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The percentage of residual DCIS in patients diagnosed with primary invasive breast cancer treated with neoadjuvant systemic therapy: A nationwide retrospective study

R.A.W. Ploumen [a, b, *], K.B.M.I. Keymeulen [a], L.F.S. Kooreman [b, c], S.M.J. van Kuijk [d], S. Siesling [e, f], M.L. Smidt [a, b], T.J.A. van Nijnatten [g]

[a] Department of Surgery, Maastricht University Medical Centre+, 6202 AZ, Maastricht, the Netherlands
[b] GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre+, 6200 MD, Maastricht, the Netherlands
[c] Department of Pathology, Maastricht University Medical Centre+, 6202 AZ, Maastricht, the Netherlands
[d] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+, 6202 AZ, Maastricht, the Netherlands
[e] Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, 7522 NH, Enschede, the Netherlands
[f] Department of Research and Development, Netherlands Comprehensive Cancer Organisation, 3511 DT, Utrecht, the Netherlands
[g] Department of Radiology and Nuclear Medicine, Maastricht University Medical Centre+, 6202 AZ, Maastricht, the Netherlands

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ABSTRACT

Introduction: Neoadjuvant systemic therapy (NST) is increasingly applied in breast cancer to improve surgical and oncological outcome. Approximately 21% of patients receiving NST achieve pathological complete response (pCR) of the breast. There is disagreement on the definition of pCR with respect to residual DCIS (ypT0 versus ypT0/is). The aim of this retrospective study was to determine the percentage of breast pCR (ypT0) and residual DCIS (ypTis), and its association with clinicopathological variables, in patients treated with NST and surgery.

Materials and methods: Patients with invasive breast cancer treated with neoadjuvant chemotherapy, with or without targeted therapy, in the period of 2010–2019 were selected from the Netherlands Cancer Registry (NCR). Descriptive statistics and multivariable logistic regression analyses were used to analyse the percentage of ypT0 and ypTis and its association with clinicopathological variables.

Results: From the NCR database, 20495 patients were included, of whom 5847 (28.5%) achieved breast pCR (ypT0) and 881 (4.3%) showed residual DCIS (ypTis). The percentage of ypTis was highest in HER2+ tumour subtypes (ER+HER2+ 7.9%, ER-HER2+ 9.8%, ER+HER2- 2.1%, triple negative 3.3%, $p < 0.001$). Multivariable logistic regression analyses demonstrated high tumour grade (OR 2.00, $p = 0.003$) and HER2+ tumour subtype (ER+HER2+ OR 3.58, ER-HER2+ OR 4.37, $p < 0.001$) as independent predictors for ypTis.

Conclusion: pCR (ypT0) was achieved in 5847 (28.5%) patients receiving NST and residual DCIS (ypTis) was found in 881 (4.3%) patients. Consequently, the rate of pCR may be affected by ypTis when not excluded from the definition. The percentage of ypTis is highest in HER2+ subtypes.

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1. Introduction

Neoadjuvant systemic therapy (NST) was once reserved for locally advanced or inoperable breast cancer to reduce tumour extent. Nowadays, NST is increasingly applied in the treatment of early-stage breast cancer with the main goal of downsizing the tumour and improving surgical and oncological outcome [1–3]. Approximately 21% of patients treated with NST achieve pathological complete response (pCR) of the breast [4]. However, the current definition of pCR differs among published studies. The most

* Corresponding author. Department of Surgery Maastricht University Medical Centre+, P.O. Box 5800, 6202 AZ, Maastricht, the Netherlands.
E-mail addresses: r.ploumen@maastrichtuniversity.nl (R.A.W. Ploumen), k.keymeulen@mumc.nl (K.B.M.I. Keymeulen), loes.kooreman@mumc.nl (L.F.S. Kooreman), sander.van.kuijk@mumc.nl (S.M.J. van Kuijk), s.siesling@iknl.nl (S. Siesling), m.smidt@mumc.nl (M.L. Smidt), thiemo.nijnatten@mumc.nl (T.J.A. van Nijnatten).

