Quality assurance in breast cancer care and breast implant surgery

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CHAPTER 5

Breast conserving therapy after neoadjuvant chemotherapy; data from the Dutch Breast Cancer Audit

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ABSTRACT

Introduction: NAC has led to an increase in breast conserving surgery (BCS) worldwide. This study aims to analyse trends in the use of neoadjuvant chemotherapy (NAC) and the impact on surgical outcomes.

Methods: We reviewed all records of cT1-4N0-3M0 breast cancer patients diagnosed between July 2011 and June 2016 who have been registered in the Dutch National Breast Cancer Audit (NBCA) (N=57.177). The surgical outcomes of 'BCS after NAC' were compared with 'primary BCS', using a multivariable logistic regression model.

Results: Between 2011 and 2016, the use of NAC increased from 9% to 18% and 'BCS after NAC' (N = 4170) increased from 43% to 57%. We observed an involved invasive margin rate (IMR) of 6,7% and a re-excision rate of 6,6%. As compared to 'primary BCS', the IMR of 'BCS after NAC' is higher for cT1 (12,3% versus 8,3%; $p < 0.005$), equal for cT2 (14% versus 14%; $p=0.046$) and lower for cT3 breast cancer (28,3% versus 31%; $p<0.005$). Prognostic factors associated with IMR for both 'primary BCS' as for 'BCS after NAC' are: lobular invasive breast cancer and a hormone receptor positive receptor status (all $p<0,005$).

Conclusion: The use of NAC and the incidence of 'BCS after NAC' increased exponentially in time for all stages of invasive breast cancer in the Netherlands. This nationwide data confirms that 'BCS after NAC' compared to 'primary BCS' leads to equal surgical outcomes for cT2 and improved surgical outcomes for cT3 breast cancer. These promising results encourage current developments towards de-escalation of surgical treatment.

INTRODUCTION

Neoadjuvant chemotherapy in breast cancer patients has resulted in an increased rate of breast conserving treatment (BCT) consisting of breast conserving surgery (BCS) and radiation treatment[1-3]. Due to down-staging of the tumour by NAC, patients who were initially planned for mastectomy could receive BCS. The advantages of BCS compared to mastectomy obviously include less morbidity and thereby improved aspects of quality of life[3-5]. Another benefit of NAC includes the opportunity to deescalate surgical treatment of the axilla[6-8]. BCS after NAC introduces challenges as identification of original tumour location and monitoring tumour response using imaging[9,10]. The efficacy of NAC to downsize or achieve a pathologic complete response (pCR) has improved due to more efficient targeted drug regimens, and pCR rates of up to 60-80% in the triple negative and HR-/ HER2. subtypes are now being reached[11,12]. These promising results have led to challenging new trials investigating the potential of non-operative therapy for invasive breast cancer by utilizing accurate image-guided percutaneous biopsy to document pathologic complete response[13-15].

While improved breast imaging and the promising concept of non-operative therapy in patients that reach pCR after NAC are currently being investigated, surgical management with the primary goal to remove the (residual) tumour with clear margins is still the standard of care. In the present study, we analyse trends in the surgical performance after NAC for breast cancer in the Netherlands between 2012 and 2016 (1), we describe the surgical outcomes including margins and re-excision rates for BCS after NAC compared to primary BCS (2) and identify prognostic factors associated with involved margins for both groups (3).

METHODS

The NBCA

The NABON Breast Cancer Audit (NBCA) is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of patients who are surgically treated for newly diagnosed breast cancer in the Netherlands. All 89 hospitals in the Netherlands participating in breast cancer care participate in this nationwide registry. Data completeness of the NBCA is estimated to be at least 95%. Available data from the NBCA dataset include demographic variables (year of incidence, age), tumour variables (histologic subtype, clinical tumour stage, clinical nodal stage and hormone receptor status) and treatment variables (use of systemic therapy, radiotherapy and type of surgery). Furthermore, the volume and type of hospital is being registered. Hospital volume was based on the surgical volume, which was defined as the mean annual number of breast cancer surgeries during the period 2012-2016. The cut-off points of <150 and 300<, were based on those reported in a publication of the European Society of Breast Cancer Specialist (EUSOMA)[16]. Hospital type was described as academic, teaching and general. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents.

