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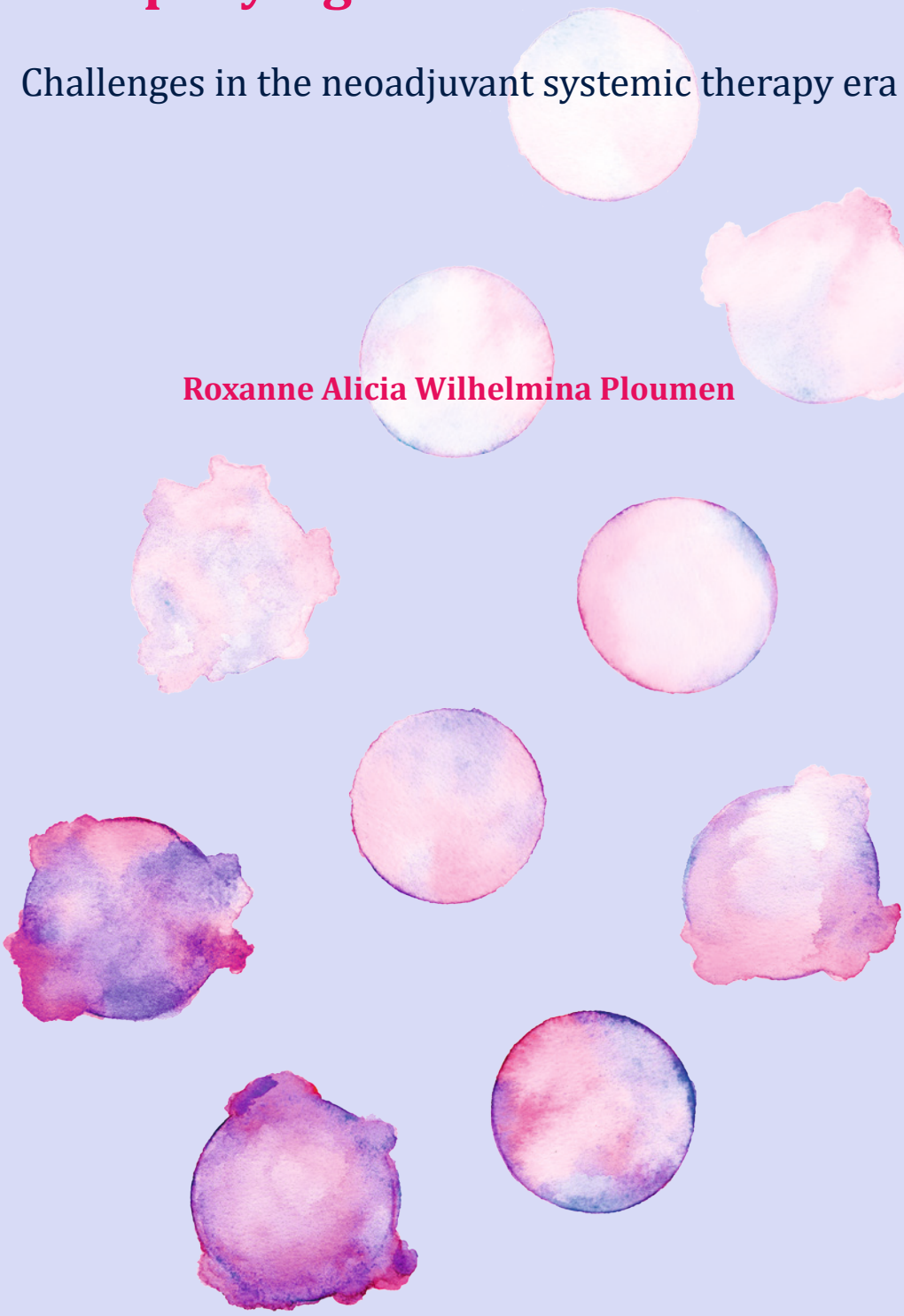
Challenges in the neoadjuvant systemic therapy era

Roxanne Alicia Wilhelmina Ploumen



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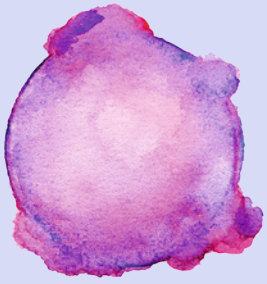

CHAPTER 1

General introduction and Thesis outline

General introduction

Breast cancer is the most common cancer among women in the Netherlands. Per year, approximately 16000 women are newly diagnosed, resulting in a lifetime risk of 1 in 7 women developing this disease.[1] Another 2300 women per year are diagnosed with ductal carcinoma in situ (DCIS). DCIS is a non-invasive proliferation of ductal epithelial cells that can potentially progress to invasive breast cancer. Consequently, DCIS is locally treated to prevent the risk of developing invasive breast cancer. The histopathology of these entities and the current treatment is described in the following introduction.

Histopathology of breast cancer

The female breast consists of lobules, ducts, and surrounding adipose tissue. Lobules are fibroglandular structures that can produce milk in response to hormones during pregnancy and lactation. The ducts serve to transfer the milk towards the nipple. Figure 1 shows an overview of the anatomy of the breast and a cross-section of a duct, consisting of three layers. The outer layer is the basement membrane, which is covered on the inside by a layer of myoepithelial cells. The inner layer consists of ductal epithelial cells.[2] A neoplastic proliferation of ductal epithelial cells can occur, leading to an accumulation of these cells within the duct. The process of this neoplastic proliferation is shown in Figure 1. Atypical Ductal Hyperplasia (ADH) is the first step in which proliferative epithelial cells are limited to less than two contiguous ducts, or when the lesion extent is less than 2mm.[3] ADH can increase in size and involve more ducts. This condition is called Ductal Carcinoma in Situ (DCIS), a lesion that is considered a non-obligate precursor of invasive breast cancer, and is still surrounded by the basement membrane. Once the neoplastic cells eventually invade through the basement membrane, the condition is called invasive ductal carcinoma.[2] Breast cancer comprises various morphological subtypes, but this dissertation primarily focuses on the most common invasive ductal carcinoma (also known as invasive carcinoma of no special type), hereafter referred to as invasive breast cancer.

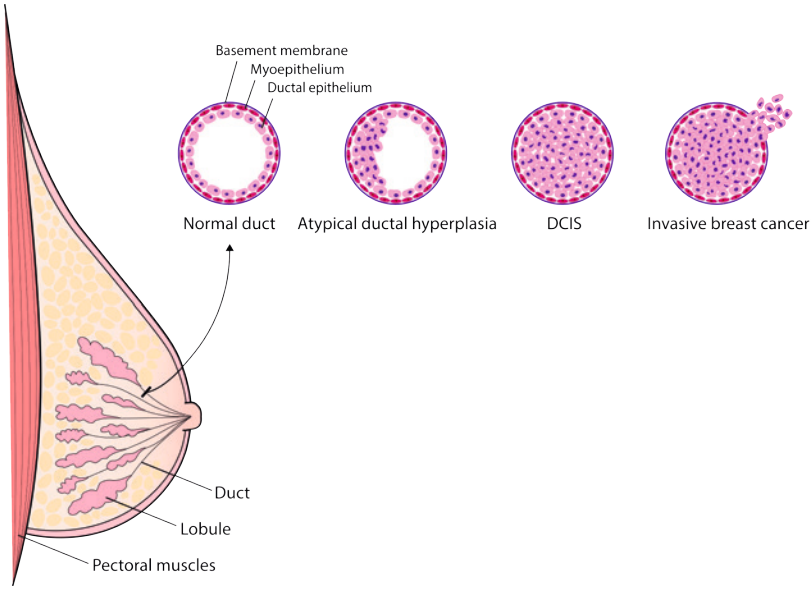

Figure 1: Anatomy of a sagittal view of the breast and histopathology of a duct, showing different stages of neoplastic proliferation

By histopathological examination, DCIS and invasive breast cancer can be classified based on different characteristics. Both DCIS and invasive breast cancer are classified by grade, scored from 1-3. Grade 1 corresponds to a low-aggressive tumor whose cells still most closely resemble normal ductal cells, and grade 3 is an aggressive tumor, consisting of highly abnormal and proliferating cells.[4]

Furthermore, invasive breast cancer is commonly classified based on the TNM classification and the presence of various receptors within the tumor cell or on its membrane. The TNM classification describes the tumor size (T), presence of metastasis in the axilla (N) and presence of distant metastasis (M). The TNM classification is preoperatively referred to as cTNM (clinical); postoperatively as pTNM (pathological); and following neoadjuvant therapy and surgery, it is denoted as ypTNM. The most important receptors are estrogen receptor (ER), progesterone receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2). HER2 is a membrane receptor tyrosine kinase that regulates the growth and division of normal breast cells. In HER2+ breast cancer, the HER2 protein expression can be 40-100 fold increased, which causes extensive cell proliferation, differentiation, invasion and metastasis.[5, 6] The estrogen and progesterone receptor are collectively called hormone receptors (HR), and both enhance tumor growth in the presence of the hormones.[7] In the Dutch guideline, the combination of mainly the ER and HER2 receptor is used to classify four main subtypes of invasive breast cancer, in order of incidence: ER+HER2- (77%), ER-HER2- (11%), ER+HER2+ (8%), and ER-HER2+ (4%).[1] The ER-HER2- subtype is also referred to as triple negative

breast cancer (TNBC), in case of absence of progesterone receptor. The invasive cancer subtype is highly related to the patient's prognosis, and the more aggressive HER2+ and triple negative subtypes show poorer survival outcomes compared to less aggressive hormone receptor positive breast cancer.[8, 9] Currently, the receptor status of DCIS is not routinely determined in clinical practice and is assessed only for research purposes.

Detection and treatment of Ductal Carcinoma in Situ

DCIS comprises a heterogeneous group of different entities, with varying histopathological characteristics including grade, receptor status, and presence of comedonecrosis and calcifications.[10, 11] Calcifications are caused by passive and active processes that leave calcium deposits within the duct. They can be detected on mammography, and depending on the morphology can be considered benign or suspicious. Suspicious mammographic calcifications can represent the presence of DCIS, especially in the case of fine pleiomorphic or fine linear calcifications that are distributed in segmental and linear pattern.[10, 12] An example of suspicious calcifications on mammography related to DCIS is shown in Figure 2. The majority of DCIS cases present without symptoms, as it is typically non-palpable. Consequently, the introduction of the national screening program has led to an increase in DCIS diagnoses, primarily based on the detection of mammographic calcifications.[13, 14] In 10-20% of DCIS cases, no mammographic calcifications are detected.[15]

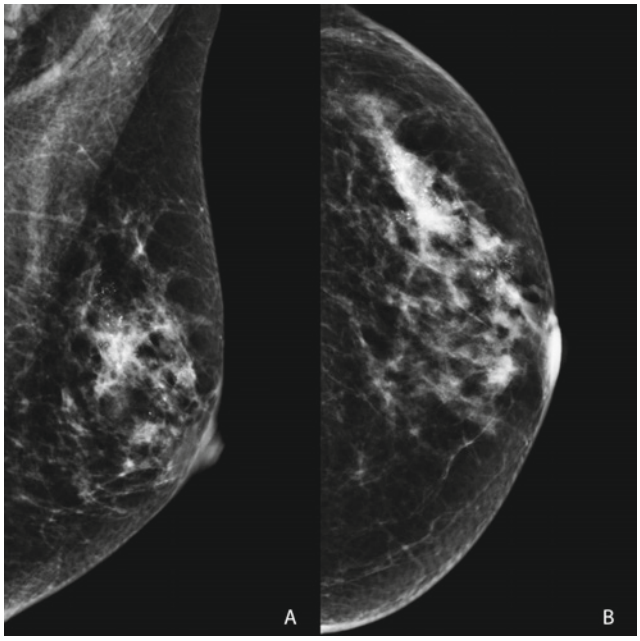

Figure 2: Mammography of the left breast in mediolateral oblique view (A) and craniocaudal view (B) showing an area of pleiomorphic calcifications, suspicious for DCIS

DCIS is considered a non-obligate precursor of invasive breast cancer, but the exact pathophysiology of progression from DCIS to invasive cancer remains unknown and different models are hypothesized.[16, 17] In addition, the risk of progression to invasive breast cancer varies widely in literature, ranging from 10 to 60%.[18, 19] Given that a substantial part of DCIS lesions will never progress to invasive breast cancer, the international PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) consortium was established to reduce overtreatment of these low risk DCIS tumors.[20] The safety of active surveillance in patients with low-grade DCIS is currently being investigated in the non-inferiority LORIS trial (ISRCTN27544579)[21], COMET trial (NCT02926911)[22], and Dutch LORD study (NCT02492607)[23]. Current standard of care treatment of all DCIS lesions still consists of surgery, with or without radiation therapy.[24] The recently initiated Direct-DCIS project will investigate whether it is possible to predict the risk of DCIS progression using artificial intelligence.[25]

Diagnosis of invasive breast cancer

Patients can be diagnosed with invasive breast cancer based on abnormalities detected in the national screening program, or when they present with symptoms, such as a palpable lump in the breast. After clinical examination, different imaging modalities can be used. Full-field digital mammography (FFDM) can detect breast cancer based on anatomical abnormalities such as masses, suspicious calcifications, or asymmetries. Breast MRI detects tumors based on angiogenesis, which refers to the development of new blood vessels in order to favor tumor growth. These vessels often leak, causing the intravenous contrast to accumulate around the tumor, resulting in 'enhancement' on MRI.[26, 27] A more novel imaging technique is contrast-enhanced mammography (CEM): combining a mammography imaging technique with administration of an intravenous contrast agent. This technique enables the evaluation of calcifications and enhancement, making it particularly valuable for diagnosing both DCIS and invasive breast cancer.[28] The accuracy of CEM in detecting breast cancer seems comparable to breast MRI, although evidence is still preliminary and limited.[29, 30] After the detection of abnormalities on imaging, biopsies are taken to establish the diagnosis, and in case of breast cancer, evaluate the histopathological characteristics.

Previous literature shows that approximately half of invasive breast cancer patients have an accompanying DCIS component.[31-33] The presence of a DCIS component differs among breast cancer subtypes and it is more frequently detected in patients with a relatively lower age[31-33] Of the previous described invasive tumor subtypes, the percentage of a DCIS component is highest in HER2+ subtypes (ER+HER2+ 59.1%, ER-HER2+ 57.4%) and lowest in the triple negative subtype (ER-HER2- 34.1%).[31, 32] Because of the high rates in HER2+ disease, this patient population represents a major subject of this thesis.

Surgical treatment

The surgical treatment of invasive breast cancer mainly consists of two methods: breast-conserving surgery, or mastectomy. In the early 20th century, all breast cancer patients were treated with primary surgery, consisting of the Halsted radical mastectomy, removing the complete mammary gland, both pectoral muscles and all axillary lymphnodes.[34] Over the past decades, the extent of surgical treatment of the breast has been reduced to a simple mastectomy, preserving the pectoral muscles. Nowadays, breast-conserving surgery is also an option, allowing for the removal of only the tumor. In the current guidelines, all patients treated with breast-conserving surgery are subsequently treated with radiation therapy. Patients treated with breast-conserving surgery followed by radiation therapy have similar, and in some cases even better, survival outcomes compared to mastectomy patients.[35-37] Moreover, better quality of life and less complications have been reported.[38, 39] Therefore, breast-conserving surgery is increasingly used, when clinically feasible and in consultation with the patient's wishes. The presence of a DCIS component accompanying invasive breast cancer has been shown to affect surgical treatment, in which patients are more often treated with mastectomy.[33, 40]

Neoadjuvant systemic therapy and pathologic complete response

Systemic therapy includes the administration of chemotherapy, targeted therapy, hormone therapy or immunotherapy. The goal is to eliminate any remaining undetected microscopic tumor cells that may have spread throughout the body.[41, 42] Previously, systemic therapy was administered after surgery, called adjuvant systemic therapy. In the late 1990's, neoadjuvant systemic therapy (NST) has been introduced, concerning the administration of systemic therapy before surgery.[43] Various trials have shown that NST had similar survival outcomes to adjuvant systemic therapy, but added the potential of downstaging disease in both the breast and axilla.[44-46] This allowed for less invasive surgery, and patients who were initially candidates for mastectomy, became able to undergo breast-conserving surgery due to a reduction in tumor extent. In addition, the in vivo sensitivity of the tumor to the administered systemic therapy could be evaluated.[46, 47]

In a subset of patients, a condition called pathological complete response (pCR) is achieved, in which the tumor completely responds to NST, and no remaining malignant cells are found in the resection specimen. Previous literature indicates that the achievement of pCR is associated with improved survival outcomes.[48] The response of the tumor to NST varies between different tumor morphologies and subtypes.[49-51] Overall, HER2+ tumors achieve the highest rate of pCR of the primary breast tumor; of up to 65% in patients treated with chemotherapy in combination with dual anti-HER2 therapy, as shown in the TRAIN-2 trial and the TRYPHAENA study.[52, 53] The definition of pCR varies in literature, mainly on the topic whether presence of residual DCIS should be considered pCR or not. The most commonly used definition describes the complete

disappearance of invasive tumor cells, irrespective of the presence of remaining DCIS (ypT0/is). Other studies use a more strict definition, wherein both the invasive tumor and DCIS must be completely eradicated (ypT0).[54] A large previously published meta-analysis, including 11955 patients, demonstrates that there is no difference in event-free and overall survival between the two definitions.[48]

In case of a decrease in tumor extent, it is important to adequately monitor tumor response with imaging to adjust surgical treatment. The most accurate imaging modality for evaluating tumor response is considered to be breast MRI.[55, 56] Despite a great amount of research and improvements of MRI techniques, the sensitivity and specificity of breast MRI in predicting pCR are approximately 0.80 and 0.83, respectively.[57, 58] Only few studies have evaluated CEM in monitoring of invasive tumor response on NST, but results seem promising when compared to breast MRI.[59-61] The use of FFDM is limited in the neoadjuvant setting as contrast-enhanced imaging is preferred.[62]

In patients with accompanying DCIS, it was previously thought that the DCIS component was poorly responsive to NST, because of the intact basement membrane, and less malignant characteristics.[63] Nevertheless, a recent meta-analysis of six studies showed that also DCIS can be completely eradicated by NST, reporting a complete response in 40.5% of HER2+ invasive breast cancer patients.[64] Yet thus far, this meta-analyses showed that only small populations have been studied.

In summary, DCIS is a non-obligate precursor for invasive breast cancer, which can present solely or accompany invasive breast cancer, with the highest rate in HER2+ subtypes. Currently, HER2+ invasive breast cancer is often treated with NST, and the response of the invasive tumor can be evaluated by various imaging techniques. This thesis will further elaborate on the concomitant challenges of an accompanying DCIS component during NST.

Thesis outline

Part I investigates the presence of a DCIS component in patients with invasive breast cancer treated with NST. **Chapter 2** presents results from a nationwide cohort study of invasive breast cancer patients who received NST, reporting the percentage of residual DCIS and its association with invasive tumor subtypes. **Chapter 3** focuses on HER2+ invasive breast cancer patients with a DCIS component, analyzing the percentage of complete response of DCIS after NST, based on a national pathology database.

Part II explores imaging modalities for the detection and monitoring of invasive breast cancer patients with a DCIS component. **Chapter 4** provides a systematic review of imaging findings for DCIS components on mammography, breast MRI, and contrast-enhanced mammography, both before and after NST. **Chapter 5** specifically evaluates the detection of a DCIS component in HER2+ invasive breast cancer using contrast-enhanced mammography.

Part III examines the impact of a DCIS component on surgical treatment and prognosis following NST. **Chapter 6** presents 10-year trends in surgical treatment after NST in HER2+ invasive breast cancer patients, with a specific focus on the influence of a DCIS component. **Chapter 7** investigates the surgical outcomes and 5-year survival follow-up of HER2+ invasive breast cancer patients, with or without a DCIS component, who were treated with breast-conserving surgery after NST.

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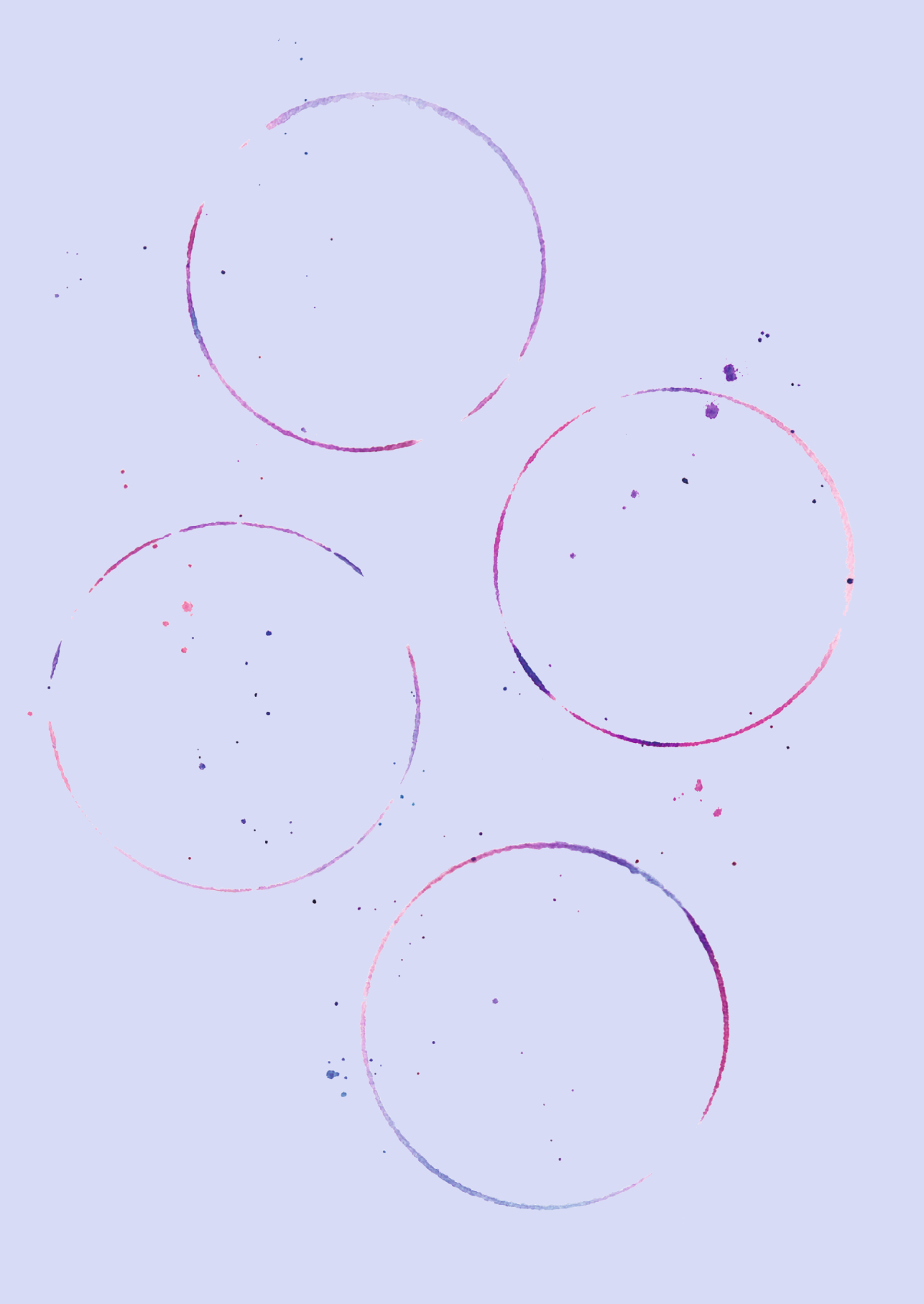
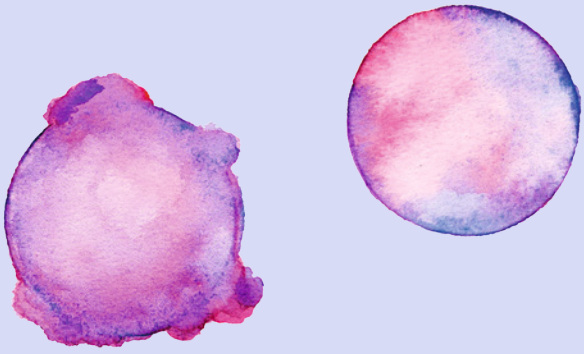


PART I

PATHOLOGY



CHAPTER 2

The percentage of residual DCIS in patients diagnosed with primary invasive breast cancer treated with neoadjuvant systemic therapy

A nationwide retrospective study

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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 analyze 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+ tumor 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 tumor grade (OR 2.00, p=0.003) and HER2+ tumor 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.

Introduction

Neoadjuvant systemic therapy (NST) was once reserved for locally advanced or inoperable breast cancer to reduce tumor extent. Nowadays, NST is increasingly applied in the treatment of early-stage breast cancer with the main goal of downsizing the tumor 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 common interpretation in the literature is the absence of invasive tumor 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+ tumors, ranging from 31.1-50.3%. 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.

Materials and methods

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, tumor 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.

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 tumor status, neoadjuvant endocrine or irradiation treatment, or no surgical treatment. Collected data comprise information on patient characteristics (age at diagnosis), tumor characteristics (grade according to Bloom and Richardson, histological type, clinical and pathological TNM stage and estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) receptor status) and details on systemic therapy and surgery.

Neoadjuvant systemic therapy and surgical procedure

Neoadjuvant systemic therapy (NST) consisted of neoadjuvant chemotherapy (NAC) with or without targeted therapy. According to the Dutch 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 tumor (cN+) or clinical node negative tumor (cN0) in combination with: (1) tumor size > 2cm or > 1 cm in patients younger than or equal to 35 years, (2) grade 2 tumors of 1-2 cm, or (3) HER2 positive tumor > 0.5cm. 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 tumor size >2 cm.[16-18] Surgical treatment after NST consisted of breast conserving surgery or mastectomy.[16-18]

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. Tumor 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 tumor 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 tumor 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 tumor. In case of postoperative residual invasive tumor, classified as ypT1-4, there was no information available regarding the presence of DCIS.

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.

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 tumor characteristics and to calculate the percentage of ypT0 and ypTis after NST and surgery, overall and per invasive tumor subtype. Patients were divided into four subgroups based on receptor status, namely ER+HER2+, ER-HER2+, ER+HER2- and triple negative. Pearson's χ^2 test was used to test for differences in the percentage of ypT0, ypTis and ypT1-4 between the invasive tumor 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.

Results

In the period of 2010-2019, 20929 women received NST for a total of 21488 primary invasive breast tumors in the Netherlands. After exclusion of ineligible patients, 20495 patients were included in the study population (Figure 1).

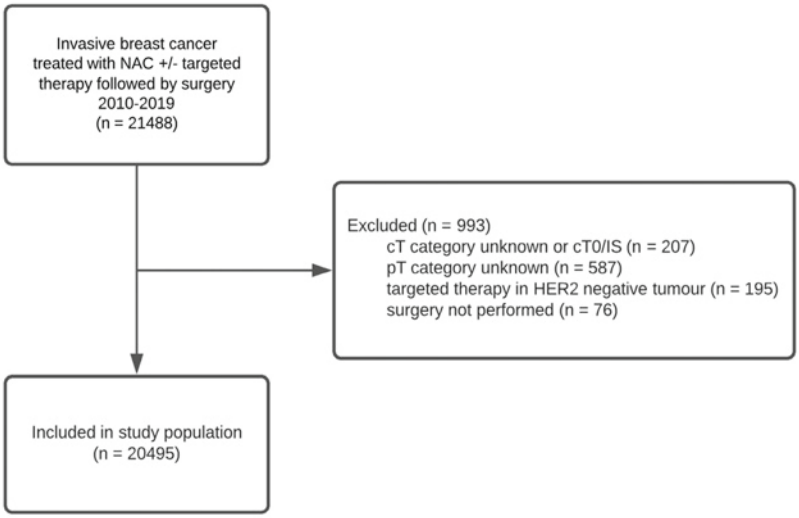

Figure 1: Flowchart of patient selection.

General characteristics and postoperative pathology

An overview of patient and tumor characteristics is shown in Table 1. The median age was 50 years. The majority of patients was diagnosed with cT2 tumor (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 tumor 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+ tumors, 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.

Table 1: Patient and tumor 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)

Table 1: Patient and tumor characteristics (*continued)*

Characteristics	Overall study sample (n = 20495) n (%)
Clinical tumor status	
T1	3470 (16.9)
T2	11555 (56.4)
T3	3880 (18.9)
T4	1590 (7.8)
Tumor grade	
1	1213 (8.4)
2	6996 (48.6)
3	6184 (43.0)
Unknown	6102
Tumor 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*	5544 (96.5)
Surgery	
Breast conserving therapy	10422 (50.9)
Mastectomy	9558 (46.6)
Both	515 (2.5)

* (in case of HER2+ disease)

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)

Association of invasive tumor subtype, morphology and postoperative pathology
Figure 2 shows the percentages of ypT0, ypTis and ypT1-4 per tumor subtype. The percentage of pCR was significantly different between the tumor 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+ tumors, 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 tumor (Appendix A). 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) (Figure 3).

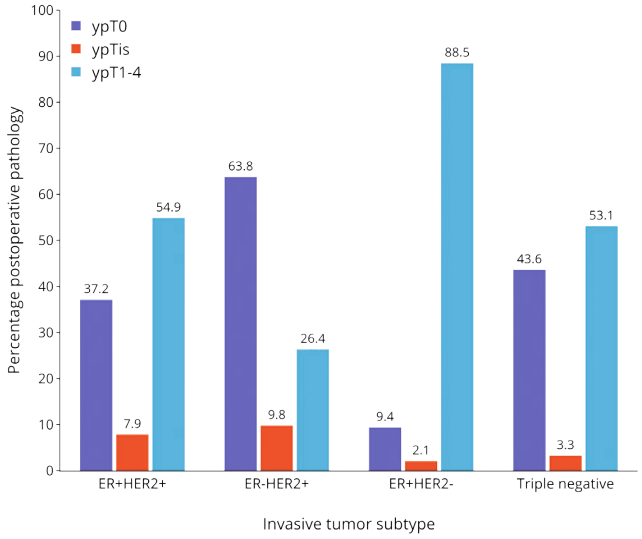

Figure 2: Percentages of ypT0, ypTis and ypT1-4 per tumor subtype

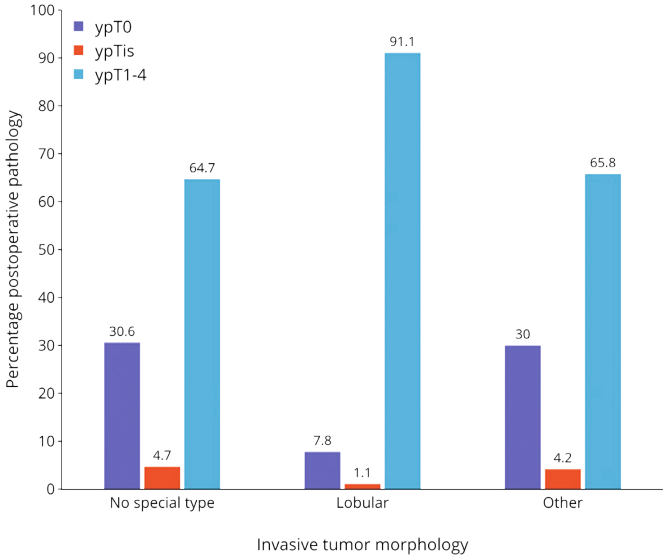

Figure 3: Percentages of ypT0, ypTis and ypT1-4 per tumor morphology

Association of clinicopathological variables and ypTis

Multivariable logistic regression analysis demonstrated higher tumor 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+ tumor 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).

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	REF	0.585-0.990	0.042	REF		
35-49	0.761	0.552-0.928	0.011	0.874	0.624-1.223	0.432
50-74	0.716	0.433-1.687	0.651	0.877	0.630-1.219	0.435
>75	0.855			0.636	0.262-1.543	0.317
Year of diagnosis						
2010-2013	REF			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

Table 3: Univariable and multivariable regression analyses of ypTis *(continued)*

	Univariable Analysis			**Multivariable Analysis**		
	OR	95% CI	p-value	OR	95% CI	p-value
Clinical tumor status						
T1	REF			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
Tumor grade						
1	REF			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**
Tumor subtype						
ER+HER2-	REF			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	REF			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	REF			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*	3.736	3.257-4.284	<0.001			

* Excluded from multivariable analyses due to collinearity with tumor subtype.