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Abbreviations

DCIS	Ductal Carcinoma in Situ
IKNL	Netherlands Comprehensive Cancer Organization (NCCO)
ISH	In Situ Hybridization
NCR	Netherlands Cancer Registry
NST	Neoadjuvant Systemic Therapy
pCR	Pathological Complete Response

common interpretation in the literature is the absence of invasive tumour regardless of residual ductal carcinoma in situ (DCIS) (ypT0/is) [5–7]. Far fewer studies exclude DCIS from the definition of pCR (ypT0) [8–10].

The percentage of pCR is affected by clinicopathological characteristics [11]. pCR rates are highest in triple negative and HER2 positive tumours, ranging from 31.1 to 50.3%. In contrast, pCR is only achieved in 7.5–9% of the hormone receptor positive subtypes [11–13]. Previous studies demonstrated improved disease-free and overall survival in case of pCR when compared to non-pCR [8,11,14]. As a result, pCR is used in the literature as a potential surrogate for long-term outcomes [5,6]. In contrast, a limited number of studies explicitly report the number of patients with residual DCIS (ypTis) and its effect on prognosis remains controversial [11,15].

In summary, the definition of pCR is inconsistent regarding residual DCIS and its prognostic outcomes may vary [5,15]. In order to clarify the definition, it is important to specifically outline the group of patients with ypTis. Therefore, the aim of the current study was to determine the percentage of ypT0 and ypTis in patients diagnosed with primary invasive breast cancer, treated with NST, in a retrospective nationwide study in the Netherlands. Secondary, clinicopathological variables potentially associated with ypTis were examined.

2. Materials and methods

2.1. Data source

The Netherlands Comprehensive Cancer Organization (IKNL) provides a nationwide cancer registry (Netherlands Cancer Registry, NCR) in which trained registrars collect data on patient, tumour and treatment characteristics of all newly diagnosed cancer patients, directly from electronic patient files in all Dutch hospitals. After approval of a Committee of Privacy, the collected data can be used in retrospective studies.

2.2. Study population

From the NCR, all patients diagnosed with primary invasive breast carcinoma treated with NST, followed by surgery in the period of 2010–2019, were selected. Exclusion criteria were age under 18 years, male sex, unknown clinical or pathological tumour status, neoadjuvant endocrine or irradiation treatment, or no surgical treatment. Collected data comprise information on patient characteristics (age at diagnosis), tumour characteristics (grade according to Bloom and Richardson, histological type, clinical and pathological TNM stage and oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) receptor status) and details on systemic therapy and surgery.

2.3. Neoadjuvant systemic therapy and surgical procedure

Neoadjuvant systemic therapy (NST) consisted of neoadjuvant chemotherapy (NAC) with or without targeted therapy. According to the guideline [16–18], NAC may be considered in cases with prior indication for adjuvant systemic therapy. In general, this applies to patients with clinical node positive tumour (cN+) or clinical node negative tumour (cN0) in combination with: (1) tumour size > 2 cm or > 1 cm in patients younger than or equal to 35 years, (2) grade 2 tumours of 1–2 cm, or (3) HER2 positive tumour >0.5 cm. Trastuzumab was prescribed as targeted therapy for a total of 1 year, of which partly preoperative. As from 2017, pertuzumab was advised as dual anti-HER2 therapy in case of tumour size >2 cm [16–18]. Surgical treatment after NST consisted of breast conserving surgery or mastectomy [16–18].

2.4. Pathological analysis

Pathological examination was performed locally according to the Dutch guideline. In general, morphology and receptor status were determined in the primary core biopsy samples. Tumour grade was determined on the resection specimen, unless the grade was higher in the biopsy, in which case the highest grade was recorded.

ER and PR receptor status were determined using immunohistochemistry and considered positive if >10% of tumour cells stained positive. HER2 status was examined by immunohistochemistry or in situ hybridization (ISH), or in a combination, following ASCO CAP guidelines [16–19]. When targeted therapy was applied in cases of equivocal HER2 status, these cases were also considered HER2 positive. PR receptor status was not included in ER/HER2 subtype differentiation, but was assured negative in the triple negative subtype.

Morphology was classified as invasive carcinoma of no special type (also known as ductal NOS), invasive lobular carcinoma and other (for example, mucinous adenocarcinoma, metaplastic carcinoma, et cetera). There was no information regarding presence of DCIS in the pre-NST biopsy and therefore no distinction was made between pure invasive breast cancer or invasive breast cancer in the presence of DCIS.

