNB (negative = 27,200 or positive = 5154) without an ALND and (c)ALND (n=4572). Obviously, the proportion of patients with a positive SLNB as definitive axillary staging procedure increased from 6% (n=282) in 2011 to 18% (n=1411) in 2015 ( $P < 0.001$ ). In these cT1-4N0M0 sentinel node-positive breast cancer patients, a cALND was omitted.

Rarely, in a proportion of patients with a negative SLNB (n= 27,526), a cALND was performed (1%, n=326). This percentage remained unchanged over the years and was not associated with either age or clinical tumor stage. Apart from this, 861 out of



**Figure 3.** Trends in the definitive axillary staging in cT1-4N0M0 breast cancer patients in the Netherlands from 2011 to 2015.

all 37,520 (2.3%) cT1-4N0M0 breast cancer patients received ALND directly, without previous axillary staging. Overall, percentages of SLNB as definitive axillary staging increased from 72% in 2011 to 93% in 2015, and percentages of (c)ALND as definitive axillary staging declined from 24% in 2011 to 6% in 2015 ( $P < 0.001$ ).

### ***Trends in Axillary Surgery in cT1-2N0M0 Sentinel Node-positive Breast Cancer Patients***

A subgroup analysis was performed in cT1-2N0M0 breast cancer patients with 1 to 2 (and 1.8% >2) positive sentinel lymph nodes; a group comparable with the ACOSOG-Z0011 and AMAROS trial population. A total of 8191 out of 36,641 cT1-2N0M0 patients were sentinel node-positive with a median age of 60 years (22–96).

The clinical, pathological, and hospital characteristics of this population are shown in Table 1. Most of these patients underwent breast-conserving surgery (61%,  $n=4959$ ) and were classified with a ductal, unifocal, hormone receptor-positive, and human epidermal growth receptor (HER)2-negative breast tumor. The majority (84%,  $n=5939$ ) of the cT1-2N0M0 sentinel node-positive patients received radiotherapy on any region and 62% ( $n=4646$ ) of the patients received adjuvant chemotherapy.

**Table 1.** Clinical- pathological and hospital characteristics of cT1-2N0M0 sentinel node positive patients (N=8191) and percentages of complementary axillary lymph node dissection (cALND), 2011 -2015.

	N	cALND		p-Value
<b>Incidence year</b>				
2011	1111	833	75%	<0.001
2012	1815	947	52%	
2013	1905	723	38%	
2014	1730	430	25%	
2015	1630	276	17%	
<b>Age</b>				
<40	326	183	56%	<0.001
40-50	1309	624	48%	
50-75	5394	2035	38%	
75+	1162	367	32%	
<b>Histologic subtype</b>				
ductal	7112	2721	38%	<0.001
lobular	1079	488	45%	
<b>Clinical tumor stage</b>				
cT1	5159	1807	35%	<0.001
cT2	3032	1402	46%	
<b>Multifocality</b>				
unifocal	6893	2583	37%	<0.001
multifocal	1298	626	48%	
<b>Receptor status</b>				
triple -	456	225	49%	<0.001
HR -, Her2+	212	102	48%	
HR+, Her2+	650	267	41%	
HR+, Her2-	6361	2374	37%	
unknown	512	241	47%	
<b>Grade</b>				
I	1753	586	33%	<0.001
II	4217	1634	39%	
III	2101	933	44%	
unknown	120	56	47%	
<b>Initial surgery</b>				
mastectomy	3232	1691	52%	<0.001
breast conserving treatment (BCT)	4959	1518	31%	
<b>Radiotherapy (on any region)</b>				
no	1138	672	59%	<0.001
yes	5939	1760	30%	
Unknown	785	554	71%	

Table 1. (continued)