Data selection

Data records of patients aged 18-98 years diagnosed with cT1-4N0-3M0 invasive breast cancer between July 2011 and June 2016 were abstracted from the NBCA. We excluded patients with a prior cancer diagnosis or unknown timing of chemotherapy. Neoadjuvant chemotherapy (NAC)was defined as chemotherapy given within four weeks prior to surgery. In accordance with international guidelines, the Dutch national breast cancer guidelines indicate NAC for patients with locally advanced disease (stage III) and recommended it in patients with stage II disease with an indication for systemic treatment[17,18]. Trends in the use of NAC and the surgical performance after NAC during the years were analysed.

Surgical performance

Type of surgery (BCS or mastectomy) and the pathology report of the surgical specimen was derived from the NBCA database. Resection margins of the surgical specimen were defined according to the Dutch guidelines and in accordance with the definition

of the quality indicator defined by the NBCA audit[19]. In the Dutch guidelines, the definition for focally involved margins for invasive breast cancer is described as residual tumour in the resection surface over a maximum length of 4 mm. More than focally involved margins is defined as residual tumour in the resection surface over more than 4 mm. According to the Dutch guidelines, focally involved margins do not mandate re-excision. In case of more than focally involved (positive) margins, a re-excision is indicated unless the positive margin is the dorsal margin and the fascia has been resected. In addition to radiation after BCS, a radiation therapy boost may be applied when one or more of the following indications is present: age <50 years, an estimated local recurrences risk 1% per year, grade 3, positive tumour margins and lymphvascular space invasion[20,21].

Statistical analysis

Statistical analysis was performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA). Descriptive analyses were used to report on the trends in the use of NAC and in the surgical outcomes after NAC. Bivariate comparisons of surgical outcomes of BCS with and without NAC were performed with chi-square tests. Secondly, a multivariable logistic regression model was used to determine which factors were independent associated for tumour involved margins in BCS with and without NAC. Statistical tests were 2-sided and statistical significance was defined as a p value <0.05.

RESULTS

Overall, 62.982 patients were diagnosed with cT1-4N0-3M0 invasive breast cancer in the Netherlands between July 2011 and June 2016, and registered in the NBCA registry. Patients with a prior cancer diagnosis (N=5661) or unknown timing of chemotherapy (N=144) were excluded for further analyses, resulting in data of 57.177 patients available for our study. Median age was 62 years (range 19-98) and most of the patients were diagnosed with a clinical tumour stage of cT1 (N=34.678; 60,7%) or cT2 (N=18.482; 32,3%), without nodal involvement (N=47.512; 83,1%).

Primary surgery without NAC was performed in 85.8% of all patients (N=49.712); of which 65% were treated with BCS (N=32.305) and 35% with a mastectomy (N=17.407).

Table 1. Clinical-pathological and hospital characteristics of patients with invasive cT1-4M0 breast cancer (N=8195) who have received NAC followed by surgery (2012-2016).

	NAC + BCS		NAC + Mastectomy		
	(N=4170)		(N=4025)		
Year of incidence					*<0,005*
2012 (07-2011 – 06-2012)	424	*43%*	553	57%	
2013 (07-2012 – 06-2013)	626	*47%*	716	53%	
2014 (07-2013 – 06-2014)	836	*50%*	838	50%	
2015 (07-2014 – 06-2015)	1086	*52%*	1008	48%	
2016 (07-2015 – 06-2016)	1198	*57%*	910	43%	
Age					*<0,005*
<40	395	*39%*	626	*61%*	
40-50	1307	*49%*	1341	*51%*	
50-60	1462	*55%*	1173	*45%*	
60-70	872	*55%*	704	*45%*	
70-100	132	*42%*	181	*58%*	
Histologic subtype					*<0,005*
Ductal	3633	*53%*	3287	48%	
Lobular	331	*41%*	482	59%	
DCIS component					*0,009*
No	2684	*52%*	2463	*48%*	
Yes	1486	*49%*	1562	*51%*	
Clinical tumor stage					*<0,005*
cT1	706	*59%*	488	*41%*	
cT2	2948	*63%*	1763	*37%*	
cT3	442	*26%*	1246	*74%*	
cT4	74	*12%*	528	*88%*	
Clinical nodal stage					*<0,005*
cN0	1976	*59%*	1401	41%	
cN1	1921	*47%*	2164	53%	
cN2	80	*38%*	128	62%	
cN3	192	*37%*	329	63%	
Hormone receptor status					*0,007*
Triple -	890	*55%*	743	*45%*	
HR -, HER2+	338	*48%*	367	*52%*	
HR +, HER2+	610	*54%*	529	*46%*	
HR +, HER2-	2237	*50%*	2267	*50%*	
Type of hospital					*0,016*
General-	1356	*50%*	1331	*50%*	