Breast pCR was defined as the absence of both invasive tumour and DCIS in postoperative pathology, classified as ypT0. Postoperative residual DCIS, classified as ypTis, was based on pathology reports from the NCR database and defined as presence of DCIS in the absence of residual invasive tumour. In case of postoperative residual invasive tumour, classified as ypT1-4, there was no information available regarding the presence of DCIS.

2.5. Study objectives

Primary endpoint was the overall percentage of pCR (ypT0) and residual DCIS (ypTis), after NST and surgery, in patients initially diagnosed with invasive breast cancer. Secondary endpoints were the percentage of ypT0 and ypTis per breast cancer subtype and identification of clinicopathological variables associated with ypTis.

2.6. Statistical analysis

We performed statistical analyses using the Statistical Package for the Social Sciences (SPSS, version 26, Armonk, New York). Descriptive analyses were used to summarize baseline patient and tumour characteristics and to calculate the percentage of ypT0 and ypTis after NST and surgery, overall and per invasive tumour subtype. Patients were divided into four subgroups based on receptor status, namely ER+HER2+, ER-HER2+, ER+HER2- and triple

negative. Pearson's X^2 test was used to test for differences in the percentage of ypT0, ypTis and ypT1-4 between the invasive tumour subtypes. Univariable logistic regression analysis was performed to determine clinicopathological variables associated with the odds of ypTis. Subsequently, multivariable logistic regression analyses were performed to adjust for possible confounders. Cases with missing data were excluded from multivariable logistic regression analyses. A p-value of ≤ 0.05 was considered statistically significant.

3. Results

In the period of 2010–2019, 20 929 women received NST for a total of 21 488 primary invasive breast tumours in the Netherlands. After exclusion of ineligible patients, 20 495 patients were included in the study population (Fig. 1).

3.1. General characteristics and postoperative pathology

An overview of patient and tumour characteristics is shown in Table 1. The median age was 50 years. The majority of patients was diagnosed with cT2 tumour (56.4%), followed by cT3 (18.9%), cT1 (16.9%) and 7.8% cT4. Clinical nodal status was 1 in 47.4%, 0 in 41.6% and 2–3 in 11% of the patients. Most common tumour subtype was ER+HER2- (47.8%) and most common morphology was invasive carcinoma of no special type (83.5%). Of the total of 5747 HER2+ tumours, 5544 (96.5%) were additionally treated with targeted therapy. Postoperative pathology results are shown in Table 2. After NST and surgery, 5847 patients (28.5%) achieved pCR (ypT0) and another 881 patients (4.3%) had ypTis.

3.2. Association of invasive tumour subtype, morphology and postoperative pathology

Fig. 2 shows the percentages of ypT0, ypTis and ypT1-4 per tumour subtype. The percentage of pCR was significantly different between the tumour subtypes and highest in ER-HER2+ subtype (63.8%, $p < 0.001$). The percentage of ypTis in HER2+ subtypes is significantly higher than in the ER+HER2-and triple negative subtype (7.9–9.8% compared to 2.1% and 3.3%, respectively, $p < 0.001$). Of the total of 5747 HER2+ tumours, 5544 (96.5%) were additionally treated with targeted therapy. HER2+ patients not receiving targeted therapy had a lower percentage of pCR (11.7% compared to 49.3%) and ypTis (1.3% compared to 9.0%). In addition, these patients had a significantly higher percentage of residual invasive tumour (Appendix A, Table A.1). The percentage of ypT0 and ypTis was lower in lobular carcinoma compared to invasive carcinoma of no special type (7.8% and 1.1% compared to 30.6% and 4.7%, $p < 0.001$) (Fig. 3).

3.3. Association of clinicopathological variables and ypTis

Multivariable logistic regression analysis demonstrated higher tumour grade as an independent predictor of ypTis (grade 2 versus 1: OR 1.993, $p = 0.003$, grade 3 versus 1: 2.003, $p = 0.003$) (Table 3). HER2+ tumour subtypes were the most important predictors of ypTis with an odds ratio of 3.577 for ER+HER2+ and an odds ratio of 4.365 for ER-HER2+ ($p < 0.001$). Lobular carcinoma was associated with significant lower odds for ypTis (OR 0.345, $p < 0.001$).