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 tumor 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] analyzed 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 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).

In comparison to previous studies reporting patients with ypTis, this is the first study to focus on its association with clinicopathological variables. Tumor subtype analysis shows HER2+ subtypes achieve the highest percentage of ypTis, ranging from 7.9-9.8%. 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 tumor grade as an independent predictor for ypTis. HER2 positivity and higher tumor 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 tumors 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 tumors 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 tumor. 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 tumor 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.

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+ tumor 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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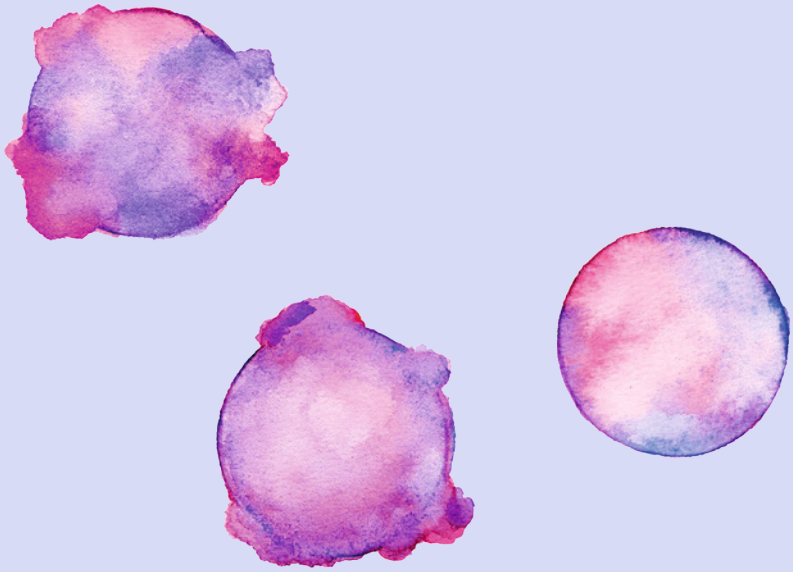
Supplementary material

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)



CHAPTER 3

Pathologic complete response of ductal carcinoma in situ to neoadjuvant systemic therapy in HER2+ invasive breast cancer patients

A nationwide analysis

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Abstract

Purpose: Ductal carcinoma in situ (DCIS) is present in more than half of HER2+ invasive breast cancer (IBC). Recent studies show that DCIS accompanying HER2+ IBC can be completely eradicated by neoadjuvant systemic therapy (NST). Our aim was to determine the percentage of pathologic complete response of the DCIS component in a nationwide cohort and to assess associated clinicopathologic variables. Furthermore, the impact on surgical treatment after NST was investigated.

Methods: Women diagnosed with HER2+ IBC, treated with NST and surgery, between 2010-2020, were selected from the Netherlands Cancer Registry. Pre-NST biopsy and postoperative pathology reports were obtained from the Dutch Nationwide Pathology Databank and assessed for presence of DCIS. Clinicopathologic factors associated with DCIS response were assessed using logistic regression analyses.

Results: A DCIS component was present in the pre-NST biopsy in 1403 (25.1%) of 5598 included patients. Pathologic complete response of the DCIS component was achieved in 730 patients (52.0%). Complete response of DCIS occurred more frequently in case of complete response of IBC (63.4% versus 33.8%, $p<0.001$). ER-negative IBC (OR 1.79; 95%CI 1.33-2.42) and more recent years of diagnosis (2014-2016 OR 1.60; 95%CI 1.17-2.19, 2017-2019 OR 1.76; 95%CI 1.34-2.34) were associated with DCIS response. Mastectomy rates were higher in IBC+DCIS compared to IBC (53.6% versus 41.0%, $p<0.001$).

Conclusion: Pathologic complete response of DCIS occurred in 52.0% of HER2+ IBC patients and was associated with ER-negative IBC and more recent years of diagnosis. Future studies should investigate imaging evaluation of DCIS response to improve surgical decision-making.

Introduction

Neoadjuvant systemic therapy (NST) has gained an important role in the treatment of invasive breast cancer (IBC). Earlier, NST was reserved for locally advanced or inoperable breast cancer, while nowadays NST can be considered in early stage breast cancer.[1] The main goal of NST is to improve oncologic outcomes and additionally to reduce tumor extent in order to improve breast-conserving surgery rates.[2, 3] The response rate depends on the breast cancer subtype, with the highest rates of pathologic complete response (pCR) in HER2+ or triple negative IBC.[4]

In case of HER2+ IBC, a ductal carcinoma in situ (DCIS) component accompanies the invasive tumor in 57.4%-71.6% of patients.[5, 6] Some studies show that in IBC patients with a DCIS component, the pCR rate is lower, while others did not find an association between presence of DCIS and pCR.[7-9] DCIS was previously considered insensitive to NST, due to its protective basal membrane, less dense micro-vasculature and lower proliferative state as opposed to IBC.[10] Subsequently, IBC patients with a DCIS component were less likely to undergo breast-conserving surgery, both in case of primary surgery and after NST.[6, 11]

Recently, a few studies have shown that the DCIS component accompanying HER2+ IBC can respond to NST. Von Minckwitz et al. demonstrated that in their population including 59 HER2+ IBC patients with a DCIS component, 30 (50.8%) showed a pCR of the DCIS component.[7] Groen et al. investigated 138 HER2+ IBC patients with a DCIS component and showed a pCR of DCIS in 46% of patients after NST.[12] In conclusion, current literature suggests response of the DCIS component in HER2+ IBC, but these few articles only concerned small study populations.

Therefore, the aim of this study was to determine the rate of pCR of a DCIS component in HER2+ IBC in a large cohort of patients by performing a nationwide analysis. In addition, the influence of clinicopathologic variables on the rate of pCR of the DCIS component and the impact of the DCIS component on surgical treatment was investigated.

Materials and methods

Data sources and study population

A database from the Netherlands Cancer Registry (NCR) was used for this nationwide retrospective study. Since 1989, trained registrars from the Netherlands Comprehensive Cancer Organization (IKNL) have been collecting data regarding patient, tumor, and treatment characteristics of all newly diagnosed cancer patients in the Netherlands. Upon request, the collected data can be used for research after approval by the privacy board of the IKNL.

Women aged 18 years or older, diagnosed with primary HER2+ IBC, treated with neoadjuvant chemotherapy and targeted therapy followed by surgery between January 2010 and December 2019 in the Netherlands, were included from the NCR for the present study. This population was subsequently linked to PALGA, the Dutch Nationwide Pathology Databank.[13] In this way, all pre-NST biopsy and postoperative pathology reports were collected. Patients were excluded in case of missing pre-NST or postoperative pathology reports or when treatment differed from the Dutch guidelines at the year of diagnosis.

Neoadjuvant systemic therapy and surgical procedure

NST regimens were based on the national guidelines in the year of diagnosis.[14-16] In HER2+ IBC, NST is recommended in case of tumor size ≥5mm or node positive IBC. In general, NST consisted of anthracyclines followed by docetaxel or paclitaxel, in combination with trastuzumab. From 2016 onwards, patients with tumor size ≤2cm received only paclitaxel in combination with trastuzumab for 12 weeks, based on the study by Tolaney et al.[17] Trastuzumab was in all patients continued after NST and surgery in the adjuvant setting for one year in total. Dual anti-HER2 blockade consisting of trastuzumab with pertuzumab was administered from 2017 onwards.

Surgical treatment after NST consisted of breast-conserving surgery or mastectomy and was at the discretion of the treating surgeon in consultation with the patient.

Pathologic assessment of IBC, DCIS and response

Pathologic examination was performed locally according to the Dutch guideline.[14-16] The majority of the pathology laboratories use the Dutch Pathology Module (PALGA) for synoptic reporting, and standard work-up includes tumor subtyping, receptor status and grading. Receptor status was evaluated for IBC, not for the DCIS component. ER status was determined using immunohistochemistry and considered positive if ≥10% of tumor cells stained positive. HER2 status was examined by immunohistochemistry or in situ hybridization, or in a combination, following ASCO CAP guidelines.[18] Tumor grade of IBC was classified according to the modified Bloom-Richardson guideline.[19, 20] In this study population of neoadjuvant treated patients, in general, the IBC grade of the postoperative specimen is recorded in the NCR. In case patients achieve pCR, or when the grade in the biopsy is higher, the grade of the biopsy is recorded.

From PALGA, the presence of a DCIS component was collected from the pre-NST and postoperative pathology reports per patient. The grade of the DCIS component and the presence of comedonecrosis and/or calcifications was assessed in the pre-NST biopsy. In case the presence/absence of comedonecrosis and/or calcifications was not described, these variables were not classified as absent but as “missing value”.

Patients with a recorded DCIS component present in the pre-NST biopsy report were classified as IBC+DCIS and included in the analysis on complete response of DCIS. Complete response was defined as the absence of any DCIS in the postoperative specimen. Resection specimens below 30 grams are embedded entirely for microscopic review. Larger specimens are sampled at at least 1 slide per cm of the expected tumor region.

Study objectives

Primary endpoint was the percentage of pCR of DCIS in HER2+ IBC patients with a DCIS component in the pre-NST biopsy. Secondary endpoints were: association between complete response of IBC and complete response of DCIS, association of other clinicopathologic variables with complete response of DCIS, and impact of the presence of a DCIS component pre-NST on surgical treatment after NST.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 26, Armonk, New York). Descriptive statistics were used to summarize the study population. Complete response of the DCIS component was calculated as percentage of the patients with IBC+DCIS in the pre-NST biopsy. Pearson's χ^2 test was used to compare IBC response with DCIS response, and in this analysis IBC response was defined as absence of invasive breast cancer after NST (ypT0/is). Clinicopathologic variables associated with complete response of DCIS were determined by univariable logistic regression analyses. Subsequently, multivariable logistic regression analyses were performed to adjust for potential confounders. A complete case analysis was performed, in which patients with missing data were excluded from the univariable and multivariable analyses. Surgical treatment was compared between patients with IBC+DCIS and patients with pure IBC in the pre-NST biopsy using Pearson's χ^2 test. A p-value < 0.05 was considered statistically significant.

Results

In the period of 2010-2020, 6380 women with HER2+ IBC received NST followed by surgical treatment in the Netherlands. After exclusion of ineligible patients (n=782), 5598 patients were included in the study population (Figure 1). Subsequently, pathology reports were assessed for the presence of DCIS and 1403 patients (25.1%) showed a DCIS component in the pre-NST biopsy. These patients were included in the analysis on pathologic complete response of the DCIS component. The other 4195 patients (74.9) did not show a DCIS component in the pre-NST biopsy and were excluded from further analyses on DCIS response. An overview of the patient inclusion and classification based on pathology reports is shown in Figure 1.

Patient characteristics

Baseline characteristics of the 1403 patients with IBC+DCIS are shown in Table 1. Patients were most commonly diagnosed with cT2 tumor (50.7%), ER-positive (63.2%) and morphology of invasive carcinoma no special type (91.9%). IBC grade was most commonly grade 3 (47.7%), followed by grade 2 (46.1%). Patients with clinical tumor status Tis (n=8) were included in the study population, since they had clinically node positive disease and were treated with NST. Patients were classified as cTX (n=18) when IBC was detected in pre-NST biopsy but cT status could not be determined on imaging.

Histopathologic characteristics of the DCIS component in the pre-NST biopsies are also shown in Table 1. Comedonecrosis and calcifications were present in 521 (76.8%) and 457 (61.7%) patients, respectively. The DCIS component was most often grade 3 (n=774, 62.3%). DCIS grade and IBC grade were concordant in 61.8% of patients (616/997 patients, Supplementary Table 1).

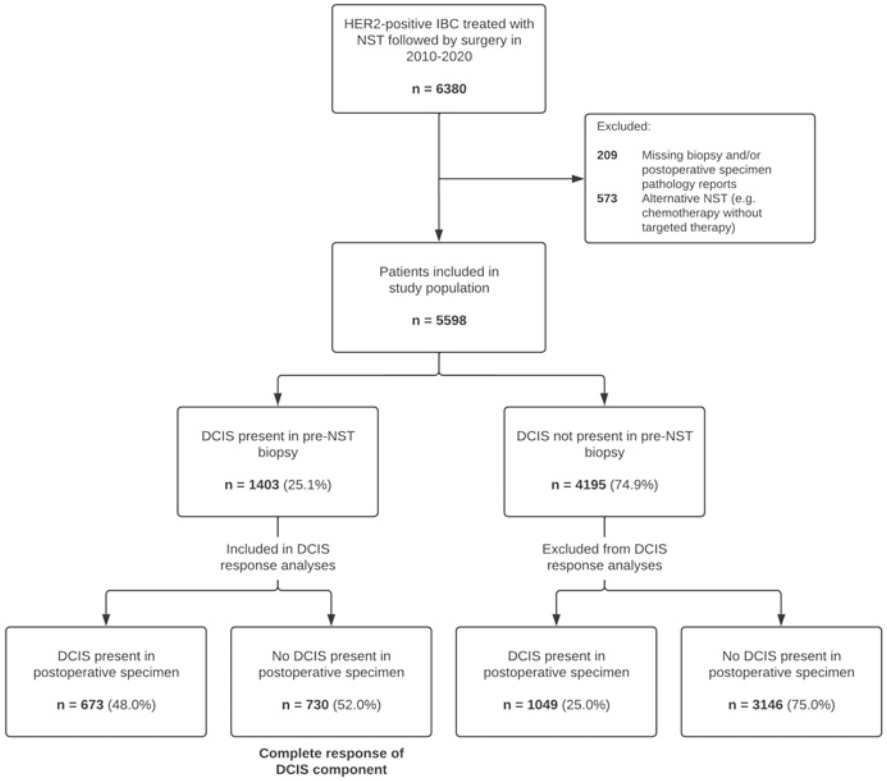

Figure 1: Flowchart of patient selection.

Association between clinicopathologic variables and the complete response of DCIS to NST

As presented in Figure 1, 52.0% of the patients with a DCIS component in the pre-NST biopsy showed pCR of the DCIS component. The number of patients with complete response of IBC (ypT0/is) in comparison to complete response of the DCIS component is shown in Table 2. Complete response of the DCIS component occurred significantly more often in case of complete response IBC compared to patients with residual IBC (63.4% versus 34.1%, p<0.001).

Table 1: Baseline characteristics of patients with IBC with a DCIS component

Characteristics	**IBC + DCIS (n=1403) n (%)**
Age at diagnosis in years (median [range])	48 [22-84]
Year of diagnosis	
2010-2013	259 (18.5)
2014-2016	410 (29.2)
2017-2019	734 (52.3)
Clinical tumor status	
T1	258 (18.4)
T2	711 (50.7)
T3	325 (23.2)
T4	81 (5.8)
Tis[a]	8 (0.6)
TX[a]	18 (1.3)
Missing	2
Clinical nodal status	
N0	618 (44.3)
N1	609 (43.7)
N2-3	167 (12.0)
Missing	9
IBC morphology	
Invasive carcinoma of no special type	1289 (91.9)
Lobular	5 (0.4)
Other	109 (7.7)
IBC grade	
1	68 (6.1)
2	512 (46.1)
3	530 (47.7)
Missing	293

Table 1: Baseline characteristics of patients with IBC with a DCIS component *(continued)*

Characteristics	IBC + DCIS (n=1403) n (%)
IBC ER status	
ER-positive	886 (63.2)
ER-negative	515 (36.8)
Missing	2
DCIS grade	
1	41 (3.3)
2	428 (34.4)
3	774 (62.3)
Missing	160
Comedonecrosis	
Present	521 (76.8)
Absent	157 (23.2)
Missing	725
Calcifications	
Present	457 (61.7)
Absent	284 (38.3)
Missing	662

[a] Diagnosed with cN+ disease and treated with NST

Table 2: Comparison of complete pathologic response of IBC and the DCIS component in the postoperative specimen after NST

No. (%) Total n=1443	Complete response of DCIS	Residual DCIS	p-value
	n = 730/1403 (52.0%)	n = 673/1403 (48.0%)	
Complete response of IBC n = 858/1403 (61.2%)	544/858 (63.4%)	314/858 (36.6%)	**<0.001**
Residual IBC n = 545/1403 (38.8%)	186/545 (34.1%)	359/545 (65.9%)	

The univariable and multivariable logistic regression analyses for clinicopathologic variables associated with complete response of DCIS are shown in Table 3. In univariable analyses, age at diagnosis above 50 (OR 1.41; 95% CI 1.14-1.75), year of diagnosis between 2014-2016 (OR 1.60, 95% CI 1.17-2.19) and between 2017-2019 (OR 1.76, 95% CI 1.34-2.34), clinical tumor status T3 (OR 0.59; 95% CI 0.43-0.82), and ER-negative IBC (OR 1.65; 95% CI 1.33-2.06) were significantly associated with complete DCIS response. Of the pathologic characteristics of the DCIS component, presence of both

comedonecrosis (OR 0.66; 95% CI 0.46-0.94) and calcifications (OR 0.58; 95% CI 0.43-0.78) were significantly associated with a complete response of DCIS to NST. DCIS grade and IBC grade were not associated with DCIS response.

In multivariable logistic regression analyses, year of diagnosis between 2014-2016 (OR 1.64; 95% CI 1.06-2.54) and 2017-2019 (OR 1.83; 95% CI 1.23-2.72, and ER-negative IBC (OR 1.81; 95% CI 1.36-2.39) were independently associated with higher odds for pCR of the DCIS component. Clinical tumor status T3 was independently associated with lower odds for pCR of the DCIS component (OR 0.57; 95% CI 0.39-0.85). The other abovementioned univariable clinicopathologic variables did not reach significance after multivariable logistic regression analysis. Comedonecrosis and calcifications were not included in the multivariable logistic regression analysis because of high numbers of missing data, resulting in too many patients being excluded from the analysis.

Surgical treatment after NST

Surgical treatment differed significantly between patients with IBC+DCIS (n=1403) and patients with pure IBC (n=4195) in the pre-NST biopsy. Mastectomy was more often performed as primary surgical treatment in patients with IBC+DCIS (n=742, 52.9%) compared to pure IBC (n=1681, 40.1%) (p<0.001). Postoperative pathology outcomes (ypT status) are shown in Supplementary Table 2, for IBC patients and for IBC+DCIS patients, according to primary surgery treatment (BCS versus mastectomy). Of the total of 2423 patients receiving primary mastectomy, 1027 (42.4%) showed complete response (ypT0) in the postoperative pathology specimen.

Table 3: Association of clinicopathologic variables with complete response of DCIS to NST in univariable and multivariable regression analyses

Clinicopathologic factors	Complete response of DCIS n/total (%)	Univariable analysis			Multivariable analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Age at diagnosis							
<50	384/795 (48.3%)	REF			REF		
≥50	346/608 (56.9%)	1.41	1.14 – 1.75	0.001	1.24	0.95 – 1.61	0.11
Year of diagnosis							
2010-2013	107/259 (41.3%)	REF			REF		
2014-2016	217/410 (52.9%)	1.60	1.17 – 2.19	0.003	1.64	1.06 – 2.54	**0.03**
2017-2019	406/734 (55.3%)	1.76	1.32 – 2.34	<0.001	1.83	1.23 – 2.72	**0.003**

Table 3: Association of clinicopathologic variables with complete response of DCIS to NST in univariable and multivariable regression analyses *(continued)*

Clinicopathologic factors	Complete response of DCIS n/total (%)	Univariable analysis			Multivariable analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Clinical tumor status							
T1	148/258 (57.4%)	REF			REF		
T2	374/711 (52.6%)	0.83	0.62 – 1.10	0.19	0.77	0.55 – 1.08	0.12
T3	144/325 (44.3%)	0.59	0.43 – 0.82	0.002	0.57	0.39 – 0.85	**0.006**
T4	50/81 (61.7%)	1.20	0.72 – 2.00	0.49	1.19	0.60 – 2.35	0.62
Tis[a]	4/8 (50.0%)	0.74	0.18 – 3.04	0.68	1.37	0.12 – 15.46	0.80
TX[a]	9/18 (50.0%)	0.74	0.29 – 1.93	0.54	1.05	0.22 – 4.94	0.95
IBC grade							
1	34/68 (50.0%)	REF			REF		
2	269/512 (52.5%)	1.11	0.67 – 1.84	0.69	0.78	0.43 – 1.41	0.41
3	287/530 (54.2%)	1.18	0.71 – 1.96	0.52	0.82	0.44 – 1.51	0.52
ER status							
Positive	420/886 (47.4%)	REF			REF		
Negative	308/515 (59.8%)	1.65	1.33 – 2.06	<0.001	1.81	1.36 – 2.39	**<0.001**
DCIS grade							
1	15/41 (36.6%)	REF			REF		
2	215/428 (50.2%)	1.75	0.90 – 3.40	0.10	1.72	0.80 – 3.72	0.17
3	372/774 (48.1%)	1.60	0.84 – 3.08	0.16	1.48	0.69 – 3.19	0.32
Comedonecrosis							
Absent	95/157 (60.5%)	REF			[b]		
Present	261/521 (50.1%)	0.66	0.46 – 0.94	0.02			
Calcifications							
Absent	171/284 (60.2%)	REF			[b]		
Present	213/457 (46.6%)	0.58	0.43 – 0.78	<0.001			

[a] = diagnosed with cN+ disease and treated with NST, [b] = comedonecrosis and calcifications were not included in multivariable analysis due to high number of missing values.
Abbreviations: OR odds ratio, *REF* reference

Discussion

In current studies investigating response to NST in breast cancer treatment, only a few studies have been conducted on the pathologic response of DCIS to NST. To the best of our knowledge, this is the first nationwide analysis investigating a large cohort of HER2+ IBC patients with a DCIS component, and a pCR of DCIS was found in 52.0% of 1403 patients. In addition, we demonstrated that pCR of the DCIS component was associated with complete response of IBC, ER negativity of IBC and a more recent year of breast cancer diagnosis within this study cohort. Patients with a DCIS component in the pre-NST biopsy were significantly more often treated with mastectomy after NST compared to patients without a DCIS component.

The rate of pCR of the DCIS component is consistent with the outcomes of previous, smaller studies. Groen et al. and von Minckwitz et al. investigated the response of a DCIS component in HER2+ IBC patients and found a complete response in 46% and 51% of these patients, respectively.[7, 12] Sun et al. found a slightly lower response rate of 35.7% in their population of 129 HER2-postive IBC patients.[8] Goldberg et al. investigated the response of a DCIS component in IBC patients treated with NST and found a response rate of 33%. This lower response rate can be explained by the study population consisting of different IBC subtypes, including HER2-negative. In comparison to these previous studies, a significantly larger number of patients was included in our study. Therefore, this study may be seen as a confirmation of previous results.

In addition, the potential association between clinicopathologic variables and DCIS response was investigated. First, it was found that complete response of the DCIS component occurred significantly more often in case of complete response of IBC (63.4% versus 34.1%, $p<0.001$). Previous studies show a high concordance in receptor status and grade between IBC and the accompanying DCIS component.[21-23] In our multivariable analysis, ER-negative IBC was found to be significantly associated with complete response of DCIS, which is also associated with higher rates of pCR of the invasive tumor in previous studies.[4, 24] Given that IBC and the accompanying DCIS are comparable in morphology, their response could be affected by the same factors.[21-23] In addition, year of diagnosis between 2014-2016 and 2017-2019 was significantly associated with complete response of DCIS. This could be explained by the continuous improvements in NST in the recent years, including dual anti-HER2 blockade from 2017 onwards. Unfortunately, our database did not include information on treatment with single or dual anti-HER2 blockade. Yet, Groen et al. did find an independent association of dual anti-HER2 blockade with DCIS response in their analysis of 138 HER2+ IBC patients with a DCIS component.[12]

This study has strengths and limitations. A strength is the nationwide database of the NCR combined with the Dutch Nationwide Pathology Databank that allowed for

evaluation of DCIS response on a large scale, in comparison to previous smaller study populations. Second, various clinicopathologic variables were taken into consideration, which enabled evaluation of association between clinicopathologic variables and complete response of the DCIS component.

There are certain limitations worth mentioning. First, due to the retrospective nature of our database, some variables are missing because of insufficient reporting, in particular regarding the pathologic characteristics of the DCIS component. The presence of a DCIS component in the postoperative specimen is a mandatory field in the Dutch Pathology Module since 2009. Unfortunately, the presence of a DCIS component in the pre-NST biopsy is not a mandatory field in completing the module. However, it has been added as an optional field as of 2016 and is often additionally described in the report. Nevertheless, this could have led to an underreporting of the DCIS component pre-NST by the pathologist focusing on the invasive tumor. Moreover, previous research shows there is a high inter-observer variation between pathologists and laboratories in grading DCIS, and the receptor status of the DCIS component is not yet a standard determination.[25] Therefore, these pathologic characteristics of the DCIS component could not be investigated properly in relation to response.

Second, the pre-NST biopsy collection generates another limitation. Since DCIS can appear outside of the area of the invasive tumor, there may be a risk of missing the DCIS component, when targeting the invasive tumor during biopsy. The presence of a DCIS component can therefore be underestimated and this may affect the complete response rate. Moreover, the location and size of the DCIS component outside of the invasive tumor can influence the possibility to perform breast-conserving surgery, but this was not possible to investigate based on the pre-NST pathology reports. Lastly, the higher mastectomy rate in the patients with a DCIS component could not be further evaluated because our database did not include relevant clinical data (e.g. gene expression, extent of mammographic calcifications, the use of oncoplastic and reconstructive surgery, and patients' preference regarding surgical treatment).

Further research into complete response of DCIS in HER2+ IBC is important, because our study confirms the increased mastectomy rate found in previous studies in patients with IBC+DCIS versus patients without a DCIS component (52.9% versus 40.1%, $p<0.001$).[6, 11] In order to implement the potential response of the DCIS component in personalizing surgical treatment after NST, future studies should evaluate whether it is possible to monitor response of the DCIS component by imaging modalities. Moreover, a thorough investigation of pathologic characteristics of the DCIS component in relation to response could be useful to predict DCIS response before start of NST.

Conclusion

In conclusion, in this nationwide retrospective study, we demonstrated that pCR of DCIS to NST occurred in 52.0% of the HER2+ IBC patients with a DCIS component in pre-NST biopsy. These findings are important to create awareness that the presence of a DCIS component in particular should not necessarily indicate the need for mastectomy. Future studies should investigate the evaluation of DCIS response by imaging and the possibility of increasing the chance of breast-conserving surgery. In addition, further assessment of specific pathologic characteristics of DCIS related to response could possibly predict the chance of pCR.

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Supplementary Materials

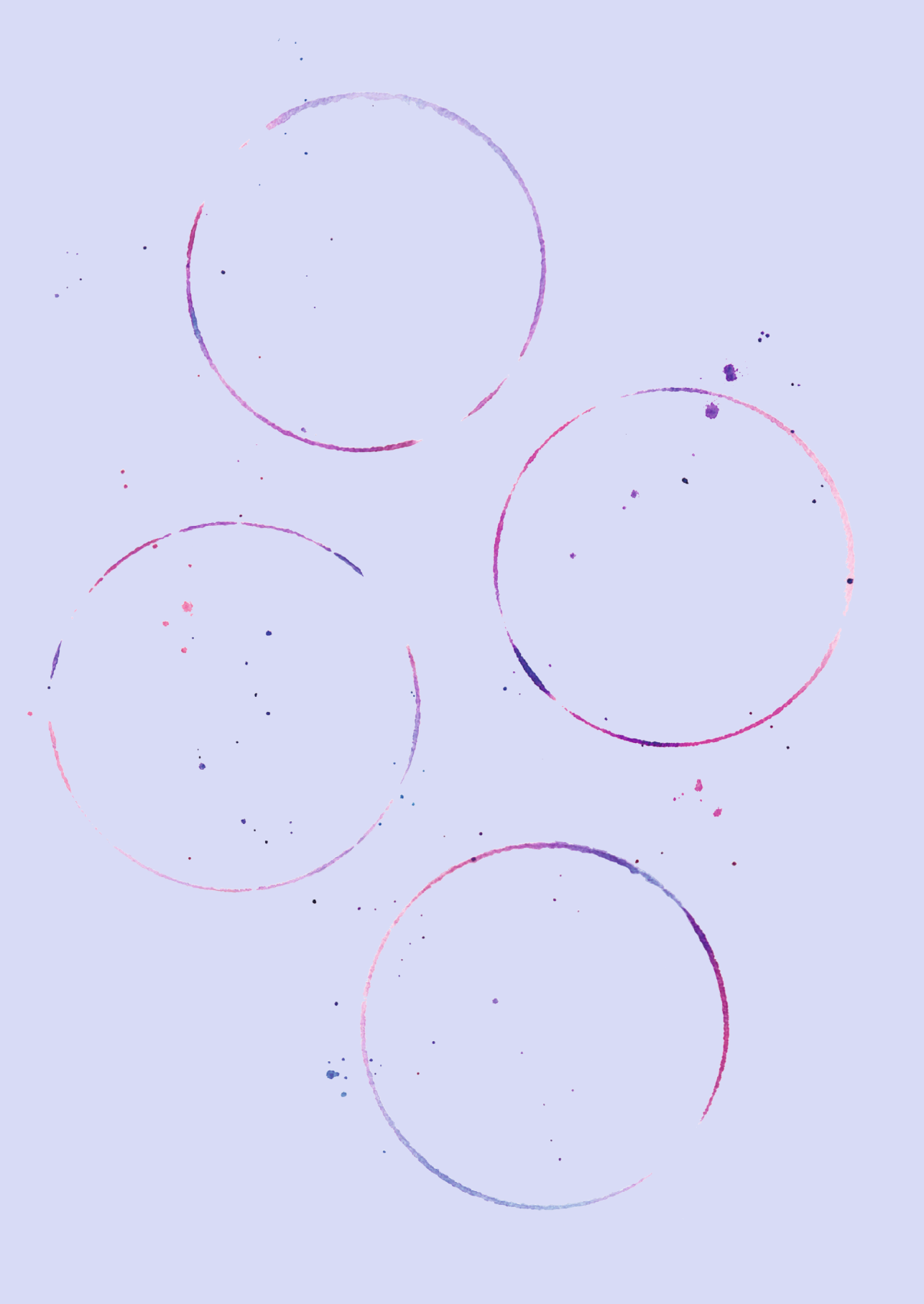
Supplementary Table 1: Comparison of tumor grade between IBC and DCIS

		DCIS grade			Total
		1	*2*	*3*	
IBC grade	*1*	**9**	27	18	54
	2	15	**228**	212	455
	3	8	101	**379**	488
Total		32	356	609	997

In case of concordant tumor grade in DCIS and IBC, numbers are in bold.

