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Correlation Between Pathologic Complete Response in the Breast and Absence of Axillary Lymph Node Metastases After Neoadjuvant Systemic Therapy

Sanaz Samiei, MD,†‡ Thiemo J. A. van Nijnatten, MD, PhD,†‡ Linda de Munck, MSc,§ Kristien B. M. I. Keymeulen, MD,* Janine M. Simons, MD,¶ Loes F. S. Kooreman, MD,‡|| Sabine Siesling, MD, PhD,§** Marc B. I. Lobbes, MD, PhD,†‡ and Marjolein L. Smidt, MD, PhD*‡*

Objective: The aim was to investigate whether pathologic complete response (pCR) in the breast is correlated with absence of axillary lymph node metastases at final pathology (ypN0) in patients treated with neoadjuvant systemic therapy (NST) for different breast cancer subtypes.

Background: Pathologic complete response rates have improved on account of more effective systemic treatment regimens. Promising results in feasibility trials with percutaneous image-guided tissue sampling for the identification of breast pCR after NST raise the question whether breast surgery is a redundant procedure. Thereby, the need for axillary surgery should be reconsidered as well.

Methods: Patients diagnosed with cT1-3N0-1 breast cancer and treated with NST, followed by surgery between 2010 and 2016, were selected from the Netherlands Cancer Registry. Patients were compared according to the pathologic response of the primary tumor with associated pathologic axillary outcome. Multivariable analysis was performed to determine clinicopathological variables correlated with ypN0.

Results: A total of 4084 patients were included for analyses, of whom 986 (24.1%) achieved breast pCR. In clinically node negative patients (cN0), 97.7% (432/442) with breast pCR had ypN0 compared with 71.6% (882/1232) without breast pCR ($P < 0.001$). In clinically node positive patients (cN1), 45.0% (245/544) with breast pCR had ypN0 compared with 9.4% (176/1866) without breast pCR ($P < 0.001$). The odds of ypN0 was decreased in case of clinical T3 stage (OR 0.59, 95% CI 0.40–0.87), cN1 (OR 0.03, 95% CI 0.02–0.04) and ER+HER2- subtype (OR 0.30, 95% CI 0.20–0.44), and increased in case of breast pCR (OR 4.53, 95% CI 3.27–6.28).

Conclusions: Breast pCR achieved after NST is strongly correlated with ypN0 in cN0 patients, especially in ER+HER2+, ER-HER2+, and triple negative subtypes. These results provide data to proceed with future clinical trials to investigate if axillary surgery can be safely omitted in these selected patients when image-guided tissue sampling identifies a breast pCR.

Keywords: axillary surgery, breast cancer, neoadjuvant systemic therapy, pathologic complete response

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Over recent years, systemic therapy in the treatment of breast cancer has increasingly been administered in the neoadjuvant setting. The indication of neoadjuvant systemic therapy (NST) has evolved from inoperable and locally advanced breast cancer to early stage breast cancer patients with unfavorable tumor profiles.[1] NST allows treatment response to be clinically assessed and can lead to the treatment plan being modified in cases of poor response.[2] It also offers the advantages of downsizing the primary tumor, decreasing the incidence of positive lymph nodes, or even results in complete eradication of cancer, so-called pathologic complete response (pCR) of the breast tumor (hereinafter referred to as breast pCR) and/or the axillary lymph nodes (ypN0).[3,4] As well as these NST advantages, previous studies have reported that pCR in the breast and axilla is associated with superior survival outcomes.[5–7]

Over the past decade, improvements in the efficacy of chemotherapy and targeted therapies have increased pCR rates. A meta-analysis, performed by Cortazar et al, found that breast pCR was achieved in 22.0% of patients after NST with higher pCR rates in HER2+ and triple negative breast cancer subtypes.[8] Concerning axillary lymph nodes, NST can eradicate metastases in clinically node positive patients with a reported axillary pCR rate of 37.0%.[9] The axillary pCR rate for HER2+ patients increases with the use of HER2-targeted therapy to between 43% and 74%.[6,7,10,11] Patients who achieved axillary pCR were more likely to have breast pCR.[6,11,12]

At present, surgery is the gold standard for determining whether pCR after NST is achieved in breast cancer patients. However, research is increasingly being conducted with the focus on reducing or eliminating breast and/or axillary surgery. Promising results in feasibility trials with percutaneous image-guided biopsy for identifying breast pCR after NST raise the question of whether breast surgery is becoming a redundant procedure in selected group of patients with breast pCR.[13–15] Since correlation between breast pCR and axillary pCR has been suggested, the need for axillary surgery should be reconsidered in the case of breast pCR.[13,14] Evidence for this correlation is limited, however, and not yet studied for different breast cancer subtypes.

