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Original article

Variation in use of neoadjuvant chemotherapy in patients with stage III breast cancer: Results of the Dutch national breast cancer audit

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ABSTRACT

Objectives: Neoadjuvant chemotherapy (NAC) is important in the optimal treatment of patients with locally advanced (stage III) breast cancer (BC). The objective of this study was to examine the clinical practice of NAC for stage III BC patients in all Dutch hospitals participating in BC care.
Materials and methods: All patients aged 18–70 years who received surgery for stage III BC from January 2011 to September 2015 were selected from the national multidisciplinary NABON Breast Cancer Audit. Multivariable logistic regression was used to assess independent predictors of NAC use, focussing on hospital factors.
Results: A total of 1230 out of 1556 patients with stage III BC (79%) received NAC prior to surgery. The use of NAC did not change over time. We observed a large variation of NAC use between hospitals (0–100%). Age <50 years, breast MRI, large tumour size, advanced nodal disease, negative hormone receptor status and hospital participation in neoadjuvant clinical studies were significant independent predictors of NAC use (all $P < 0.001$). NAC use in stage III BC was not influenced by hospital type and hospital surgical volume. After adjustment for all independent predictors, variation in NAC use between hospitals remained (0% to 97%).
Conclusion: NAC was used in 79% of patients with stage III BC, which represent a high quality of care in the NL. Patient, tumour, clinical management and hospital factors could not explain considerable variation in its use between hospitals. Hospital participation in neoadjuvant studies did show to improve the use of NAC in daily practice.

1. Introduction

Locally advanced or stage III breast cancer (BC) is defined as a bulky tumour of the breast and/or extensive nodal disease. The prognosis of stage III BC is worse than early stage disease showing a ten-year overall survival in only 56% of patients [1]. As multimodality treatment improves the outcome of Stage III BC, neoadjuvant chemotherapy (NAC) has become an important initial treatment strategy. NAC aims to downsize the tumour to improve the possibility of a radical resection or even to enable breast conservation surgery [2–4]. Other potential advantages of NAC include the opportunity to investigate tumour biology, to monitor response and adapt to suboptimal response. Several studies have demonstrated that NAC, when compared to adjuvant chemotherapy, leads to similar overall and disease-free survival [5–8] and may even improve survival in triple-negative and HER2 positive BC subtypes when pCR is achieved [9]. In accordance with international guidelines [10,11], the Dutch national breast cancer guideline recommends NAC for patients with stage III BC aged <70 years [12].

The NABON Breast Cancer Audit (NBCA) is a multidisciplinary nationwide registry of all diagnostic and treatment modalities of

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patients who are surgically treated for BC in the Netherlands since 2011. This audit provides the opportunity to gain insight into patterns of practice in different hospitals by creating a national benchmark. Knowledge of variation in the use of NAC for stage III BC and the reasons for this variation may help in bringing down barriers to use upfront chemotherapy and to improve outcome in these patients. The objective of the present study was therefore to examine the use of NAC in patients with stage III BC in the Netherlands and to assess which patient, tumour and hospital related factors influence clinical practice.

1.1. Patients and methods

The NBCA is a nationwide registry that captures 100% of all newly diagnosed and surgically treated breast cancer patients in the Netherlands. We selected data from the NBCA database on all patients aged 18–70 years diagnosed with stage III BC (clinical cT1-4N2, cT3N1-3, cT4N0, M0) from January 2011 to September 2015. In the given time frame, 63.315 patients with invasive breast cancer are registered in the NBCA, which means a proportion of 2,46% stage III patients aged 18–70 years. Tumour stage was defined according to the 7th edition of the International Union Against Cancer tumour node metastasis (TNM) classification [13]. We excluded patients with a prior cancer diagnosis or unknown sequence of chemotherapy and surgery. Patients aged 70 years and older were also excluded, because the use of NAC is not considered standard treatment in the elderly [12]. Patients who received both neoadjuvant- and adjuvant chemotherapy were not excluded from this study.

1.2. Construction of variables

The primary outcome of the study was the use of NAC, defined as chemotherapy given within four weeks prior to surgery, for stage III BC in the different hospitals in the Netherlands. The hospital of treatment was defined as the hospital where the first therapeutic surgical intervention was conducted. Available data from the NBCA dataset regarding the use of NAC includes factors of the patient (year of incidence, age), the tumour (histologic subtype, clinical tumour stage, clinical nodal stage and hormone receptor status), clinical management and various hospital related factors. The surgical volume of a hospital was defined as the mean annual number of breast cancer surgeries during the period 2011–2015; divided into low-volume (<150), mid-range (150–300) and high-volume (>300) categories. Type of hospital was described as academic, teaching and general hospitals. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents. Between 2011 and 2015, there were three clinical trials regarding neoadjuvant therapy in which participation was possible: NEO-ZOTAC, TRAIN-2 and TEAM IIa [14]. Information on tumour grade was excluded, because of missing data.