Table 1. (continued)

	NAC + BCS		NAC + Mastectomy		
	(N=4170)		(N=4025)		
Teaching-	1987	*50%*	2004	*50%*	
Academic-	827	*55%*	690	*45%*	
Hospital surgical volume					*0,472*
< 150	1043	*51%*	988	*49%*	
150-300	1557	*50%*	1531	*50%*	
> 300	1562	*51%*	1493	*49%*	

In 14.2% of patients NAC was applied before surgery (N=8195); of which 50.9% were treated with BCS (N=4170) and 49.1% with a mastectomy (N=4025). Clinical-pathological and hospital characteristics of patients treated with NAC are shown in **Table 1**. Women who received NAC followed by BCS instead of a mastectomy tended to be older (>50 yrs of age), except of patients aged >70 years of age. Tumour characteristics associated with NAC followed by BCS are ductal invasive histologic subtype, no multifocality, a cT1-2 clinical tumour stage and cN0 disease (all P<0.005).

Between 2011 and 2016, there were 37 general-, 43 teaching and 9 academic hospitals in the Netherlands; divided into low-volume <150 (N=44), mid-range 150-300 (N=34) and high-volume 300< (N=11) hospitals. NAC was most often applied in academic hospitals (26% NAC; N=1517) compared to teaching- (13% NAC; N=3991) and general hospitals (12% NAC; N=2687). The type or volume of hospital is not associated with the type of surgery received after NAC [Table 1].

Trends in the surgical performance after NAC

In the last 5 years the use of NAC increased from 9% in 2012 to 18% in 2016 and applies to the clinical tumour stages cT1-3 [**Table 2**]. There is no increasing trend in the use of NAC for cT4 breast cancer (a stable percentage around 63% over the years). A greater upward trend per tumour stage in the use of NAC is seen in the sub selection of patients with nodal involvement (N=9665); the use of NAC increased from 38% (N=636) in 2012 to 61% (N=1168) in 2016; for cT1N+ from 17% (N=80) to 38% (N=169), for cT2N+ from 35% (N=289) to 63% (N= 613) and for cT3N+ from 67% (N=159) to 80% (N=283).

Table 2. Patients with invasive cT1-4M0 breast cancer who have received NAC followed by surgery, per tumour stage; 2012 compared to 2016.

	Total	NAC	%	Followed by surgery		No NAC	%	Primary surgery	
2012				BCS	Mastectomy			BCS	Mastectomy
cT1	6600	129	2%	52%	48%	6471	98%	74%	26%
cT2	3445	508	15%	60%	40%	2937	85%	44%	56%
cT3	475	216	45%	20%	80%	259	55%	5%	95%
cT4	197	124	63%	8%	92%	73	37%	8%	92%
cT1-4	10717	977	9%	43%	57%	9740	91%	63%	37%
2016									
cT1	7161	335	5%	65%	35%	6828	95%	79%	21%
cT2	3768	1271	33%	66%	34%	2526	67%	48%	52%
cT3	666	432	62%	35%	65%	256	38%	9%	91%
cT4	198	153	62%	19%	81%	75	38%	17%	83%
cT1-4	11793	153	18%	57%	43%	9685	82%	68%	32%

As presented in Table 1, 'BCS after NAC' increased from 43% in 2012 to 57% in 2016, which is a relative increase of 33%. For 'Primary BCS', an increased percentage of 63% in 2012 to 69% in 2016 is observed, which is a relative increase of only 9,5%. As depicted in **Fig. 1A**, an upward trend of 'BCS after NAC' for cT1N0 breast cancer is described from 43% (N=20) to 61% (N=99), for cT2N0 from 65% (N=139) to 70% (N=437) and for cT3N0 from 30% (N=14) to 43% (N=54). Shown in **Fig. 1B**, an equal upward trend of 'BCS after NAC' is seen in the sub selection of patients with nodal involvement; for cT1N+ from 58% (N=46) to 69% (N=116), for cT2N+ from 56% (N=161) to 62% (N=377) and for cT3N+ from 18% (N=29) to 31% (N=87). The group of cT4 breast cancer patients treated is too small for reliable analyses (N<110 of patients treated with NAC per year).