4. Discussion

The aim of this study was to examine the percentage pCR (ypT0) and residual DCIS (ypTis), in patients with invasive breast cancer treated with NST. In our nationwide retrospective database concerning 20 495 patients, 5874 patients (28.5%) achieved ypT0 and 881 patients (4.3%) demonstrated ypTis. The percentage of ypTis was highest in the HER2+ invasive tumour subtypes (ranging 7.9–9.8%).

To the best of our knowledge, this is the first nationwide study focusing on the incidence of ypTis in patients treated with NST for invasive breast cancer. We found ypTis in 4.3% of all patients, which is consistent with the reported outcomes in previous studies. Jones et al. [9] observed ypTis in 5% of 435 patients treated with NAC and Von Minckwitz et al. [15] performed a pooled analysis of 7 clinical trials (n = 6377) in which 6.4% of patients showed ypTis. Sun et al. [20] analysed 280 HER2+ patients receiving NST and demonstrated ypTis in 17.9% of all patients. Except for the fact that they selected a HER2+ study population, there is no explanation for this higher rate of ypTis and the authors do not discuss this further. In comparison to the previous literature, a significantly larger number of

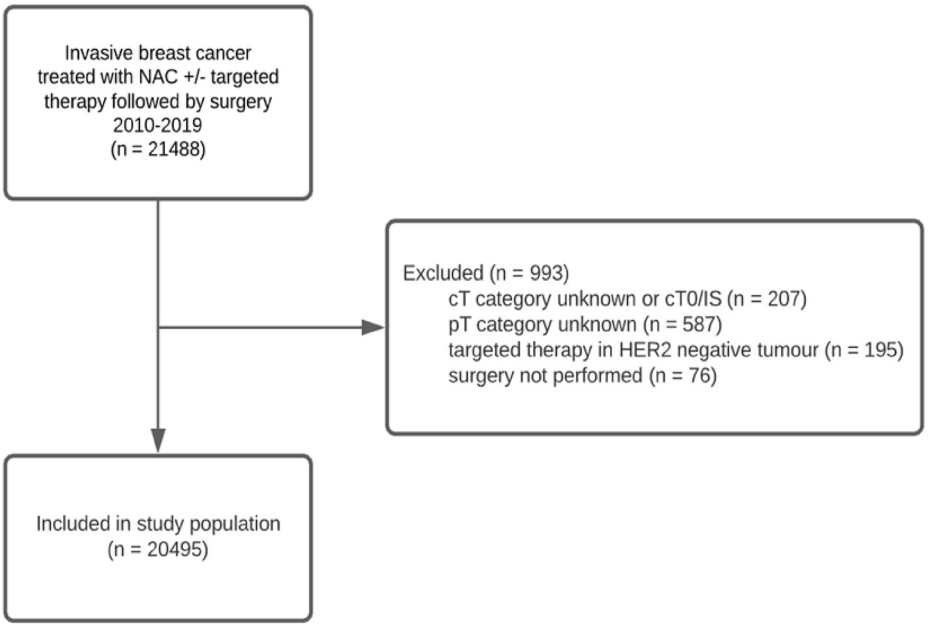

Fig. 1. Flowchart of patient selection.

Table 1
Patient and tumour characteristics.

Characteristics		Overall study sample (n = 20495) N (%)
Age in years, median [range]		50 [18–89]
Year of inclusion		
	2010–2013	4939 (24.1)
	2014–2016	6953 (33.9)
	2017–2019	8603 (42.0)
Clinical tumour status		
	T1	3470 (16.9)
	T2	11555 (56.4)
	T3	3880 (18.9)
	T4	1590 (7.8)
Tumour grade		
	1	1213 (8.4)
	2	6996 (48.6)
	3	6184 (43.0)
	Unknown	6102
Tumour subtype		
	ER+HER2+	3476 (17.3)
	ER-HER2+	2271 (11.3)
	ER+HER2-	9614 (47.8)
	Triple negative	4749 (23.7)
	Unknown	385
Clinical nodal status		
	0	8485 (41.6)
	1	9652 (47.4)
	2–3	2244 (11.0)
	Unknown	114
Multifocality		315 (1.5)
Morphology		
	No special type	17123 (83.5)
	Lobular	1852 (9.0)
	Other	1520 (7.5)
Neoadjuvant targeted therapy[a]		5544 (96.5)
Surgery		
	Breast conserving therapy	10422 (50.9)
	Mastectomy	9558 (46.6)
	Both	515 (2.5)

[a] (in case of HER2+ disease).

patients were included in the current study, making it possible to specifically outline and examine the group of patients with ypTis.