1.2.1. Statistical analysis

The Pearson's Chi-square test was applied to test associations of the use of NAC and the covariates in the entire study population. A multivariable logistic regression model was used to determine whether patient, tumour, clinical management and hospital factors were independent predictors associated with the odds of receiving NAC in comparison with patients who were treated only surgically with our without adjuvant therapy. The multivariable logistic regression model was used to quantify the percentage of NAC in daily practice and to reveal the variation among the 89 Dutch hospitals adjusted for the predictors [15]. Statistical significance was defined as a two-sided p value < 0.05. All analyses were performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA).

2. Results

We identified 1556 surgically treated patients with stage III BC aged 18–70 between 2011 and 2015 in the Netherlands. A total of 1230 patients (79%) with stage III BC received NAC. The rate of NAC did not significantly change over time.

Table 1a shows the patient, tumour and clinical management factors according to the use of NAC. The median age of patients with stage III disease was 51 years (range 19–70 years). The median age of treated patients in general hospitals was 53.0 years compared to 51.4 years in teaching hospitals and 49.1 years in academic hospitals ($p < 0.001$). In case a breast MRI was performed or when the patient had been discussed in a preoperative MDT, a significantly higher rate of NAC use was observed (84% versus 57%, $p < 0.001$; 79% versus 68%, $p = 0.038$). Of notice, a total of 227 patients (87%) in which a breast conservation surgery was performed, received NAC compared to 1003 patients (77%) in which a mastectomy was performed ($p < 0.001$).

Hospital factors regarding NAC use are depicted in Table 1b. The median number of surgically treated patients with stage III BC per hospital was 15 (range 2–99). Significant more patients in academic hospitals received NAC (88%) as compared to patients in teaching hospitals (79%) or in general hospitals (75%) ($p < 0.001$). The use of NAC in hospitals participating in neoadjuvant clinical studies was significantly higher (83%) than in hospital not doing so (73%) ($p < 0.001$).

To determine the independent predictors of NAC use, a multivariable logistic regression analysis was conducted (Table 2). Age <50 years, breast MRI, large tumour size, advanced nodal disease,

Table 1A
Factors of patient, tumour and clinical management regarding the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (n = 1556).

		Stage III (n)	NAC		*P-value*
			(n)	%	
Year of incidence	*2011*	204	158	77%	0,283
	2012	306	244	80%	
	2013	357	271	76%	
	2014	377	299	79%	
	2015	312	258	83%	
Age	*<40*	162	137	85%	0,000
	40–50	547	462	84%	
	50–60	470	362	77%	
	60–70	377	269	71%	
Histologic subtype	*ductal*	1293	1044	81%	0,000
	lobular	263	186	71%	
Clinical tumor stage	*cT1*	20	7	35%	0,000
	cT2	48	31	65%	
	cT3	995	768	77%	
	cT4	493	424	86%	
Clinical nodal status	*cNx/N0*	116	85	73%	0,000
	cN1	1250	992	79%	
	cN2	95	64	67%	
	cN3	95	89	94%	
Hormone receptorstatus	*triple -*	235	200	85%	0,000
	HR− HER2+	171	152	89%	
	HR + HER2+	214	165	77%	
	HR + HER2-	936	713	76%	
Preoperative MDT	*No*	60	41	68%	0,038
	Yes	1496	1189	79%	
Breast MRI	*No*	284	162	57%	0,000
	Yes	1272	1068	84%	
Type of surgery	*BCS*	260	227	87%	0,000
	Mastectomy	1296	1003	77%	

MDT = multidisciplinary team.
BCS = breast conservation surgery.

Table 1B
Factors on hospital level regarding the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (n = 1556).

		Hospitals (n)	Stage III (n)	NAC		*P-value*
				(n)	%	
Type of hospital	*General*	37	390	291	75%	0,001
	Teaching	43	957	755	79%	
	Academic	9	209	184	88%	
Hospital surgical volume	*<150*	44	455	348	76%	0,148
	150–300	34	692	547	79%	
	>300	11	409	335	82%	
PET-CT available	*No*	56	700	538	77%	0,055
	Yes	33	856	692	81%	
Hospital study participation	*No*	48	604	440	73%	0,000
	Yes	41	952	790	83%	

Table 2
Multivariable logistic regression of the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (n = 1556).