For 'Primary BCS', increased percentages of more BCS per tumour stage is observed. However, this increase is to a lesser extent; from 76% to 80% for cT1N0, from 49% to 51% for cT2N0 and from 6% to 11% for cT3N0. For patients with nodal involvement: from 51% to 58% for cT1N+, from 24% to 26% for cT2N+ and from 4% to 6% for cT3N+.

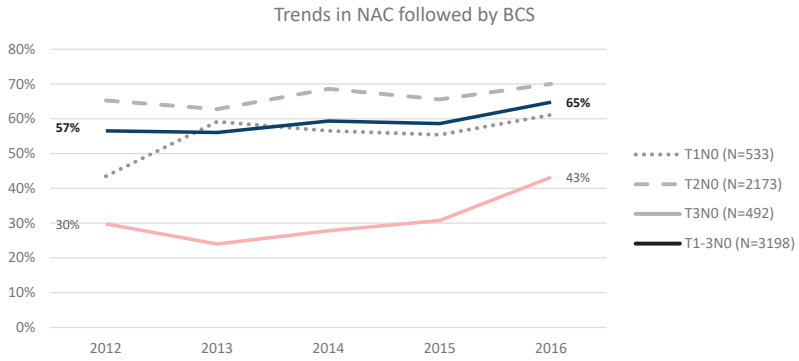

Figure 1a. Trends in NAC followed by BCS per tumour stage in patients with cN0 disease; 2012-2016.
*N= patients treated with NAC.

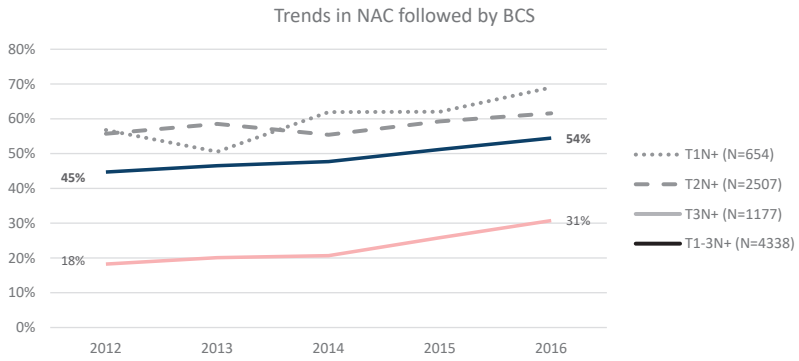

Figure 1b. Trends in NAC followed by BCS per tumour stage in patients with nodal involvement; 2012-2016.
*N= patients treated with NAC.

Surgical outcomes of BCS after NAC

Table 3 shows the surgical outcomes of 'BCS after NAC' in terms of focally or more than focally involved invasive margins and re-excision rates. Of all patients treated with BCS after NAC between 2011 and 2016 (N=4170), 8,5% (N=355) had focally involved invasive margins and 6,7% (N=281) had more than focally involved invasive margins. The re-excision rate was 6,6%; consisting of almost all patients with more than focally involved margins. For primary BCS (N=32.305), these percentages are 6,3% and 3,1% respectively, resulting in a 5,3% overall re-excision rate.