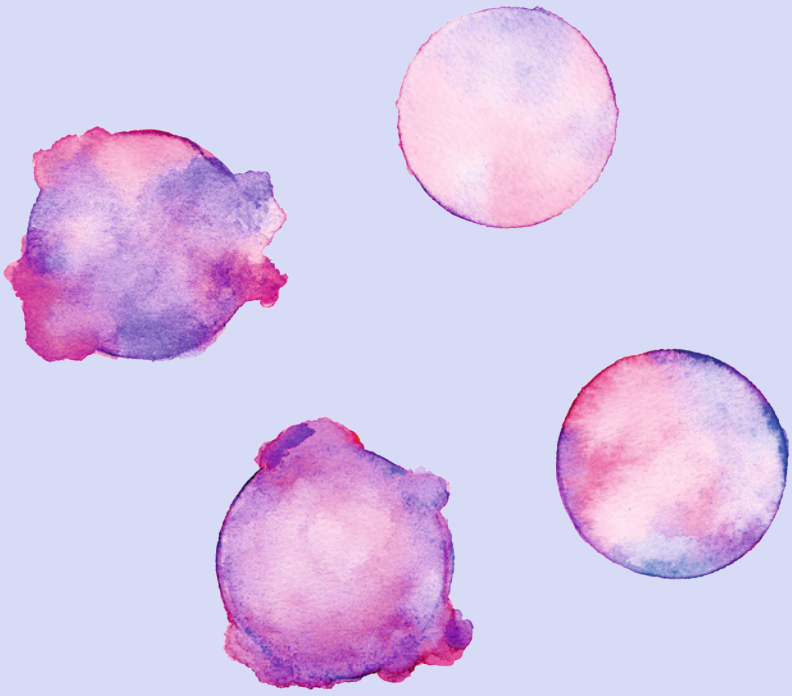
Supplementary Table 2: Postoperative pathology of IBC and IBC+DCIS per primary surgical treatment after NST

	Primary surgical treatment IBC		Primary surgical treatment IBC+DCIS		Total (n (%))
	Breast conserving surgery (n (%))	Mastectomy (n (%))	Breast conserving surgery (n (%))	Mastectomy (n (%))	
ypT status					
ypT0	1231 (49.0)	755 (44.9)	275 (41.6)	272 (36.7)	2533 (45.2)
ypTis	245 (9.7)	185 (11.0)	122 (18.4)	193 (26.0)	745 (13.3)
ypT1-2	663 (26.4)	428 (25.5)	91 (13.8)	77 (10.4)	1259 (22.5)
ypT1-2 + DCIS	360 (14.3)	227 (13.5)	169 (25.6)	174 (23.4)	930 (16.6)
ypT3-4	11 (0.4)	58 (3.5)	1 (0.2)	14 (1.9)	84 (1.5)
ypT3-4 + DCIS	4 (0.2)	28 (1.6)	3 (0.4)	12 (1.6)	47 (0.9)
Total	2514	1681	661	742	5598



PART II

RADIOLOGY



CHAPTER 4

Imaging findings for response evaluation of ductal carcinoma in situ in breast cancer patients treated with neoadjuvant systemic therapy

A systematic review and meta-analysis

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Abstract

Objectives: In approximately 45% of invasive breast cancer (IBC) patients treated with neoadjuvant systemic therapy (NST), ductal carcinoma in situ (DCIS) is present. Recent studies suggest response of DCIS to NST. The aim of this systematic review and meta-analysis was to summarize and examine the current literature on imaging findings for different imaging modalities evaluating DCIS response to NST. More specifically, imaging findings of DCIS pre- and post-NST, and the effect of different pCR definitions will be evaluated on mammography, breast MRI and contrast enhanced mammography (CEM).

Methods: PubMed and Embase databases were searched for studies investigating NST response of IBC, including information on DCIS. Imaging findings and response evaluation of DCIS were assessed for mammography, breast MRI and CEM. A meta-analysis was conducted per imaging modality to calculate pooled sensitivity and specificity for detecting residual disease between pCR definition no residual invasive disease (ypT0/is) and no residual invasive or in situ disease (ypT0).

Results: Thirty-one studies were included. Calcifications on mammography are related to DCIS, but can persist despite complete response of DCIS. In 20 breast MRI studies, an average of 57% of residual DCIS showed enhancement. A meta-analysis of 17 breast MRI studies confirmed higher pooled sensitivity (0.86 versus 0.82) and lower pooled specificity (0.61 versus 0.68) for detection of residual disease when DCIS is considered pCR (ypT0/is). Three CEM studies suggest the potential benefit of simultaneous evaluation of calcifications and enhancement.

Conclusions and Clinical Relevance: Calcifications on mammography can remain despite complete response of DCIS and residual DCIS does not always show enhancement on breast MRI and CEM. Moreover, pCR definition effects diagnostic performance of breast MRI. Given the lack of evidence on imaging findings of response of the DCIS component to NST, further research is demanded.

Introduction

In recent decades, neoadjuvant systemic therapy (NST) has gained an increasing role in the treatment of both early-stage and locally advanced invasive breast cancer (IBC). The advantages of NST are in vivo evaluation of response to NST regimens and the decrease in tumor size, thereby increasing the likelihood of breast-conserving surgery and improving long-term outcomes.[1-3] Monitoring response to NST with the use of accurate imaging modalities is therefore important in surgical planning and estimation of prognosis.[4] Previous literature has indicated breast MRI is currently the most accurate imaging modality to monitor response of the primary tumor, yet a recent meta-analysis estimated similar accuracy of contrast-enhanced mammography (CEM) as well.[5-9]

In approximately 45-60% of patients with IBC, a ductal carcinoma in situ (DCIS) component is present in the biopsy specimen at diagnosis.[10-12] DCIS has variable presentation, which hinders easy detection on imaging.[13, 14] On mammography, malignant calcifications or calcifications outside or adjacent to the mass can be considered suspicious for the presence of DCIS. However, 25% of DCIS cases do not contain mammographic calcifications.[15, 16] On breast MRI, DCIS tends to present as non-mass enhancement (NME), however, low grade DCIS might lack enhancement.[17, 18] On CEM, DCIS can be detected based on the presence of enhancement and/or calcifications.[19]

Many previous studies investigating response monitoring focused on predicting response of IBC rather than the presence of residual DCIS. Moreover, varying definitions for pathological complete response (pCR) are used in which residual DCIS is most often considered pCR.[20] On the contrary, accurate detection of residual DCIS is relevant, as it can be a cause for recurrence.[21] It was previously assumed that DCIS responds poorly to NST.[22] However, recent retrospective studies have demonstrated that DCIS adjacent to IBC can be fully eradicated after NST.[12, 23, 24] Consequently, the need to monitor the response of DCIS to NST by imaging, in addition to IBC response assessment, has increased in order to improve surgical planning.

Therefore, the aim of this systematic review and meta-analysis is to summarize and examine the current literature on imaging findings for different imaging modalities evaluating DCIS response to NST. More specifically, imaging findings of DCIS pre- and post-NST, and the effect of different pCR definitions will be evaluated on mammography, breast MRI and CEM.

Materials and methods

Literature search

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[25] PubMed and Embase databases were searched for eligible studies, and the last search was performed on 09.08.2022. Studies reporting mammography, breast MRI and CEM results in predicting response to NST in the presence of IBC were included using the following keywords: breast neoplasm, ductal carcinoma in situ, mammography, contrast enhanced mammography, magnetic resonance imaging, neoadjuvant systemic therapy, and other synonyms. References of included studies and relevant systematic reviews or meta-analyses were searched for additional eligible studies. There was no limitation for the year of publication, but only studies written in English were included. Supplemental tables S1 and S2 show the full-search strategies used.

Study selection

After removal of duplicates, titles and abstracts were screened and assessed for eligibility by two independent reviewers (R.P. and T.v.N.). Subsequently, full texts were read and considered eligible for inclusion if they met the predefined inclusion criteria: 1) mammography (MG), breast MRI, or CEM performed (before and) after completion of NST; 2) imaging findings correlated to postoperative pathology; 3) a clear description of the definition of pCR; and 4 information on the DCIS component related to imaging. It was decided to exclude conference abstracts, case reports and case series, animal studies, reviews and articles on alternative treatment (e.g. neoadjuvant radiation therapy) or alternative imaging modalities (ultrasound, computed tomography). Regarding MRI methods, only dynamic contrast-enhanced (DCE) MRI data were used while diffusion-weighted imaging (DWI) was excluded. Any discrepancies during study selection were resolved in a consensus meeting between the reviewers.

Studies were eligible for meta-analysis when: 1) the number of patients with pCR (ypT0) and residual DCIS without residual invasive tumor (ypTis) was reported, and 2) post-NST data on true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases were provided per pCR definition (ypT0 versus ypT0/is). Studies were also included in the meta-analysis when the above-mentioned information could be deduced from reported diagnostic performances.

Data extraction and quality assessment

Data extraction was performed by two reviewers (R.P. and C.M.d.M.) independently and any discrepancies were resolved by discussion with a third reviewer (T.v.N.). Collection of study information concerned study design, number and type of participants included, years of patient inclusion and neoadjuvant treatment administered. For the imaging modalities used, information on vendor, settings and imaging protocols was collected.

Image evaluation during NST was summarized regarding subtraction images, region of interest analyses, computer aided detection and enhancement evaluation (subjective and/or objective, and specific late phase enhancement evaluation for DCIS detection[26, 27]). Definitions used for radiological complete response (rCR) and pCR in the included studies were summarized and evaluated. The definition of pCR was recorded as: absence of residual invasive and in situ component (ypT0) or absence of residual invasive tumor, irrespective of the presence of residual DCIS (ypT0/is).

Quality of the included studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[28] This tool comprises four domains: patient selection, index test, reference standard, and flow and timing. Domains were tested for risk of bias and concerns regarding applicability.

Statistical Analysis

For each imaging modality (mammography, breast MRI and CEM), information on three topics was summarized: imaging findings of DCIS pre-NST, imaging findings of DCIS post-NST and response evaluation of DCIS. Response evaluation consisted of studies investigating the response of DCIS according to imaging findings (i.e. pre- versus post-NST or correlation of imaging findings to potential response at histopathology of the surgical specimen).

The effect of pCR definition on diagnostic performance was investigated in a meta-analysis. Studies that reported data on TP, TN, FP and FN cases per pCR definition were included for meta-analysis per imaging modality. With this information, two-by-two contingency tables were extracted per pCR definition. Positive was regarded as residual disease at final pathology or imaging and negative as either a pCR or rCR. Subsequently, the pooled sensitivity and pooled specificity with corresponding 95% confidence intervals (95% CIs), were calculated separately for both definitions of pCR (i.e. ypT0 and ypT0/is). The heterogeneity among the included studies was explored using Cochran's Q test and the inconsistency index (I^2), with $P<0.05$ or $I^2 >50\%$ indicating the presence of substantial heterogeneity. All statistical analyses were carried out using statistical software STATA (version 17.0; Stata Corp.).

Results

Study selection

A total of 5247 studies were found by searching the Pubmed and Embase databases. After duplicates had been removed, titles and abstracts were screened, and 3847 studies were excluded as irrelevant. The remaining 301 full texts were read and another 270 studies were excluded for various reasons (Figure 1). Finally, 31 studies (4987 patients in total) were included in this systematic review, of which 17 were used for meta-analysis.

Figure 1 includes a flowchart showing the literature selection. Table 1 provides an overview of included studies.

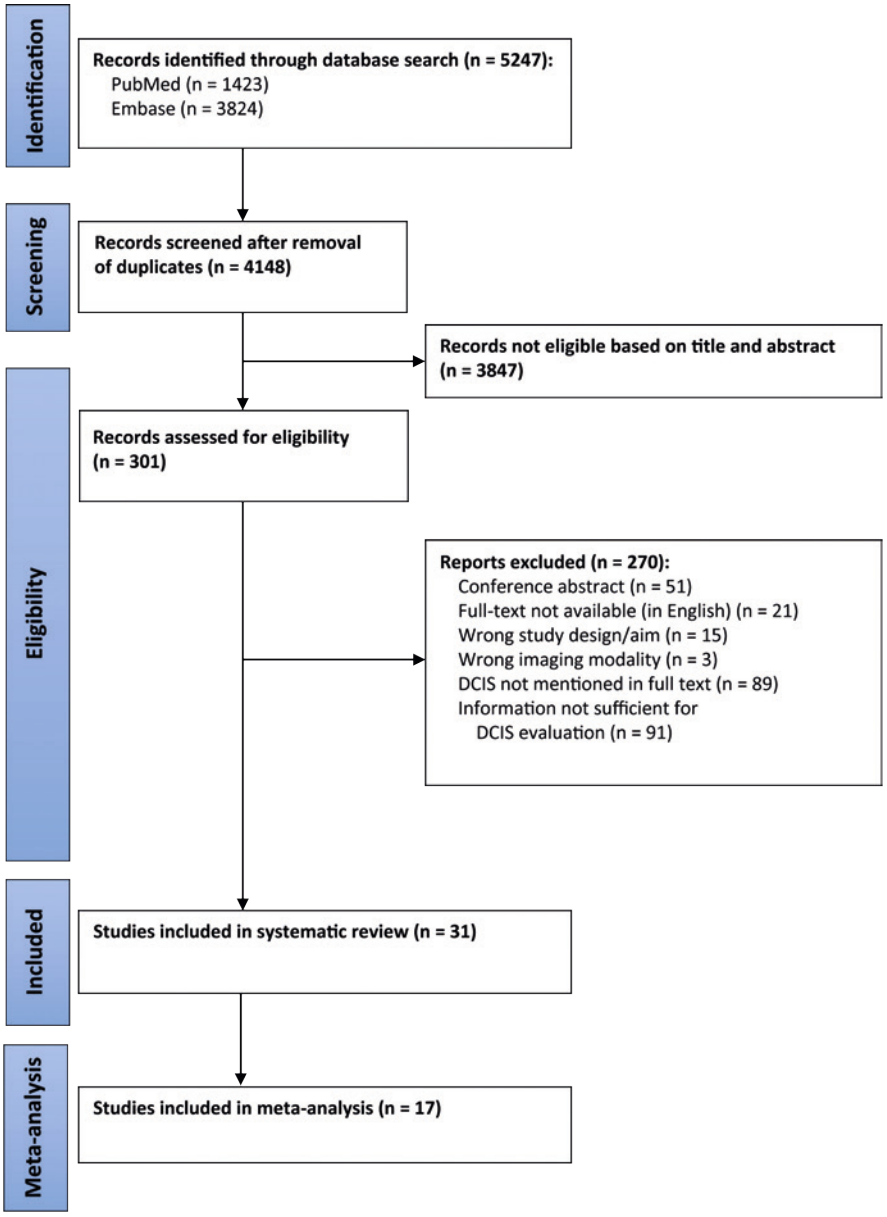

Figure 1: Overview of study selection

Table 1: Characteristics of included studies

Study (year)	Country	Study design	Patients	Imaging modality	pCR definition
Adrada (2015)[29]	USA	Retrospective	106	MG	ypT0
An (2017)[30]	Korea	Retrospective	29	MG	ypT0
Bernardi (2022)[31]	Italy	Prospective	51	MRI+CEM	ypT0
Bodini (2004) [32]	Italy	Prospective	73	MRI	ypT0[a]
Böttcher (2014)[33]	Germany	NR	54	MRI	ypT0
Chen (2008)[34]	USA	NR	51	MRI	ypT0/is
Choi (2012)[35]	Korea	Retrospective	46	MG+MRI	ypT0/is
De Los Santos (2011)[36]	USA	NR	81	MRI	ypT0 & ypT0/is
Feliciano (2017)[37]	USA	Retrospective	90	MG	ypT0
Gampenrieder (2019)[38]	Austria	Retrospective	246	MRI	ypT0/is N0
Goldberg (2017)[23]	Israel	Prospective	92	MG	ypT0
Groen (2021)[12]	Netherlands	Retrospective	316	MG+MRI	ypT0[a]
Hahn (2014)[39]	South Korea	Retrospective	78	MRI	ypT0/is
Hayashi (2013)[40]	Japan	NR	264	MRI	ypT0/is
Iotti (2017)[41]	Italy	Prospective	54	CEM	ypT0
Iotti (2021)[42]	Italy	Retrospective	36	CEM	ypT0 & ypT0/is
Iwase (2018)[43]	Japan	Retrospective	201	MRI	ypT0
Khazindar (2021)[44]	SAU	Retrospective	52	MRI	ypT0 & ypT0/is
Kim (2020)[45]	Korea	Retrospective	96	MG	ypT0
Lee (2017)[46]	USA	Prospective	30	MRI	ypT0
Li (2014)[47]	China	Retrospective	187	MG	ypT0 & ypT0/is
Mirza (2016)[48]	UK	NR	67	MRI	ypT0 & ypT0/is
Mistry (2015)[49]	India	Retrospective	446	MG	NR
Nakamura (2007)[50]	Japan	NR	115	MRI	ypT0
Negrão (2019)[51]	Brazil	Retrospective	219	MRI	ypT0/is
Park (2016)[52]	Korea	Retrospective	117	MG+MRI	ypT0/is
Santamaria (2019)[53]	Spain	Retrospective	81	MRI	ypT0 & ypT0/is
van Ramshorst (2017)[54]	Netherlands	Retrospective	330	MRI	ypT0/is
Vinnicombe (1996)[55]	UK	Retrospective	95	MG	ypT0[a]
Woodhams (2010)[56]	Japan	NR	69	MRI	ypT0[a]
Zhang (2020)[57]	China	Retrospective	1219	MRI	ypT0 & ypT0/is

[a]: not reported, derived from text. Abbreviations: MG = mammography, MRI = magnetic resonance imaging,
CEM = contrast-enhanced mammography, NR = not reported

Quality of included studies

The results per category and study are reported in Table S3 and Figure 2 summarizes the risk of bias and applicability concerns. Overall, there was a low risk of bias regarding patient selection, index test and reference standard. The risk of bias was often unclear for "flow and timing" because studies did not report time between imaging post-NST and surgery.

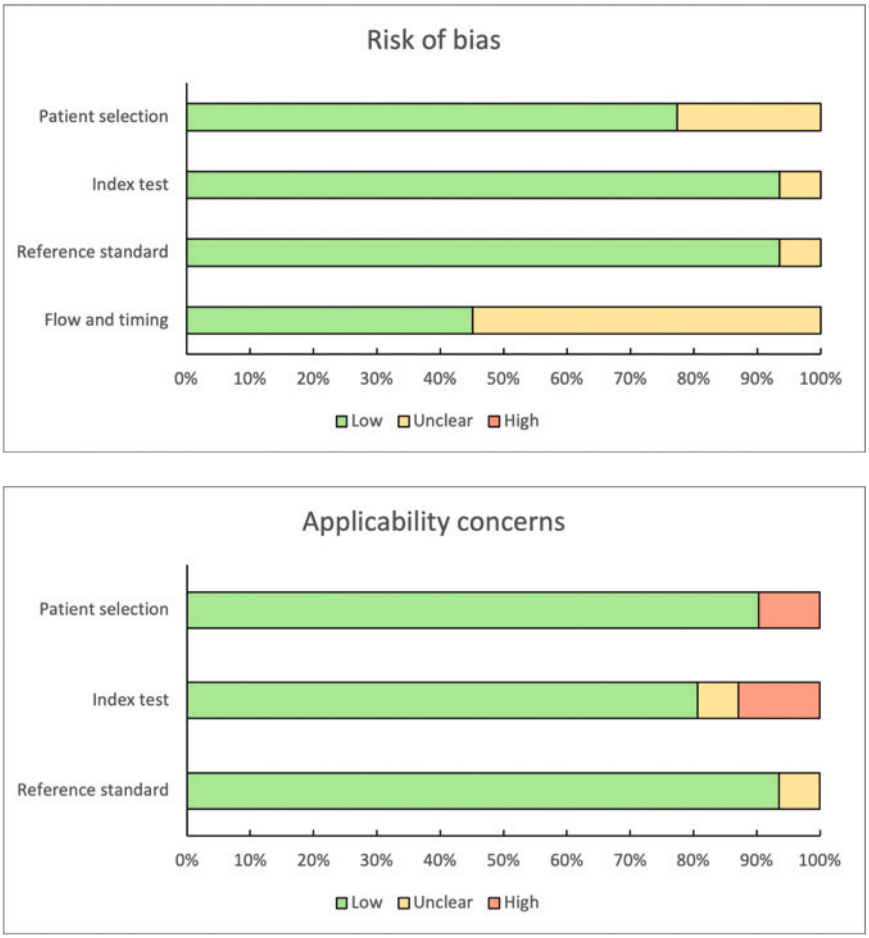

Figure 2: Risk of bias and applicability concerns

Imaging findings of DCIS

Table 2 presents a summary of imaging findings pre- and post-NST per imaging modality. The characteristics of the imaging modalities, image evaluation, and the definitions used for rCR are reported in Table S4.

Table 2: Pre-NST and post-NST imaging findings per modality

Study (year)	**Patients (n)**	**Pre-NST findings of DCIS**	**Post-NST findings of DCIS**		
Mammography		*% of calcifications related to a DCIS component*	*% of calcifications related to a DCIS component*	*% of DCIS without calcifications*	*% of calcifications related to benign pathology*
Adrada (2015)	106	64.1%	29.2%	48.4%	40.6%
An (2017)	29	NR	34.5%	NR	44.8%
Choi (2012)	46	NR	45.8%	26.7%	54.2%
Feliciano (2017)	90	53.3%	36.7%	34%	62.2%
Groen (2021)	316	50.3%	NR	NR	NR
Kim (2020)	96	NR	50%	15.8%	38.5%
Li (2014)	187	NR	NR	NR	NR
Mistry (2016)	446	NR	60%	55.3%	NR
Vinnicombe (1996)	95	NR	42.1%	41.2%	NR
Breast MRI		*Pre-NST MRI findings of a DCIS component*	*Number of patients with ypTis*	*% ypTis with MRI enhancement*	*% ypTis without MRI enhancement*
Bernardi (2022)	51	NR	12	66.7%	33.3%
Bodini (2004)	73	NR	4	75%	25%
Böttcher (2014)	54	NR	6	33.3%	66.7%
Chen (2008)	51	NR	6	16.7%	83.3%
Choi (2012)	46	NR	15	93.3%	6.7%
De Los Santos (2011)	81	NR	9	66.7%	33.3%
Gampenrieder (2019)	246	NR	11	36.4%	63.6%
Hahn (2014)	78	NR	6	100%	0%
Hayashi (2013)	260	NR	32	78.1%	21.9%
Iwase (2018)	201	NR	14	64.3%	35.7%
Khazindar (2021)	52	NR	11	45.5%	54.5%
Lee (2017)	30	NR	2	0%	100%
Mirza (2016)	69	NR	6	33.3%	66.7%
Nakamura (2007)	115	NR	11	72.7%	27.3%
Negrão (2019)	219	NR	9	66.7%	33.3%
Park (2016)	117	NR	50	68%	32%
Santamaria (2019)	81	NR	8	75%	25%
Van Ramshorst (2017)	296	NR	69	23.2%	76.8%
Woodhams (2010)	69	NR	7	57.1%	42.9%
Zhang (2020)	1219	NR	60	68.3%	31.7%

Table 2: Pre-NST and post-NST imaging findings per modality *(continued)*

Study (year)	**Patients (n)**	**Pre-NST findings of DCIS**	**Post-NST findings of DCIS**		
CEM		*Pre-NST CEM findings of a DCIS component*	*Number of patients with ypTis*	*% enhancement in patients with ypTis*	*% calcifications in patients with ypTis*
Bernardi (2022)	51	NR	12	58.3%	NR
Iotti (2017)	46	NR	3	33.3%	NR
Iotti (2021)	36	NR	5	40%	100%

Abbreviations: DCIS = ductal carcinoma in situ, NST = neoadjuvant systemic therapy, MRI = magnetic resonance imaging, CEM = contrast-enhanced mammography, ypTis = residual DCIS in absence of residual invasive tumor, NR = not reported.

Pre-NST

Three mammography studies have reported imaging findings on pre-NST mammograms of patients with invasive breast cancer with a DCIS component.[12, 29, 37] More than half of the calcifications found on pre-NST mammography (50.3%-64.1%) were related to a DCIS component.

Two studies on mammography and breast MRI investigated a study population of patients achieving pCR (ypT0/is) after NST.[35, 52] Pre-NST imaging findings of mammography and breast MRI were compared between the patients with ypT0 and ypTis: patients achieving ypTis more often had calcifications on mammography (54%-87%) pre-NST compared to patients achieving ypT0 (16%-35%). In addition, non-mass enhancement on breast MRI pre-NST was more frequent in patients achieving ypTis (28%-80%) versus ypT0 (12%-32%).

The remaining included breast MRI and CEM studies reported no imaging findings related to a DCIS component prior to NST.

Post-NST

Eight mammography studies have investigated the post-NST mammography findings of DCIS.[29, 30, 35, 37, 45, 47, 49, 55] Calcifications on mammography post-NST were related to DCIS (adjacent to IBC or residual DCIS only) in 29.2%-60%.[29, 30, 35, 37, 45, 49, 55] Compared to ypT0, patients with ypTis more often show calcifications on post-NST mammography (73.3% versus 41.9%).[35] Of the DCIS components in the surgical specimen post-NST, 15.8%-55.3% are not related to calcifications on mammography.[29, 35, 37, 45, 49, 55] In addition, 38.5%-62.2% of calcifications post-NST were related to benign pathology.[29, 30, 35, 37, 45] Li et al. showed that calcifications post-NST outside the mass and calcifications that increased in size after NST had the highest percentage of ypTis (11.5% and 22.2%, respectively).[47]

The included breast MRI studies only described imaging findings of patients with ypTis rather than residual IBC with a DCIS component. Twenty breast MRI studies have investigated the percentage of patients with ypTis that showed enhancement on breast MRI (Table 2). The average percentage of ypTis that enhanced on MRI in these studies was 57.4% (200/348 patients).[31-36, 38-40, 43, 44, 46, 48. 50-54, 56, 57] Two breast MRI studies demonstrated that ypTis was more frequently observed (68%-93.3%) as residual disease on breast MRI post-NST compared to ypT0 (37-64.5%).[35, 52] Choi et al. found a significant correlation between residual DCIS size on breast MRI post-NST and histopathology (r=0.81, P=0.0003).[35]

The three CEM studies included showed the varying presentation of ypTis and discrepancy in comparison to MRI regarding enhancement.[31, 41, 42] The study by Iotti et al. published in 2017 showed that MRI estimated the three patients with ypTis as complete response, while CEM showed residual enhancement in one.[41] The study by Bernardi et al. showed that CEM demonstrated enhancement in 7 of 12 patients with ypTis, compared to 8 patients with enhancement on MRI.[31] The other study by Iotti et al. published in 2021 demonstrated that on CEM, 3 out of 5 patients with ypTis had no residual enhancement, but all patients had residual pleiomorphic calcifications.[42]

Response evaluation of DCIS

Two studies have investigated the imaging findings of patients with response of DCIS.[12, 23] Goldberg et al. investigated imaging findings of patients with response of DCIS on mammography. In their prospective cohort, 10 of 36 patients with a DCIS component pre-NST achieved pCR. In addition, 92% of calcifications remained on post-NST mammography despite complete response of the DCIS component.[23]

Groen et al. investigated mammography and breast MRI findings associated with response of DCIS. Mammography was performed only pre-NST and not post-NST. They defined rCR on MRI as no residual enhancement within the original tumor bed after NST and near complete response as only minimal residual enhancement in the original tumor bed, without any components clearly identifiable as original tumor. Multivariable logistic regression analyses reported absence of suspicious calcifications on pre-NST mammography (OR 3.51 (1.32-9.32)) and (near) complete response post-NST on breast MRI (OR 4.14 (1.36-12.59)) as independent factors associated with response of DCIS.[12]

A clinical example of mammography and MRI images of a patient with pCR of both IBC and DCIS during NST is presented in Figure 3. Mammography post-NST showed a persisting area of pleiomorphic calcifications, while on breast MRI post-NST no persisting enhancement was found, classified as rCR.

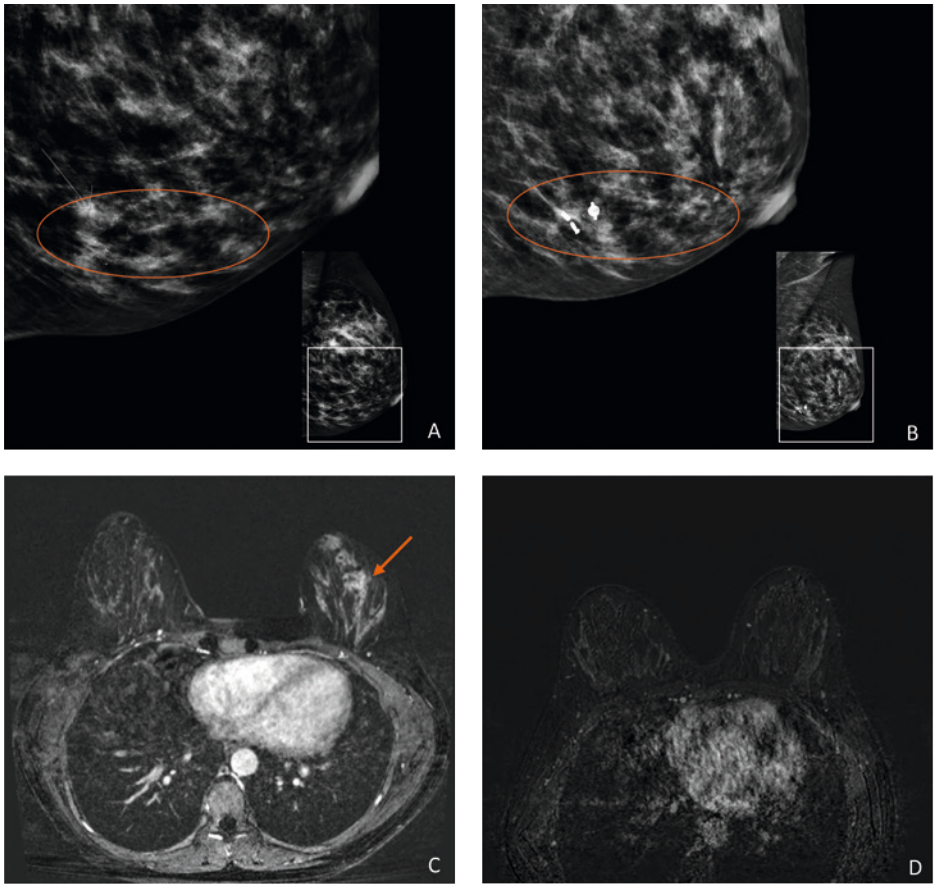

Figure 3: Pre- (a, c) and post-NST (b, d) mammography and MRI images of a patient with pCR of both IBC and DCIS. Fine pleiomorphic calcifications remained on mammography (a, b, orange circle), while NME (c, orange arrow) disappeared, classified as rCR on MRI

Meta-analysis of diagnostic performance in different pCR definitions

Table 1 presents the definition of pCR used in the included studies. The mammography studies most frequently used ypT0 (7/11 studies) as pCR definition. In the MRI studies, 8 used ypT0/is, 8 used ypT0, and 5 used both definitions. In the 3 CEM studies included, two used ypT0 and one used both definitions. Seventeen breast MRI studies were included in the meta-analysis.[31-34, 36, 38-40, 46, 48, 50, 51, 53, 54, 56, 57] Meta-analyses for mammography and CEM could not be performed, due to limited amount of studies including data on pCR definitions. In total, 787 patients in 17 studies achieved ypT0 and 269 patients had ypTis. Of the patients with ypTis, 143 out of 269 (53.2%) showed enhancement on MRI (Table S5). Figure 4 shows the pooled sensitivity and specificity per pCR definition. When ypT0/is is used, and DCIS is thus considered residual disease, sensitivity is slightly higher (0.85 versus 0.83) and specificity is lower (0.61 versus 0.69)

compared to pCR defined as ypT0. There is a high heterogeneity in both groups, with I^2 ranging from 84.2%-95.6% (Figure 4).