It is of great importance to distinguish between ypT0 and ypTis, not only to clarify the definition of pCR, but also in the context of recent research on omitting surgery after NST. Several studies are investigating whether it is possible to eliminate breast surgery after NST in subgroups with high pCR rates, for example by measuring response in image-guided biopsies [20–22]. In this case, it is important to identify patients with ypTis, as this could be a nidus for recurrence. With regard to the axilla, a study by Kahler-Ribeiro-Fontana et al. demonstrated that a sentinel node biopsy is acceptable in clinically node positive patients who become cN0 after NST [23]. In addition, outlining patients with ypTis is interesting to further investigate the effect of ypTis on prognosis [24]. Cortazar et al. demonstrated no difference in event-free and overall survival between the pCR definitions ypT0 ypN0 and ypT0/is ypN0 in the CTneoBC pooled analysis [11]. In contrast, Von Minckwitz et al. [15] showed a lesser disease-free survival of patients with ypTis ypN0 compared to ypT0 ypN0 in a pooled analysis of seven randomized trials (n = 6377).

Table 2
Postoperative pathology results in the overall study population.

Pathology		Overall study sample n = 20495 N (%)
ypT		
	0 (pCR)	5847 (28.5)
	is	881 (4.3)
	1	8110 (39.6)
	2	4123 (20.1)
	3	1277 (6.2)
	4	257 (1.3)

In comparison to previous studies reporting patients with ypTis, this is the first study to focus on its association with clinicopathological variables. Tumour subtype analysis shows HER2+ subtypes achieve the highest percentage of ypTis, ranging from 7.9 to 9.8%. This is in line with a study by von Minckwitz et al. [15], which showed HER2+ subtype was most prevalent in the group of patients with ypT0/is, however, they did not distinguish ypTis from ypT0. The association between HER2+ invasive breast cancer and higher rates of ypTis can be explained by the higher incidence of additional DCIS to HER2+ invasive breast cancer compared to the HER2- and triple negative subtypes [25,26]. Moreover, our multivariable logistic regression analysis demonstrated higher tumour grade as an independent predictor for ypTis. HER2 positivity and higher tumour grade are associated with better response to NST in invasive breast cancer [12,27,28]. A subsequent hypothesis would be that ypTis is most common in invasive tumours with frequent additional DCIS and high rates of pCR. This is in line with our multivariable logistic regression analysis showing that lobular carcinoma was associated with lower odds for ypTis and previous literature demonstrating a lower pCR rate in this morphological subtype [29–31]. However, this hypothesis does not consider the possible effect of NST on DCIS. Because of its non-invasive characteristics, it was previously believed in literature that DCIS responds poorly to NST [32]. In contrast, recent studies do show response of DCIS to NST in a certain amount [10,33]. Groen et al. investigated 138 patients with additional DCIS on pretreatment biopsy in HER2+ invasive breast cancer and showed complete eradication of DCIS in 46% of patients treated with NST [34]. Von Minckwitz et al. demonstrated 50.8% of invasive tumours with adjacent DCIS showing complete eradication of DCIS after NST [10]. The degree of response of DCIS to NST affects the percentage of pCR and ypTis and is therefore of interest to investigate further.

The strengths of this nationwide database study are the large number of patients and the various clinicopathological variables included, that enabled evaluation of potential correlation with ypTis. In contrast, there are a few relevant limitations to mention. Due to the lack of information on DCIS in the pre-NST biopsy, it is not possible to distinguish between pure invasive breast cancer or invasive breast cancer in the presence of DCIS. In addition, there is no information on the percentage of DCIS in case of residual invasive tumour. This would be interesting to examine in the context of the effect of NST on DCIS, however, the primary aim of this study was to determine the percentage of ypTis in a nationwide study. Moreover, it is not possible to complete all missing data due to the nature of the dataset obtained from the NCR. In particular tumour grade was poorly recorded in a subset of patients. Missing data may affect the multivariable logistic regression analyses, though this is not expected in such a large cohort. Lastly, this dataset does not contain information on chemotherapy or targeted therapy regimen, dosage or duration.