Therefore, we aimed to investigate whether breast pCR is correlated with ypN0 in patients treated with NST for different breast cancer subtypes.

From the *Department of Surgery, Maastricht University Medical Center+, Maastricht, The Netherlands; †Department of Radiology and Nuclear Medicine, Maastricht University Medical Center+, Maastricht, The Netherlands; ‡GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, The Netherlands; §Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands; ¶Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands; ||Department of Pathology, Maastricht University Medical Center+, Maastricht, The Netherlands; and **Department of Health Technology and Services Research, Technical Medical Center, University of Twente, Enschede, The Netherlands.

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Reprints: Sanaz Samiei, MD, Department of Surgery, Maastricht University Medical Center+, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: sanaz.samiei@mumc.nl.

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METHODS

In this study, 4084 consecutive patients were included who had all been diagnosed with primary invasive breast cancer in the Netherlands and treated with NST (chemotherapy with or without trastuzumab) between January 2010 and September 2016. To be considered for final analyses, patients needed to be staged as cT1-3N0-1 breast cancer prior to NST administration. After the completion of NST, all patients underwent standard breast and axillary surgery. Patients were excluded if the sentinel lymph node biopsy (SLNB) had been performed before NST administration. Other exclusion criteria were unknown pathological tumor stage, distant metastases at primary breast cancer diagnosis or within 91 days after surgery, unknown breast cancer subtype, neoadjuvant endocrine therapy, or unknown number of lymph node metastases at final pathology (Fig. 1).

The axillary nodal status was determined before NST administration by axillary ultrasound. If axillary ultrasound showed no suspicious lymph nodes, patients were defined as clinically node negative (cN0). If suspicious lymph nodes were confirmed with additional fine-needle aspiration cytology (FNAC) or core needle biopsy, patients were defined as clinically node positive (cN1).

If the patient was defined as cN0 before NST administration, the patient underwent SLNB after NST. If the patient was classified as cN1 before NST administration, the patient underwent axillary lymph node dissection (ALND) after NST.

The 2008 and 2012 Dutch national guidelines were applied during the 2010 to 2016 study period.[16,17] These guidelines recommended systemic therapy consisting of the following chemotherapeutic regimens: 6 cycles of TAC (Taxotere, Adriamycin, Cyclofosfamide), or 3 cycles of FEC (Fluorouracil (5FU), Epirubicin, Cyclophosphamide), or 4 cycles of AC (Adriamycine, Cyclophosphamide) followed by 12 cycles of paclitaxel or 4 cycles of docetaxel. In the case of HER2+ breast cancer, trastuzumab was recommended as the targeted therapy in addition to chemotherapy and continued until 1 year after the start. In the time frame 2010 to 2016 no HER2-targeted therapy was advised in addition to trastuzumab.

HER2 status was evaluated with immunohistochemistry (IHC). The IHC score of 0 or 1+ was considered negative (<10% of the tumor cells are stained, or >10% of the tumor cells are stained, with no circumferential staining and weak color intensity). In case of a 2+ IHC score (>10% circumferential membrane staining with moderate intensity), fluorescence in situ hybridization (FISH) was mandatory in addition to IHC and the result of FISH overruled. The IHC score of 3+ was considered positive (>30% of cells with strong intensity circumferential membrane staining).

Data were obtained from the Netherlands Cancer Registry (NCR) after this study had been approved by the Privacy Review Board of NCR, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). On site trained registrars from the NCR extract data from patients' medical records after notification. Data were