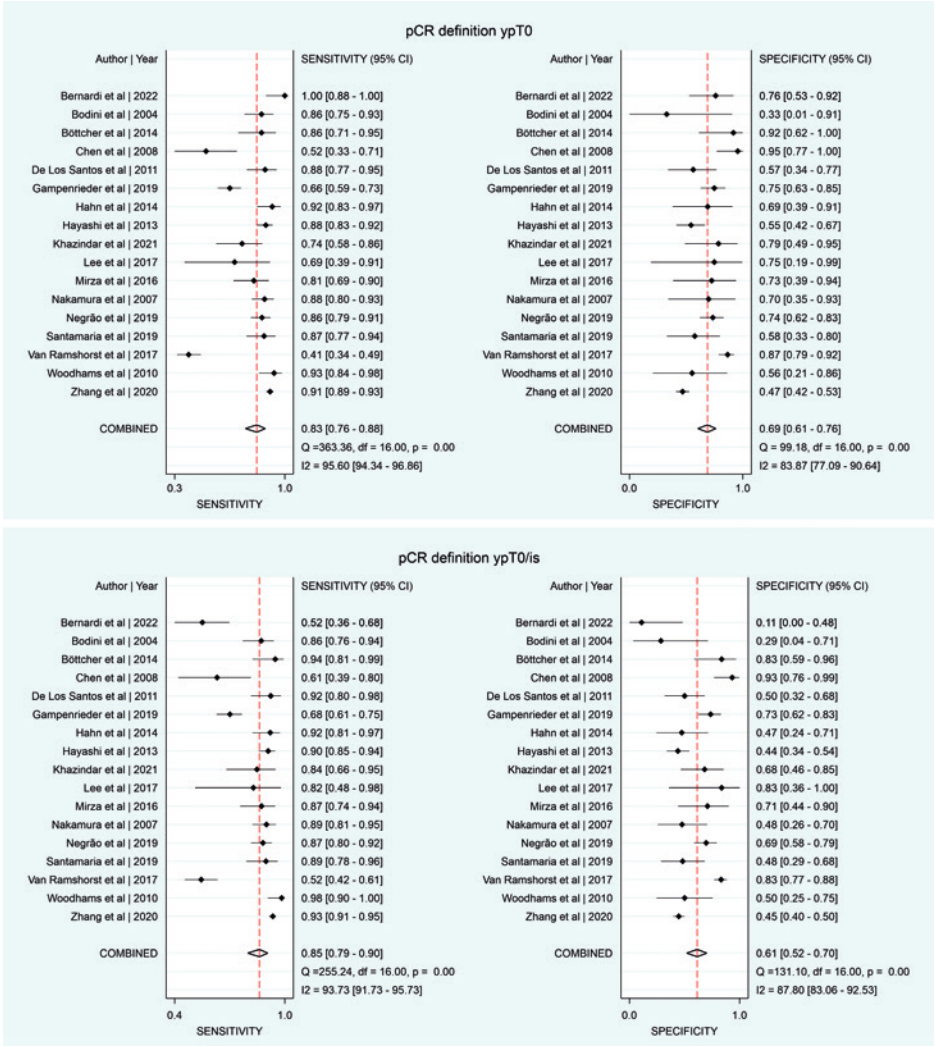

Figure 4: Pooled sensitivity and specificity for detection of residual disease by MRI between pCR defined as ypT0 and ypT0/is

Discussion

Since recent literature indicates potential response of DCIS to NST, accurate evaluation of both DCIS and IBC during NST is important for surgical planning. According to our knowledge, this is the first review to summarize the literature on response evaluation of the DCIS component in IBC patients with the imaging modalities mammography, breast MRI and CEM. The 31 included studies did not specifically investigate imaging findings of DCIS response. Therefore, this review summarized additional information regarding pre- and post-NST imaging findings of a DCIS component and the influence of pCR definition on diagnostic performance. In general, we demonstrated that different findings per imaging modality are related to a DCIS component during NST.

On mammography, calcifications pre-NST are most often related to a DCIS component. In contrast, up to 50% of DCIS post-NST did not have calcifications and calcifications post-NST can remain without associated DCIS or IBC.[29, 37] Therefore, remaining calcifications should not generally be considered as residual DCIS but may represent a necrotic tumor bed in case of complete response of DCIS and IBC.[58, 59] Morphology of the calcifications can add important information to distinguish between malignant and benign findings. Previous mammographic studies have shown that fine-linear branching and fine pleiomorphic calcifications are most suspicious for high-grade DCIS with or without invasive breast cancer.[15, 60, 61] However, there were no studies correlating the morphology of calcifications to a DCIS component during NST.

On breast MRI, contrast enhancement of residual DCIS is varying. Overall in this review, 57% of the cases with residual DCIS (ypTis) demonstrated enhancement post-NST. There are a few possible explanations for the variable enhancement of residual DCIS. First, the sensitivity for detection of DCIS adjacent to IBC on MRI ranges between 39% and 84.9%.[62, 63] Another explanation might be the influence of the grade of DCIS on imaging findings. Previous literature showed that high-grade DCIS more often presents as an enhancing mass, while low-grade DCIS shows non-mass or no enhancement.[17] Moreover, MRI sensitivity is higher for high grade DCIS than for low grade DCIS (98% compared to 80%).[62] It is important to note that, as presented in Table S4, the definition of rCR and the evaluation of enhancement differed between studies, which could have also contributed to the varying percentages of enhancement in patients with residual DCIS (Table 2).

No included studies described MRI findings of DCIS pre-NST. Considering a potential response of DCIS to NST, it is important to detect the DCIS component pre-NST and future studies should evaluate the change of imaging findings during NST compared to DCIS response.

Regarding CEM, only three studies were included in this review presenting information on a DCIS component. These three studies demonstrated a possible benefit of combining evaluation of calcifications and enhancement to detect residual DCIS. Compared to the other imaging modalities, CEM has been introduced more recently and overall less research has been conducted. Studies investigating CEM findings of pure DCIS described that enhancement and calcifications features can contribute to differentiating between invasive breast cancer, DCIS and benign lesions. Absence of enhancement in the presence of calcifications is mainly related to low-grade DCIS, although high-grade DCIS, like IBC, usually shows enhancement.[64, 65] This is in line with CEM studies in this systematic review in which part of the residual DCIS cases would have been missed on the basis of enhancement alone. The included CEM studies did not specify whether the evaluation of enhancement was based on objective or subjective assessment.

In general, most studies on NST response evaluation adhere to the pCR definition ypT0/is, thus considering residual DCIS as pCR. Our meta-analysis including 17 breast MRI studies demonstrated a slightly higher pooled sensitivity and a lower pooled specificity for detection of residual disease when DCIS was considered pCR (ypT0/is). This difference is explained by the higher numbers of false positives in pCR definition ypT0/is, because more than half of residual DCIS (53.2%) showed enhancement. A previous meta-analysis by Marinovich et al. demonstrated similar results, with an increase in accuracy (i.e., a lower number of false positives and/or negatives) found when residual DCIS was excluded from the pCR definition.[6] However, it is important to emphasize that the differences in pooled sensitivity and specificity are small and that there is a high heterogeneity between included studies. More research is needed to investigate potential factors influencing the enhancement of residual DCIS, as this affects the diagnostic performance.

This meta-analysis further highlights the importance of distinguishing pCR from ypTis to establish true pCR. In our nationwide analysis of patients treated with NST, an average of 4.3% had ypTis, increasing up to 9.8% in HER2+ invasive tumors.[66] Various clinical trials (e.g., NCT04578106) are investigating the possibility of omitting surgery in patients with expected pCR. Although no difference in prognosis between ypT0 and ypTis was reported in previous studies, it remains important to detect residual DCIS in these patients since this might cause positive surgical margins or even a recurrence of invasive cancer.[67, 68] Moreover, von Minckwitz et al. demonstrated that ypT0/is has an increased risk of recurrence compared to ypT0.[69] Current ongoing trials on fine needle aspiration or vacuum-assisted core biopsies (NCT03188393, NCT02945579) investigate the potential of biopsies near the clip marker post-NST. However, an in situ component outside of the invasive tumor should be considered.

There are certain limitations to this review. First, there was a significant heterogeneity overall and per imaging modality. Between studies, the populations, imaging protocols,

image evaluation, and study outcomes differed notably. Since this is the first review on this topic, this heterogeneity was expected in advance. Second, this review is influenced by the quality of the included studies, and despite an overall low risk of bias determined by the QUADAS-2 tool, there were applicability concerns for patient selection and the index test. Third, the results regarding the evaluation of the DCIS component during NST were often only described as secondary outcomes. Apart from the studies by Choi et al.[35] and Park et al.[52] aiming to distinguish between ypT0 and ypTis, the described imaging protocols of the included studies did not address detecting (residual) DCIS. For example, specific late phase enhancement evaluation, described as typical for DCIS in previous studies[26, 27], was only performed in two included studies.[33, 53] This makes some of the results difficult to interpret and additional information on extent or imaging characteristics of DCIS were partially under-reported. However, due to the systematic approach of this review, we were able to summarize and evaluate the most important features of DCIS on imaging during NST. Future research should focus on DCIS adjacent to IBC to investigate possible influencing factors on diagnostic performance of imaging modalities.

Conclusion

In conclusion, different imaging findings on mammography, breast MRI and CEM are related to a DCIS component. Most important to note is that residual calcifications do not necessarily indicate residual DCIS and that approximately 57% of residual DCIS shows enhancement on breast MRI. The meta-analysis shows a higher sensitivity and a lower specificity for detection of residual disease when DCIS is considered pCR (ypT0/is). Combining the imaging findings of calcifications and enhancement on CEM can be of potential benefit for evaluation of DCIS adjacent to IBC. This review provides a rationale for further research into imaging of DCIS adjacent to IBC during NST, given the current lack of evidence on imaging findings of response of the DCIS component.

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Supplementary Materials

Supplemental 1: Pubmed search

("breast neoplasms"[MeSH Terms] OR (("breast"[MeSH Terms] OR "breast*"[Title/Abstract] OR "mamma*"[Title/Abstract]) AND ("neoplas*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "cancer*"[Title/Abstract] OR "malign*"[Title/Abstract] OR "carcinom*"[Title/Abstract])) OR ("carcinoma, intraductal, noninfiltrating"[MeSH Terms] OR "ductal carcinoma in situ"[Title/Abstract] OR "DCIS"[Title/Abstract] OR "intraductal carcinom*"[Title/Abstract])) AND ("magnetic resonance imaging"[MeSH Terms] OR "magnetic resonance imaging"[Title/Abstract] OR "MRI"[Title/Abstract] OR "magnetic resonance image"[Title/Abstract] OR "nmr imaging"[Title/Abstract] OR "mr tomography"[Title/Abstract] OR "nmr tomography"[Title/Abstract] OR ("mammography"[MeSH Terms] OR "digital breast tomosynthesis"[Title/Abstract] OR "digital mammograph*"[Title/Abstract] OR "mammograph*"[Title/Abstract]) OR ("contrast media"[MeSH Terms] OR "contrast enhanced mammography"[Title/Abstract] OR "CESM"[Title/Abstract] OR "contrast enhanced spectral mammography"[Title/Abstract])) AND ("neoadjuvant therapy"[MeSH Terms] OR "neoadjuvant chemotherapy"[Title/Abstract] OR "neoadjuvant chemotherapy treatment"[Title/Abstract] OR "neoadjuvant systemic therapy"[Title/Abstract] OR "neoadjuvant systemic treatment"[Title/Abstract] OR "neoadjuvant treatment"[Title/Abstract] OR "neoadjuvant endocrine therapy"[Title/Abstract] OR "neoadjuvant targeted therapy"[Title/Abstract] OR (("hormone therapy"[Title/Abstract] OR "endocrine therapy"[Title/Abstract] OR "targeted therapy"[Title/Abstract]) AND "Neoadjuvant"[Title/Abstract]) OR "preoperative chemotherapy"[Title/Abstract])

Supplemental 2: Embase search

1	breast tumor/	24	CESM.ti,ab,kw.
2	breast/	25	22 or 23 or 24
3	breast*.ti,ab,kw.	26	nuclear magnetic resonance imaging/
4	mamma*.ti,ab,kw.	27	magnetic resonance imaging*.ti,ab,kw.
5	2 or 3 or 4	28	MRI*.ti,ab,kw.
6	malignant neoplasm/	29	26 or 27 or 28
7	(neoplas* or tumor* or tumor* or cancer* or malign* or carcinom*).ti,ab,kw.	30	21 or 25 or 29
8	6 or 7	31	exp neoadjuvant therapy/
9	5 and 8	32	preoperative treatment/
10	1 or 9	33	preoperative chemotherapy/
11	exp intraductal carcinoma/	34	31 or 32 or 33

Supplemental 2: Embase search *(continued)*

12	intraductal carcinom*.ti,ab,kw.	35	(neoadjuvant* or neo adjuvant* or preoperative* or pre operative*).ti,ab,kw.
13	ductal carcinoma in situ.ti,ab,kw.	36	chemotherapy/
14	DCIS.ti,ab,kw.	37	systemic therapy/
15	11 or 12 or 13 or 14	38	immunotherapy/
16	10 or 15	39	molecularly targeted therapy/
17	exp mammography/	40	antineoplastic agent/
18	exp digital mammography/	41	(chemotherap* or systemic therap* or immunotherap* or targeted therap* or antineoplastic).ti,ab,kw.
19	mammograph*.ti,ab,kw.	42	36 or 37 or 38 or 39 or 40 or 41
20	digital breast tomosynthes*.ti,ab,kw.	43	35 and 42
21	17 or 18 or 19 or 20	44	34 or 43
22	contrast enhanced spectral mammograph*.ti,ab,kw.	45	16 and 30 and 44
23	contrast enhanced mammograph*.ti,ab,kw.		

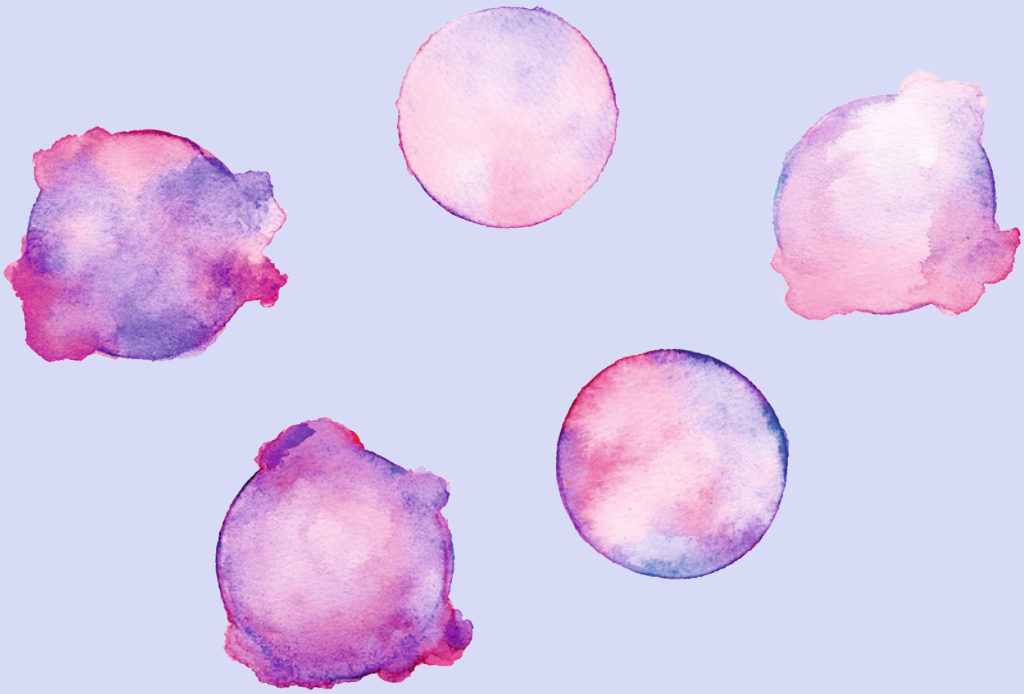
Supplemental 3 & 4

Available online, via https://link.springer.com/article/10.1007/s00330-023-09547-7 or scan the QR code below

Supplemental 5

Table S5: Patients with ypT0 and ypTis in meta-analysis and MRI enhancement of ypTis

Study	Total number of patients	ypT0 (n)	ypTis (n)	ypTis enhanced on MRI (n (%))	TP ypT0	TN ypT0	FP ypT0	FN ypT0	TP ypT0/is	TN ypT0/is	FP ypT0/is	FN ypT0/is
Bernardi (2022)	51	16	12	8 (66.7)	30	16	0	5	22	20	8	1
Bodini (2004)	73	3	4	3 (75.0)	60	1	2	10	57	2	5	9
Böttcher (2014)	54	12	6	2 (33.3)	36	11	1	6	34	15	3	2
Chen (2008)	51	22	6	1 (16.7)	15	21	1	14	14	26	2	9
De Los Santos (2011)	81	23	9	6 (66.7)	51	13	10	7	45	16	16	4
Gampenrieder (2019)	246	68	11	4 (36.4)	118	51	17	60	114	58	21	53
Hahn (2014)	78	13	6	6 (100)	60	9	4	5	54	9	10	5
Hayashi (2013)	264	66	32	25 (78.1)	175	36	30	23	150	43	55	16
Khazindar (2021)	56	14	11	5 (45.5)	31	11	3	11	26	17	8	5
Lee (2017)	17	4	2	0 (0)	9	3	1	4	9	5	1	2
Mirza (2016)	69	11	6	2 (33.3)	47	8	3	11	45	12	5	7
Nakamura (2007)	115	10	11	8 (72.7)	92	7	3	13	84	10	11	10
Negrao (2019)	219	76	9	6 (66.7)	123	56	20	20	117	59	26	17
Santamaria (2019)	82	19	8	6 (75.0)	55	11	8	8	49	13	14	6
Van Ramshorst (2017)	297	112	69	16 (23.3)	76	97	15	109	60	150	31	56
Woodhams (2010)	70	9	7	4 (57.1)	57	5	4	4	53	8	8	1
Zhang (2020)	1031	309	60	41 (68.3)	657	146	163	65	616	165	204	46
Total	2854	787	269	143 (53.2)								



CHAPTER 5

Evaluation of a DCIS component accompanying HER2+ invasive breast cancer on contrast-enhanced mammography

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Abstract

Objectives: A DCIS component can be present accompanying HER2+ invasive breast cancer (IBC) in approximately 57% of patients. Until now, no contrast-enhanced mammography (CEM) studies have investigated the detection of a DCIS component, which is important for surgical decision-making. This study aimed to investigate imaging findings of a DCIS component in HER2+ IBC on CEM.

Methods: Women with HER2+ IBC with a DCIS component that underwent CEM between 2013-2021 were included. Two independent radiologists retrospectively reassessed CEM exams, and a breast pathologist reassessed histopathology specimen. The percentage and extent of suspicious calcifications and non-mass enhancement (NME) on CEM, and interobserver agreement between radiologists was determined. In the primary surgery group, the detection rate of DCIS outside of the invasive tumor was determined, and maximum diameter of imaging findings was compared to histopathology.

Results: Sixty-two patients were included. CEM showed suspicious calcifications (27.4%), NME (16.1%), both (27.4%) or no findings (29.0%), related to DCIS. In the primary surgery group (n=45), CEM detected 27 of 35 DCIS components present outside of the invasive tumor (77.1%). NME was a better predictor for DCIS diameter (ICC=0.65) compared to suspicious calcifications (ICC=0.43). Inter-observer agreement on detection of imaging findings was better for suspicious calcifications (κ=0.81) compared to NME (κ=0.47), while reliability between size measurements was comparable (ICC=0.89 versus ICC=0.80, respectively).

Conclusion: CEM was able to detect 77.1% of DCIS present outside of the invasive tumor. NME is the most accurate predictor of DCIS diameter, but requires improvements regarding inter-observer agreement.

Introduction

Contrast-enhanced mammography (CEM) has been increasingly investigated in the diagnosis of breast malignancies in recent decades.[1] CEM facilitates the assessment of both calcifications and enhancement by combining standard full-field digital mammography (FFDM) with intravenous contrast administration. This is particularly useful in evaluating ductal carcinoma in situ (DCIS), which in approximately 75% of cases presents as either suspicious calcifications or non-mass enhancement.[2, 3] CEM has demonstrated greater accuracy in identifying both invasive breast cancer (IBC) and DCIS compared to FFDM and it approaches the accuracy of breast MRI.[4-6] Moreover, early results for monitoring response of IBC to neoadjuvant systemic therapy (NST) are promising.[7]

A DCIS component can be present accompanying an invasive tumor, with the highest percentage of approximately 58% in HER2+ IBC.[8] The detection of a DCIS component accompanying IBC is important for surgical decision-making, as prior studies show a higher rate of positive surgical margins after breast-conserving surgery compared to patients without a DCIS component.[9, 10] Furthermore, since recent studies report a pathologic complete response of DCIS in 50% of HER2+ IBC patients after NST, identifying the DCIS component on imaging at time of diagnosis has become important to monitor this response.[11] A study by Kuhl et al. investigated the accuracy of preoperative breast MRI in detecting a DCIS component and reported an overall sensitivity of 85%, with a range of 56.8%-100%, influenced by the extent and grade of the DCIS component.[12] Until now, no previous CEM studies have specifically investigated the detection of a DCIS component accompanying HER2+ IBC in both primary setting or after NST.

The aim of the current study was to investigate the imaging findings of a DCIS component accompanying HER2+ IBC on CEM, in patients treated with primary surgery or NST followed by surgery. In the primary surgery group, the detection rate of a DCIS component outside of the invasive tumor was investigated, and the diameter of imaging findings on CEM compared to DCIS size in histopathology. Lastly, the inter-observer reliability to detect and measure the imaging findings related to the DCIS component was assessed.

Materials and methods

This is a single-center retrospective cohort study performed at the Maastricht University Medical Center+. The study was approved by the local ethics committee and informed consent was waived due to the retrospective nature of the study (decision number: METC 2023-0164).

Patient selection
All consecutive women diagnosed with HER2+ IBC of no special type between January 2013 and December 2021 were selected from the hospital's electronic patient files. Patients were screened and included in the study population when a CEM was performed as part of the diagnostic work-up, and a DCIS component was present in either the biopsy or the postoperative specimen. Based on local policy, all patients recalled from breast cancer screening undergo CEM as part of diagnostic work-up. In addition, CEM can be considered in patients in which conventional mammography was inconclusive or contrast-enhanced imaging is preferred, for instance because of neoadjuvant response monitoring. In the present study, patients were treated with primary surgery or neoadjuvant systemic therapy followed by surgery. Exclusion criteria were as follows: 1) image quality not eligible for reassessment, 2) neoadjuvant endocrine or radiation therapy, or 3) distant metastasis at diagnosis.

Imaging protocol
All CEM exams were performed on a Senographe Essential unit with Senobright CEM upgrade (GE Healthcare, Chalfont St Giles, United Kingdom). A non-ionic, monomeric, low-osmolar contrast agent (iopromide; Ultravist® 300, Bayer Healthcare, Germany) was used at a dose of 1.5 mL/kg body weight, with a maximum of 120cc, and administered with a flow rate of 3 mL/s, followed by a saline flush. Bilateral MLO and CC views were obtained, consisting of a low-energy image (LEI) and a recombined image (RCI), and additional images were made at the request of the reporting radiologist.

Image analysis
Two breast radiologists (TvN and IMR), with both more than 3 years of CEM experience, independently reassessed the CEM images on a dedicated workstation. Image analysis was performed using a scoring tool based on the American College of Radiology (ACR) Breast Imaging Reporting and Data System supplement on CEM (BI-RADS CEM), shown in Supplemental A.[13]

During CEM image analysis, the evaluator first read the LEIs to report on mass, suspicious calcifications, asymmetry and/or architectural distortion. Secondly, the RCIs were evaluated and combined with the LEIs to report on contrast enhancement related to the mass, asymmetry, or architectural distortion, or to report on non-mass enhancement (NME). Reported imaging findings were measured in maximum diameter in millimeter. In addition, breast density and background parenchymal enhancement (BPE) according to ACR BI-RADS were recorded.[14] After both radiologists independently completed the reassessments, a consensus meeting was held to resolve any discrepancies between them and finalize a combined reassessment for final analysis. The individual reassessments were used to evaluate inter-observer reliability. The radiologists were aware of the study population consisting of only patients with HER2+ with a DCIS component, but were unaware of the localization and size of the DCIS component

and other clinical information (e.g. symptoms or histopathological features). The DCIS component was differentiated from the invasive component on imaging based on the presence of suspicious calcifications or NME. From all patients, baseline CEM images at time of diagnosis were evaluated. In patients treated with NST, mid and post-NST images were not taken into consideration in the light of the current study aim.

Histopathology analysis

All histopathological reports from the included patients were reviewed. HER2-positivity was examined by immunohistochemistry or in situ hybridization, or in a combination, following ASCO CAP guidelines.[15] The presence of a DCIS component was based on the biopsy or the postoperative specimen. The following characteristics of the DCIS component were included in the database: grade (based on the WHO classification[16]), presence of comedonecrosis and/or calcifications, maximum diameter in mm (in postoperative pathology), and whether it was present within or outside of the invasive tumor. When multiple scattered foci of DCIS were found, the total diameter of the area with scattered foci was recorded. In case of any missing data, our experienced breast pathologist reassessed the histopathology of the biopsy and/or postoperative specimen. Additional characteristics of the invasive tumor that were obtained from the pathology reports were: invasive tumor size, grade according to Bloom and Richardson, and estrogen receptor (ER) status.

The maximum diameters of the invasive tumor and the DCIS component in histopathology were compared to calculate a size ratio of the DCIS component versus the invasive tumor. Hence, a ratio above 1 means that the DCIS component is larger than the invasive tumor, and a ratio below 1 vice versa.

Study Endpoints

The primary outcome was to determine the imaging findings on CEM of an accompanying DCIS component. Patients were subsequently divided into two groups based on presence of either suspicious calcifications and/or NME, and patients without imaging findings of DCIS. Radiological and histopathological characteristics were compared between the two groups. In addition, patients treated with primary surgery were used to investigate the detection rate of a DCIS component present outside of the invasive tumor on CEM, and to compare size of imaging findings to histopathological size of DCIS. Regarding tumor size measurements and detection of the DCIS component outside of the invasive tumor, patients treated with NST were excluded. Inter-observer reliability between the two independent radiologists was determined for detection and measurement of imaging findings in the whole population.

Statistical analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS, version 26, Armonk, New York, USA). Descriptive statistics were used to

summarize the baseline characteristics of the study population, and to calculate the percentages of different imaging findings reported. Pearson's χ^2 or Fisher's Exact tests were used for categorical variables, and unpaired T-test or Mann-Whitney U for continuous variables.

In the primary surgery group, the extent of the imaging findings (suspicious calcifications and non-mass enhancement) on CEM was compared to DCIS size in histopathology. The margin of error to classify concordance, over- and underestimation was set at 10mm, based on previous literature.[17] In addition, intraclass correlation coefficients and Bland-Altman plots were used to assess agreement between the radiological and pathological size of DCIS per imaging finding.

Lastly, inter-observer agreement between the two radiologists for detection of the imaging findings (dichotomous) was assessed using Cohen's kappa.[18] Agreement on measurements of the maximum diameters of imaging findings was assessed using intraclass correlation coefficient (ICC), based on absolute agreement and a two-way mixed effects model, as well as Bland-Altman plots.[19, 20] A p-value < 0.05 was considered statistically significant.

Results

A total of 216 patients were diagnosed with HER2+ invasive breast cancer with a DCIS component between 2013-2021 in the Maastricht University Medical Centre+. After exclusion of ineligible patients, the study population consisted of 62 patients. A flowchart of patient selection and reasons for exclusion is shown in Figure 1.

Baseline characteristics

Baseline characteristics are shown in Table 1. Median age was 60 years old. Most patients were diagnosed with a cT1 (64.5%) cN0 (85.7%) tumor. The invasive tumor was mostly grade 3 (48.4%) and ER positive (83.9%). The DCIS component was found in the biopsy alone in 6 patients, in the postoperative specimen alone in 18 patients, and in both the biopsy and postoperative specimen in 38 patients. The DCIS component was mostly grade 3 (66.1%), and calcifications and comedonecrosis were present in 64.5% and 75.8%, respectively. Forty-five patients underwent primary surgery and the other 17 patients received NST, of which 4 patients achieved ypT0.

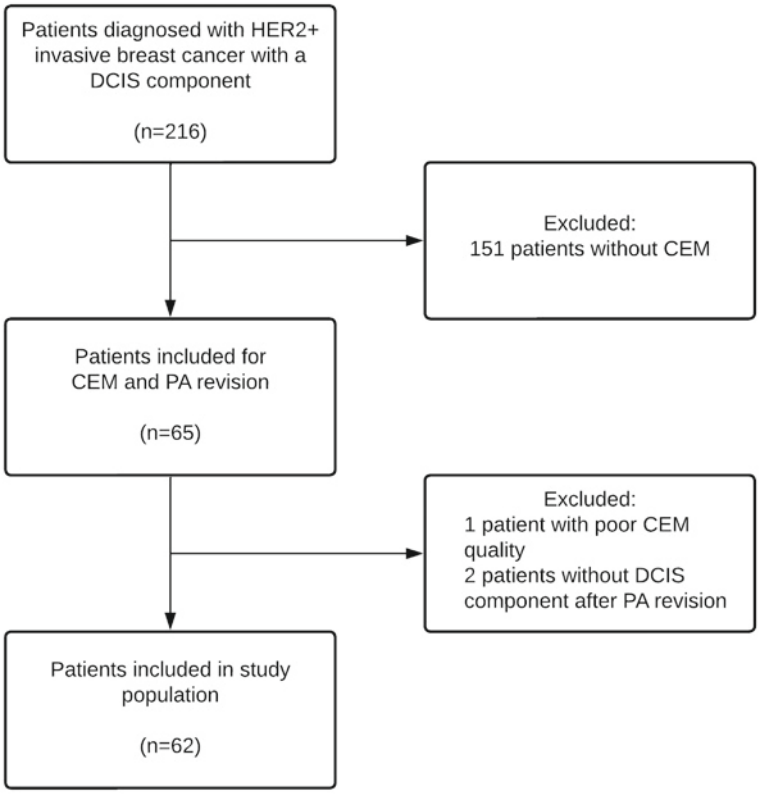

Figure 1: Flowchart of study population

Table 1: Baseline characteristics

Baseline characteristics	**Total population (n = 62) n (%)**
Age (Median (IQR))	60 (56-67)
cT	
1	40 (64.5)
2	14 (22.6)
3	1 (1.6)
IS[a]	6 (9.7)
X[a]	1 (1.6)
cN	
0	53 (85.5)
1	8 (12.9)
2	0
3	1 (1.6)

Table 1: Baseline characteristics *(continued)*

Baseline characteristics	Total population (n = 62) n (%)
Invasive tumor grade	
1	4 (6.4)
2	28 (45.2)
3	30 (48.4)
Invasive tumor ER status	
Positive	52 (83.9)
Negative	10 (16.1)
Presence of DCIS	
In biopsy	6 (9.7)
In postoperative specimen	18 (29.0)
In both biopsy and postoperative specimen	38 (61.3)
DCIS grade	
1	1 (1.6)
2	20 (32.3)
3	41 (66.1)
DCIS histopathology	
Presence of both comedonecrosis and calcifications	34 (54.8)
Presence of only comedonecrosis	13 (21.0)
Presence of only calcifications	6 (9.7)
No comedonecrosis or calcifications	9 (14.5)
Treatment	
Primary surgery	45 (72.6)
Neoadjuvant systemic therapy	17 (27.4)
Time between CEM and surgery in days (median (IQR))	
Primary surgery	31 (20-40)
Neoadjuvant systemic therapy	204 (164-209)
(y)pT	
0	4 (6.4)
1	46 (74.2)
2	5 (8.1)
3	2 (3.2)
IS	5 (8.1)
Histopathological size ratio DCIS/IBC [b] (Median (IQR))	1.56 (0.97, 4.00)

[a] postoperative pathology showed IBC + DCIS [b] in patients treated with primary surgery
Abbreviations: DCIS ductal carcinoma in situ, ER estrogen receptor IBC invasive breast cancer, IQR interquartile range

Imaging findings of a DCIS component on CEM

Following the consensus meeting between the two radiologists, the imaging findings of the 62 patients on CEM were summarized (Supplemental Table 1). Imaging findings that were considered related to the DCIS component were suspicious calcifications and/or NME. Overall, suspicious calcifications were observed in 54.8% of patients, while non-mass enhancement (NME) was observed in 43.5%. When categorizing patients based on imaging findings, 17 (27.4%) had only suspicious calcifications, 10 (16.1%) had only NME, and 17 (27.4%) showed both findings (Figure 2). In 18 of the 62 patients (29.0%), neither calcifications nor NME were detected.

When comparing the imaging and histopathological characteristics of patients with detected DCIS (n=44) to undetected DCIS (n=18), based on presence of suspicious calcifications and/or NME, patients with presence of comedonecrosis and calcifications in histopathology were more often detected (Table 2). An example of imaging and histopathology of a detected and undetected DCIS component are shown in Supplemental Figure 1 and 2, respectively.