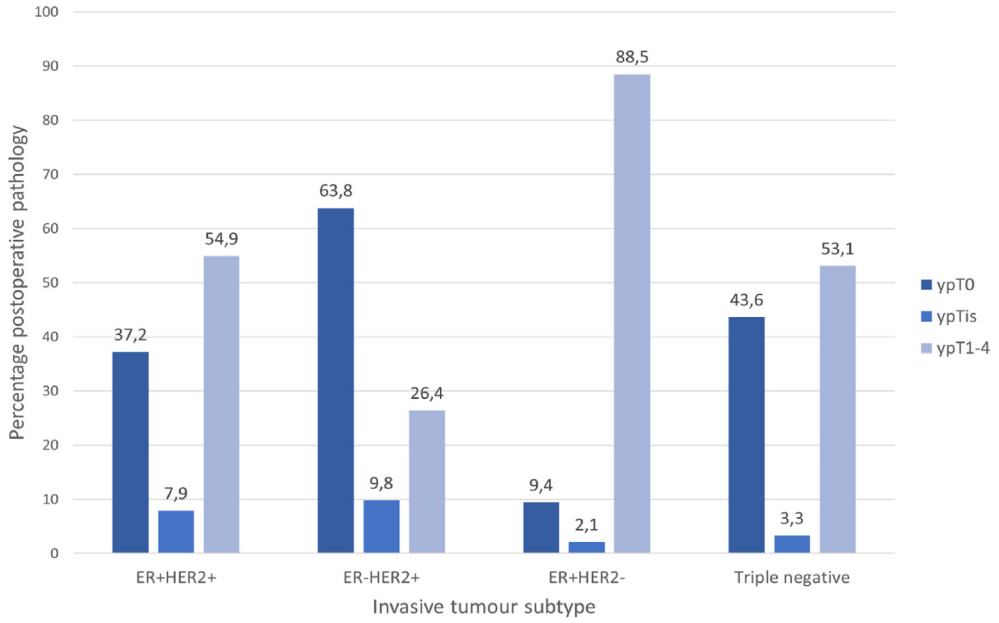

Fig. 2. Percentages of ypT0, ypTis and ypT1-4 per tumour subtype.

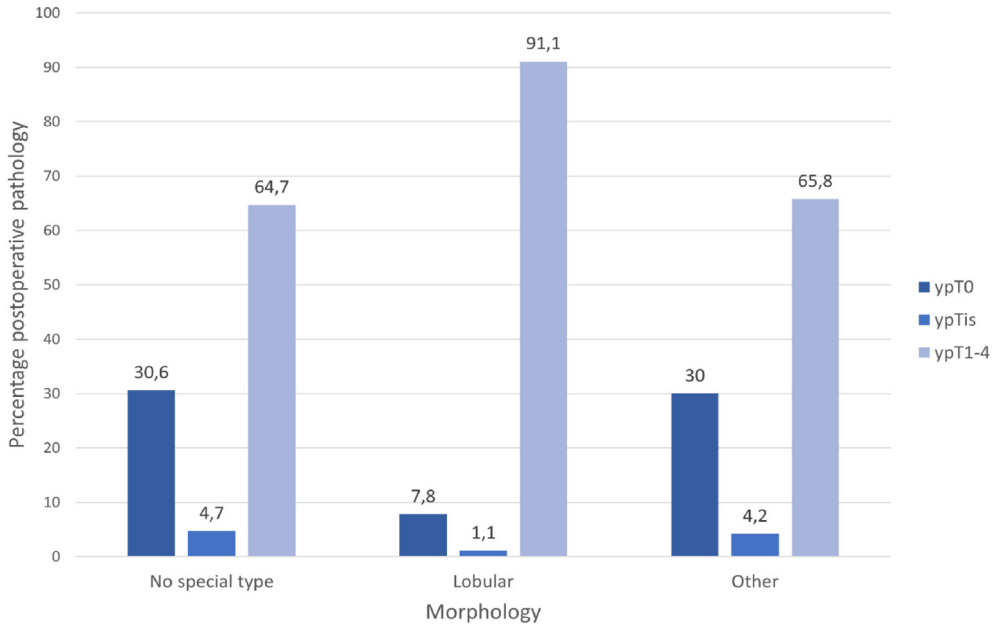

Fig. 3. Percentages of ypT0, ypTis and ypT1-4 per tumour morphology.