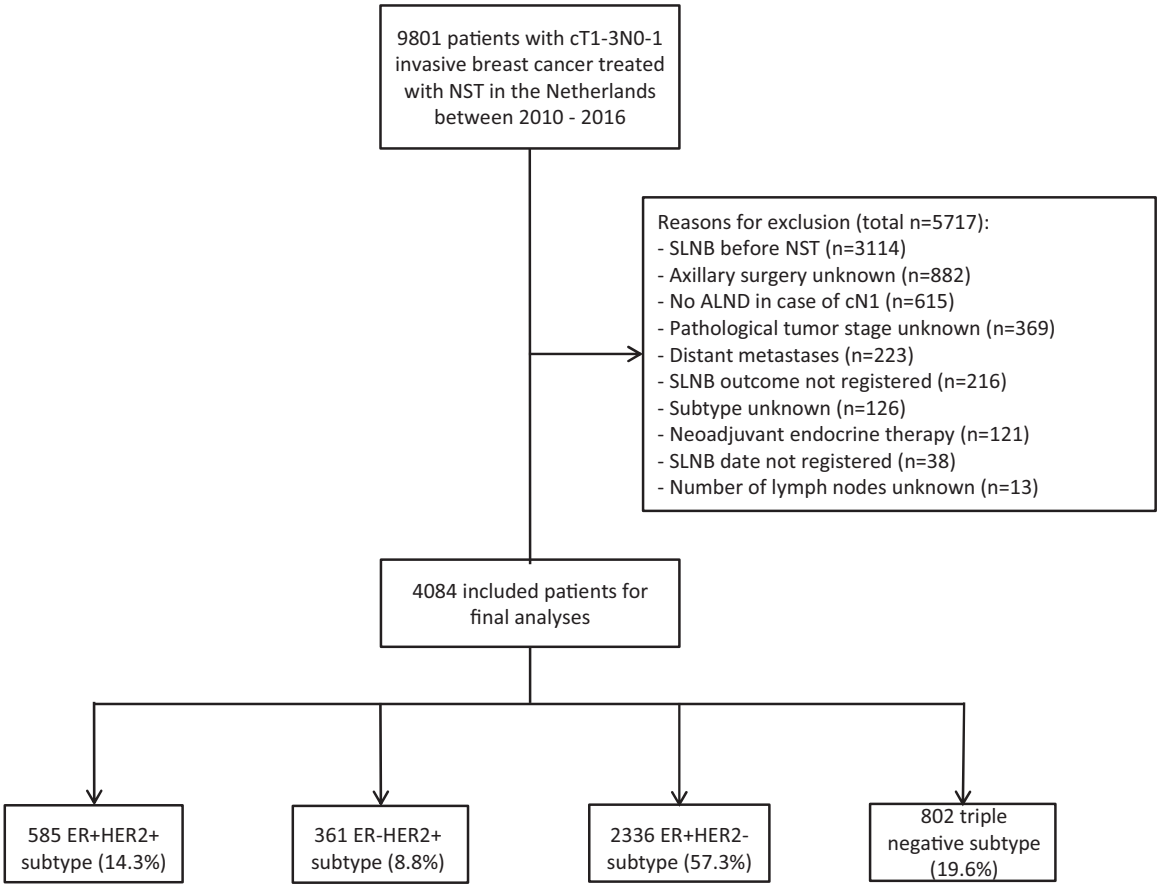

FIGURE 1. Flow diagram of patient inclusion. ALND indicates axillary lymph node dissection; cN1, clinically node positive; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; Triple negative, negative for ER, PR and HER2.

collected on age, tumor histology, receptor status, surgical procedures, systemic therapy, radiation therapy, clinical TNM stage, and pathology results, including stage after NST (ypTNM), tumor grade and number of axillary lymph nodes with and without metastases. Breast pCR was defined as the absence of both invasive and in situ breast cancer, with ypN0 being defined as the absence of both macro- and micrometastases in the axillary lymph nodes.[18] Isolated tumor cells were considered as ypN0.[18]

Statistical analyses were performed by using Statistical Package for the Social Sciences software (SPSS, version 24, IBM, Armonk, NY). Patients were subdivided into breast pCR or without breast pCR for the following breast cancer subtypes: ER positive(+)HER2+, ER negative(−)HER2+, ER+HER2−, and triple negative. For each subtype, the number of axillary lymph nodes with and without metastases at final pathology was reported. The χ^2 test and Fisher exact test were used to compare patients with breast pCR and without breast pCR. Univariable logistic regression analysis was conducted to determine the association between relevant clinicopathological variables and ypN0. Multivariable analysis was performed to identify the independent clinicopathological variables correlated with ypN0. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Two-sided P values of <0.05 were considered statistically significant.