Table 3. Surgical outcomes of patients with invasive cT1-4M0 breast cancer who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).
* This is excl. patients with invasive cT1-4M0 breast cancer without DCIS involvement

	NAC + BCS (N=4170)		Primary BCS (N=32.305)		
Involved margins (Invasive or DCIS)					*<0,005*
> focally	286	6,9%	1075	3,3%	
Focally	439	10,5%	3124	9,7%	
No	3391	81,3%	27994	86,7%	
Involved invasive margins					*<0,005*
> focally invasive	281	6,7%	1001	3,1%	
Focally invasive	355	8,5%	2021	6,3%	
No	3480	83,5%	29171	90,3%	
Involved DCIS margins*					*0,107*
> focally DCIS	32	2,3%	510	3,3%	
Focally DCIS	126	9,1%	1423	9,3%	
No	1229	88,6%	13342	87,3%	
Re-excision					*<0,005*
No	3823	91,7%	29309	90,7%	
Yes	275	6,6%	1699	5,3%	
missing	72	1,7%	1297	4,0%	
Type of re-excision					*0,661*
BCS	146	53,1%	933	54,9%	
Mastectomy	129	46,9%	764	45,0%	

On multivariable analysis, prognostic factors associated with involved invasive margins for both patients treated with primary BCS as for BCS after NAC are: lobular invasive breast cancer, an increasing clinical tumour stage and a hormone receptor positive receptor status (all p<0,005; **Table 4**). The type of hospital, the year of incidence, a DCIS component and nodal involvement are only associated with involved invasive margins for primary BCS (all p<0,005). From a sub-analysis on re-excision rates, lobular invasive breast cancer was the only significant factor associated with a mastectomy if a re-excision was performed because of involved margins in BCS after NAC.

As shown in Fig. 2, there is a significant difference in involved invasive margins (in terms of focally or more than focally) in patients treated with BCS after NAC compared to patients treated with primary BCS per tumour stage. While the percentage of involved

Table 4. Multivariable logistic regression for the odds of involved invasive margins in patients with invasive cT1-4M0 breast cancer who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

	NAC + BCS (N=4116)				Primary BCS (N=32.193)			
		95% CI				95% CI		
	OR	Lower	Upper		OR	Lower	Upper	
Year of incidence				*0,318*				*<0,005*
2012	ref.				ref.			
2013	1,158	0,784	1,712		0,823	0,721	0,939	
2014	0,881	0,602	1,291		0,79	0,694	0,9	
2015	1,186	0,828	1,698		0,831	0,73	0,947	
2016	1,113	0,78	1,587		0,793	0,696	0,904	
Age				*0,561*				*0,038*
<40	0,912	0,62	1,343		0,977	0,703	1,359	
40-50	1,02	0,805	1,292		1,126	0,973	1,302	
50-60	ref.				ref.			
60-70	1,107	0,856	1,431		0,919	0,825	1,023	
70-100	0,649	0,335	1,258		1,05	0,939	1,174	
Histologic subtype				*<0,005*				*<0,005*
Ductal	ref.				ref.			
Lobular	4,684	3,559	6,165		2,912	2,602	3,259	
DCIS component				*0,024*				*<0,005*
No	ref.				ref.			
Yes	1,273	1,032	1,57		1,182	1,081	1,292	
Clinical tumor stage				*<0,005*				*<0,005*
cT1	ref.				ref.			
cT2	1,275	0,966	1,683		1,676	1,523	1,844	
cT3	2,622	1,837	3,744		3,202	1,853	5,532	
cT4	3,333	1,805	6,157		2,904	1,365	6,178	
Clinical nodal stage				*0,017*				*<0,005*
cN0	ref.				ref.			
cN1	1,291	1,054	1,581		1,664	1,419	1,952	
cN2	2,013	1,06	3,822		2,639	1,187	5,867	
cN3	1,49	0,928	2,393		4,776	1,736	13,138	
Hormone receptor status				*<0,005*				*<0,005*
Triple -	1,311	0,627	2,742		0,523	0,433	0,633	
HR -, HER2+	ref.	0,064	0,233		ref.	0,064	0,233	
HR +, HER2+	2,908	1,444	5,86		0,709	0,523	0,962	
HR +, HER2-	8,184	4,29	15,612		0,844	0,714	0,998	
Type of hospital				*0,035*				*<0,005*
General-	1,118	0,88	1,421		1,148	1,044	1,263	

Table 4. (continued)

	NAC + BCS (N=4116)				Primary BCS (N=32.193)			
		95% CI				95% CI		
	OR	**Lower**	**Upper**		**OR**	**Lower**	**Upper**	
Teaching-	ref.				ref.			
Academic-	1,405	1,086	1,817		1,254	1,085	1,449	
Hospital surgical volume				*0,956*				*0,031*
< 150	ref.				ref.			
150-300	0,986	0,752	1,294		1,029	0,921	1,151	
> 300	1,021	0,787	1,325		0,907	0,812	1,012	

invasive margins (IMR) for cT1 patients treated with BCS after NAC is higher than after primary BCS (12,3% compared to 8,3%; p<0,005) and comparable for cT2 patients (14,0% compared to 13,7%; p=0,046), the percentage of IMR is significant lower for cT3 patients treated with BCS after NAC compared to primary BCS (28,3% versus 31,0%; p<0.005).