Table 2: Comparison of imaging and histopathology characteristics between patients with detected and undetected DCIS

	Detected DCIS (n=44) n (%)	**Undetected DCIS (n=18) n (%)**	**p-value**
Imaging			
ACR			0.309
A-B	39 (68.4)	18 (31.6)	
C-D	5 (100.0)	0	
BPE			0.152
Minimal-mild	34 (66.7)	17 (33.3)	
Moderate-marked	10 (90.9)	1 (9.1)	
Histopathology			
Grade DCIS			0.346
Low (1-2)	14 (63.6)	8 (36.4)	
High (3)	30 (75.0)	10 (25.0)	
Presence of comedonecrosis			**0.002**
Yes	38 (80.9)	9 (19.1)	
No	6 (40.0)	9 (60.0)	

Table 2: Comparison of imaging and histopathology characteristics between patients with detected and undetected DCIS *(continued)*

	Detected DCIS (n=44) n (%)	**Undetected DCIS (n=18) n (%)**	**p-value**
Presence of histopathologic calcifications			**0.001**
Yes	34 (85.0)	6 (15.0)	
No	10 (45.5)	12 (54.5)	

Abbreviations: ACR American College of Radiology, BPE background parenchymal enhancement, DCIS ductal carcinoma in situ, IBC invasive breast cancer

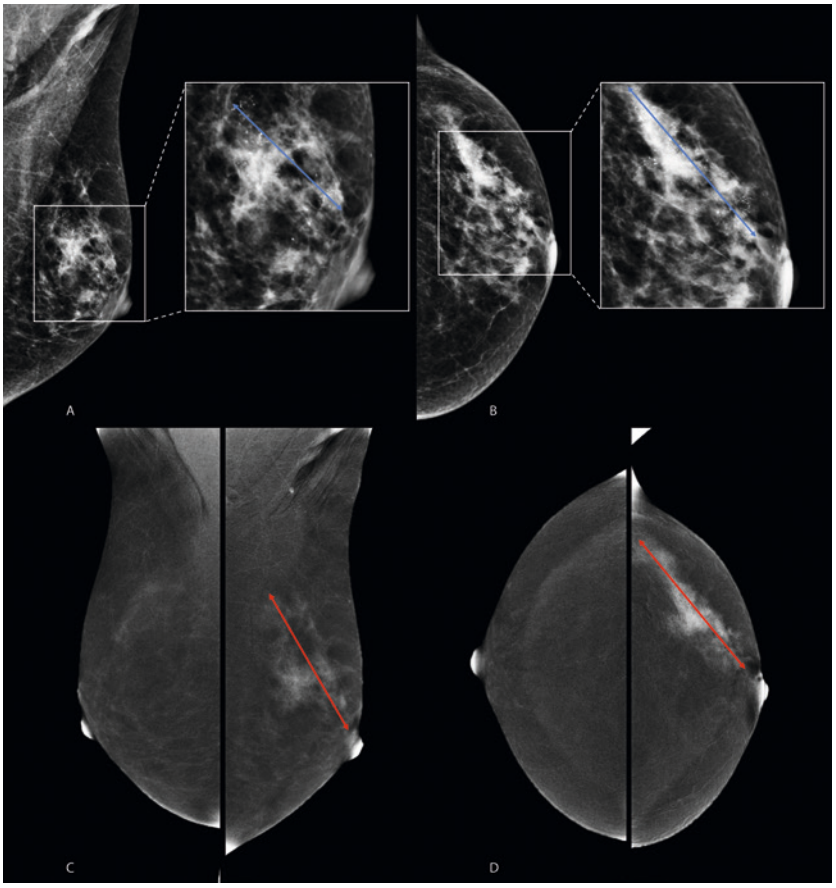

Figure 2A (Mediolateral oblique view (MLO)) and 2B (Craniocaudal view (CC)): low energy images of the left breast showing suspicious calcifications in an area of 68mm (blue dimension line). Figure 2C (MLO) and 2D (CC): recombined images of both breasts, showing the presence of non-mass enhancement in the left breast of 71mm (red dimension line) compared to only minimal background parenchymal enhancement in the right breast.

Detection of DCIS outside of the invasive tumor

Of the 45 patients treated with primary surgery, 35 had a DCIS component present outside of the invasive tumor. The detection rate of this DCIS component, based on suspicious calcifications and/or NME, was 77.1% (27/35), which was significantly higher compared to 30% (3/10) in patients with a DCIS component inside of the invasive tumor (p<0.001). Of these 27 patients with a detected DCIS component outside of the invasive tumor, NME was reported in 7 (25.9%), suspicious calcifications in 8 (29.6%), and 12 patients (44.4%) had both imaging findings.

The DCIS component outside of the invasive tumor that was not detected (n=8) was significantly smaller compared to the detected DCIS (median size 12mm (IQR 9.25-23.75) vs 40mm (IQR 20-70), p=0.001). The DCIS/IBC size ratio was also significantly lower compared to the DCIS component that was detected (median 1.06 vs 3.13, p<0.001).

Measurement of DCIS size on CEM compared to postoperative histopathology

In the 45 patients that underwent primary surgery, the size of the different imaging findings was compared to the size of the DCIS component in histopathology (Table 3). For the 22 patients with suspicious calcifications, the percentage size concordance (error within margin of 10mm) was 59.1% (13/22). The intraclass correlation coefficient for suspicious calcifications was 0.43. For the 21 patients with non-mass enhancement, 47.6% (10/21) of patients had a size difference of ≤10 mm. The intraclass correlation coefficient for NME was 0.65. Suspicious calcifications more often underestimated the DCIS component size in pathology, while NME both over- and underestimated the DCIS size (Table 3).

Table 3: Size measurement of the DCIS component on CEM compared to histopathology in patients treated with primary surgery

	Mean diameter in mm	Correct measurement n (%)	Under-estimation n (%)	Over-estimation n (%)	ICC (95% CI)
Suspicious calcifications n=22	31.09	13 (59.1)	7 (31.8)	2 (9.1)	0.43 (0.04-0.71)
Histopathology size DCIS n=22	41.95				
NME n=21	48.71	10 (47.6)	6 (28.6)	5 (23.8)	0.65 (0.30-0.84)
Histopathology size DCIS n=21	50.71				

Abbreviations: DCIS ductal carcinoma in situ, ICC intraclass correlation coefficient, NME non-mass enhancement

Figure 3 shows the Bland Altman plots for suspicious calcifications and NME in comparison to histopathology diameter. In both suspicious calcifications and NME, agreement was worse in higher mean size of the lesions. For both imaging findings, a linear regression was performed that confirmed no proportional bias with a p-value of more than 0.05 (p=0.43 for suspicious calcifications and p=0.65 for NME).

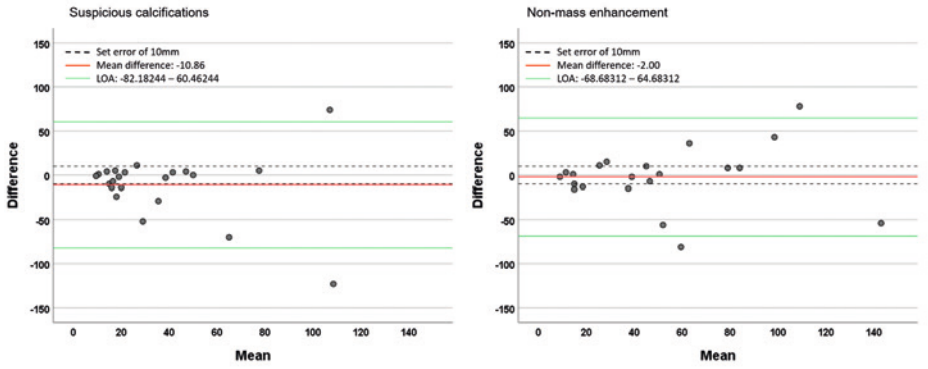

Figure 3: Bland Altman plots for the diameter on imaging based on suspicious calcifications and NME in comparison to pathological size of DCIS component. LOA = limits of agreement. Size in mm.

Inter-observer reliability

The inter-observer reliability was investigated in all patients, on both detection and measurement of imaging findings. In 90.3% (56/62) of cases, the independent radiologists agreed on the presence or absence of suspicious calcifications, with a kappa of 0.81. The ICC for measured diameter of suspicious calcifications was 0.89, in the 30 patients in which both measurements were performed. In 74.2% (46/62) of cases, the independent radiologists agreed on the presence or absence of NME, with a kappa of 0.47. The ICC for measured diameter of NME was 0.80, in the 17 patients in which both measurements were performed. Figure 4 shows the Bland Altman plots for the diameter measurement between the two independent radiologists. For both imaging findings linear regression showed no proportional bias (p=0.93 for suspicious calcifications and p=0.37 for NME).

In addition to the imaging findings for detection of the DCIS component, the inter-observer reliability was tested for the other imaging findings (Table 4). The percentage of agreement was highest for the presence of contrast enhancement (91.9%), and for the size measurement of mass on LEI (ICC=0.91).

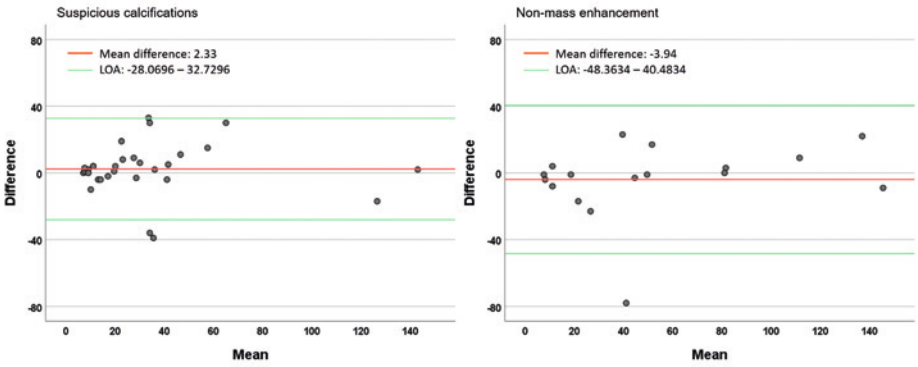

Figure 4: Bland Altman plots for diameter measurement between radiologists for suspicious calcifications and NME. LOA = limits of agreement. Size in mm.

Table 4: Inter-observer agreement of CEM imaging findings

Imaging findings	Detection agreement	Size agreement (95%CI)
Suspicious calcifications (LEI)	56/62 cases (90.3%) κ = 0.81	ICC = 0.89 (0.78-0.95) Mean difference: 2.33 mm
NME (RCI)	46/62 cases (74.2%) κ = 0.47	ICC = 0.80 (0.54-0.92) Mean difference: -3.94 mm
Mass (LEI)	54/62 cases (87.1%) κ = 0.70	ICC = 0.91 (0.83-0.95) Mean difference: 0.21 mm
Asymmetry [a] (LEI)	56/62 cases (90.9%)	
Architectural distortion (LEI)	56/62 cases (90.3%) κ = 0.37	ICC = 0.96* (0.77-0.99) Mean difference: 11.50 mm
Contrast enhancement (RCI)	57/62 cases (91.9%) κ = 0.76	ICC = 0.80 (0.66-0.88) Mean difference: -1.04
BPE (low versus high [b]**)** (RCI)	57/62 cases (91.9%) κ = 0.69	

[a] Too limited data for further analysis
[b] Minimal and mild BPE = low, moderate and marked BPE = high
Abbreviations: κ = kappa, ICC intraclass correlation coefficient, LEI low energy image, NME non-mass enhancement, RCI recombined image

Discussion

This single center retrospective study aimed to evaluate the imaging findings of a DCIS component accompanying HER2+ IBC on CEM, using both low energy and recombined images. In 71.0% of patients, either suspicious calcifications or NME was present on CEM. In patients treated with primary surgery, CEM detected 77.0% of the DCIS components present outside of the invasive tumor, that are of importance for surgical management. The measurement of NME was most accurate in comparison to histopathological size of the DCIS component, with an ICC of 0.65 compared to 0.43 in suspicious calcifications, yet 95% confidence intervals overlap in this small population. Inter-observer agreement for detecting NME was lower compared to suspicious calcifications; however, the size measurements of the radiologists for both types of findings were similarly accurate.

To the best of our knowledge, this is the first study focusing on imaging findings of a DCIS component accompanying invasive breast cancer on CEM. One previous study by Kuhl et al. investigated the ability of breast MRI in the detection of a DCIS component in 539 patients. The sensitivity of breast MRI for the detection of a DCIS component was 84.9%, which was significantly higher than conventional imaging (36.7%).[12] Sensitivity of CEM in the current study was lower than breast MRI but higher than the reported sensitivity of conventional imaging by Kuhl et al (36.7%). Moreover, in the study by Kuhl et al. sensitivity increased with a larger size and higher grade of DCIS.[12] This is in line with the current study, demonstrating that the sensitivity increased to 77.0% for the detection of a DCIS component outside of the invasive tumor, which is of more clinical relevance compared to DCIS within the invasive tumor. When the extent of DCIS exceeds the invasive tumor, it increases the risk of positive surgical margins if not detected properly on imaging.[21] In contrast to Kuhl et al., grade of DCIS was not significantly different in our results, probably due to the small study population. However, patients with detected DCIS had a significant higher percentage of comedonecrosis, which is related to a higher grade.[22] The challenge in detecting a DCIS component is partly due to the degree of contrast enhancement, as 56.5% of patients in this study showed no NME. Previous studies on the detection of pure DCIS using CEM and breast MRI have reported an absence of enhancement up to 55% of patients, typically in smaller and less aggressive lesions, as observed in our study.[6, 23, 24] The percentage of patients with pure DCIS showing suspicious calcifications on LEI is higher in previous studies, ranging from 67.3% to 90%, compared to 55.6% in the current study.[6, 25, 26] Notably, other imaging findings, such as a mass or architectural distortion, may also be associated with a DCIS component. However, these are reported in only about 10% of cases and are more commonly linked to the invasive tumor.[3, 27, 28] Consequently, this study focused on the presence of suspicious calcifications and NME for detecting the accompanying DCIS component.

Size measurements of the DCIS component on CEM compared to histopathology demonstrated only moderate reliability for NME (ICC = 0.65) and poor reliability for suspicious calcifications (ICC = 0.43), with both findings underestimating the histopathological size of the DCIS component in 28.6% and 31.8% of cases, respectively. Previous studies on CEM measuring pure DCIS size show better results, suggesting that particularly the combination of IBC with a DCIS component is challenging.[6, 29] Two prior CEM address this specific study population. Travieso-Aja et al. investigated CEM size measurements of 204 breast cancers, including both pure IBC, DCIS and IBC+DCIS, and reported overestimation of 47% compared to histopathology size, using a more strict error margin of 5mm.[30] The Spearman correlation coefficient was highest for pure DCIS (0.872), followed for IBC (0.865) and lowest for IBC+DCIS (0.783).[30] Schouten van der Velden et al. investigated the ability of breast MRI in size measurement of IBC with an extensive intraductal component and reported a Spearman correlation coefficient of 0.65 in breast MRI, with an over- and underestimation in 22% and 30% of the cases respectively.[31] These studies only measured the maximum tumor sizes, without specifically distinguishing the extent of the DCIS component. This may explain the slightly better results compared to the current study. Factors that are previously reported to influence DCIS size measurement are scattered morphology of DCIS, BPE, tumor size, and compression of the breast during CEM examination.[6, 32, 33]

The inter-observer reliability differed between the individual imaging findings on CEM, with the highest kappa for detection of a suspicious calcifications on LEI (κ=0.81). The inter-observer agreement for NME was low (κ=0.47), which is consistent with previous studies on breast MRI, yet no data are available for NME assessment on CEM. El Khoury et al. found substantial agreement in classifying lesions as mass or NME (Krippendorff's α: 0.71), however, only slight to fair agreement was found in further describing the characteristics of NME (Krippendorff's α: 0.18-0.38).[34] Grimm et al. reported a moderate inter-observer reliability for NME on breast MRI (κ=0.49), which is comparable to the kappa of 0.47 found in our study.[35] Previous breast MRI studies describe the difficulty in distinguishing BPE from NME, resulting in a low agreement between readers.[33, 36] In the 16 cases with inter-observer disagreement on NME in the current study, 25% had mild BPE, 12.5% moderate and 6.3% marked BPE. The inter-observer agreement between low and high BPE in the current study was good (k=0.693), which is comparable to previous studies.[37, 38]

The strengths of this study are the previously understudied focus on imaging of the DCIS component combined with the comprehensive reassessment of both radiology and pathology. In contrast, this retrospective study presents with certain limitations. The study population was small, resulting in limited statistical power, and therefore results should be interpreted with caution. Subsequently, some meaningful differences in the results did not reach significance, and wide 95% confidence intervals and limits of agreement were found. The patients treated with NST could not be included in the

analyses on the detection of DCIS outside of the invasive tumor and the size comparison between imaging and histopathology, because pretreatment CEM findings could not be confirmed in the postoperative specimen after NST. Since this was a first study focused on imaging findings of a DCIS component on CEM it was particularly aimed at summarizing imaging findings as a foundation for further research in a larger, preferably multicenter, population. Moreover, radiologists were aware of the presence of a DCIS component, which could have led to confirmation bias. However, we tried to prevent this by conducting the re-evaluation in a structured manner according to the BI-RADS lexicon.

Conclusion

This study highlights the key findings related to a DCIS component in HER2+ invasive breast cancer on CEM, with 71.0% of patients showing either suspicious calcifications or NME. CEM was able to detect 77.0% of DCIS components located outside of the invasive tumor, which is of clinical relevance for surgical margins. NME was the most accurate measure for estimating the size of DCIS in histopathology, although only moderate reliability was observed. Inter-observer agreement was generally good, particularly for suspicious calcifications; however, NME detection was less consistent, potentially influenced by definition and BPE. Future prospective studies should include patients both with and without a DCIS component to further evaluate diagnostic performance of CEM.

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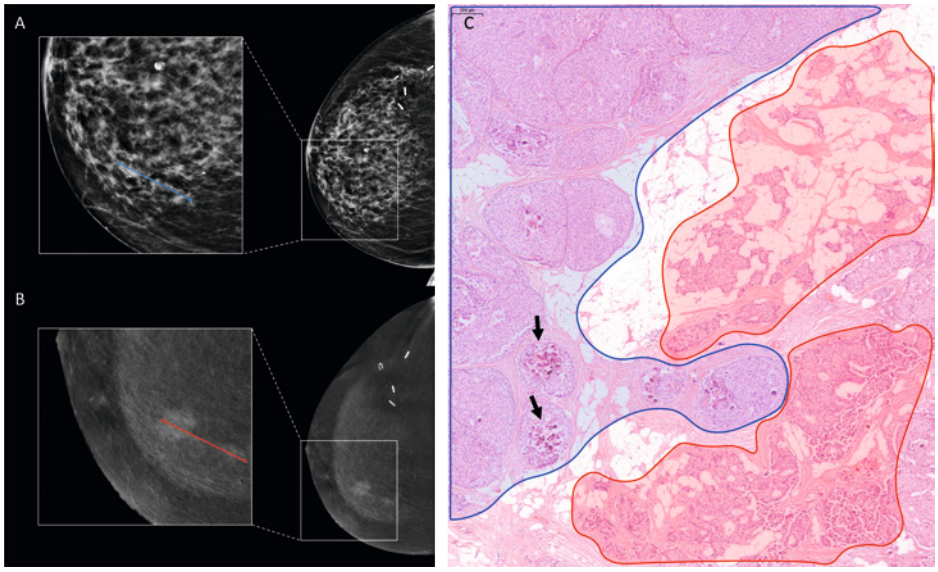
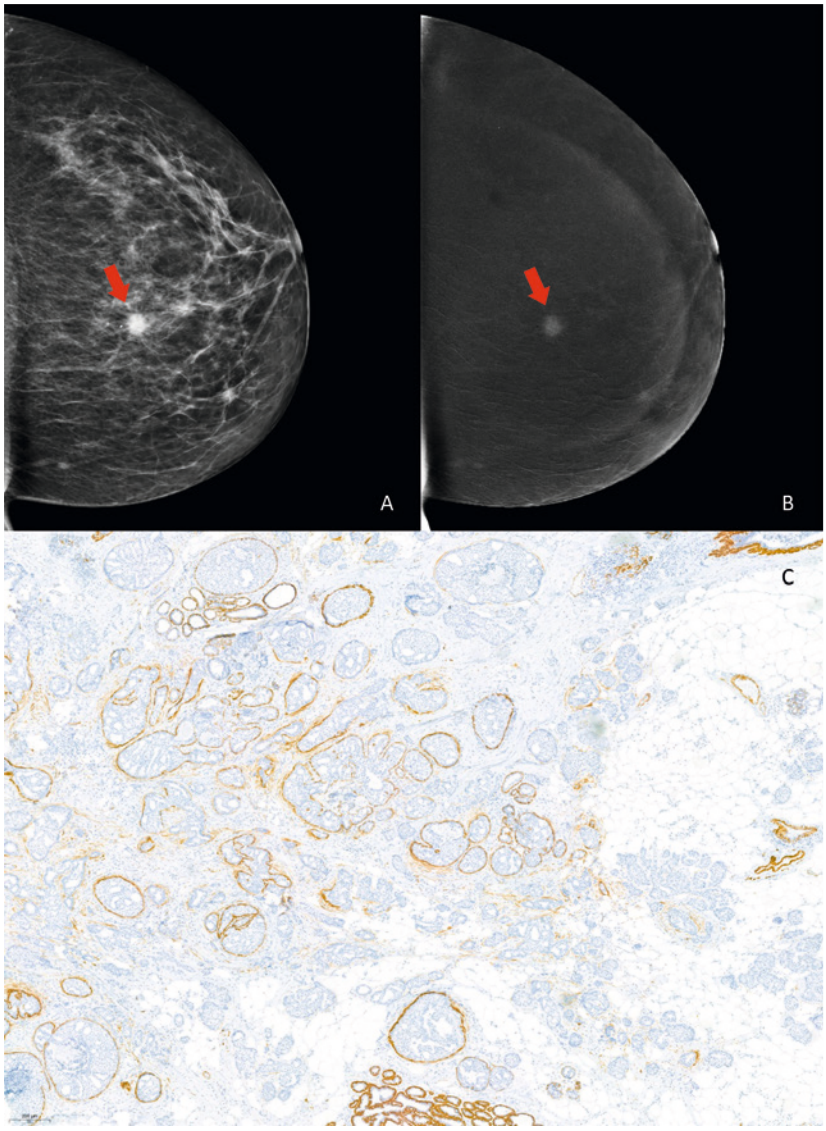
Supplementary Materials

Supplemental Figure 1:
A: CEM image of a detected DCIS component in the right breast showing suspicious calcifications (blue dimension line, picture A) on LEI and NME (red dimension line, picture B) on RCI. (Clips from previous breast surgery present in upper left quadrant)
C: Corresponding histopathology image showing area of invasive carcinoma (red) along with DCIS (blue), with calcifications (black arrows). DCIS/IBC size ratio in histopathology was 2.86.



Supplemental Figure 2:
A&B: CEM images of an undetected DCIS component in the left breast showing only a mass on CEM (A LEI CC view, B RCI CC view, red arrows), without suspicious calcifications and NME on CEM.
C: Corresponding histopathology slice with E-cadherin staining, showing a DCIS component intermixed with invasive breast cancer, with a DCIS/IBC size ratio of 0.53. The DCIS component displays a clear brown alignment of E-cadherin staining along the cell membranes, while the invasive component shows reduced or absent staining.



Supplemental Table 1: Scoring form for reassessment of Contrast-Enhanced Mammography

Patient data			**General data**				
Study number			**Name radiologist**			**Date**	…… - …… - ……
CEM							
Date of CEM exam		…… - …… - ……					
Mamma		0 Left	0 Right				
Density (ACR)		0 A	0 B	0 C	0 D		
Morphology lesion Low energy image	**Massa** **0 Yes 0 No**	Maximum diameter	…… mm				
		Location	0 UOQ	0 LOQ	0 LIQ	0 UIQ	0 Central
		Shape	0 Round	0 Oval	0 Irregular		
		Margins	0 Circumscribed	0 Obscured	0 Microlobulated	0 Spiculated	0 Indistinct
		Density	0 High	0 Equal	0 Low	0 Fat-containing	
	Suspicious calcifications **0 Yes 0 No**	Maximum diameter	…… mm				
		Morphology	0 Amorphous	0 Fine pleiomorphic	0 Coarse heterogeneous	0 Fine linear	0 Linear branching
		Distribution	0 Diffuse	0 Regional	0 Grouped	0 Linear	0 Segmental
		Location in relation to lesion	0 Inside of lesion	0 Outside of lesion, distance to lesion …… mm, on the …… side			0 Not applicable
	Asymmetry **0 Yes 0 No**	Maximum diameter	…… mm				
		Morphology	0 Asymmetry	0 Focal asymmetry	0 Global asymmetry		
	Architectural distortion **0 Yes 0 No**	Maximum diameter	…… mm				

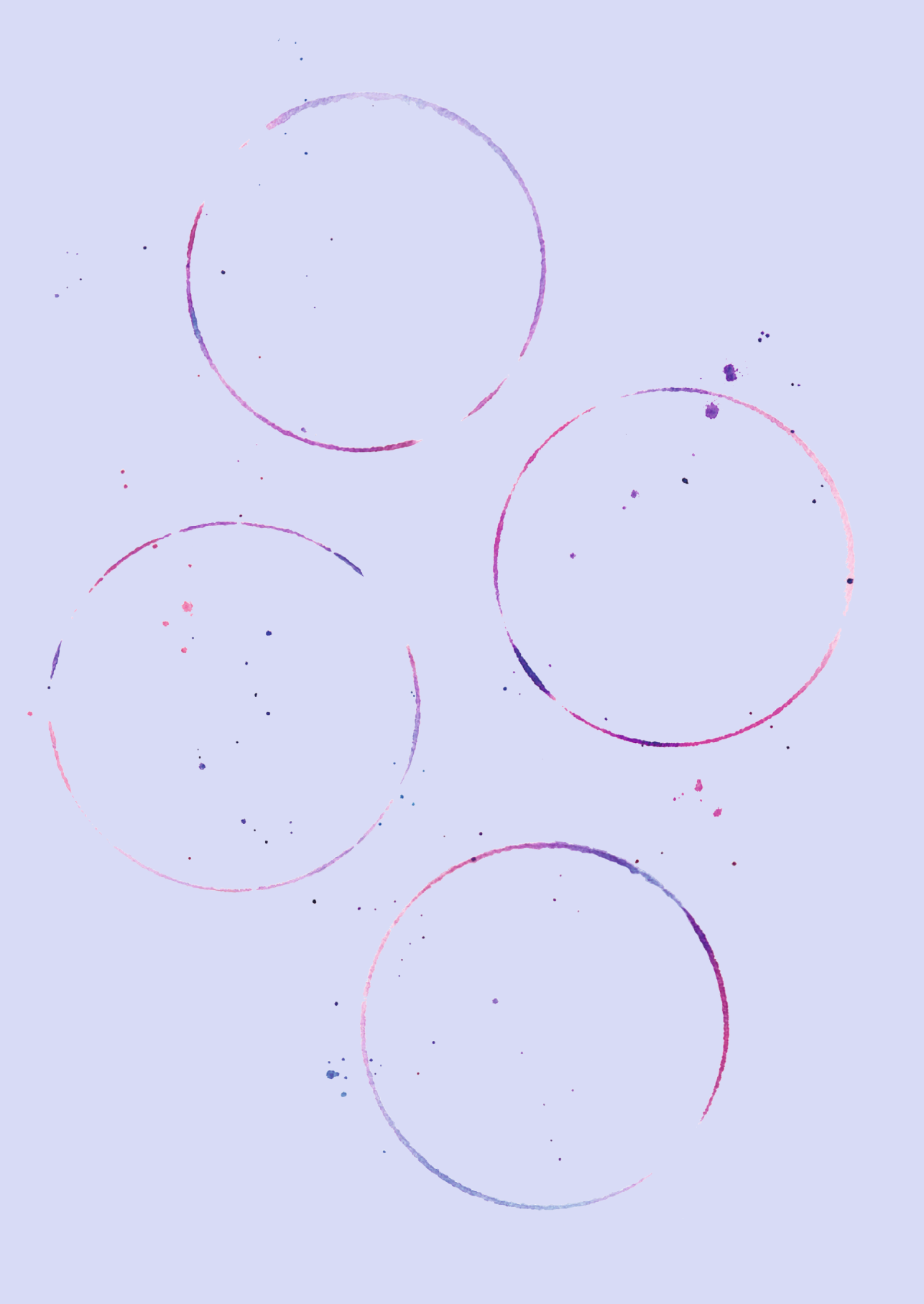
Supplemental Table 1: Scoring form for reassessment of Contrast-Enhanced Mammography *(continued)*

Patient data			**General data**					
Study number			**Name radiologist**			**Date**	…… - …… - ……	
CEM								
Recombined image	**Contrast enhancement 0 Yes 0 No**	Maximum diameter of **mass / asymmetry / architectural distortion**	…… mm					
		Enhancement **primary lesion**	0 Weak	0 Moderate	0 Strong			
			0 Homogeneous	0 Heterogeneous	0 Rim enhancement			
	NME 0 Yes 0 No	Maximum diameter **NME**	…… mm					
		Distribution **NME**	0 Focal	0 Regional	0 Multiple regions	0 Linear	0 Segmental	0 Diffuse
		Enhancement **NME**	0 Weak	0 Moderate	0 Strong			
			0 Homogeneous	0 Heterogeneous	0 Clumped	0 Clustered ring		
	BPE	Degree	0 Minimal	0 Mild	0 Moderate	0 Marked		
		Symmetry	0 Symmetric	0 Asymmetric				
Multifocality:	**0 Yes 0 No**	Number of lesions …..						
		Multicentric	0 Yes	0 No				

Supplemental Table 2: Imaging findings on CEM in study population

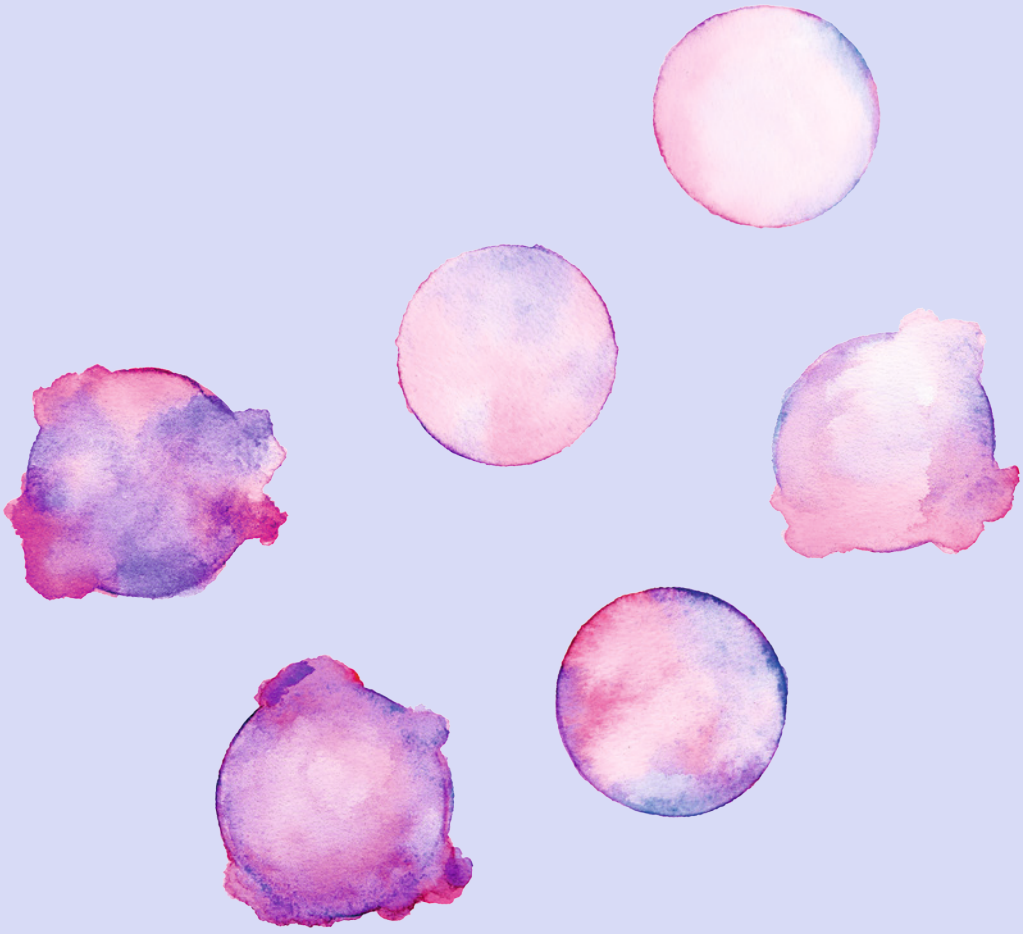
Imaging finding	Total study population (n=62) n (%)
Density according to ACR	
A	5 (8.1)
B	52 (83.8)
C	5 (8.1)
D	0
Mass	42 (66.7)
Suspicious calcifications	34 (54.8)
Asymmetry	1 (1.6)
Architectural distortion	7 (11.3)
Contrast enhancement of mass	45 (72.6)
Non-mass enhancement	27 (43.5)
BPE	
Minimal	41 (66.1)
Mild	10 (16.1)
Moderate	8 (12.9)
Marked	3 (4.9)

Abbreviations: ACR American College of Radiology, BPE Background Parenchymal Enhancement



PART III

SURGERY AND PROGNOSIS



CHAPTER 6

Surgical treatment after neoadjuvant systemic therapy for HER2+ invasive breast cancer in the Netherlands

10-year trends and the influence of an accompanying DCIS component

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Abstract

Background: The presence of a DCIS component accompanying invasive breast cancer (IBC) is associated with a higher rate of primary mastectomy compared to IBC without DCIS. After neoadjuvant systemic therapy (NST), HER2+ IBC patients show high response rates, allowing for increasing breast-conserving surgery rates. The aim of this study was to examine surgical trends after NST in a Dutch nationwide HER2+ cohort, and the influence of a DCIS component on mastectomy rate.