RESULTS

Of the 4084 patients (median age, 49 yrs; range, 18–83 yrs) included for analyses, 585 patients had ER+HER2+, 361 ER-HER2+, 2336 ER+HER2− and 802 had triple negative breast cancer subtype. A total of 1674 (41.0%) patients were cN0 and 2410 (59.0%) were cN1. Breast conserving surgery was performed in 1835 (44.9%) patients and 2249 (55.1%) underwent mastectomy. SLNB was performed in 1483 (36.3%) patients and 2601 (63.7%) underwent ALND (Table 1).

Overall, 986 out of 4084 patients (24.1%) achieved breast pCR. Of the patients with breast pCR, 68.7% (677 of 986) had ypN0 compared with 34.2% (1058 of 3098) without breast pCR ($P < 0.001$). In the case of cN0, 97.7% (432/442) with breast pCR had ypN0 compared with 71.6% (882/1232) without breast pCR ($P < 0.001$). In the case of cN1, 45.0% (245/544) with breast pCR had ypN0 compared to 9.4% (176/1866) without breast pCR ($P < 0.001$) (Table 2).

In univariable analysis, clinicopathological variables associated with lower odds of ypN0 were age 35 to 50 years (OR 0.70, 95% CI 0.54–0.90, $P < 0.006$), age 50 to 75 years (OR 0.60, 95% CI 0.47–0.79, $P < 0.001$), clinical T3 stage (OR 0.51, 95% CI 0.41–0.62, $P < 0.001$), cN1 stage (OR 0.06, 95% CI 0.05–0.07, $P < 0.001$), ER+HER2− subtype (OR 0.32, 95% CI 0.27–0.39, $P < 0.001$), and triple negative subtype (OR 0.31, 95% CI 0.26–0.37, $P < 0.001$). Tumor grade 3 (OR 1.67, 95% CI 1.28–2.19, $P = 0.045$) and breast pCR (OR 4.22, 95% CI 3.62–4.93, $P < 0.001$) were associated with higher odds of ypN0. In multivariable analysis after correcting for confounders, the odds of ypN0 was decreased in the case of clinical T3 stage (OR 0.59, 95% CI 0.40–0.87, $P < 0.007$), cN1 (OR 0.03, 95% CI 0.02–0.04, $P < 0.001$) and ER+HER2− subtype (OR 0.30, 95% CI 0.20–0.44, $P < 0.001$), and increased in the case of breast pCR (OR 4.53, 95% CI 3.27–6.28, $P < 0.001$) (Table 3).

ER+HER2+ subtype

Trastuzumab in neoadjuvant setting was administered in 531 out of 585 (90.8%) ER+HER2+ patients. In this subtype, 236 out of 585 (40.3%) patients achieved breast pCR. In all ER+HER2+ patients with breast pCR, 76.3% (180 of 236) had ypN0 compared to 48.4% (169 of 349) without breast pCR ($P < 0.001$). In the case of cN0 with breast pCR, only 2 out of 124 patients (1.6%) had 1 axillary lymph node metastasis at final pathology, compared to 15.0% (23 of

TABLE 1. Overview of Patient, Tumor, and Treatment Characteristics

	Total (n = 4084)	ER+HER2+ (n = 585)	ER-HER2+ (n = 361)	ER+HER2− (n = 2336)	Triple Negative (n = 802)
Median age (yrs; range)	49 (18–83)	48 (18–75)	51 (23–81)	50 (24–76)	49 (24–83)
Clinical stage (%)					
T1N0	294 (7.2)	59 (10.1)	15 (4.2)	159 (6.4)	61 (7.6)
T1N1	355 (8.7)	42 (7.2)	29 (8.0)	210 (9.8)	74 (9.2)
T2N0	1057 (25.9)	172 (29.4)	88 (24.4)	557 (20.2)	240 (30.0)
T2N1	1354 (33.2)	181 (30.9)	120 (33.2)	773 (36.2)	280 (34.9)
T3N0	323 (7.9)	46 (7.9)	25 (6.9)	216 (7.6)	36 (4.5)
T3N1	701 (17.1)	85 (14.5)	84 (23.3)	421 (19.8)	111 (13.8)
Tumor histology (%)					
Ductal	3242 (79.4)	510 (87.2)	318 (88.1)	1725 (73.8)	689 (85.9)
Lobular	439 (10.7)	29 (5.0)	8 (2.2)	388 (16.6)	14 (1.7)
Mixed ductal and lobular	103 (2.5)	11 (1.9)	2 (0.6)	88 (3.8)	2 (0.2)
Other*	300 (7.4)	35 (5.9)	33 (9.1)	135 (5.8)	97 (12.2)
Tumor grade (%)					
1	293 (7.1)	25 (4.3)	10 (2.8)	253 (10.8)	5 (0.6)
2	1090 (26.7)	170 (29.1)	60 (16.6)	764 (32.7)	96 (12.0)
3	864 (21.2)	126 (21.5)	105 (29.1)	258 (11.0)	375 (46.8)
Unknown	1837 (45.0)	264 (45.1)	186 (51.5)	1061 (45.5)	326 (40.6)
Breast surgery (%)					
Breast conserving surgery	1835 (44.9)	304 (52.0)	169 (46.8)	967 (41.4)	395 (49.3)
Mastectomy	2249 (55.1)	281 (48.0)	192 (53.2)	1369 (58.6)	407 (50.7)
Axillary surgery (%)					
SLNB	1483 (36.3)	257 (43.9)	123 (34.1)	791 (33.9)	312 (38.9)
ALND	2601 (63.7)	328 (56.1)	238 (65.9)	1545 (66.1)	490 (61.1)
Breast pCR (%)	986 (24.1)	236 (40.3)	247 (68.4)	208 (8.9)	295 (36.8)