		OR	95% C.I.		Sig.
			Lower	Upper	
Age	*<40*	ref.			0,000
	40–50	1,12	0,679	1849	
	50–60	0,677	0,41	1118	
	60–70	0,458	0275	0,762	
Histologic subtype	*ductal*	ref.			0,021
	lobular	0,674	0482	0,942	
Clinical tumor stage	*cT1*	0,091	0025	0,337	0000
	cT2	0,228	0078	0,664	
	cT3	ref.			
	cT4	2,46	1653	3662	
Clinical nodal status	*cN0*	0,398	0227	0,698	0000
	cN1	ref.	1195	4,19	
	cN2	1671	0,671	4158	
	cN3	5,13	1734	15,178	
Hormone receptorstatus	*triple -*	ref.			0,004
	HR -, HER2+	1502	0,8	2821	
	HR+, HER2-	0,675	0445	1025	
	HR+, HER2+	0,567	0342	0,94	
Preoperative MDT	*No*	ref.			0,495
	Yes	1927	1043	3559	
Type of hospital	*General-*	ref.			0,058
	Teaching-	1,04	0,708	1527	
	Academic-	1824	1042	3194	
Hospital surgical volume	*<150*	ref.			0,999
	150–300	1,01	0,674	1515	
	>300	1013	0,596	1721	
PET-CT available	*No*	ref.			0,517
	Yes	0,881	0,6	1293	
Study participation	*No*	ref.			0,000
	Yes	1832	1366	2457	

MDT = multidisciplinary team.

negative HR status and hospital participation in neoadjuvant clinical studies remained significant (all $p < 0.001$). Hospital type and hospital surgical volume were not independently associated with the use of NAC.

The variation between hospitals in the Netherlands in the percentage of patients with stage III BC receiving NAC during 2011–2015 is depicted in Fig. 1. The median is 48,3% and a large variation in its use was observed (0–100%). After adjusting for independent predictors according to our multivariable model, the rate of NAC per hospital over the period 2011–2015 were modified from minus 8,9% to plus 22%. One hospital with only two patients with stage III BC, neither of whom received NAC, accounted for the number of 0%. According to the 95% confidence interval (CI), three hospitals were negative outliers (significant lower rates than average).

3. Discussion

In this nationwide population-based study from 2011 to 2015 in the Netherlands, we observed that 1230 out of 1556 of women aged 18–70 years with stage III BC (79%) were treated with NAC prior to surgery. Various recent studies reveal an international trend on the increasing implementation for NAC in patients with BC. The high rate of NAC in The Netherlands did not significantly change over time. Our data compare favourably with those reported from cancer registries in other countries. For stage III BC, Mougalian et al. used data from the National Cancer Data Base of America and reported a mean use of NAC in 41.6% of 71,433 patients during 2003–2011, while they observed an increase to 59.3% in 2011 [16]. Recent studies from the United States on patients with all stages of BC showed a major increase in the use of NAC during the last decade, with a proportion of 10–20% of BC patients treated with NAC [2,17]. A similar increase was seen in a population study of 10 Dutch hospitals in which the use of NAC for BC increased from 2.5% in 2003 to 13% in 2012 [18]. During this time span, the use of NAC for cT3 BC increased from 30.6% to 70.9%. A French survey reported the use of NAC in 16.3% of patients with BC in 2010, but data on stage of disease were incomplete [19].

In line with other studies [16,17,20]; we found the following predictive patient and tumour factors for the use of NAC in patients with BC: young age, large tumour size, advanced nodal disease and a negative hormone receptor status. Going beyond the scope of prior studies, we also assessed factors at hospital level and observed that the surgical volume and type of hospital was not independently associated with the use of NAC in the Netherlands. This has been previously observed by a study in the Netherlands on variation in adjuvant chemotherapy [19] and is presumably due to the consultancy of experts in oncology meetings between academic, teaching and general hospitals. Of notice, we observed a significantly higher use of NAC in hospitals participating in neoadjuvant clinical studies (83% versus 73%). Study participation is an instrument of cultural change. It creates more awareness among physicians and it narrows the gap between the best available evidence and current practice. Moreover, it also requires an adjustment of the current pattern of care and may facilitate the implementation of new therapeutic concepts.

Variation in the use of NAC between hospitals is in line with international literature [16,20], except that these studies did not adjust for hospital related factors and did not exclude patients >70 years of age with possible contraindications [2,16,20]. After adjustment according to our multivariable model, we observed a constant proportion of 77% and considerable variation between 89 hospitals remained.