5. Conclusion

In conclusion, in this large nationwide study 28.5% of patients achieved pCR (ypT0) and 4.3% showed residual DCIS (ypTis) after treatment with NST and surgery. The percentage of ypTis is highest in HER2+ tumour subtypes, up to 9.8%. This should be considered in future clinical decision making as well as future trials regarding response to NST.

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CRediT authorship contribution statement

R.A.W. Ploumen: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **K.B.M.I. Keymeulen:** Conceptualization, Writing – review & editing, Visualization. **L.F.S. Kooreman:** Conceptualization, Investigation, Writing – review & editing, Visualization. **S.M.J. van Kuijk:** Formal analysis, Investigation, Writing – review & editing, Visualization. **S. Siesling:** Validation, Resources, Writing – review &

Table 3
Univariable and multivariable regression analyses of ypTis.

	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	P Value	OR	95% CI	P Value
Age						
<35	1 [ref]			1 [ref]		
35–49	**0.761**	**0.585–0.990**	**0.042**	0.874	0.624–1.223	0.432
50–74	**0.716**	**0.552–0.928**	**0.011**	0.877	0.630–1.219	0.435
>75	0.855	0.433–1.687	0.651	0.636	0.262–1.543	0.317
Year of diagnosis						
2010–2013	1 [ref]			1 [ref]		
2014–2016	**1.275**	**1.053–1.543**	**0.013**	1.026	0.767–1.372	0.863
2017–2019	**1.381**	**1.151–1.657**	**0.001**	0.979	0.742–1.291	0.880
Clinical tumour status						
T1	1 [ref]			1 [ref]		
T2	1.008	0.835–1.218	0.932	1.069	0.851–1.343	0.568
T3	1.095	0.875–1.369	0.428	1.237	0.928–1.649	0.147
T4	1.002	0.745–1.346	0.992	1.216	0.818–1.807	0.334
Tumour grade						
1	1 [ref]			1 [ref]		
2	**2.291**	**1.478–3.550**	**<0.001**	**1.993**	**1.266–3.136**	**0.003**
3	**2.731**	**1.763–4.230**	**<0.001**	**2.003**	**1.262–3.180**	**0.003**
Tumour subtype						
ER+HER2-	1 [ref]			1 [ref]		
ER+HER2+	**3.908**	**3.248–4.703**	**<0.001**	**3.577**	**2.836–4.511**	**<0.001**
ER-HER2+	**4.948**	**4.069–6.017**	**<0.001**	**4.365**	**3.387–5.624**	**<0.001**
Triple negative	**1.551**	**1.256–1.916**	**<0.001**	1.312	0.995–1.728	0.054
Morphology						
No special type	1 [ref]			1 [ref]		
Lobular	**0.224**	**0.143–0.349**	**<0.001**	**0.345**	**0.196–0.608**	**<0.001**
Other	0.900	0.694–1.168	0.429	1.009	0.701–1.450	0.963
Clinical nodal status						
N0	1 [ref]			1 [ref]		
N1	0.920	0.797–1.062	0.256	0.855	0.710–1.029	0.097
N2-3	1.021	0.816–1.277	0.854	0.824	0.621–1.095	0.183
Targeted therapy[a]	**3.736**	**3.257–4.284**	**<0.001**			

[a] Excluded from multivariable analyses due to collinearity with tumour subtype.

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Declaration of competing interest

None declared.

6. Appendix A

Table A.1
Postoperative pathology results in HER2+ patients.

Pathology	NAC (n = 239) N (%)	NAC + targeted therapy (n = 5508) N (%)
ypT		
0 (pCR)	28 (11.7)	2714 (49.3)
is	3 (1.3)	493 (9.0)
1	119 (49.8)	1689 (30.7)
2	66 (27.6)	477 (8.6)
3	18 (7.5)	109 (2.0)
4	5 (2.1)	26 (0.4)

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