*Includes adenocarcinoma not further defined, mucinous adenocarcinoma, medullary carcinoma, metaplastic carcinoma among other things.

ALND indicates axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; Triple negative, negative for ER, PR, and HER2.

TABLE 2. Overview of Number of Lymph Node Metastases for Each Breast Cancer Subtype Differentiated Between Breast pCR and Without Breast pCR After NST

		Number of Lymph Node Metastases on Final Pathology (%)				
Breast pCR (n = 986)		**0**	**1**	**2**	**3**	**≥4**
ER+HER2+ (n = 236)	cT1N0	29 (100)	0	0	0	0
	cT2N0	73 (99)	1 (1)	0	0	0
	cT3N0	20 (95)	1 (5)	0	0	0
	cT1N1	9 (60)	6 (40)	0	0	0
	cT2N1	33 (53)	26 (42)	0	2 (3)	1 (2)
	cT3N1	16 (46)	17 (48)	0	1 (3)	1 (3)
ER-HER2+ (n = 247)	cT1N0	13 (100)	0	0	0	0
	cT2N0	72 (100)	0	0	0	0
	cT3N0	12 (100)	0	0	0	0
	cT1N1	12 (48)	13 (52)	0	0	0
	cT2N1	33 (43)	42 (55)	1 (1)	1 (1)	0
	cT3N1	25 (52)	23 (48)	0	0	0
ER+HER2− (n = 208)	cT1N0	27 (94)	1 (3)	1 (3)	0	0
	cT2N0	44 (94)	3 (6)	0	0	0
	cT3N0	12 (92)	1 (8)	0	0	0
	cT1N1	4 (17)	12 (49)	4 (17)	0	4 (17)
	cT2N1	25 (35)	33 (46)	6 (8)	2 (3)	6 (8)
	cT3N1	9 (39)	10 (43)	0	2 (9)	2 (9)
Triple negative (n = 295)	cT1N0	29 (97)	0	1 (3)	0	0
	cT2N0	99 (100)	0	0	0	0
	cT3N0	2 (67)	1 (33)	0	0	0
	cT1N1	16 (49)	15 (45)	1 (3)	0	1 (3)
	cT2N1	47 (47)	45 (44)	6 (6)	1 (1)	2 (2)
	cT3N1	16 (55)	10 (35)	2 (7)	0	1 (3)
		Number of Lymph Node Metastases on Final Pathology (%)				
No Breast pCR (n = 3098)		**0**	**1**	**2**	**3**	**≥4**
ER+HER2+ (n = 349)	cT1N0	25 (83)	5 (17)	0	0	0
	cT2N0	87 (89)	8 (8)	2 (2)	0	1 (1)
	cT3N0	18 (72)	5 (20)	1 (4)	0	1 (4)
	cT1N1	9 (33)	10 (37)	2 (7)	1 (4)	5 (19)
	cT2N1	15 (13)	63 (53)	10 (8)	7 (6)	24 (20)
	cT3N1	15 (30)	13 (26)	4 (8)	3 (6)	15 (30)
ER-HER2+ (n = 114)	cT1N0	2 (100)	0	0	0	0
	cT2N0	14 (88)	2 (12)	0	0	0
	cT3N0	12 (92)	0	1 (8)	0	0
	cT1N1	2 (50)	0	0	2 (50)	0
	cT2N1	14 (33)	13 (30)	6 (14)	4 (9)	6 (14)
	cT3N1	9 (25)	14 (39)	6 (17)	4 (11)	3 (8)
ER+HER2− (n = 2128)	cT1N0	97 (75)	24 (18)	5 (4)	0	4 (3)
	cT2N0	341 (67)	124 (24)	23 (4)	10 (2)	12 (3)
	cT3N0	107 (53)	58 (29)	11 (5)	4 (2)	23 (11)
	cT1N1	7 (4)	63 (34)	34 (18)	19 (10)	63 (34)
	cT2N1	36 (5)	217 (31)	111 (16)	88 (13)	249 (35)
	cT3N1	22 (6)	72 (18)	45 (11)	46 (12)	213 (53)
Triple negative (n = 507)	cT1N0	27 (87)	4 (13)	0	0	0
	cT2N0	126 (89)	12 (8)	2 (2)	1 (1)	0
	cT3N0	26 (79)	4 (12)	2 (6)	0	1 (3)
	cT1N1	5 (12)	15 (37)	4 (10)	5 (12)	12 (29)
	cT2N1	35 (20)	64 (36)	20 (11)	15 (8)	45 (25)
	cT3N1	7 (9)	18 (22)	10 (12)	7 (9)	40 (52)