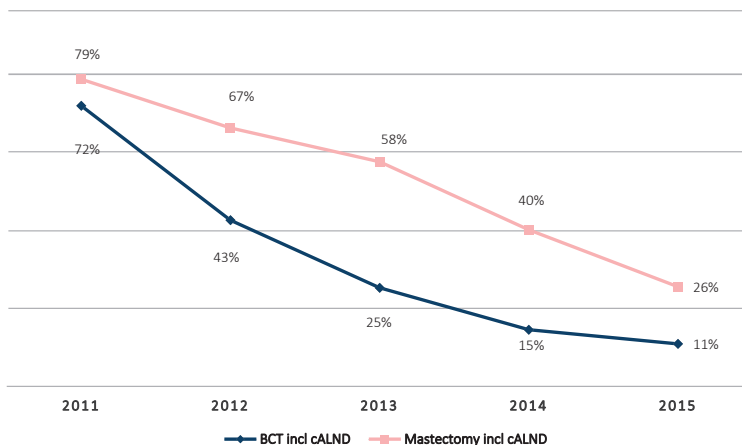
	N	cALND		p-Value
<b>Adjuvant chemotherapy</b>				
no	2937	781	27%	<0.001
yes	4646	2135	46%	
unknown	607	293	48%	
<b>Type of hospital</b>				
general non-teaching	2993	1353	45%	<0.001
teaching hospital	4582	1684	37%	
academic	616	172	28%	
<b>Hospital surgical volume</b>				
<150	2450	1076	44%	<0.001
150-300	3060	1113	36%	
>300	1988	732	37%	
unknown	693	288	42%	

cALND complementary axillary lymph node dissection, cT clinical tumor, HR hormone receptor, Her2 human epidermal growth receptor 2

As shown in Table 1, within this subgroup of cT1-2N0M0 sentinel node-positive patients, the performance of a cALND decreased from 75% in 2011 (ACOSOG-Z0011 published), to 25% in 2014 (AMOROS published) and 17% in 2015. In cT1-2N0M0 sentinel node-positive breast cancer patients, younger patients were more likely to receive a cALND. Over time, the rate of cALND for patients aged <40 decreased from 89.6% in 2011 to 61.8%, 47.0%, 37.7%, and 39.6% in 2012, 2013, 2014, and 2015, respectively. The rate of cALND for patients aged 50 to 75 decreased from 76.4% in 2011 to 51.1%, 37.1%, 23.3%, and 15.9% in 2012, 2013, 2014, and 2015, respectively.

Regarding the receptor status, triple negative patients had a higher probability in receiving cALND. Over time, the rate of cALND in triple negative patients declined from 79.0% in 2011 to 56.6%, 50.0%, 33.7%, and 25.3% in 2012, 2013, 2014, and 2015, respectively.

In case of breast-conserving therapy, a cALND was omitted more often (69%) compared with mastectomy (48%) ( $P < 0.001$ ). **Figure 4** shows the type of primary surgery of cT1-2N0M0 sentinel node-positive patients treated with a cALND from 2011 to 2015. The proportion of patients receiving cALND declined for both types of surgery over the years, but notable is the slower adaptation of omitting cALND in the mastectomy group.



**Figure 4.** Percentages of cT1-2N0M0 sentinel node positive breast cancer patients in which a complementary axillary lymph node dissection (cALND) was performed; breast conserving therapy (BCT) versus mastectomy.

### *Prognostic Factors Omitting a cALND in cT1- 2N0M0 Sentinel Node-positive Patients*

A multivariable logistic regression analysis was used to determine independent predictors in omitting cALND (Table 2). Apart from an earlier year of diagnosis, lower age and patients being treated with mastectomy, also invasive lobular subtype, increasing tumor grade and being treated in a general nonteaching hospital were independently associated with a lower probability in omitting cALND (all  $P < 0.001$ ). Hospital surgical volume and receptor status were not independently associated with omitting cALND in multivariable analysis.

**Table 2.** Univariable and multivariable analyses for the performance of complementary axillary lymph node dissection (cALND) among cT1-2N0M0 sentinel node positive patients (N=8191), 2011 -2015.

Incidence year	Univariable			Multivariable		
	Odds	CI Interval	p-Value	Odds	CI Interval	p-Value
2011	ref.		<0.001	ref.		<0.001
2012	0,364	(0,309 - 0,429)		0,359	(0,297 - 0,435)	
2013	0,204	(0,173 - 0,241)		0,206	(0,17 - 0,249)	
2014	0,111	(0,093 - 0,132)		0,092	(0,075 - 0,113)	
2015	0,068	(0,056 - 0,082)		0,059	(0,047 - 0,073)	

Table 2. (continued)