Methods: Women with HER2+ IBC, diagnosed between 2010-2019 and treated with NST and surgery were included from the Netherlands Cancer Registry. Mastectomy rate was examined over the years, and compared between patients with and without a DCIS component in the pre-NST biopsy. Multivariable logistic regression analysis was used to investigate the association of the DCIS component with mastectomy rate and likelihood of achieving ypT0.

Results: In total, 5289 patients were included. Over 10 years, mastectomy rate significantly decreased from 62.6% in 2010 to 35.1% in 2019. Patients with IBC+DCIS more often underwent mastectomy, with a rate of 48.4% in 2019, compared to 30.0% in IBC only ($p<0.001$). Percentage of ypT0 was significantly lower in patients with IBC+DCIS (38.7%), compared to IBC only (47.3%, $p<0.001$) Multivariable logistic regression analyses showed presence of DCIS (OR 1.69, 95%CI 1.47-1.95, $p<0.001$) to be independently associated with mastectomy.

Conclusion: Rate of mastectomy decreased significantly in HER2+ IBC treated with NST between 2010-2019. Presence of DCIS in the biopsy remained associated with higher mastectomy rate, yet 38.7% of these patients do achieve ypT0.

Introduction

Neoadjuvant systemic therapy (NST) strategies have been extensively studied for patients with HER2+ invasive breast cancer (IBC), showing similar survival outcomes compared to adjuvant treatment and thereby the benefit of downstaging disease.[1-3] One of the most important outcome measures is the achievement of pathologic complete response (pCR), which is mentioned in literature as a surrogate marker for survival.[4] Moreover, this downstaging allows for breast-conserving surgery in patients for whom mastectomy was initially indicated.[5] The highest pCR rates are observed in patients with HER2+ IBC treated with dual anti-HER2 therapy, up to 65% in the TRAIN-2 and TRYPHAENA studies.[6, 7] Dual anti-HER2 treatment is therefore recommended in the Dutch guideline and the ESMO Clinical Practice Guideline for patients with HER2+ IBC with a tumor larger than 2 cm.[8, 9]

In addition to the potential response to NST, surgical treatment is determined by several factors, such as tumor grade and morphology, the ratio of tumor size to breast volume, presence of multifocal disease, and, of course, patient's preference.[10] Moreover, in patients treated with primary surgery, previous literature shows that the presence of a DCIS component is associated with a higher mastectomy rate.[11-13] In approximately 60% of patients with HER2+ IBC, a DCIS component is present accompanying the invasive tumor.[14] Recent studies report a complete response of DCIS in 50% of patients with HER2+ patients after NST, suggesting that downsizing surgical treatment could be feasible in these patients.[12, 15]

The aim of this nationwide cohort study was to evaluate the trends of surgical treatment in patients with HER2+ IBC, treated with NST, between 2010 and 2019. Mastectomy rate was evaluated in relation to presence of a DCIS component in the biopsy and other clinicopathological variables. In addition, the association between clinicopathological variables and ypT0 was investigated, to compare the likelihood of pCR to the surgical treatment performed.

Materials and methods

Data collection and study population

For this retrospective nationwide cohort study, data of the Netherlands Cancer Registry (NCR) were used. Trained registrars from the Netherlands Comprehensive Cancer Organization (IKNL) collect data from all newly diagnosed cancer patients, with regard to patient, tumor and treatment characteristics. In order to use NCR data, the study protocol was assessed by the privacy board of the IKNL, and after approval, the requested database was retrieved. Pre-NST and postoperative pathology reports of

the included patients were collected from the Dutch Nationwide Pathology Databank (PALGA) after matching the NCR cohort.

All women aged 18 years or older, diagnosed with HER2+ IBC between January 2010 and December 2019, who were treated with neoadjuvant chemotherapy in combination with targeted therapy followed by surgery, were included. Exclusion criteria were: distant metastatic disease at diagnosis, missing pathology reports, and systemic treatment deviating from the Dutch guideline (e.g. neoadjuvant endocrine or radiation therapy).

Data collected from the NCR and PALGA comprised of patient characteristics (age, year of diagnosis), tumor characteristics (clinical and pathological TNM classification, grade according to Bloom and Richardson, estrogen receptor (ER), multifocal disease, presence of DCIS), and details on systemic therapy and surgical treatment.

Treatment according to Dutch guidelines

Over the 10 years, three different Dutch guidelines were applicable.[8, 16, 17] In the first guideline originating from 2008, NST was indicated for patients diagnosed with locally advanced breast cancer (stage III), and in case of a relative large tumor (approximately >3cm) in primary operable breast cancer in a patient with a wish for breast-conserving surgery. In the 2012 and 2017 guidelines, the indication for NST changed to: locally advanced breast cancer (stage III), or stage II breast cancer with an upfront indication for adjuvant systemic therapy. In HER2+ breast cancer, this corresponds to a tumor size ≥ 5mm, or node-positive disease.

Advised chemotherapy regimens consisted of carboplatin and paclitaxel, or adriamycin, cyclofosfamid and paclitaxel. Anti-HER2 targeted therapy consisted of trastuzumab, or trastuzumab in combination with pertuzumab as dual anti-HER2 therapy since 2017 in tumor size >2cm or node-positive disease. Patients might have been treated with dual anti-HER2 therapy before 2017 when included in different systemic therapy trials, conducted between 2014 and 2016.

Based on these alterations in NST indications and regimens, year of diagnosis was divided into three categories: 2010-2012, 2013-2016 and 2017-2019.

Histopathological examination

The Dutch Nationwide Pathology Databank collects and archives pathology reports from all national pathology laboratories. Local laboratories perform histopathological examination according to the Dutch guideline.[8, 16, 17] ER receptor status is determined using immunohistochemistry and is considered positive if ≥10% of tumor cells stain positive. The pre-NST and postoperative pathology reports from the included patients were reassessed for the presence of DCIS. Patients were divided into *IBC* or *IBC+DCIS* based on whether or not a DCIS component was reported in the pre-NST biopsy. When

a DCIS component was reported only in the postoperative specimen and not in the biopsy, patients were classified as *IBC*, since this DCIS component did not influence surgical decision-making. Postoperative pathology reports were reassessed to evaluate pathological response of the invasive and in situ components. Breast pCR was defined as absence of both invasive and in situ disease in the postoperative specimen (ypT0).

Study endpoints

The primary endpoint was the rate of mastectomy after NST in the years 2010-2019. The mastectomy rate was based on the first breast surgery performed after NST. Hence, patients who primarily underwent BCS and had a secondary mastectomy, e.g. because of positive surgical margins, were classified as BCS. This choice was made to investigate the primary surgical decision making, not to investigate surgical margins and outcomes.

Secondary endpoints were the comparison of mastectomy rate between patients with and without a DCIS component in the biopsy, and the association between patient and tumor characteristics and likelihood of mastectomy. In addition, clinicopathological variables associated with ypT0 were determined and compared to those associated with mastectomy.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 26, Armonk, New York). Missing data were expected to be missing at random, and multiple imputation was used to handle these missing data. Five imputed datasets were pooled according to Rubin's rules in the subsequent analyses.[18]

Descriptive statistics were used to summarize the study population. Trends in surgical treatment over the study period of 2010-2019 were compared with Pearson's Chi squared test. Univariable logistic regression analyses were used to determine patient and tumor characteristics associated with mastectomy rate. Variables that were statistically significant in univariable analyses were subsequently included in multivariable logistic regression analysis. Subsequently, the same clinicopathological variables were tested in uni- and multivariable logistic regression analyses to evaluate the likelihood of achieving ypT0. A p-value <0.05 was considered to be statistically significant.

Results

A total of 6380 patients were diagnosed with HER2+ invasive breast cancer between January 2010 and December 2019. After exclusion of ineligible patients, 5289 were included in the study population. Baseline characteristics are summarized in Table 1. Median age was 50 years and 49.0% of all patients were diagnosed between 2017-2019. Patients were most commonly diagnosed with a cT2 (56.1%), grade 2 (49.0%) tumor.

Nodal status was most commonly cN1 (46.1%), followed by cN0 (42.2%). The majority of patients (60.5%) had ER positive disease. In 1660 patients (31.4%) there was multifocal disease. A DCIS component was present in the pre-NST biopsy in 1326 patients (25.1%). Figure 1 shows the absolute numbers of patients diagnosed with HER2+ invasive breast cancer with (IBC+DCIS) and without a DCIS component (IBC) per year, showing an overall increase of patients treated with NST over the 10 years.

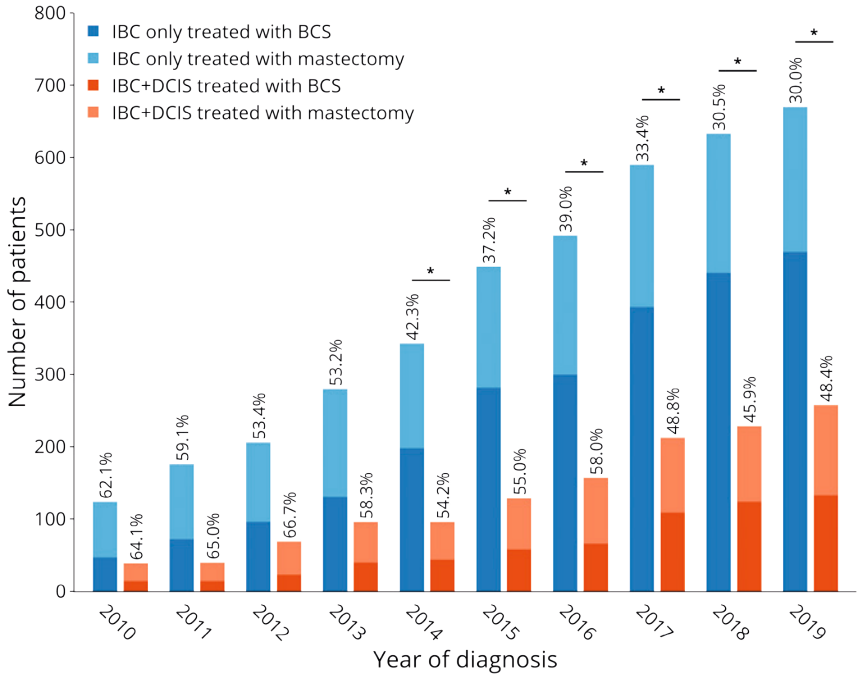

Figure 1: Incidence and surgical treatment of patients with HER2+ invasive breast cancer with (IBC+DCIS) and without (IBC) a DCIS component treated with NST and surgery per year. Percentages of mastectomy are shown per year and per patient group. Significant difference between IBC and IBC+DCIS is shown with an asterisk.

Surgical trends

In the overall study population, the mastectomy rate was 42.3% (2236/5289). Over the 10 years of inclusion, the rate of mastectomy decreased significantly, starting with 62.6% (102/163) in 2010 and 35.1% (326/928) in 2019 ($p<0.001$, Figure 2).

Table 1: Baseline characteristics

Characteristic	Total (n=5289) n (%)
Age Median (range)	50 (19-84)
Year of diagnosis	
2010-2012	654 (12.4)
2013-2016	2042 (38.6)
2017-2019	2593 (49.0)
cT status	
1	960 (18.2)
2	2968 (56.1)
3	980 (18.5)
4	381 (7.2)
cN status	
0	2234 (42.2)
1	2437 (46.1)
2	145 (2.7)
3	473 (9.0)
Grade	
1	299 (5.7)
2	2592 (49.0)
3	2398 (45.3)
ER receptor status	
Positive	3202 (60.5)
Negative	2087 (39.5)
Multifocal disease	
Yes	1660 (31.4)
No	3629 (68.6)
DCIS component in biopsy	
Yes	1326 (25.1)
No	3963 (74.9)
Anti-HER2 therapy	
Trastuzumab	2312 (43.7)
Trastuzumab + pertuzumab	2977 (56.3)

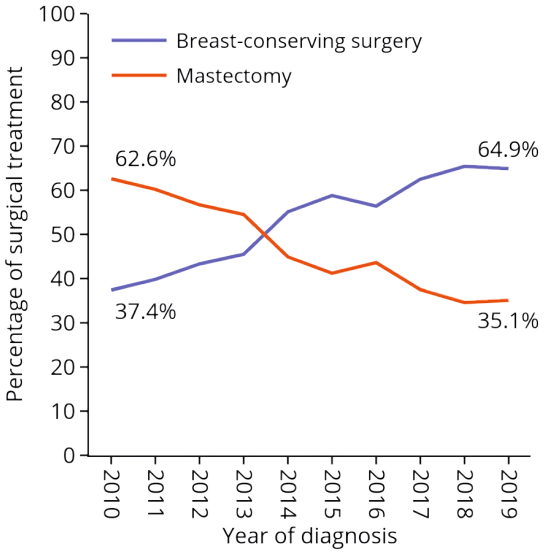

Figure 2: Percentage of breast-conserving surgery and mastectomy after NST in patients with HER2+ IBC

When comparing patients with and without a DCIS component in the biopsy over the entire study period, patients with a DCIS component were significantly more likely to be treated with mastectomy (52.9%, 701/1326) compared to those without a DCIS component (38.7%, 1535/3963, p<0.001).

In patients without a DCIS component, mastectomy rate significantly decreased from 62.1% (77/124) in 2010 to 30% (201/670) in 2019 (Figure 3, p<0.001). In patients with a DCIS component, mastectomy rate significantly decreased from 64.1% (25/39) in 2010 to 48.4% (125/258) in 2019 (Figure 3, p<0.001). The percentage undergoing mastectomy did not significantly differ between patients with and without DCIS in 2010 (p=0.821), but it did from 2014 onwards (Figure 1, Table S1).

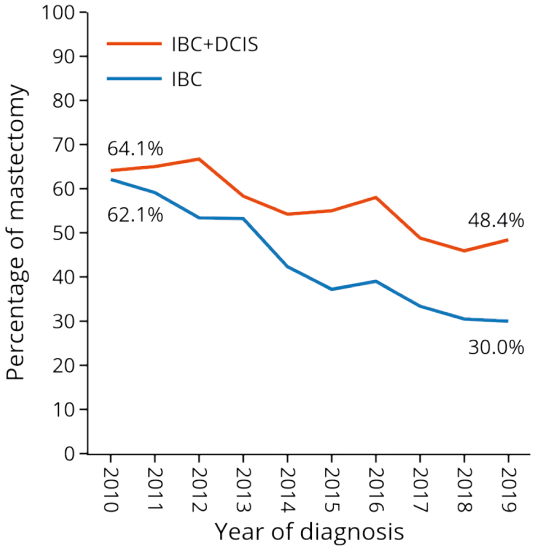

Figure 3: Mastectomy rate after NST in patients with HER2+ IBC with and without a DCIS component in the pre-NST biopsy

In multivariable logistic regression analyses, variables associated with higher mastectomy rate were: age below 50, cT3-4, cN+, ER negative disease, multifocal disease, and presence of a DCIS component (Table 2). Later year of diagnosis and treatment with dual anti-HER2 therapy was associated with lower mastectomy rate (Table 2).

Table 2: Logistic regression analyses for the association with mastectomy

	Mastectomy/ Total (%)	Univariable			Multivariable		
		OR	95% CI	p-value	OR	95% CI	p-value
Age							
≥50 years	1056/2831 (37.3)	REF			REF		
<50 years	1180/2458 (48.0)	1.55	1.39-1.73	<0.001	1.46	1.29-1.66	**<0.001**
Year of diagnosis							
2010-2012	388/654 (59.3)	REF			REF		
2013-2016	923/2042 (45.2)	0.57	0.47-0.68	<0.001	0.70	0.57-0.87	**0.001**
2017-2019	925/2593 (35.7)	0.38	0.32-0.45	<0.001	0.60	0.47-0.76	**<0.001**
cT status							
1-2	1248/3928 (31.8)	REF			REF		
3-4	988/1361 (72.6)	5.69	4.96-6.52	<0.001	5.33	4.59-6.18	**<0.001**

Table 2: Logistic regression analyses for the association with mastectomy *(continued)*

	Mastectomy/ Total (%)	Univariable			Multivariable		
		OR	95% CI	p-value	OR	95% CI	p-value
cN status							
cN0	711/2234 (31.8)	REF			REF		
cN+	1525/3055 (49.9)	2.13	1.90-2.39	<0.001	1.38	1.21-1.58	**<0.001**
Grade							
1-2	1171/2891 (40.5)	REF			REF		
3	1065/2398 (44.4)	1.17	1.01-1.36	0.04	1.03	0.88-1.20	0.72
ER status							
Positive	1278/3202 (39.9)	REF			REF		
Negative	958/2087 (45.9)	1.28	1.14-1.43	<0.001	1.20	1.05-1.37	**0.009**
Multifocal disease							
No	1242/3629 (34.2)	REF			REF		
Yes	994/1660 (59.9)	2.86	2.54-3.23	<0.001	3.08	2.69-3.52	**<0.001**
DCIS component							
No	1535/3963 (38.7)	REF			REF		
Yes	701/1326 (52.9)	1.77	1.57-2.01	<0.001	1.69	1.47-1.95	**<0.001**
Anti-HER2 therapy							
Trastuzumab	1081/2312 (46.8)	REF			REF		
Trastuzumab + pertuzumab	1155/2977 (38.8)	0.72	0.65-0.81	<0.001	0.79	0.68-0.93	**0.004**

Pathological complete response

YpT0 was achieved in 2389 (45.2%) of 5289 patients receiving NST. The rate of ypT0 increased from 31.3% (51/163) in 2010 to 46.9% (435/928) in 2019 (p<0.001), with the highest percentage in 2017 (49.4%, Figure 4). Patients with IBC with a DCIS component significantly less often achieved ypT0, with 38.7% (513/1326) compared to 47.3% (1876/3963) in IBC only (p<0.001). Mastectomy rates in patients with ypT0 were 49.7% with in patients with a DCIS component, compared to 37.0% for IBC only (p<0.001).

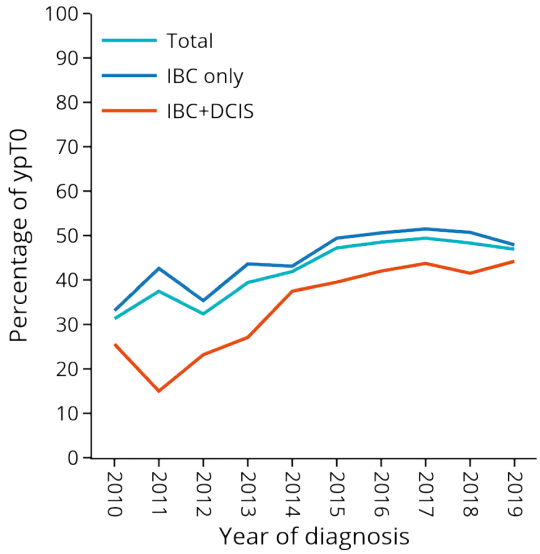

Figure 4: Percentage of patients with HER2+ IBC achieving ypT0 per year of diagnosis

Multivariable logistic regression analysis showed that diagnosis between 2013-2016, cN+ disease, grade 3 IBC, and treatment with dual anti-HER2 blockade were associated with higher likelihood of achieving ypT0 (Table 3). Patients with multifocal disease or with a DCIS component in the biopsy were associated with lower chance of achieving ypT0 (Table 3).

A comparison between Table 2 and Table 3 demonstrates that certain clinicopathological variables associated with lower odds of achieving ypT0 correspond with higher odds of undergoing mastectomy, as in patients with a DCIS component and multifocal disease. A more recent year of diagnosis and treatment with dual anti-HER2 therapy are associated with an increased likelihood of achieving ypT0 and a lower mastectomy rate. Other factors such as cT3-4 and cN+ disease show a strong association with higher odds of mastectomy, yet demonstrate a similar or even higher chance of achieving ypT0 compared to cT1-2 or cN0 disease, respectively.

Table 3: Logistic regression analyses for the association with ypT0

		Univariable			Multivariable		
	ypT0/Total (%)	OR	95% CI	p-value	OR	95% CI	p-value
Age							
≥50 years	1295/2831 (45.7)	REF					
<50 years	1094/2458 (44.5)	0.95	0.85-1.06	0.37			
Year of diagnosis							
2010-2012	221/654 (33.8)	REF			REF		
2013-2016	920/2042 (45.1)	1.61	1.34-1.93	<0.001	1.25	1.02-1.53	**0.03**
2017-2019	1248/2593 (48.1)	1.82	1.52-2.18	<0.001	1.11	0.88-1.39	0.39
cT status							
1-2	1766/3928 (45.0)	REF					
3-4	623/1361 (45.8)	1.03	0.91-1.17	0.60			
cN status							
cN0	969/2234 (43.4)	REF			REF		
cN+	1420/3055 (46.5)	1.13	1.02-1.27	0.03	1.02	0.90-1.15	0.75
Grade							
1-2	1198/2891 (41.4)	REF			REF		
3	1191/2398 (49.7)	1.39	1.24-1.56	<0.001	1.17	1.04-1.32	**0.01**
ER status							
Positive	1126/3202 (35.2)	REF			REF		
Negative	1263/2087 (60.5)	2.83	2.52-3.17	<0.001	2.71	2.41-3.06	**<0.001**
Multifocal disease							
No	1692/3629 (46.6)	REF			REF		
Yes	697/1660 (42.0)	0.83	0.74-0.93	0.002	0.82	0.72-0.93	**0.002**
DCIS component							
No	1876/3963 (47.3)	REF			REF		
Yes	513/1326 (38.7)	0.70	0.62-0.80	<0.001	0.70	0.61-0.80	**<0.001**
Anti-HER2 therapy							
Trastuzumab	831/2312 (35.9)	REF			REF		
Trastuzumab + pertuzumab	1558/2977 (52.3)	1.96	1.75-2.19	<0.001	2.03	1.76-2.35	**<0.001**

Discussion

This nationwide retrospective study examined trends in surgical treatment after NST for patients with HER2+ IBC between 2010 and 2019. Over this period, mastectomy rate significantly decreased from 62.8% in 2010 to 35.2% in 2019. Patients with a DCIS component underwent mastectomy significantly more often, with a rate of 48.6% in 2019, compared to 30% in patients with IBC only. The presence of DCIS was independently associated with a higher likelihood of mastectomy in multivariable logistic regression analyses, as well as age below 50, cT3-4, cN+ disease, ER negative disease, and multifocal disease. Both the presence of DCIS and multifocal disease were associated with lower odds of achieving ypT0, which may explain the higher mastectomy rates; however, this did not apply to age below 50, cT3-4, cN+, or ER-negative disease. A later year of diagnosis and treatment with dual anti-HER2 therapy were associated with a higher likelihood of achieving ypT0 and a lower likelihood of mastectomy, reflecting the improvements in neoadjuvant treatment effects over these 10 years.

One previous study by Li et al. evaluated the surgical treatment of 9643 patients with IBC, including all subtypes, that were treated with NST between 2010-2020.[19] An increase in BCS, and thereby decrease in mastectomy, comparable to our results was found over the included years. However, the rates of BCS compared to our population were considerably lower, with an overall rate of BCS in 2019 of 24.1%, compared to 64.8% in our study.[19] Reasons for this lower BCS rate could be inclusion of all tumor subtypes, and differences in patient preferences and health insurance between countries. A meta-analysis Karakatsanis et al. involving 1,452 patients from 7 randomized trials (1997-2012) assessed BCS eligibility after NST, which increased from 43.3% to 60.4%, yet BCS was only performed in 51.8%.[20] The meta-analysis reported the following factors to be associated with final surgical management: planned surgery before NST, multicentric or multifocal disease, tumor size before NST, and presence of residual tumor on palpation or MRI. The current study agreed on primary tumor size (cT status) and multifocal disease and its relationship to surgical treatment after NST, yet we did not have information on treatment decisions or details on clinical and radiological examination after NST. Multifocal disease is a frequently discussed topic regarding BCS in both the primary setting and after NST.[21-25] The multivariable analysis on achieving ypT0 in this study showed that multifocal disease is significantly associated with a lower likelihood of ypT0, justifying a more extensive surgical treatment after NST. Interestingly, cT3-4 disease was strongly associated with mastectomy, but the chance of achieving ypT0 was similar to cT1-2 disease (45.8% versus 45.0%, respectively). The high mastectomy rate in these patients may be attributed to the extent of the tumor and uncertainties regarding radiological complete response, prompting a more aggressive approach to ensure complete tumor removal. Importantly, BCS can be suitable for patients with residual disease if the remaining tumor is small relative to breast size;

however, the retrospective design of this cohort limited our analysis to comparisons with ypT0.

The association between presence of DCIS and surgical treatment after NST is rarely reported in the literature. In patients primarily treated with surgery, a few studies report the relation between a DCIS component and surgical treatment. Wong et al. investigated 1,355 size-matched IBC patients with versus without a DCIS component and showed that patients with a DCIS component were less likely to be treated with BCS.[13] Kole et al. included 494,801 IBC patients treated with primary surgery as well as NST and also found that the presence of DCIS was associated with mastectomy.[11] The presence of DCIS was significantly associated with a lower likelihood of ypT0 in the current study, which is in line with previous literature and explains part of the higher mastectomy rate.[26, 27] However, overall, patients with IBC with a DCIS component achieved ypT0 in 38.7%. Breast-conserving surgery could be feasible in these patients, yet imaging of potential response of the DCIS component is poorly investigated. A recent systematic review highlights the challenges in monitoring response of the DCIS component, reporting that suspicious calcifications can remain in the prior tumor region, and residual DCIS does not always show enhancement on breast MRI.[28] For the invasive tumor, breast MRI is to date the most adequate in determining tumor response, yet the pooled sensitivity and specificity range between 0.64-0.77 and 0.81-0.92 in meta-analyses, respectively.[29-31] Further research into additional imaging parameters, or the combination with radiomics and machine learning, should reveal whether it is possible to predict tumor response accurately enough to adjust surgical treatment.

In addition to the tumor characteristics discussed earlier, another important factor in deciding on surgical treatment is patient preference. Given the high percentage of ypT0 patients who still underwent mastectomy, it might be argued that this is unnecessary extensive treatment. However, despite BCS being feasible, a patient can opt for mastectomy for several reasons. Actually, literature has shown that more patient involvement in surgical decision-making was associated with a greater likelihood of mastectomy.[32] A systematic review evaluating 25 studies on factors influencing women's choice for surgical treatment concludes that the main reasons for opting mastectomy were mastectomy being the most reassuring option, avoiding radiation, and supposedly a more expedient treatment. Women chose for BCT based on body image concerns and femininity, physician recommendation, long-term survival being equivalent, and less surgery being involved.[33] Shared decision-making and appropriate risk counseling is important when presenting the patient with the surgical treatment decision, as studies report that women might feel forced to choose between feminine identity and survival.[34, 35] Nowadays, there are increasing possibilities with regard to oncoplastic reconstruction of the breast that should also be considered and discussed.[36, 37] In the Netherlands, a patient decision aid was developed in 2014 to support shared-decision making in counselling about surgical treatment, and more recently another patient

aid was develop for breast reconstruction.[38, 39] In addition to patient's preferences, the before-mentioned systematic review also reports on surgeon factors associated with surgical treatment. Female gender, higher case numbers, and individual surgeon practice, were associated with increased BCS rates.[33]

The retrospective nature of this nationwide database created certain limitations. Most importantly, patient's preference for surgical treatment could not be investigated. Moreover, there was no information on imaging findings (e.g. widespread calcifications), or (secondary) oncoplastic reconstructions that could have influenced choice for mastectomy. Reporting bias of the presence of DCIS may have occurred due to pathologists focusing on the invasive tumor, ignoring small amounts of DCIS. However, these minimal DCIS components would probably not have influenced surgical treatment. In addition, information on BRCA gene mutations was missing, since these patients often choose for (bilateral) mastectomy.[40] However, HER2-positivity is rare amongst BRCA mutation carriers with rates lower than 10% in literature.[41, 42] It is important to note that the early years had lower case numbers, which could potentially impact the trend graphs. However, this was not expected due to the absence of major outliers, thus additional analyses like moving averages were not considered necessary. An important strength of this study is that it is the first one focusing on the role of the DCIS component on surgical treatment after NST on a nationwide scale. The large population size allowed for a proper multivariable analysis, and a comparison to the likelihood of achieving pCR.

Conclusion

This nationwide retrospective study shows a significant decrease of mastectomy rate in HER2+ invasive breast cancer patients over the years 2010-2019. Patients with HER2+ IBC with a DCIS component showed a significantly higher likelihood of mastectomy after NST, and a significantly lower chance of achieving ypT0. Hence, part of these mastectomies are justified, however, 38.7% of patients with a DCIS component did reach a pathological complete response and could benefit from less extensive surgery. Future imaging studies including response evaluation of the DCIS component may contribute to surgical decision-making after NST. Mastectomy should not be eliminated, however, patients should be able to make well-informed choices about their surgical treatment.