ER indicates estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR and HER2.

153) without breast pCR ($P < 0.001$). In the case of cN1 with breast pCR, 51.8% (58 of 112) of the patients had ypN0 compared to 19.9% (39 of 196) without breast pCR ($P < 0.001$) (Table 4).

ER-HER2+ subtype

In the ER-HER2+ subtype, trastuzumab in neoadjuvant setting was administered in 336 out of 361 (93.1%) patients. In this subtype, 247 out of 361 (68.4%) patients achieved breast pCR. In patients with breast pCR, 67.6% (167 of 247) had ypN0 compared to 46.5% (53 of 114) without breast pCR ($P < 0.001$). All cN0 patients with breast pCR (n = 97) had ypN0 compared to 90.3% (28 of 31) without breast pCR ($P = 0.013$). In the case of cN1 with breast pCR, 46.7% (70 of 150) of the patients had ypN0 compared to 30.1% (25 of 83) without breast pCR ($P = 0.014$).

ER+HER2− subtype

In the ER+HER2− subtype, 208 out of 2336 (8.9%) patients achieved breast pCR of whom 58.2% (121 of 208) had ypN0

TABLE 3. Univariable and Multivariable Analyses for Clinicopathological Variables and the Outcome ypN0 After NST

	Univariable Analysis			Multivariable Analysis		
	OR	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Age						
< 35 yrs	1 [reference]			1 [reference]		
35–50 yrs	0.70	0.54–0.90	$P < 0.006$	0.91	0.55–1.50	$P = 0.72$
50–75 yrs	0.61	0.47–0.79	$P < 0.001$	0.90	0.55–1.48	$P = 0.68$
>75 yrs	0.60	0.21–1.74	$P = 0.35$	1.55	0.20–12.15	$P = 0.68$
Clinical tumor stage						
T1	1 [reference]			1 [reference]		
T2	0.89	0.75–1.06	$P = 0.20$	0.89	0.64–1.24	$P = 0.49$
T3	0.51	0.41–0.62	$P < 0.001$	0.59	0.40–0.87	$P = 0.007$
Clinical nodal stage						
N0	1 [reference]			1 [reference]		
N1	0.06	0.05–0.07	$P < 0.001$	0.03	0.02–0.04	$P < 0.001$
Tumor histology						
Ductal	1 [reference]			1 [reference]		
Lobular	0.84	0.68–1.03	$P = 0.089$	0.93	0.63 –1.37	$P = 0.70$
Other	0.98	0.79–1.21	$P = 0.83$	0.89	0.59–1.36	$P = 0.60$
Tumor grade						
1	1 [reference]			1 [reference]		
2	1.09	0.84–1.41	$P = 0.53$	1.01	0.71–1.45	$P = 0.95$
3	1.67	1.28–2.19	$P < 0.001$	1.12	0.74–1.69	$P = 0.59$
Tumor subtype						
ER+HER2+	1 [reference]			1 [reference]		
ER-HER2+	1.06	0.81–1.38	$P = 0.70$	1.16	0.68–1.98	$P = 0.60$
ER+HER2−	0.31	0.26–0.37	$P < 0.001$	0.30	0.20–0.44	$P < 0.001$
Triple negative	0.80	0.65–0.96	$P = 0.045$	0.95	0.62–1.45	$P = 0.81$
Breast Pcr						
No	1 [reference]			1 [reference]		
Yes	4.22	3.62–4.93	$P < 0.001$	4.53	3.27–6.28	$P < 0.001$