The preferences of both patient and clinician and the level of shared decision-making may be important factors in the decision to

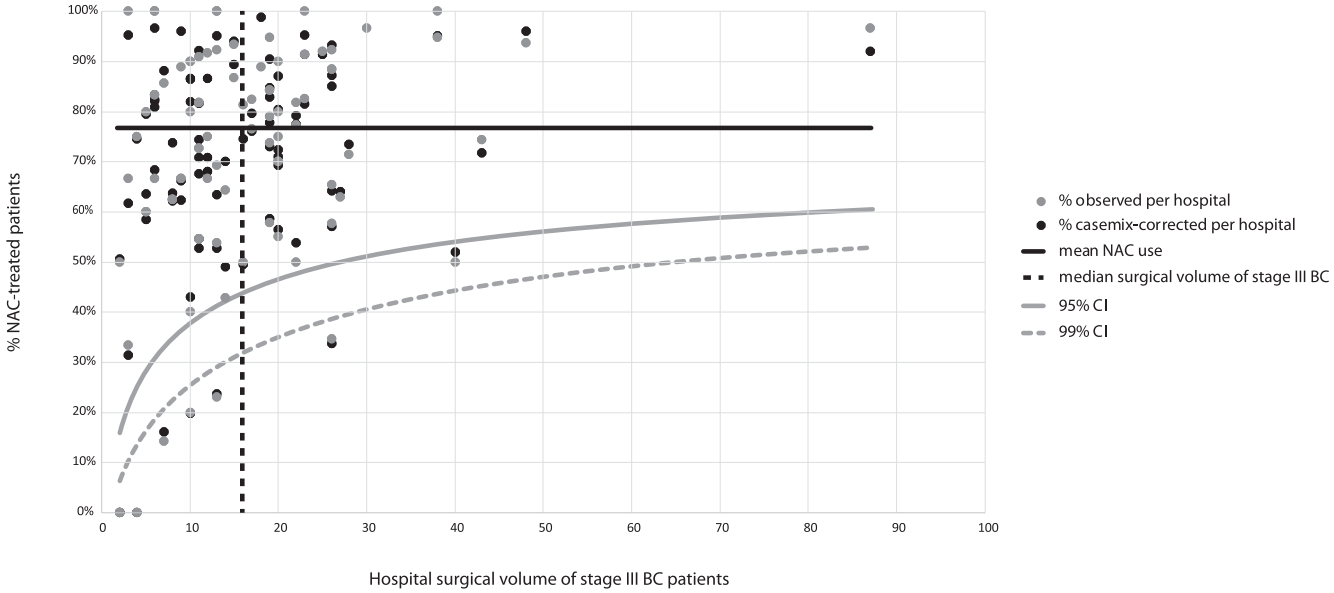

Fig. 1. Variation between hospitals in the use of neoadjuvant chemotherapy (NAC) in patients with stage III breast cancer (n = 1556) in the Netherlands in 2011–2015.

use or to refrain from NAC. It may be possible that many women prefer to undergo surgery first because of an incorrect idea of delayed surgery or because of a preference for mastectomy (in combination with a reconstruction). Patients may not realise that neoadjuvant treatment is a viable choice. It has been demonstrated that clinicians' treatment recommendations and preferences exert one of the most powerful influences over patients' decisions [21,22].

Valid options to refrain from NAC may be a contraindication for chemotherapy such as poor performance status or severe comorbidity, or the choice for neoadjuvant hormonal therapy in low-grade highly endocrine-sensitive BC. Other factors such as under capacity or financial incentives could negatively affect the implementation of NAC. In-hospital factors such as the level of training of physicians, the composition of MDT meetings and an integrated oncological care pathway for BC may also account for discrepancies between hospitals [23,24]. Confirmed by our univariate analyses, preoperative MDT is significantly associated with NAC use.

The main strength of the present study is the multivariable adjustment for hospital case mix, including factors regarding patient, tumour, clinical management and hospital level. Additionally, because our data covers all surgically treated BC patients in the Netherlands we can more reliable understand clinical practice. Unfortunately, we had no data available regarding the reason why NAC was omitted, such as patient performance status, comorbidities, genetic risk factors and other treatment decision-making factors.

In conclusion, our study shows that NAC is being used in 79% of patients with stage III BC, which stands for high quality of care compared to the international percentages of NAC use reported. Still, 21% of patients did not receive NAC prior to surgery. After adjustment for all independent predictors of NAC, a considerable variation remained between hospitals. Hospital participation in neoadjuvant clinical studies may be a major factor contributing to a more rapid implementation of NAC in daily practice.

We have deployed further research to examine the role of patient- and specialist preferences in shared-decision making on NAC in patients with BC.

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Ethical consent and the standards of animal care

Ethical approval was not required.

Disclosure

The authors have declared no conflicts of interest.

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