	Univariable			Multivariable		
	Odds	CI Interval	p-Value	Odds	CI Interval	p-Value
<b>Age</b>						
<40	ref.		<0.001	ref.		<0.001
40-50	0,712	(0,564 - 0,918)		0,723	(0,535 - 0,976)	
50-75	0,473	(0,383 - 0,602)		0,638	(0,482 - 0,845)	
75+	0,361	(0,284 - 0,464)		0,297	(0,216 - 0,407)	
<b>Histologic subtype</b>						
ductal	ref.		<0.001	ref.		0,023
lobular	1,33	(1,171 - 1,516)		1,214	(1,027 - 1,433)	
<b>Clinical tumor stage</b>						
cT1	ref.		<0.001	ref.		<0.001
cT2	1,596	(1,456 - 1,748)		1,303	(1,156 - 1,469)	
<b>Multifocality</b>						
unifocal	ref.		<0.001	ref.		0,035
multifocal	1,554	(1,38 - 1,751)		1,18	(1,012 - 1,377)	
<b>Receptor status</b>						
triple -	ref.		<0.001	ref.		0,185
HR -, Her2+	0,952	(0,687 - 1,319)		0,822	(0,557 - 1,213)	
HR+, Her2+	0,716	(0,562 - 0,911)		0,732	(0,548 - 0,978)	
HR+, Her2-	0,611	(0,505 - 0,74)		0,786	(0,617 - 1,001)	
<b>Grade</b>						
I	ref.		<0.001	ref.		0,012
II	1,968	(1,863 - 2,078)		1,052	(0,91 - 1,216)	
III	2,567	(2,425 - 2,717)		1,271	(1,068 - 1,513)	
<b>Initial surgery</b>						
mastectomy	ref.		<0.001	ref.		<0.001
nreast conserving treatment(BCT)	0,402	(0,367 - 0,441)		0,335	(0,295 - 0,381)	
<b>Type of hospital</b>						
general non-teaching	ref.		<0.001	ref.		<0.001
teaching hospital	0,704	(0,641 - 0,774)		0,664	(0,566 - 0,779)	
academic	0,47	(0,388 - 0,568)		0,335	(0,263 - 0,426)	
<b>Hospital surgical volume</b>						
<150	ref.		<0.001	ref.		0,327
150-300	0,913	(0,876 - 0,953)		1,125	(0,963 - 1,315)	
>300	0,861	(0,822 - 0,903)		1,113	(0,926 - 1,337)	

CI confidence interval, Ref reference, cT clinical tumor, HR hormone receptor, Her2 human epidermal growth receptor 2

## DISCUSSION

This study showed a trend towards less extensive axillary surgery in Dutch cT1-T4N0M0 breast cancer patients in the ACOSOG-Z0011 and AMAROS era. Particularly in cT1-T2N0M0 sentinel node-positive invasive breast cancer patients, the performance of a cALND decreased from 75% in 2011 to 17% in 2015. The downward trend observed in the use of cALND in cT1- 2N0 sentinel node-positive breast cancer patients reflects the implementation of the study concept of the ACOSOG-Z0011 and AMAROS trials in the Netherlands. In these patients, axillary surgery varied between patients treated with breast-conserving therapy and mastectomy. In 2011, the percentage of patients without a cALND was higher in the breast-conserving therapy group (28%) compared with the mastectomy group (21%). Only a small percentage of patients (0% in the ACOSOG-Z0011 and 18% in the AMAROS trial) were treated with mastectomy, which could be a reason why omitting cALND in mastectomy patients was less likely adopted by surgeons.

As expected, due to the presentation of the results of the ACOSOG-Z0011 trial, a reduction in the number of cALND performed in patients treated with breast-conserving therapy was observed. While the results of the AMAROS trial were presented in 2014, a reduction in the percentage of cALND in patients treated with mastectomy was already observed in 2013. This may reflect the confidence of physicians in the concept that not every positive axillary sentinel lymph node will develop into clinical detectable axillary disease.<sup>7,19</sup>

In some patients, physicians were still reluctant to omit cALND. As reported in this study, the probability of omitting cALND decreased when patients were younger (<40 years), were treated in a general nonteaching hospital, or had more aggressive tumor biology. The relation of younger age (<40 years) to higher cALND rates may reflect the hypothesis that treatment of the axilla should be more aggressive in younger patients to optimize overall survival. However, the prognostic relevance of young age on the occurrence of regional recurrences is controversial.<sup>20-22</sup> Physicians may extrapolate the higher risk of young patients to develop a local recurrence to the regional recurrence risk. Indeed, the occurrence of a local recurrence affects the overall survival of young patients.<sup>21,23-25</sup>