CI indicates confidence interval; ER, estrogen receptor; OR, odds ratio; Triple negative, negative for ER, PR, and HER2.

compared to 28.7% (610 of 2128) without breast pCR ($P < 0.001$). In cN0 patients with breast pCR, 6 out of 89 patients (6.7%) had 1 or 2 axillary lymph node metastases at final pathology, compared to 35.3% (298 of 843) without breast pCR ($P < 0.001$). In cN1 patients with breast pCR, 31.9% (38 of 119) of the patients had ypN0 compared to 5.1% (65 of 1285) without breast pCR ($P < 0.001$).

Triple negative subtype

In the triple negative subtype, 295 out of 802 (36.8%) patients achieved breast pCR of whom 70.8% (209 of 295) had ypN0 compared to 44.6% (226 of 507) without breast pCR ($P < 0.001$). In the case of cN0 with breast pCR, only 2 out of 132 patients (1.5%) had 1 or 2 axillary lymph node metastases at final pathology, compared to 12.7% (26 of 205) without breast pCR ($P < 0.001$). In cN1 patients with breast pCR, 48.5% (79 of 163) of the patients had ypN0 compared to 15.6% (47 of 302) without breast pCR ($P < 0.001$).

DISCUSSION

In this study, we have reported on a large cohort of cT1-3N0-1 breast cancer patients who were treated with NST and showed an overall breast pCR rate of 24.1%. We found that breast pCR achieved after NST is positively correlated with ypN0. Further, the findings showed that in the case of breast pCR, 97.7% of cN0 patients had ypN0 and in the case of cN1 45.0% converted to ypN0. Of all breast cancer subtypes, only the patients with ER+HER2- subtype were less likely to have ypN0.

TABLE 4. Overview of ypN0 in the Case of Breast pCR and Without Breast pCR After NST for the Different Breast Cancer Subtypes

	Breast pCR and ypN0	**No Breast pCR and ypN0**	***P* Value***
cT1-3N0 ER+HER2+ (n = 277)	98.4 (122/124)	85.0 (130/153)	$P < 0.001$
cT1-3N1 ER+HER2+ (n = 308)	51.8 (58/112)	19.9 (39/196)	$P < 0.001$
cT1-3N0 ER-HER2+ (n = 128)	100 (97/97)	90.3 (28/31)	$P = 0.013$
cT1-3N1 ER-HER2+ (n = 233)	46.7 (70/150)	30.1 (25/83)	$P = 0.014$
cT1-3N0 ER+HER2− (n = 932)	93.3 (83/89)	64.7 (545/843)	$P < 0.001$
cT1-3N1 ER+HER2− (n = 1404)	31.9 (38/119)	5.1 (65/1285)	$P < 0.001$
cT1-3N0 triple negative (n = 337)	98.5 (130/132)	87.3 (179/205)	$P < 0.001$
cT1-3N1 triple negative (n = 465)	48.5 (79/163)	15.6 (47/302)	$P < 0.001$

Data are presented as percentages with the numbers in parentheses.
*χ^2 test and Fisher exact test between patients with breast pCR and ypN0 versus patients without breast pCR and ypN0.
ER indicates estrogen receptor; Triple negative, negative for ER, PR, and HER2.