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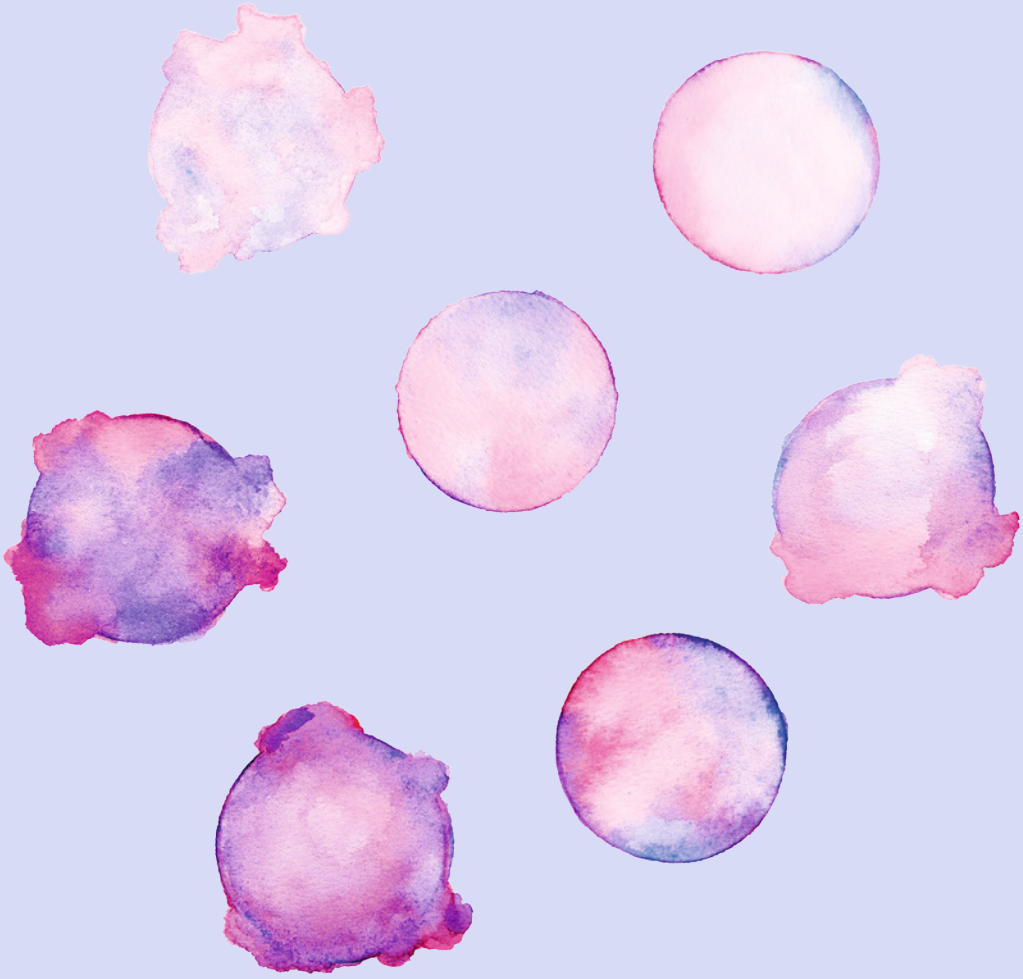
Table S1: Incidence and surgical treatment of patients with HER2+ invasive breast cancer, with (IBC+DCIS) and without (IBC) a DCIS component

Year of diagnosis	IBC, n (%)	IBC+DCIS, n (%)	BCS in IBC, n (%)	Mastectomy in IBC, n (%)	BCS in IBC+DCIS, n (%)	Mastectomy in IBC+DCIS, n (%)	p-value
2010	124 (76.1)	39 (23.9)	47 (37.9)	77 (62.1)	14 (35.9)	25 (64.1)	0.821
2011	176 (81.5)	40 (18.5)	72 (40.9)	104 (59.1)	14 (35.0)	26 (65.0)	0.491
2012	206 (74.9)	69 (25.1)	96 (46.6)	110 (53.4)	23 (33.3)	46 (66.7)	0.054
2013	280 (74.5)	96 (25.5)	131 (46.8)	149 (53.2)	40 (41.7)	56 (58.3)	0.385
2014	343 (78.1)	96 (21.9)	198 (57.7)	145 (42.3)	44 (45.8)	52 (54.2)	**0.038**
2015	449 (77.7)	129 (22.3)	282 (62.8)	167 (37.2)	58 (45.0)	71 (55.0)	**<0.001**
2016	492 (75.8)	157 (24.2)	300 (61.0)	192 (39.0)	66 (42.0)	91 (58.0)	**<0.001**
2017	590 (73.5)	213 (26.5)	393 (66.6)	197 (33.4)	109 (51.2)	104 (48.8)	**<0.001**
2018	633 (73.4)	229 (26.6)	440 (69.5)	193 (30.5)	124 (54.1)	105 (45.9)	**<0.001**
2019	670 (72.2)	258 (27.8)	469 (70.0)	201 (30.0)	133 (51.6)	125 (48.4)	**<0.001**

Abbreviations: BCS breast-conserving surgery, DCIS ductal carcinoma in situ, IBC invasive breast cancer



CHAPTER 7

Surgical outcomes and prognosis of HER2+ invasive breast cancer patients with a DCIS component treated with breast-conserving surgery after neoadjuvant systemic therapy

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Abstract

Introduction: In up to 72% of HER2+ invasive breast cancer (IBC), a ductal carcinoma in situ (DCIS) component is present. The presence of DCIS is associated with increased positive surgical margins after breast-conserving surgery (BCS). The aim of this study was to assess surgical margins, recurrence and survival in a nationwide cohort of HER2+ IBC with versus without a DCIS component, treated with neoadjuvant systemic therapy (NST) and BCS.

Materials and methods: Women diagnosed with HER2+ IBC treated with NST and BCS, between 2010-2019, were selected from the Netherlands Cancer Registry and linked to the Dutch Nationwide Pathology Databank. Kaplan-Meier and Cox regression analyses were performed to determine locoregional recurrence rate (LRR) and overall survival (OS) and associated clinicopathological variables. Surgical outcomes and prognosis were compared between IBC only and IBC+DCIS.

Results: A total of 3056 patients were included: 1832 with IBC and 1224 with IBC+DCIS. Patients with IBC+DCIS had significantly more often positive surgical margins compared to IBC (12.8% versus 4.9%, $p<0.001$). Five-year LRR was significantly higher in patients with IBC+DCIS compared to IBC (6.8% versus 3.6%, $p<0.001$), but the presence of DCIS itself was not significantly associated with LRR after adjusting for confounders in multivariable analysis. Five-year OS did not differ between IBC+DCIS and IBC (94.9% versus 95.7%, $p=0.293$).

Conclusion: The presence of DCIS is associated with higher rates of positive surgical margins, but not with LRR and lower OS when adjusted for confounders. Further research is necessary to adequately select IBC+DCIS patients for BCS after NST.

Introduction

Breast-conserving surgery (BCS), followed by radiation therapy, has become a preferred treatment for invasive breast cancer (IBC) patients, given the increased quality of life and similar survival outcomes compared to mastectomy.[1] The assessment of surgical margins after BCS is important, because in case of tumor-involved margins, local recurrence rate (LRR) increases.[2] The width of the margin does not affect recurrence rate and therefore, after a SSO/ASCO/ASTRO consensus in 2014, "no ink on tumor" is recommended after primary BCS.[2, 3] In neoadjuvant setting, fewer studies have investigated the impact of margin status, and the previously mentioned guideline does not apply to patients treated with neoadjuvant systemic therapy (NST). Cheun et al. investigated 2803 patients who underwent NST followed by BCS and whole breast irradiation, and found no significant difference in local recurrence free survival rates between patients with clear, close or involved resection margins.[4] Choi et al. and Wimmer et al. also found no association with margin width and prognosis in patients treated with BCS after NST.[5, 6]

NST is increasingly applied in HER2+ IBC patients, and one of the goals is to decrease tumor extent and increase the possibility of BCS.[7-9] A factor that potentially complicates the possibility to receive BCS after NST, is a DCIS component, which is present in more than half of HER2+ IBC patients.[10, 11] This presence of DCIS is associated with a higher rate of involved margins in previous studies on patients primarily treated with BCS.[12, 13] In the neoadjuvant setting, the impact of a DCIS component on both margin status and recurrence is less commonly investigated. Whereas it was previously thought that DCIS responds poorly to NST, recent studies show that the DCIS component can completely disappear in about 50% of HER2+ IBC patients.[14-16]

Despite the high complete response rates of DCIS in HER2+ IBC patients, important information is missing to confirm that BCS is feasible in these patients. This nationwide cohort study was conducted to investigate the rate of positive surgical margins in HER2+ IBC patients with versus without a DCIS component, treated with NST and BCS. In addition, LRR rate and overall survival will be compared between these two groups.

Methods

Data sources and study population

For this retrospective nationwide cohort study, a database was collected from the Netherlands Cancer Registry (NCR). Data managers from the Netherlands Comprehensive Cancer Organization (IKNL) collect data on all newly diagnosed cancer patients in the NCR from the electronic patient files of all hospitals in the Netherlands. After approval of the data request and study protocol by the privacy board of IKNL, a dataset was received from the NCR. This dataset included all patients diagnosed with

HER2+ IBC, treated with neoadjuvant chemotherapy and targeted therapy followed by BCS, between January 2010 and December 2019.

Subsequently, the dataset was linked to PALGA, the Dutch Nationwide Pathology Databank, and all pathology reports from the patients were collected, including pre-NST biopsies or cytology of breast/axilla, surgical specimens of breast/axilla, and biopsies of breast and axillary recurrences, or distant metastases after primary treatment.

After merging the databases, patients were excluded in case of distant metastases at diagnosis, missing pathology reports, or inability to assess surgical margins.

Treatment according to the Dutch guideline[17-19]
The administration of NST is based on age, tumor size, grade, receptor status and nodal involvement. For HER2+ IBC patients, NST is considered in case of tumor size ≥5mm or nodal involvement. Dual anti-HER2 blockade consisting of trastuzumab with pertuzumab was administered from 2017 onwards in case of tumor >2cm and/or cN+ status.

Adjuvant radiation therapy is recommended in all patients undergoing BCS after NST. An additional boost of the tumor bed is advised in case of patients younger than 50 years of age, an estimated local recurrence risk ≥1% per year, grade 3 IBC, lymph vascular invasion and/or positive surgical margins. Adjuvant systemic regimens were based on residual tumor size and nodal status.

In case of positive surgical margins, additional treatment according to the Dutch guideline is based on the width of the involved margin. Focally involved margins (tumor reaching margin in an area of <4mm) are treated with radiation therapy (with boost), where in case of more than focally involved margins (tumor reaching margin in an area of ≥4mm) reoperation is recommended.[17-19]

Pathological evaluation
All pathology reports from the included patients were reassessed to verify potential presence of a DCIS component. Patients were grouped into IBC only (no DCIS present in either the biopsy or the postoperative specimen) and IBC+DCIS (a DCIS component present in the biopsy and/or the postoperative specimen) for further analyses on surgical and prognostic outcomes.

Pathological complete response (pCR) of IBC was classified as absence of IBC in the postoperative specimen, regardless of the presence of DCIS (ypT0/is). Residual disease in the breast was defined as any remaining tumor cells, either invasive or in situ, in the postoperative pathology specimen (ypT+/is).

Surgical margins

Surgical margins were reassessed in the pathology reports and were classified as positive based on "ink on tumor" for both invasive and in situ disease. Positive surgical margins were then divided into focally positive and more than focally positive according to Dutch guidelines.[17-19]

Recurrence and survival

Locoregional recurrence (LRR) was based on pathologically proven biopsies of tumor cells (in situ/invasive) in the ipsilateral breast and axilla level I-IV that were registered in the PALGA database after surgery of the primary tumor and axilla. Contralateral tumors of the breast after primary diagnoses were not classified as recurrences, but as a second primary tumor. Contralateral metastasis in the axilla, without second primary in the contralateral breast, was classified as distant metastasis (DM).[20] Events that occurred between 0 and 90 days after primary diagnosis were classified as synchronous with the original tumor.

Five-year LRR rate was based on LRR as a first event in the first 5 years after primary diagnosis. For the LRR rate, patients were censored at the last moment of follow-up or date of death. Overall survival (OS) was determined as the time interval between primary diagnosis and death from any cause. Survivors were censored at the last moment of follow-up reported in the NCR.

End points

The primary endpoint was the rate of positive surgical margins (involved with invasive and/or in situ disease) after BCS between patients with IBC and IBC+DCIS.

Secondary endpoints were reoperation rate, 5-year LRR rate, and 5-year OS. All outcomes were compared between patients with IBC only and IBC+DCIS. Other clinicopathological variables associated with prognosis were assessed to adjust for confounding.

Statistical analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 26, Armonk, New York). Missing data were considered to be missing at random, and were consequently imputed using multiple imputation, creating five imputed datasets. For subsequent analyses, the results from these five imputed datasets were pooled according to Rubin's rules.[21]

Pearson's χ^2 test was used to compare IBC only with IBC+DCIS, and to evaluate the rate of positive surgical margins between these groups. Multivariable logistic regression analysis was used to assess the impact of DCIS on margins when adjusting for confounders.

Kaplan-Meier survival analyses were performed to determine 5-year LRR-rate and 5-year OS, and log-rank tests were used to compare IBC only and IBC+DCS. Univariable and multivariable Cox proportional hazards regression models were used to determine associated patient and tumor characteristics with LRR and OS. Statistically significant variables in univariable analyses were included in multivariable analyses. Results were presented as hazard ratio (HR) and 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant.

Results

Between January 2010 and December 2019, 3370 HER2+ IBC patients were treated with NST followed by BCS. After exclusion of ineligible patients (n=314), a total of 3056 patients were included in the study population (Figure 1). Patients were divided into IBC only (n=1832 (59.9%)) or IBC+DCIS (n=1224 (40.1%)). In the group of patients with IBC+DCIS, the DCIS component was observed in the biopsy in 630 patients, and 873 patients had residual DCIS in the postoperative specimen.

Baseline characteristics of patients with IBC compared to IBC+DCIS

Patient, tumor, and treatment characteristics were compared between patients with IBC only and IBC+DCIS (Table 1). Median age was slightly higher in patients with IBC only compared to IBC+DCIS (52 versus 50 years of age, p=0.002). Clinical tumor and nodal status were comparable between IBC and IBC+DCIS, and patients were most common diagnosed with cT2N0 grade 2 IBC. Patients with IBC+DCIS had significantly more often multifocal (25.3% versus 19.4%, p<0.001) and estrogen receptor (ER) positive disease (67.3% versus 60.0%, *p*<0.001). The percentage of patients treated with adjuvant radiation therapy was higher in the IBC group (97.5%) compared to IBC+DCIS (95.9%, p=0.011). Adjuvant chemotherapy was administered in 2.6% of IBC patients and 4.5% of IBC+DCIS patients (p<0.001). Adjuvant endocrine therapy was more often administered in IBC+DCIS patients (61.4% versus 56.7%, p=0.009).

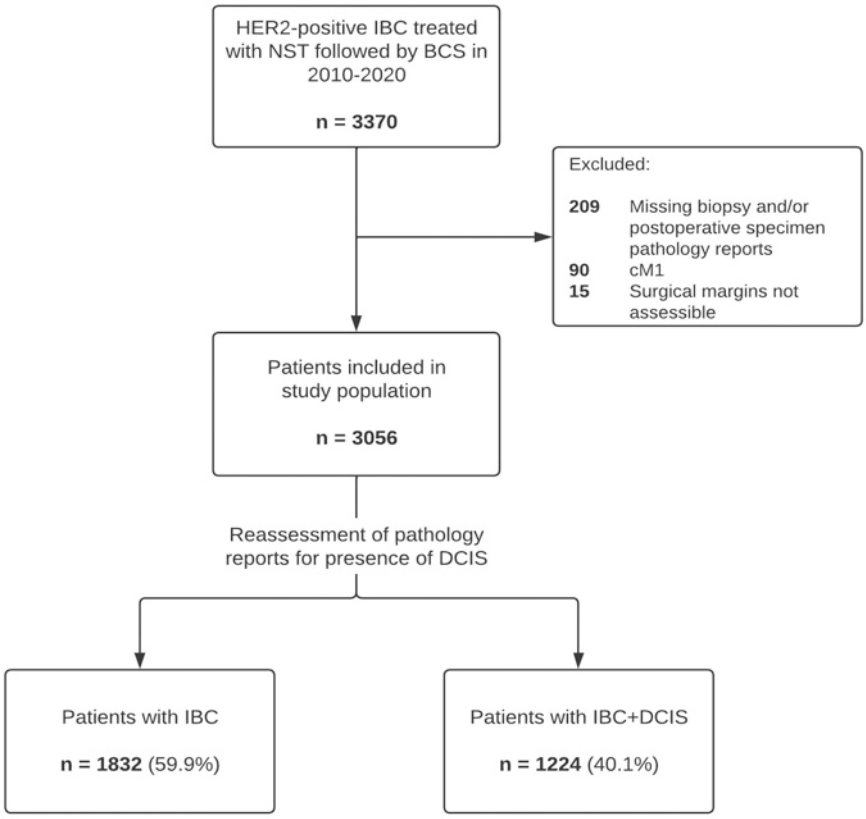


Figure 1: Flowchart of patient selection

Table 1: Baseline characteristics of patients with IBC and IBC+DCIS

	IBC (n=1832) n (%)	**IBC+DCIS (n=1224) n (%)**	**p-value**
Age in years (median (range))	52 (21-81)	50 (23-83)	**0.002**
Year of diagnosis			**0.005**
2010-2013	232 (12.7)	203 (16.6)	
2014-2016	601 (32.8)	362 (29.6)	
2017-2019	999 (54.5)	659 (53.8)	
cT status			0.702
1	388 (21.2)	260 (21.2)	
2	1228 (67.0)	811 (66.3)	
3	189 (10.3)	139 (11.4)	
4	27 (1.5)	14 (1.1)	

Table 1: Baseline characteristics of patients with IBC and IBC+DCIS *(continued)*

	IBC (n=1832) n (%)	**IBC+DCIS (n=1224) n (%)**	**p-value**
cN status			0.492
0	900 (49.1)	629 (51.4)	
1	758 (41.3)	491 (40.1)	
2	54 (3.0)	28 (2.3)	
3	120 (6.6)	76 (6.2)	
IBC grade			**0.030**
1	93 (5.1)	83 (6.8)	
2	942 (51.4)	594 (48.5)	
3	797 (43.5)	547 (44.7)	
Multifocal disease			**<0.001**
Yes	353 (19.4)	305 (25.3)	
No	1465 (80.6)	902 (74.7)	
Unknown	14	17	
ER status IBC			**<0.001**
Positive	1099 (60.0)	824 (67.3)	
Negative	733 (40.0)	400 (32.7)	
Adjuvant radiation therapy			**0.011**
Yes	1787 (97.5)	1174 (95.9)	
No	45 (2.5)	50 (4.1)	
Adjuvant chemotherapy			**0.004**
Yes	47 (2.6)	55 (4.5)	
No	1785 (97.4)	1169 (95.5)	
Adjuvant endocrine therapy			**0.009**
Yes	1038 (56.7)	752 (61.4)	
No	794 (43.3)	472 (38.6)	
Adjuvant targeted therapy			0.359
Yes	1773 (96.8)	1177 (96.2)	
No	59 (3.2)	47 (3.8)	

Abbreviations: IBC: invasive breast cancer, DCIS: ductal carcinoma in situ, ER: estrogen receptor

Table 2: Surgical outcomes after treatment with NST and BCS

	IBC (n=1832) n (%)	**IBC+DCIS (n=1224) n (%)**	**p-value**
Surgical margins [a]			**<0.001**
Positive	90 (4.9)	157 (12.8)	
Negative	1742 (95.1)	1067 (87.2)	
In case of positive surgical margins at first surgery	**IBC (n=90) n (%)**	**IBC+DCIS (n=157)** n (%)	
Extent of affected margin by IBC [b]			0.566
Focal	60 (66.7)	58 (70.7)	
More than focal	30 (33.3)	24 (29.3)	
Extent of affected margin by DCIS			
Focal		70 (71.4)	
More than focal		28 (28.6)	
Reoperation in case of positive margins			0.540
Yes	32 (35.6)	62 (39.5)	
No	58 (64.4)	95 (60.5)	
Repeat surgery			0.565
Breast-conserving surgery	18 (56.3)	31 (50)	
Mastectomy	14 (43.7)	31 (50)	
Final surgical margins [a]			**<0.001**
Positive	58 (3.2)	99 (8.1)	
Negative	1774 (96.8)	1125 (91.9)	

[a] including both invasive and in situ disease involved margins
[b] focal: *tumor reaching margin in an area of <4mm*, more than focal: *tumor reaching margin in an area of ≥4mm*

Postoperative pathology and surgical outcomes

The postoperative pathology of the included patients is shown in Table A.1. Overall, 247 patients (8.1%) had positive surgical margins after treatment with NST and BCS. The rate of positive surgical margins, involved margin width and the reoperation rate are presented in Table 2.

The rate of positive surgical margins was significantly higher in IBC+DCIS patients compared to IBC patients (12.8% versus 4.9%, p<0.001). Positive surgical margins in the IBC+DCIS group were caused by IBC in 59 (4.8%), by DCIS in 75 (6.1%) and by both in 23 patients (1.9%). When only comparing positive surgical margins for IBC, irrespective

of DCIS involved margins, patients with IBC+DCIS still had a significantly higher rate of positive margins compared to IBC only (6.7% versus 4.9%, p=0.036).

The extent of the affected margins was comparable between IBC and IBC+DCIS and margins were most frequently focally positive (66.7% and 70.1%, respectively).

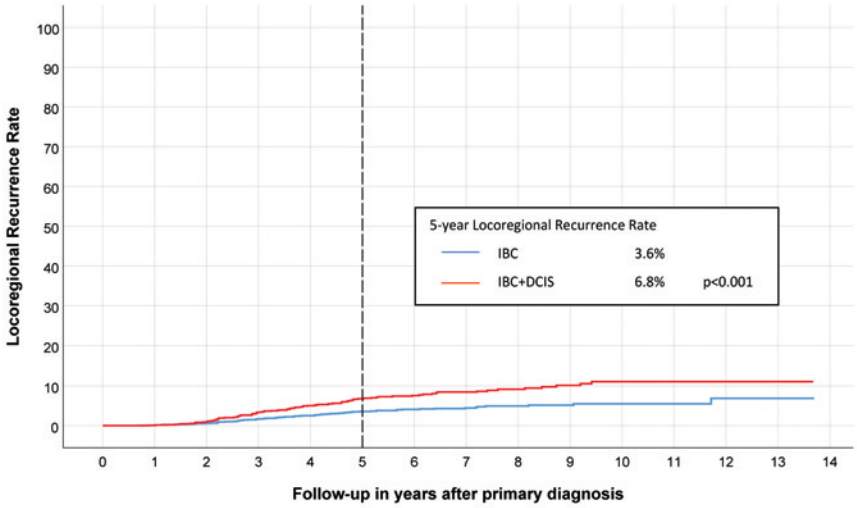
In case of positive surgical margins, the reoperation rate was 35.6% (n=32) in patients with IBC and 39.5% (n=62) in patients with IBC+DCIS (p=0.540). After reoperation, the rate of positive margins was still higher in IBC+DCIS compared to IBC only (8.1% versus 3.2%, p<0.001).

Multivariable logistic regression analyses demonstrated that presence of a DCIS component was independently associated with higher probability of positive surgical margins after adjusting for confounders (Odds Ratio (OR) 2.612, 95% CI: 1.983-3.439, p<0.001, Table A.2).

Recurrence and prognosis

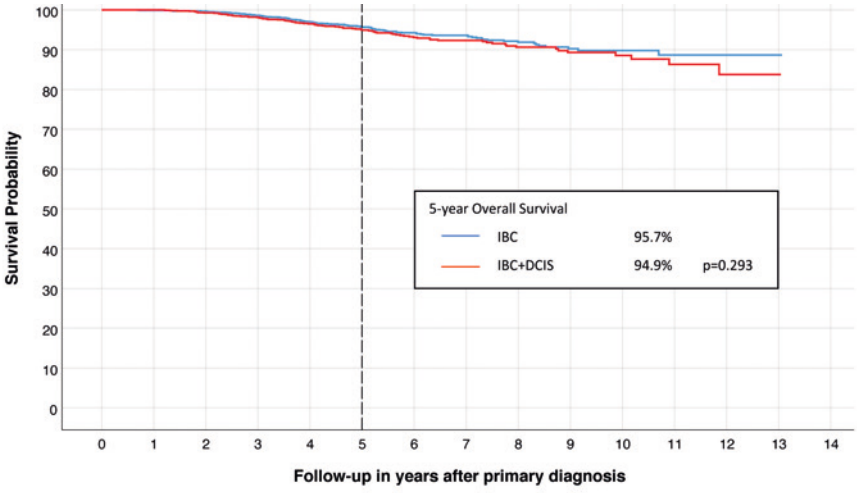
Median follow-up for recurrence and death from any cause was 6.0 (range 0.7-13.7) years. During follow-up, an ipsilateral recurrence of the breast and/or axilla was found in 172/3056 patients and a distant metastasis in 127/3056 patients. The distribution of recurrences and metastasis between the two groups is shown in Figure A.1. The histological distribution of ipsilateral breast recurrences differed between IBC and IBC+DCIS patients (Table A.3). Patients with IBC+DCIS had a significantly higher percentage of concurrent IBC+DCIS recurrence compared to patients with IBC only (35.6% versus 16.2%, p=0.007). A contralateral breast tumor was diagnosed in 52 patients during overall follow-up, of which 12 DCIS, 21 IBC and 19 IBC+DCIS. In total, 190 patients deceased during the reported follow-up.

The LRR rate was significantly higher in patients with IBC+DCIS compared to IBC only (p<0.001) with a 5-year LRR of 6.8% compared to 3.6% in IBC only (Figure 2A). Multivariable Cox Regression analysis shows that cT3-4 (HR 1.710, 95% CI 1.178-2.483, p=0.005), cN+ (HR 1.588, 95% CI 1.122-2.247, p=0.009), ypT+/is (HR 2.102, 95% CI 1.417-3.117, p<0.001), and ER negative disease (HR 1.905, 95% CI 1.082-3.355, p=0.026) are associated with higher odds for LRR. Higher age (HR 0.973, 95% CI 0.959-0.988, p<0.001), adjuvant targeted therapy (HR 0.501, 95% CI 0.277-0.908, p=0.023), and adjuvant radiation therapy (HR 0.245, 95% CI 0.153-0.393, p<0.001) are associated with lower odds for LRR. The presence of a DCIS component was significantly associated with higher odds for LRR in univariable analysis, but did not reach significance when adjusted for confounders in multivariable Cox regression (HR 1.327, 95% CI 0.940-1.874, p=0.107). Positive surgical margins, after either first surgery or final surgery, were not associated with a higher rate of LRR.



	Years after diagnosis	0	1	2	3	4	5
IBC	Number at risk (censored)	1832 (0)	1828 (2)	1800 (21)	1751 (51)	1635 (152)	1268 (503)
IBC+DCIS	Number at risk (censored)	1224 (0)	1223 (0)	1196 (16)	1149 (35)	1052 (112)	803 (344)

Figure 2 A: Locoregional Recurrence Rate for IBC and IBC+DCIS



	Years after diagnosis	0	1	2	3	4	5
IBC	Number at risk (censored)	1832 (0)	1829 (1)	1823 (2)	1803 (4)	1456 (325)	1116 (646)
IBC+DCIS	Number at risk (censored)	1224 (0)	1224 (0)	1214 (1)	1195 (6)	971 (212)	732 (439)

Figure 2 B: Overall Survival for IBC and IBC+DCIS

Table 3: Cox regression analyses of LRR

	No of events/ total	Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
Age	172/3056	0.974	0.960-0.988	<0.001	0.973	0.959-0.988	**<0.001**
Year of diagnosis	172/3056	1.021	0.953-1.093	0.555			
cT							
1-2	136/2687	REF			REF		
3-4	36/369	1.952	1.352-2.819	<0.001	1.710	1.178-2.483	**0.005**
cN							
Negative	61/1528	REF			REF		
Positive	111/1528	1.785	1.301-2.448	<0.001	1.588	1.122-2.247	**0.009**
ypT							
ypT0	52/1447	REF			REF		
ypT+/is	120/1609	2.110	1.524-2.922	<0.001	2.102	1.417-3.117	**<0.001**
ypN							
ypN0	124/2492	REF			REF		
ypN+	48/564	1.738	1.240-2.436	0.001	1.391	0.953-2.031	0.087
IBC grade							
1-2	80/1711	REF					
3	92/1345	1.489	0.983-2.257	0.060			
ER receptor							
Positive	88/1923	REF			REF		
Negative	84/1133	1.664	1.233-2.246	0.001	1.905	1.082-3.355	**0.026**
Multifocal disease							
No	131/2367	REF					
Yes	37/658	1.012	0.703-1.458	0.949			
DCIS component							
No	76/1832	REF			REF		
Yes	96/1224	1.925	1.425-2.601	<0.001	1.327	0.940-1.874	0.107
Positive surgical margins							
After first surgery	19/247	1.426	0.886-2.298	0.144			
After final surgery	14/157	1.675	0.970-2.893	0.064			
Adjuvant chemotherapy	7/102	1.492	0.700-3.183	0.300			

Table 3: Cox regression analyses of LRR *(continued)*

	No of events/ total	Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
Adjuvant endocrine therapy	81/1790	0.602	0.446-0.812	0.001	0.828	0.471-1.456	0.512
Adjuvant targeted therapy	160/2950	0.494	0.275-0.888	0.018	0.501	0.277-0.908	**0.023**
Adjuvant radiation therapy	151/2961	0.218	0.138-0.343	<0.001	0.245	0.153-0.393	**<0.001**

Kaplan-Meier curves for OS are shown in Figure 2b. OS was not significantly different between patients with IBC only and IBC+DCIS, with a 5-year survival probability of 95.7% for IBC and 94.9% for IBC+DCIS (p=0.293). Clinicopathological variables associated with worse OS in multivariable Cox regression analysis were: higher age (HR 1.029, 95% CI 1.014-1.043, p<0.001), cT3-4 (HR 1.497, 95% CI 1.030-2.175, p=0.034), ypT+/is (HR 1.602, 95% CI 1.149-2.233, p=0.005), ypN+ (HR 2.367, 95% CI 1.689-3.318, p<0.001), grade 3 (HR 1.468, 95% CI 1.085-1.985, p=0.013) and treatment with adjuvant chemotherapy (HR 2.315, 95 %CI 1.275-4.204, p=0.006). The presence of a DCIS component was not associated with OS (Table 4). Positive surgical margins were associated with worse OS in univariable analyses, but not after adjusting for confounders.

Table 4: Cox regression analyses of OS

	No of events/ total	Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
Age	190/3056	1.029	1.014-1.043	<0.001	1.029	1.014-1.043	**<0.001**
Year of diagnosis	190/3056	0.949	0.888-1.013	0.118			
cT							
1-2	155/2687	REF			REF		
3-4	35/369	1.558	1.079-2.248	0.018	1.497	1.030-2.175	**0.034**
cN							
Negative	61/1528	REF			REF		
Positive	129/1528	1.920	1.415-2.605	<0.001	1.293	0.921-1.817	0.138
ypT							
ypT0	63/1447	REF			REF		
ypT+/is	127/1609	1.737	1.284-2.350	<0.001	1.602	1.149-2.233	**0.005**

Table 4: Cox regression analyses of OS *(continued)*

	No of events/ total	Univariable			Multivariable		
		HR	95% CI	p-value	HR	95% CI	p-value
ypN							
ypN0	113/2492	REF			REF		
ypN+	77/564	2.816	2.105-3.768	<0.001	2.367	1.689-3.318	**<0.001**
IBC grade							
1-2	86/1711	REF					
3	104/1345	1.521	1.129-2.048	0.006	1.468	1.085-1.985	**0.013**
ER receptor							
Positive	106/1923	REF			REF		
Negative	84/1133	1.358	1.020-1.809	0.036	1.011	0.595-1.718	0.967
Multifocal disease							
No	150/2367	REF					
Yes	38/658	0.923	0.647-1.318	0.659			
DCIS component							
No	106/1832	REF					
Yes	84/1224	1.166	0.875-1.553	0.294			
Positive surgical margins							
After first surgery [a]	24/247	1.607	1.048-2.466	0.030			
After final surgery	17/157	1.809	1.099-2.977	0.020	1.429	0.853-2.394	0.175
Adjuvant chemotherapy	12/102	2.790	1.552-5.018	0.001	2.315	1.275-4.204	**0.006**
Adjuvant endocrine therapy	95/1790	0.677	0.509-0.899	0.007	0.614	0.364-1.035	0.067
Adjuvant targeted therapy	181/2950	0.773	0.396-1.510	0.451			
Adjuvant radiation therapy	181/2961	0.682	0.349-1.333	0.263			

[a] excluded from multivariable analysis because of collinearity with margins after final surgery

Discussion

The aim of this nationwide retrospective study was to investigate the rate of positive surgical margins between HER2+ IBC patients with and without a DCIS component, and to compare LRR and OS.

The 1224 patients with IBC+DCIS had significantly more often positive surgical margins compared to 1832 patients with IBC only (12.8% versus 4.9%, p<0.001). A higher 5-year LRR rate was found in univariate Kaplan-Meier analyses comparing IBC+DCIS (6.8%) to IBC only (3.6%). However, in multivariable Cox regression analysis, the presence of a DCIS component on its own was not significantly associated with higher odds for LRR after adjusting for confounding variables (HR 1.327, 95% CI 0.940-1.874, p=0.107). Five-year OS did not significantly differ between patients with IBC+DCIS and IBC only.

In previous literature, several studies investigated the surgical margins after NST and BCS. A systematic review by Volders et al. published in 2018 demonstrated that the rate of positive surgical margins after NST and BCS ranged widely between 2.0-39.8% in the 26 included studies published between 1999-2016.[22] Two more recently published studies by Spronk et al. (2019) and Mrdutt et al. (2022) investigated 4170 and 586 patients, treated with NST and BCS, and reported positive surgical margins in 18.7% and 7%, respectively.[23, 24] The overall positive surgical margin rate of 8.1% in our HER2+ IBC population is consistent with previous described percentages, but it remains difficult to properly compare studies because of varying margin definitions and study populations.