When we analysed the data for cT3 patients, lobular invasive breast cancer and a hormone receptor positive receptor status were associated with IMR, with no difference between patients receiving NAC and patients receiving no NAC.

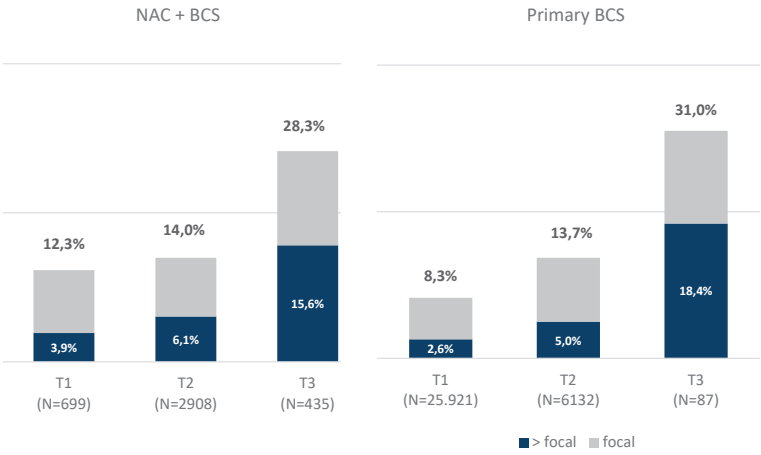

Figure 2. Percentage of patients with invasive cT1-4M0 breast cancer and involved invasive margins who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

DISCUSSION

This population-based study showed an increase in the use of NAC from 9% in 2011 to 18% in 2016 and an increase of more 'BCS after NAC' from 43% to 57% compared to 'primary BCS' from 63% to 68% in patients with primary breast cancer in the Netherlands. The increasing implementation of NAC is consistent with previous studies on the trend of NAC in breast cancer care[22-24]. Together with this international trend, it is demonstrated that NAC increases the rates of breast preservation in tumours of >2 cm[25,26]. However, this study shows an increasing trend towards more BCS after NAC not only for larger tumours but for all stages of breast cancer.

There are several explanations for this upward trend towards more 'BCS after NAC' for all stages of disease. With the increased evidence that subgroups of patients who achieve a complete pathological tumour (pCR) after NAC do have a better prognosis in terms of disease-free and overall survival, NAC is nowadays be considered as a preferred option in the treatment of triple negative and HER2. breast cancer[27-29]. Secondly, the amount of a pCR response reported has increased dramatically in the past years because of improvements of targeted therapies. Up to half of the patients in specific groups such as her2-positive patients achieve a complete remission after NAC, which has subsequently led to more BCS[30-33]. Furthermore, the development of innovative approaches to axillary staging after chemotherapy has most likely contributed to more BCS followed by NAC in patients with nodal involvement at diagnosis[6,8,34,35]. Thereby, the growing experience and confidence with NAC among clinicians due to information from nationwide clinical quality registries, the use of quality indicators providing benchmark information on surgical outcomes and the exchange of knowledge by a multidisciplinary approach and cross-border hospital collaborations may all be attributed to the upward trend towards more BCS after NAC.

The involved invasive margin rate in our study is 6,7% for 'BCS after NAC' compared to 3,1% for 'primary BCS'. The overall positive margin rate in our study is 6,9% for 'BCS after NAC' compared to 3,3% for 'primary BCS'. These rates are relatively low compared to other studies. In a systematic review performed by Volders et al. in which they aimed to determine surgical outcomes for BCS after NAC, involved margins ranged from 5% to 39.8% after NAC versus 13.1%-46% for primary BCS[36]. These percentages were

based on ten studies describing involved margins with or without NAC, but a clear comparison between these studies was not possible due to variation in terminology and variation amongst patient groups. Because of the nationwide character of our study in which all patients treated with invasive breast cancer are included, a 6,9% involved margin rate for BCS after NAC and a 3,3% involved margin rate for primary BCS is a reliable baseline for the quality of care in the Netherlands nowadays.