Recently, Tadros et al[14] have demonstrated that breast pCR is strongly correlated with axillary nodal status after NST. They showed a total breast pCR rate of 36.6% (193 of 527) with a slightly higher rate of breast pCR in the triple negative group (37.5%) compared to the HER2+ group (35.7%). In contrast to the Tadros et al study, patients with clinical T3 stage and ER+HER2− subtype were also included in the present study which can explain the lower total breast pCR rate here. We found that in the case of ER+HER2− breast cancer, pCR rates of the breast and axilla were lower compared to the other breast cancer subtypes. For this subtype, the most important systemic therapy (ie, hormonal therapy) generally follows in the adjuvant setting. Previous studies had reported breast and axillary pCR rates for the ER+HER2− subtype ranging from 7.5% to 16.5%.[4,7,8] We have shown similar breast pCR rates, but higher ypN0 rates due to the included number of cN0 patients. In the Tadros et al study, all 527 cT1-2N0 patients with HER2+ and triple negative breast cancer who achieved breast pCR after NST were found to have ypN0.[14] We have confirmed this strong correlation here between breast pCR and ypN0 in cN0 patients for ER+HER2+, ER-HER2+, and triple negative breast cancer subtypes.

Due to the presence of more effective treatment regimens, pCR rates in the breast and axilla have improved dramatically over the past decade.[19] Ongoing trials are currently evaluating the accuracy of image-guided minimally invasive techniques for predicting breast pCR in order to potentially omit surgery.[20,21] In the MICRA trial, biopsies of the original tumor bed are obtained after NST and prior to surgery in all patients with complete or partial radiologic response evaluated by MRI.[20] Preliminary results show that ultrasound-guided biopsies identify breast pCR successfully in 91.4% (43 out of 47) of the patients after NST. In a study by Kuerer et al,[22] FNAC and image-guided vacuum-assisted biopsy of the tumor bed accurately identified breast pCR after chemotherapy in 98.0% (38 out of 40) of the patients with a false negative rate (FNR) of 5.0%. The Kuerer et al findings have resulted in a prospective clinical trial evaluating omission of breast surgery after NST in patients with breast pCR confirmed by image-guided tissue sampling.[21]

Identifying breast pCR appears important for guiding axillary treatment given the previously shown correlation between breast and axillary pCR.[13,14] If breast pCR after NST can be identified prior to surgery, resulting in the complete omission of breast surgery, how should the axillary lymph nodes be handled in such patients? In recent years the focus has been on minimizing axillary surgery in an aim to reduce surgical morbidity. In this study, we observed that 97.7% of cN0 breast cancer patients who achieved breast pCR had ypN0. This implies that the risk of missing patients with axillary lymph node metastases in these selected patients is highly unlikely. Therefore, these patients should proceed to clinical trials to evaluate the safety of omission of axillary surgery when breast pCR after NST is identified by image-guided tissue sampling.[21] The requirement to proceed in these clinical trials is the determination of the axillary nodal status before NST administration by axillary ultrasound with or without biopsy.

In our study, only 45.0% of all cN1 patients who achieved breast pCR also had ypN0. Consequently, these cN1 patients remain at risk of having axillary lymph node metastases at final pathology, irrespective of breast pCR, and omission of axillary surgery would therefore be inappropriate. The performance of imaging techniques for assessing residual disease in the axillary lymph nodes after NST remains inaccurate.[23,24] As for these cN1 patients, minimally invasive surgical methods for accurately predicting the axillary status are currently under investigation. These minimally invasive techniques aim to identify ypN0 after NST resulting in less ALND and thereby preventing the associated morbidity. Caudle et al showed in a retrospective study of 85 clinically node positive patients that SLNB in combination with selective removal of metastatic marked nodes for predicting ypN0 after NST has a FNR of 2.0%.[25] The Dutch RISAS trial is a currently ongoing prospective multicenter study to validate this combined procedure of SLNB and MARI (marking the axillary lymph nodes with radioactive seeds) for identifying ypN0 after NST in clinically node positive patients.[26]

Limitations

This study included patients from all institutions in the Netherlands and thereby an advantage is generalizability of the results. However, our study has certain limitations. Due to the retrospective nature of the data, there can be no guarantee that all patients completed NST and, therefore, were treated sufficiently, since this may have contributed to not obtaining breast and/or axillary pCR. Additionally, the number of excluded patients as a consequence of missing data could have affected our results, such as unknown pathological tumor stage and breast cancer subtype.

CONCLUSIONS

These results indicate that cN0 patients who achieve breast pCR after NST are highly likely to achieve ypN0, especially in ER+HER2+, ER-HER2+, and triple negative breast cancer subtypes. Besides guiding omission of breast surgery, identifying breast pCR may guide de-escalating axillary treatment with the potential to omit axillary surgery in selected patients. Future clinical trials should investigate if omission of axillary surgery in these selected patients is safe when image-guided tissue sampling identifies breast pCR after NST.

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