



## 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.

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## 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 neo-adjuvant- 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 neo-adjuvant 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.

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