On the contrary, the ACOSOG-Z0011 10-year follow-up data showed that the number of regional recurrence is very low in both the ALND group (0.5%) and the SLNB-only group (1.5%), and no association of young age (<50 years) with loco-regional recurrences was observed.<sup>9</sup> Hence, it does not seem justified to be reluctant to omit a cALND based only on the age of the patient. This study reported that triple negative breast cancer patients with a positive SLNB were more likely to receive a cALND compared with hormone receptor-positive patients. This practice may be based on the criticism that in the ACOSOG-Z0011, only small numbers of patients with triple negative breast cancer were included and thus the results were not applicable for triple negative patients.<sup>26,27</sup> However, several studies do not support such an aggressive approach. Firstly, van Roozendaal et al questioned in their study whether triple negative patients with a clinically T1-2N0 status were more at risk for regional recurrences. Their 5-year follow-up showed a regional and distant recurrence rate of 2.9% and 12.2%, respectively. It was concluded in this study that triple negative tumors rarely recur regionally and that their disease-free survival was more threatened by distant recurrence.<sup>28</sup> Secondly, being at high risk to develop distant metastasis does not necessarily mean being at high risk for axillary nodal recurrence.<sup>26</sup> Thirdly, a recent follow-up study on the ACOSOG-Z0011 eligible patients was publicized. It was reported that after a median follow-up of 31 months, high-risk patients (ie, triple negative tumors, HER2-positive tumors, and age <50 years) compared with average-risk patients had the same risk of regional recurrence, but a higher risk of developing distant metastasis.<sup>27</sup> Hence, although longer follow-up data are preferable, it does not seem justifiable to perform a cALND based on receptor status only.

We evaluated a significant variation in omitting cALND between different types of hospitals, revealing the presence of early and late adopters. While the first hospitals started omitting cALND in 2011, other hospitals still performed this procedure in 2015, as has been reported by other authors.<sup>29-31</sup> van Steenberg et al<sup>29</sup> evaluated in 2010 the implementation of SLNB in the Netherlands and showed that general nonteaching hospitals were late adopters of the SLNB procedure by performing ALND more frequently than other hospitals. This variation might be explained by the degree of dedication of the multidisciplinary breast cancer treatment teams within a hospital or whether a radiotherapy center was located nearby the treating hospital. Within the current study, there was no information about these possible influencing factors which

should be evaluated in future studies. This variation is not favorable, but unfortunately the implementation process following the presentation of evidence-based studies and guidelines is seldom monitored and reasons for nonadherence are largely unknown.

Another notable pattern of care was the downward trend of cALND in cT3-4N0M0 sentinel node-positive breast cancer patients, which was in line with the decreasing trend in cT1-2N0M0 sentinel node-positive breast cancer patients. No randomized trials have been published to justify less extensive axillary surgery in cT3-4N0M0 sentinel node-positive breast cancer patients. Nonetheless, the decreasing trend in the numbers of cALNDs performed in all tumor stadia might reflect the growing argument for less extensive surgery in the axilla of breast cancer patients.

In addition, this study revealed an increase in the use of SLNB, especially in cT3 and cT4 patients, from 68% to 87% and 29% to 70%, respectively. This increasing trend in the use of SLNB for nodal staging in breast cancer patients reflects the growing confidence in the concept of this procedure, even in patients with T3 and T4 tumors. The accuracy in performing SLNB in cT3 tumors seems to be comparable to T1 and T2 tumors according to the available literature. Although, the evidence supporting this practice is debatable, since only small studies were published.<sup>4,5</sup> No conclusive data are available on the accuracy of SLNB in cT4N0M0 breast cancer patients.

To our knowledge, this is the largest study demonstrating patterns of care of axillary surgery in breast cancer patients. It shows that trial results of the ACOSOG-Z0011 and AMAROS were progressively implemented in axillary treatment plans of breast cancer patients nowadays. Our study is limited by its retrospective nature and by incomplete information on radiation therapy and fields. Therefore, we could not explore the potential effect of radiation on the axilla. These considerations should be taken into account when discussing axillary treatment options. Excluding neoadjuvant treated patients could result in biased underuse of cALND through the omission of high-stage breast cancer patients who underwent neoadjuvant treatment. Despite the discussion on both trials, we observed a notable early adoption and increasing trend in omitting the use of cALND in sentinel node-positive cT1-2N0M0 breast cancer patients, both treated with breast-conserving surgery and mastectomy.