An important result of this nationwide data is that BCS after NAC leads to equal surgical outcomes for cT2 and improved outcomes for cT3 invasive breast cancer compared to primary BCS. Boughey et al. already described in 2006 using data from 1998 to 2005, that NAC reduces the volume of tissue excised in patients with T2 and T3 breast cancer treated with BCS, without an increase in rates of reexcision[37]. Ever since, improvements of targeted therapies to achieve a pathologic complete response (pCR) in combination with improvements in the identification of the original tumour location have led to more BCS after NAC with less involved invasive margins and a lower re-operation rates[9-12,22].

Our multivariable analyses detailed important prognostic factors associated with a higher risk of involved invasive margins for patients who will receive BCS after NAC: lobular invasive breast cancer, an increasing clinical tumour stage and a hormone receptor positive receptor status. A decreased feasibility for successful BCS has been described in the setting of lobular histology, multicentricity and diffuse calcifications noted on preoperative mammography[38]. And, it is known that HR-positive subtypes are associated with the lowest rates of pathological complete response (pCR)[30]. Another interesting assumption made by Landscaper et al. is that cancer subtypes may have an independent association with a surgical outcome, reported that triple-negative patients not receiving NAC had the lowest reoperation rate. This result correlates with our findings that a positive hormone receptor status was clearly associated with involved invasive margins for cT3 tumours, with no difference between patients receiving NAC and patients receiving no NAC. Because larger tumour size and higher grade are characteristics commonly reported on triple negative patients and because NAC is the standard of care for many of these patients[39], this will have contributed to the lower rate of involved margins for cT3 invasive breast cancer patients treated with NAC as seen in our study. Moreover, it supports the biologic heterogeneity of invasive breast cancer with its own approach and expected surgical outcomes.

Unaddressed issues are recurrence rates and cosmetic outcomes for patients treated with BCS after NAC, which we were unable to investigate in this study. A strong association of improved long-term outcomes in patients with pCR compared to patients with residual invasive tumour at the time of surgery has been consistently reported by many groups[11,30,40,41]. However, the surrogacy of pCR as an endpoint for long-term clinical outcome has not been established[42]. Future analyses of randomized trials of targeted agents in homogeneous tumour subtypes will help elucidate whether there is a significant association between pCR and long-term outcomes. Cosmetic outcomes for NAC followed by BCS have only been reported in retrospectives studies and no conclusions can be drawn yet[43,44]. Several studies do describe a lower resected volume in patients treated with neoadjuvant therapy compared to adjuvant therapy, what potentially could lead to better cosmetic outcomes and an improved quality of life. Although we did not specify resection volumes and cosmetic outcome in this study, we emphasize the fact that follow-up on this subject is necessary and of major impact in delivering quality care to patients. A poor cosmetic outcome after BCS should be avoided at any time. Work has been established to link patient reported outcome measurements (PROMS) to clinical data of patients treated with BCS after NAC and will eventually show the patients' satisfaction and long term cosmetic outcomes. This information will be of great value empowering patients to be effective advocates for their health, and that they can make informed decisions in light of it.

To our knowledge, this is one of the largest studies on a nationwide level demonstrating a trend of more BCS after NAC in relation to surgical outcomes. However, our study is limited by the retrospective nature and incomplete information on tumour response after NAC. Also, we were unable to retrospectively determine the percentage of patients eligible for BCS at the time of diagnosis.

CONCLUSION

The increasing implementation of NAC have led to an increase in 'BCS after NAC' in the Netherlands between 2011 and 2016. Moreover, this nationwide data confirms that BCS after NAC results in equal surgical outcomes for cT2 and improved surgical outcomes for cT3 invasive breast cancer compared to primary BCS. In view of the trend towards de-escalation of surgical treatment in selected patients with excellent pathologic response, these promising results confirm that clinicians are increasingly able to perform 'BCS after NAC' while maintaining good surgical outcomes.

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Table A. Clinical-pathological and hospital characteristics of cT1-4M0 breast cancer patients (N=36.475) who have received breast conserving surgery with or without chemotherapy upfront (2012-2016).