## CONCLUSIONS

This study shows a trend towards less extensive axillary surgery in Dutch cT1-T4N0M0 breast cancer patients, illustrated by an overall increase of SLNB and decrease in cALND. Despite this decreasing trend particularly noticed in cT1-2N0M0 sentinel nodepositive patients after the presentation of the ACOSOG-Z0011 and AMAROS trial, hospital-related variation in axillary surgery is still present. This emphasizes the need for a uniform implementation strategy after the publication of national guidelines which includes an education program for surgeons and patients, to minimize variations in patterns of care in oncologic breast cancer surgery.

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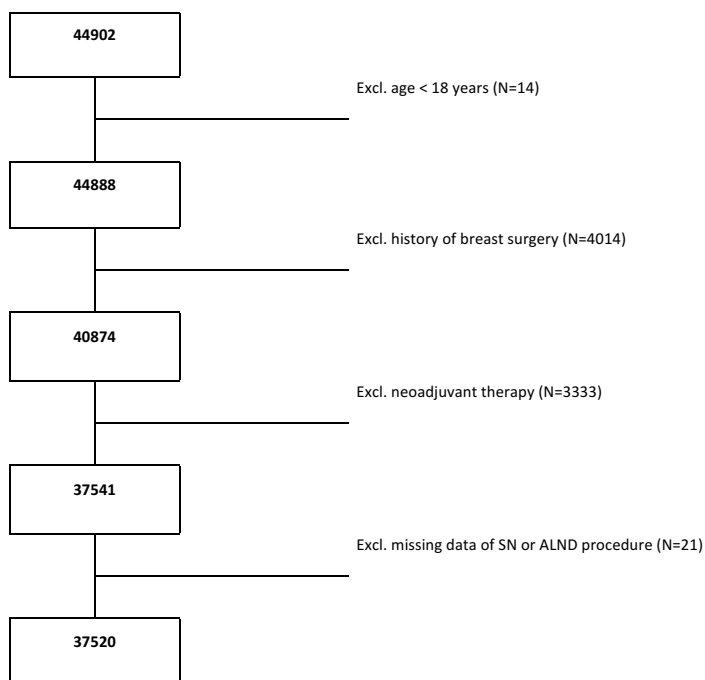
## SUPPLEMENTAL

**Table A.** Clinical- pathological and hospital characteristics of all cT1-4N0M0 patients (N=37520) and percentages of an axillary lymph node dissection (ALND), 2011 -2015.

	N	ALND		p-Value
<b>Incidence year</b>				
2011	4663	1100	24%	<0.001
2012	8097	1346	17%	
2013	8507	1029	12%	
2014	8362	653	8%	
2015	7891	444	6%	
<b>Age</b>				
<40	1135	227	20%	<0.001
40-50	4615	806	17%	
50-75	26435	2770	10%	
75+	5335	769	14%	
<b>Histologic subtype</b>				
ductal	32804	3793	12%	<0.001
lobular	4716	779	17%	
<b>Clinical tumor stage</b>				
cT1	27066	2367	9%	<0.001
cT2	9575	1866	19%	
cT3	743	284	38%	
cT4	136	55	40%	
<b>Multifocality</b>				
unifocal	32919	3564	11%	<0.001
multifocal	4601	1008	22%	
<b>Receptor status</b>				
triple -	3323	376	11%	<0.001
HR -, Her2+	1024	160	16%	
HR+, Her2+	2686	356	13%	
HR+, Her2-	28159	3320	12%	
unknown	2328	360	15%	
<b>Grade</b>				
I	9797	818	8%	<0.001
II	17528	2298	13%	
III	9289	1369	15%	
unknown	904	87	10%	
<b>Initial surgery</b>				
mastectomy	11961	2719	23%	<0.001
breast conserving treatment (BCT)	25559	1853	7%	
<b>Radiotherapy on any region</b>				
no	6183	1014	16%	<0.001

**Table A.** (continued)

	N	ALND		p-Value
yes	26566	2373	9%	
unknown	3419	846	25%	
<b>Adjuvant chemotherapy</b>				
no	20958	1412	7%	<0.001
yes	12317	2670	22%	
unknown	4242	490	12%	
<b>Type of hospital</b>				
general non-teaching	13393	1971	15%	<0.001
teaching	21208	2372	11%	
academic	2919	229	8%	
<b>Hospital surgical volume</b>				
<150	11384	1584	14%	<0.001
150-300	13745	1606	12%	
>300	9175	989	11%	
unknown	3216	393	12%	



**Figure A.** Flowchart of exclusion criteria.  
 Excl exclusion, SN sentinel node, ALND axillary lymph node dissection