	BCS		BCS after NAC		
	(N=32.305)		(N=4170)		
Year of incidence					*<0,005*
2012	6118	19%	424	*10%*	
2013	6466	20%	626	*15%*	
2014	6720	21%	836	*20%*	
2015	6368	20%	1086	*26%*	
2016	6633	21%	1198	*29%*	
Age					*<0,005*
<40	617	*2%*	395	*9%*	
40-50	3308	*10%*	1307	*31%*	
50-60	8787	*27%*	1462	*35%*	
60-70	10852	*34%*	872	*21%*	
70-100	8735	*27%*	132	*3%*	
Histologic subtype					*<0,005*
Ductal	26920	90%	3633	*92%*	
Lobular	2979	10%	331	*8%*	
DCIS component					*<0,005*
No	16487	*51%*	2684	*64%*	
Yes	15818	*49%*	1486	*36%*	
Clinical tumor stage					*<0,005*
cT1	26003	*80%*	706	*17%*	
cT2	6156	*19%*	2948	*71%*	
cT3	92	*0%*	442	*11%*	
cT4	54	*0%*	74	*2%*	
Clinical nodal stage					*<0,005*
cN0	30678	95%	1976	*47%*	
cN1	1558	5%	1921	*46%*	
cN2	42	0%	80	*2%*	
cN3	26	0%	192	*5%*	
Hormone receptor status					*<0,005*
Triple -	2793	*9%*	890	*22%*	
HR -, HER2+	707	*2%*	338	*8%*	
HR +, HER2+	2113	*7%*	610	*15%*	
HR +, HER2-	25000	*82%*	2237	*55%*	
Type of hospital					*<0,005*
General-	12635	*39%*	1356	*33%*	
Teaching-	17019	*53%*	1987	*48%*	
Academic-	2651	*8%*	827	*20%*	
Hospital surgical volume					*<0,005*
< 150	8635	*27%*	1043	*25%*	
150-300	12202	*38%*	1557	*37%*	
> 300	11163	*35%*	1562	*38%*	

Table B. Clinical-pathological and hospital characteristics associated with tumour free margins in cT1-4M0 breast cancer patients who have received breast conserving surgery after neoadjuvant chemotherapy (N= 4116).

	No involved margins (N=3835)		Involved margins (N=281)		
Year of incidence					*0,823*
2012	395	*94%*	25	*6%*	
2013	567	*93%*	43	*7%*	
2014	777	*94%*	52	*6%*	
2015	1004	*93%*	74	*7%*	
2016	1092	*93%*	87	*7%*	
Age					*0,017*
<40	377	*96%*	14	*4%*	
40-50	1203	*93%*	86	*7%*	
50-60	1337	*93%*	108	*7%*	
60-70	791	*92%*	68	*8%*	
70-100	126	*97%*	4	*3%*	
Histologic subtype					*<0,005*
Ductal	3419	*95%*	169	*5%*	
Lobular	239	*73%*	87	*27%*	
DCIS component					*0,606*
No	2473	*93%*	177	*7%*	
Yes	1362	*93%*	104	*7%*	
Clinical tumor stage					*<0,005*
cT1	672	*96%*	27	*4%*	
cT2	2731	*94%*	177	*6%*	
cT3	367	*84%*	68	*16%*	
cT4	65	*88%*	9	*12%*	
Clinical nodal stage					*0,024*
cN0	1837	*94%*	113	*6%*	
cN1	1752	*92%*	145	*8%*	
cN2	69	*87%*	10	*13%*	
cN3	176	*93%*	13	*7%*	
Hormone receptor status					*<0,005*
Triple -	865	*98%*	16	*2%*	
HR -, HER2+	333	*99%*	3	*1%*	
HR +, HER2+	590	*98%*	15	*2%*	
HR +, HER2-	1958	*89%*	244	*11%*	
Type of hospital					*<0,005*
General-	1242	*93%*	90	*7%*	
Teaching-	1855	*94%*	113	*6%*	
Academic-	738	*90%*	78	*10%*	
Hospital surgical volume					*0,672*
< 150	950	*93%*	74	*7%*	
150-300	1438	*94%*	98	*6%*	
> 300	1440	*93%*	108	*7%*	