Resection margins of HER2+ IBC patients with a DCIS component after BCS and NST have been far less studied. One study by Groen et al. investigated a smaller population of 77 patients HER2+ IBC+DCIS and reported a rate of 13% positive surgical margins after NST and BCS, which is in line with the rate in our study (12.8%).[15] Furthermore, the current study demonstrates that the presence of a DCIS component is independently associated with positive surgical margins, with an OR of 2.659 (95%CI 2.021-3.497), after adjusting for confounders. Likewise, Spronk et al. investigated prognostic factors for involved invasive margins for both patients treated with NST+BCS and primary BCS. The presence of a DCIS component was independently associated with involved invasive margins in primary BCS, and there was a positive association with involved surgical margins in NST+BCS, however not statistically significant, due to their use of a significance cut-off of <0.005 (p=0.024).[23] Previous studies on patients with primary DCIS describe possible reasons for an increased rate of positive surgical margins. DCIS is commonly non-palpable, consisting of multi-focal lesions with normal ducts in between, and is usually detected only by calcifications on mammography, all contributing to a more difficult assessment of its extent.[25-27]

Many studies have investigated the prognosis of HER2+ IBC patients. Achieving pCR is one of the most important prognostic factors for HER2+ tumors and has been proposed as an informative surrogate to improved survival.[28-30] This is in line with the results of our multivariable analyses, where residual disease in the breast (ypT+/is) and axilla (ypN+) was associated with worse outcomes for both LRR and OS. The presence of a DCIS component was not associated with statistically significant worse LRR and OS in multivariable Cox regression analysis. The higher LRR rate for IBC+DCIS in Kaplan-Meier analyses can be explained by the current study and previous literature demonstrating that patients with a DCIS component achieve a lower rate of pCR (Table A.1).[16, 31] Margin status was not found to be associated with prognosis in our multivariable analyses, and this is in line with previous studies.[4, 5]

Future studies should focus on improved patient selection for BCS after NST in patients with a DCIS component, given the increased rate of positive surgical margins. Although OS did not significantly differ, patients require additional treatment in case of positive surgical margins, which is associated with increased patient burden and health care costs.[32, 33] One possibility to improve surgical decision-making is to further investigate imaging evaluation of DCIS during NST. A recently published systematic review shows that to date there are no specific imaging findings that can be used to properly monitor the response of DCIS, because calcifications can persist in complete response of DCIS and residual DCIS does not always show enhancement on MRI.[34] This is important because in case of adequate selection, more patients could potentially benefit from BCS, especially given the high complete response rates of DCIS in HER2+ IBC+DCIS patients in previous literature and the current study.[15, 35]

There are certain limitations worth mentioning. First, the retrospective nature of this combined population and pathology database contributes to the presence of missing data. In this study, multiple imputation was used to handle these missing data in the best possible way. However, the presence of a DCIS component was based solely on its notation in the pathology reports. This could lead to an underestimation of IBC+DCIS in case of a DCIS component outside of the biopsy area, or due to reporting bias of the pathologist focusing on the invasive tumor. Moreover, data on mammographic calcifications was lacking, and the extent of the DCIS component in pathology was poorly reported. Therefore, no distinction could be made from an extensive intraductal component, which is more commonly described in literature in relation to positive surgical margins and local recurrence in primary BCS, but is less often reported after NST.[36, 37] Lastly, it is important to note that the presence of a recurrence was based on pathology reports of biopsy proven recurrent tumor cells. This implies that patients with a suggestion of recurrent disease on imaging, in whom was decided not to perform biopsy, were not included in this population.

On the contrary, the strengths of this study are the large nationwide study population in combination with re-assessment of all histopathology reports. This allowed for evaluation of important clinicopathological variables in the assessment of margin status and prognosis of HER2+ IBC patients with and without DCIS.

Conclusion

This study shows that the presence of a DCIS component is independently associated with positive surgical margins in HER2+ IBC patients treated with NST and BCS, but not with higher 5-year LRR rate or worse OS. Further research into response prediction and imaging evaluation is necessary to select IBC+DCIS patients for BCS after NST more adequately, in order to provide better surgical outcomes and to avoid additional treatment and costs.

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Supplementary Material

Table A.1: Postoperative pathology, after treatment with NST and BCS, of patients with IBC and IBC+DCIS

	IBC (n=1832) n (%)	IBC+DCIS (n=1224) n (%)	p-value[a]
ypT status			
ypT0	1185 (64.7)	262 (21.4)	pCR ypT0: **p<0.001**
ypTis	0	351 (28.7)	pCR ypT0/is: **p<0.001**
ypT1	526 (28.7)	486 (39.7)	
ypT2	90 (4.9)	117 (9.5)	
ypT3	8 (0.4)	8 (0.7)	
ypT4	1 (0.1)	0	
ypTX[b]	22 (1.2)	0	

[a] Pearson's χ2 test was used to compare pCR rate between IBC and IBC+DCIS, for two different definitions.
[b] Postoperative specimen were classified as ypTX when scattered invasive tumor cells were found but size could not be determined.

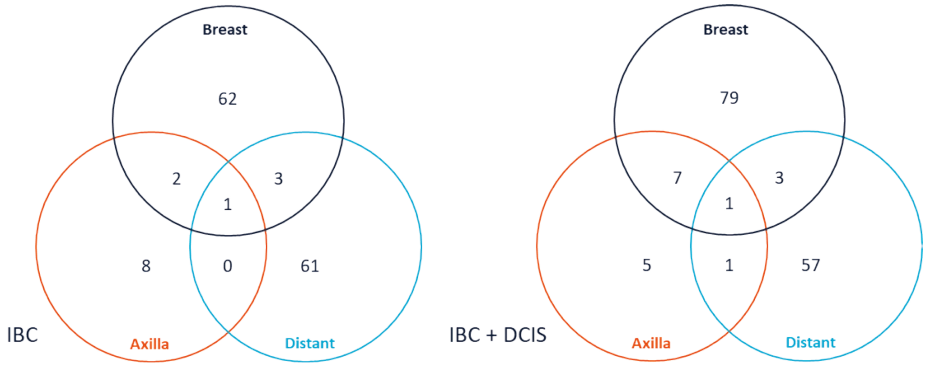


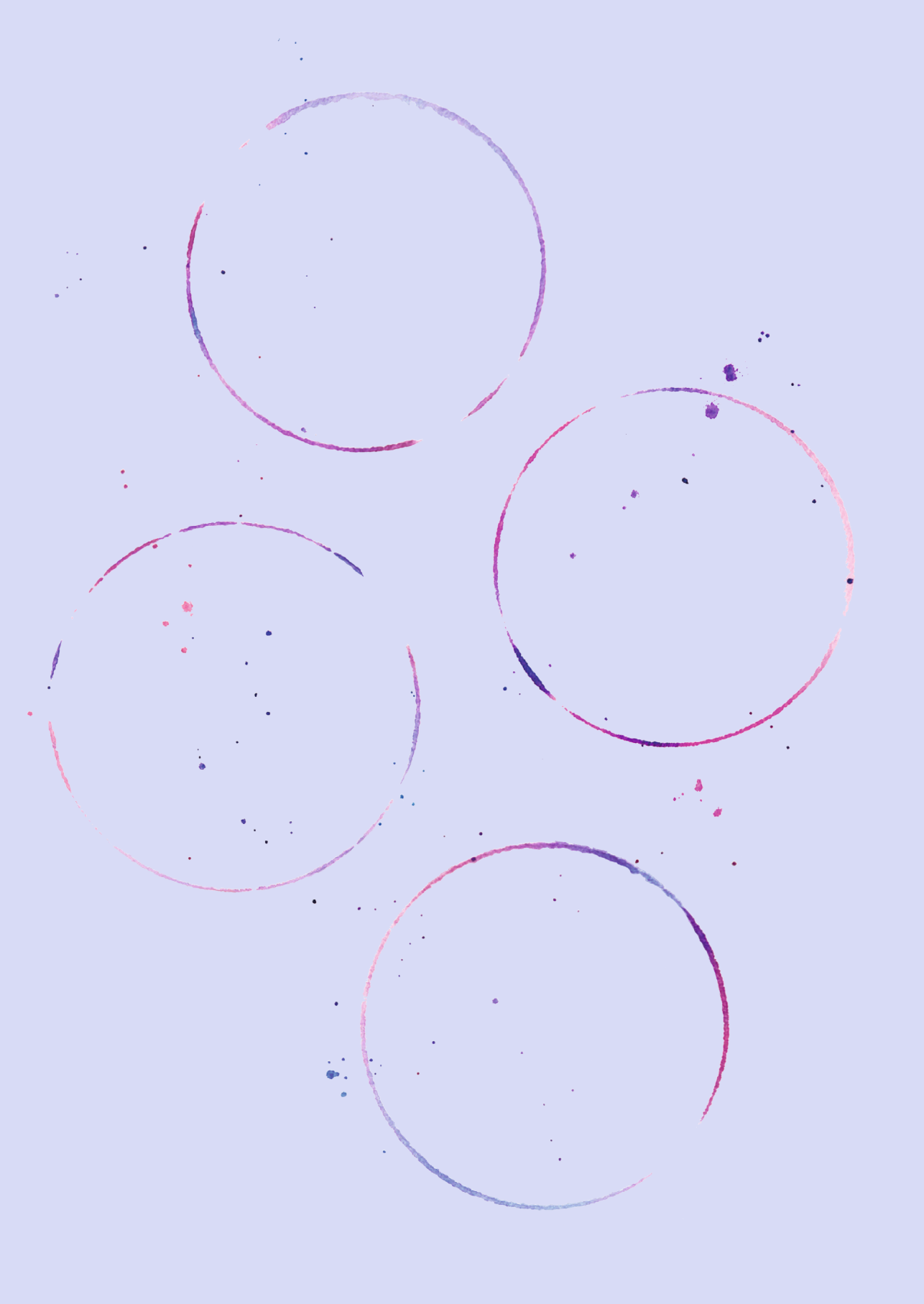
Figure A.1: Distribution of the site of ipsilateral recurrences and distant metastasis in patients with IBC and IBC+DCIS.

Table A.2: Logistic regression analyses for clinicopathological variables associated with positive surgical margins after first surgery

	Positive margins n (%)	Univariable			Multivariable		
		OR	95%CI	p-value	OR	95%CI	p-value
Age	247 (8.1)	0.978	0.966-0.990	<0.001	0.985	0.972-0.998	**0.021**
Year of diagnosis	247 (8.1)	0.964	0.914-1.017	0.181			
cT status							
cT1-2	203 (7.6)	REF			REF		
cT3-4	44 (11.9)	1.655	1.171-2.339	0.004	1.712	1.187-2.470	**0.004**
cN status							
Negative	117 (7.7)	REF					
Positive	130 (8.5)	1.114	0.857-1.448	0.419			
Multifocal disease	78 (11.9)	1.772	1.334-2.353	<0.001	1.626	1.214-2.178	**0.001**
IBC grade							
1-2	160 (9.4)	REF			REF		
3	87 (6.5)	0.676	0.513-0.891	0.005	0.743	0.556-0.994	**0.045**
ER status IBC							
Positive	205 (10.7)	REF			REF		
Negative	42 (3.7)	0.323	0.230-0.454	<0.001	0.373	0.262-0.529	**<0.001**
Presence of DCIS	157 (12.8)	2.848	2.174-3.731	<0.001	2.612	1.983-3.439	**<0.001**

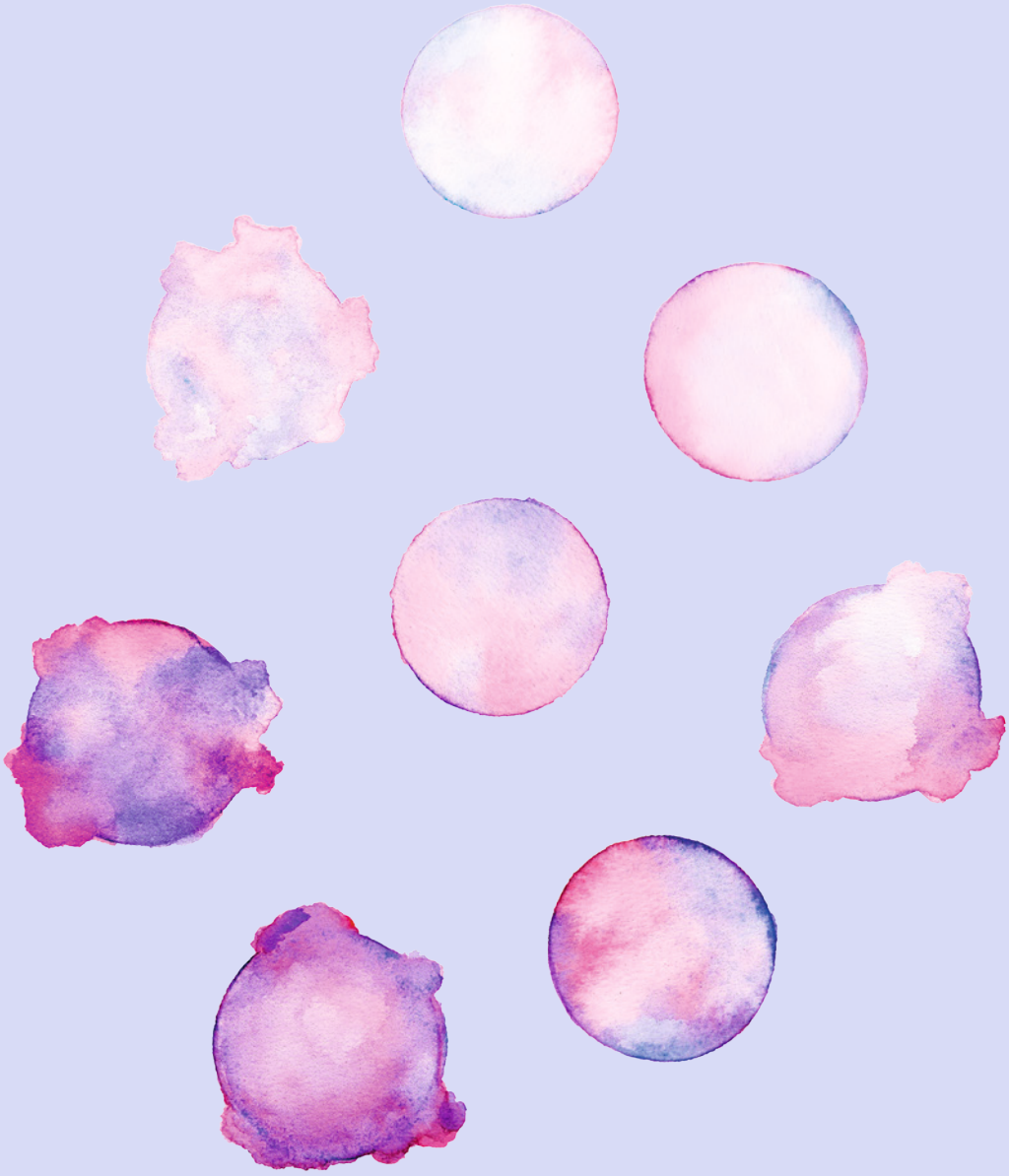
Table A.3: Pathology of ipsilateral local recurrences in the breast for patients with IBC and IBC+DCIS

	IBC (n=68) n (%)	IBC+DCIS (n=90) n (%)	p-value
Ipsilateral breast recurrence			
IBC	42 (61.8%)	46 (51.1%)	0.182
DCIS	15 (22.1%)	12 (13.3%)	0.149
IBC+DCIS	11 (16.2%)	32 (35.6%)	**0.007**



PART IV

DISCUSSION, FUTURE PERSPECTIVES AND IMPACT



CHAPTER 8

Summary and General discussion

The aim of this thesis was to evaluate the current treatment and challenges of an accompanying DCIS component in patients diagnosed with invasive breast cancer (IBC). Both patients treated with primary surgery as well as patients undergoing neoadjuvant systemic therapy (NST) were subjects of the studies, but the focus was particularly on the latter group. The results of the performed studies as presented in this thesis were organized into three distinct parts, focusing on pathology (part I), imaging (part II), and surgery and prognosis (part III). Chapter 8 is structured similarly, each part beginning with a summary of the results presented in this thesis, followed by a detailed comparison with existing literature and an examination of ongoing issues in the field.

Part I Pathology

Summary

The two studies reported in the first part of this thesis focus on patients with invasive breast cancer that were treated with NST. The aim of **Chapter 2** was to investigate the percentage of patients with only residual DCIS (ypTis) after treatment with NST. A retrospective database was obtained from the Netherlands Cancer Registry, including all patients diagnosed with primary IBC, treated with NST between 2010-2019. The study population consisted of 20495 patients, of which 5847 (28.5%) achieved a pathological complete response (pCR=ypT0) and 881 (4.3%) had residual DCIS (ypTis). The percentage of ypTis was highest in HER2+ IBC and in cases with a higher grade of the invasive tumor. Both HER2 positivity and higher tumor grade are associated with increased rates of achieving pathological complete response (pCR) in the invasive tumor, often leaving only the DCIS component remaining in the breast. However, since the presence of DCIS in the biopsy was unknown in our study, the potential response of the DCIS component itself could not be taken into account.

Consequently, the aim of our next study, presented in **Chapter 3**, was to investigate the potential response of a DCIS component accompanying HER2+ invasive breast cancer. All women diagnosed with HER2+ IBC treated with neoadjuvant chemotherapy and targeted therapy, followed by surgery, between 2010-2019 were included. By combining the data from the Netherlands Cancer Registry to pathology reports received from the Dutch Nationwide Pathology Databank, we were able to examine the presence of a DCIS component in the biopsy and postoperative specimen. In the total study population of 5598 patients, 1403 had a DCIS component in the biopsy and were eligible for further analysis on response. A pCR of the DCIS component was found in 52.0% of these patients, and was associated with complete response of IBC, ER-negative IBC, and a more recent year of breast cancer diagnosis. Given the 10-year inclusion period between 2010 and 2019, the association between year of diagnosis and likelihood of DCIS component pCR is most likely related to improvement in NST regimens, for

example the introduction of dual anti-HER2 therapy in a subset of patients from 2017 onwards.

Literature review and discussion

The results of **Chapter 2 and 3** suggest that the invasive tumor and the DCIS component demonstrate comparable characteristics. To gain deeper insight into this relationship, it is essential to review the literature on the progression of DCIS to IBC. As appointed in the general introduction, DCIS is considered a non-obligate precursor of IBC, yet the exact progression of DCIS to IBC remains poorly understood. Four models on the progression of DCIS to invasive breast cancer have been proposed. A schematic overview based on the described models in the article by van Seijen et al. is shown in Figure 1.[1]

The convergent phenotype model presumes that different DCIS subtypes can give rise to different invasive tumors with a similar phenotype. The evolutionary bottleneck model suggests that only a small proportion of DCIS will undergo genetic events and clonal selection to progress to IBC. The multiclonal invasion model on the other hand describes that multiple DCIS cells undergo different mutations and co-migrate to generate an invasive tumor. Lastly, the independent lineage model presumes that DCIS and IBC progress from two distinct cell lines and are not related, opposing the theory that DCIS is the precursor of IBC.[1-3]

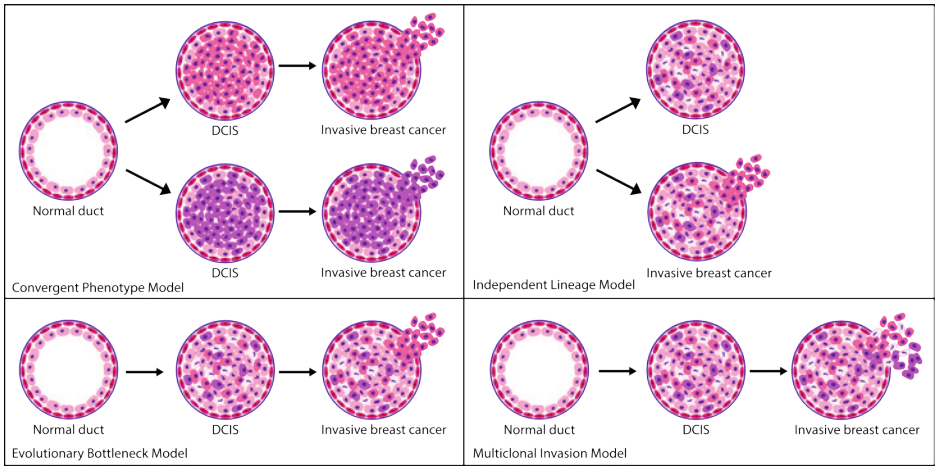


Figure 1: Hypothesized models of progression from DCIS to IBC

Given that **Chapter 1** discussed how HER2 overexpression increases cell proliferation, and since DCIS is most prevalent in HER2+ IBC, one might assume a link between HER2 positivity and DCIS progression to IBC. However, although HER2-positivity in pure DCIS is associated with poor prognostic factors (e.g. larger tumor size, higher nuclear grade) and increased risk of in situ recurrence, it does not seem to be associated with invasive

recurrence.[4] Moreover, HER2 positivity is higher in pure DCIS than in IBC (35-50% vs. 10-20%), suggesting it may not drive progression to invasive disease.[5, 6] In contrast, Roses et al. found that HER2 expression was associated with invasive foci in DCIS lesions, and one study by Visser et al. found that HER2 was associated with subsequent ipsilateral IBC recurrence.[7, 8] Hence, the role of HER2 in progression from DCIS to IBC remains controversial.

Unfortunately, we were unable to investigate the HER2-receptor status of the DCIS components in the nationwide databases of **Chapter 2 and 3**, as this is not routinely examined in the Netherlands. However, previous studies show a high concordance rate for the HER2 receptor between IBC and the accompanying DCIS component, up to 99%.[9, 10] Moreover, the higher likelihood of pCR of the DCIS component in later years of diagnosis seems to be related to the introduction of dual anti-HER2 therapy in 2017, also indicating a similarity in HER2 receptor. It would be interesting to investigate the receptor status of the DCIS component to confirm the proposed relationship with complete response. A systematic assessment of literature on HER2-positivity of pure DCIS by Van Bockstal et al. describes the advantage of determining HER2 status in decreasing interobserver variability in DCIS grading and facilitating personalized therapy.[11] Likewise, in patients with a DCIS component accompanying IBC, this could assist in prediction of complete response and influence surgical decision-making.

The association between the complete response of DCIS and IBC demonstrated in **Chapter 3** further reinforces the relationship between these two entities. Moreover, the factors associated with a pCR of DCIS in logistic regression analyses are in previous literature also reported to be associated with pCR of IBC (e.g. ER-negativity). Furthermore, tumor grade is known to correspond between IBC and the accompanying DCIS, and high grade DCIS would more often progress to high grade IBC.[12-14] This aligns with our results in **Chapter 3**, in which 61.8% of IBC and accompanying DCIS are similar in grade, with most classified as grade 3.

The question remains whether the DCIS component accompanying IBC is morphologically similar to pure DCIS. One previous study suggested that DCIS may respond poorly to systemic therapy, due to the more benign characteristics of pure DCIS.[15] Moreover, in clinical practice, patients with IBC with a DCIS component are more often treated with mastectomy.[16] Studies have compared the molecular characteristics of pure DCIS and DCIS accompanying IBC, and show that pure DCIS exhibits fewer mutations and genetic events, suggesting that the DCIS component accompanying IBC is more aggressive.[17, 18] This could help explain the unexpected high pCR rate of the DCIS component to NST, reported in **Chapter 3**.

In summary, the results from **Chapters 2 and 3** suggest an association between IBC and the accompanying DCIS component, supporting the previous evidence that DCIS serves

as a precursor to IBC. Consequently, IBC and the accompanying DCIS component likely exhibit morphological similarities, which may explain the observed response of the DCIS component. These results should be considered when making treatment decisions for patients with a DCIS component, comparing this type of DCIS to a more progressive variant that shares similarities with the invasive tumor, rather than to pure DCIS.

Part II Imaging

Summary

The second part of this thesis covers two articles on imaging of the DCIS component. In **Chapter 4**, a systematic review was performed to evaluate imaging findings of the potential response of DCIS accompanying invasive breast cancer during NST. Via a systematic approach of two databases, 31 articles on mammography, breast MRI, and contrast-enhanced mammography (CEM) studies were included. Results on imaging findings pre- and post-NST and any information on response monitoring of the DCIS component were collected. In general, few studies focused on the DCIS component and most studies lacked information for actual response evaluation. On mammography, comparison of pre- and post-NST imaging revealed that more than 50% of calcifications pre-NST are related to a DCIS component. However, on post-NST mammography, calcifications were mostly related to benign pathology, located in the necrotic tumor bed in patients with complete response of both the invasive tumor and DCIS component. On breast MRI, the included studies only reported post-NST imaging findings of the DCIS component, in which on average 57.4% of the residual DCIS component showed enhancement, and 42.6% did not. This is especially important in predicting pCR based on imaging. A subsequent meta-analysis of 17 breast MRI studies indicated that when DCIS is considered pCR (definition ypT0/is), the specificity for detecting residual disease decreases. This decline in specificity can be attributed to a higher rate of false positives, as more than half of the patients with residual DCIS showed enhancement on breast MRI, and are categorized as pCR in that definition. Only three CEM studies were included, suggesting a potential benefit of simultaneous assessment of calcifications and enhancement to detect or exclude residual disease.

The aim of **Chapter 5** was to evaluate key findings of a DCIS component on CEM in a retrospective cohort of HER2+ breast cancer patients in the Maastricht University Medical Centre+. Two independent radiologists reassessed the CEM images according to a protocol based on the BI-RADS lexicon, and a dedicated breast pathologist reassessed histopathology. In the total population of 62 patients, 71.0% showed either suspicious calcifications or non-mass enhancement (NME) on CEM. A subgroup analysis was performed on 45 patients undergoing primary surgery. CEM was able to detect 77.0% of the DCIS components outside of the invasive tumor, which is important for surgical decision-making. When comparing the size of imaging findings to DCIS size in

histopathology, NME was a better predictor of DCIS size than suspicious calcifications, yet overall imaging underestimated the DCIS size. The inter-observer agreement on detection of imaging findings was worse for NME compared to suspicious calcifications, although the inter-observer reliability on measurement of imaging findings was good.

Literature review and discussion

In short, in the second part of this thesis, three imaging modalities are discussed: mammography, breast MRI and contrast-enhanced mammography.

As already described in the introduction, mammography is widely used in the diagnosis of breast cancer, both in population screening and in symptomatic patients. The relationship between DCIS and suspicious calcifications has been highlighted several times in studies, but how can the development of calcifications be explained? Two mechanisms are described in literature.[3, 19] The first one is a passive process in which trauma to the breast leads to degenerative or dystrophic calcifications, caused by post-traumatic necrosis or hematoma. The second mechanism is an active process of secretion within the ducts and can be divided into two types based on the composition. Type I calcifications consisting of calcium oxalate are usually associated with benign processes, such as sclerosing adenosis or hyperplasia. Type II calcifications composed of calcium hydroxyapatite are endoluminal necrotic material consisting of cell debris and secretions, associated with neoplastic lesions such as high-grade DCIS.[20-23] These latter calcifications particularly occur in the terminal ductal-lobular unit, the region between the lobule and ducts where DCIS can develop. Based on the size, morphology and distribution of the calcifications, the BI-RADS lexicon defines suspicious calcifications, with a higher probability of malignancy, as calcifications smaller than 1 millimeter, with fine, pleiomorphic, heterogeneous, or amorphous morphology, and linear, clustered, segmental, or regional distribution.[24] In IBC patients with a DCIS component primarily treated with surgery, literature shows an overall moderate to good correlation between size of calcifications on mammography and total tumor extent in histopathology, yet in patients without calcifications MRI is advised.[25-27] Unfortunately, this good correlation does not apply in the neoadjuvant setting, as described in **Chapter 4**, because the DCIS component may disappear but calcifications persist on imaging. Moreover, the study by Groen et al. evaluating complete response of DCIS to NST showed that an absence of calcifications on mammography pre-NST is associated with response of DCIS to NST.[28] Therefore, mammography has no role in the evaluation of a DCIS component in the neoadjuvant systemic therapy era.

Breast MRI is an imaging modality that uses the neoangiogenesis associated with malignancy leading to increased vascularity to visualize the tumor. These newly formed vessels often show high permeability, causing leakage of the intravenous contrast agent into the region of interest surrounding the tumor.[29, 30] In case of DCIS, two types of neovascularization occur, 1) periductal, manifesting a network of microvessels on the

basement membrane, and 2) stromal, more diffusely present between the lesions.[31] The sensitivity for pure DCIS on breast MRI is lower than for invasive breast cancer, which can be explained by DCIS being a heterogeneous disease, in which low-grade DCIS shows more benign enhancement kinetics.[32] In contrast, high-grade DCIS is more likely to be detected on breast MRI, because previous literature shows that vessel density is higher in the more high grade lesions.[33, 34] The typical non-mass enhancement in DCIS is believed to result from contrast agent (e.g. gadolinium) collecting within the ducts due to basement membrane permeability, causing this segmentally or linearly distributed imaging characteristic.[35, 36] For pure DCIS, breast MRI has been shown to more accurately correlate with pathologic size compared to mammography. However, in general the preoperative use of breast MRI may increase mastectomy rates by identifying additional lesions without improving surgical outcomes.[37, 38] This leads to ongoing discussions on whether breast MRI should be used for patient selection for breast-conserving surgery.[39] However, Kuhl et al. performed a study in IBC patients with a DCIS component and shows that breast MRI improves detection of the DCIS component, with subsequent low rates of positive surgical margins and mastectomies.[40]

In the neoadjuvant setting, breast MRI remains the most effective imaging modality for assessing residual disease, which is crucial for tailoring surgical treatment to tumor response.[30, 41] Unfortunately, as discussed in **Chapter 4**, no studies have specifically focused on the imaging evaluation of the DCIS response, as this is a relatively new topic in literature. Notably, the studies that did report on imaging residual DCIS (ypTis) have shown inconsistent results, with enhancement detected in an average of 57% of cases (ranging from 0% to 100%). These variations in DCIS enhancement can be attributed to multiple factors, including the size of the residual DCIS component, grade of the DCIS, and the quality of the MRI.[42, 43]

Compared to mammography and breast MRI, CEM is a more novel technique, originating from 2011. It offers unique advantages in evaluating DCIS, either isolated or accompanying invasive breast cancer, by providing a combined assessment of both calcifications and lesion enhancement. A large study including 644 breast lesions showed that CEM demonstrated a higher sensitivity of 93.2% and specificity of 84.4% compared to full-field digital mammography (FFDM) (sensitivity 82.5% and specificity 68.6%).[44] In a retrospective study of 180 cases with only suspicious calcifications, CEM demonstrated a sensitivity of 98.5% and a specificity of 81.8% in identifying high-grade DCIS lesions, with and without invasion.[45] The advantage of CEM compared to FFDM is even higher in patients with dense breasts that are difficult to assess on FFDM.[46, 47] A systematic review comparing the diagnostic performance of CEM to breast MRI showed comparable results of pooled sensitivity (96% versus 97%, respectively) and pooled specificity (77% for both modalities).[48] To date, no studies have specifically evaluated DCIS accompanying invasive breast cancer on CEM, hence our interest in this topic in **Chapter 5**. Given that this study only included patients with a confirmed DCIS component

to evaluate its findings on CEM, future studies should explore diagnostic performance in a cohort that includes patients both with and without a DCIS component.

Fewer studies have been conducted on CEM in the neoadjuvant setting, but the available results indicate comparable effectiveness to breast MRI in monitoring tumor response and identifying residual disease.[49-51] One might assume that the combined evaluation of suspicious calcifications and enhancement provides an advantage in determining residual disease after NST. However, as previously mentioned in the discussion on mammography, calcifications can persist even after a complete response of the tumor. This suggests that the assessment of calcifications may not offer additional value in this context; yet, they could serve as markers for the locations where the DCIS component was present. Remaining non-mass enhancement in these areas of fine pleomorphic calcifications after NST could potentially indicate the presence of residual DCIS. Nevertheless, it is important to consider that up to 20% of DCIS cases are non-calcified[52], and the degree of enhancement depends on the grade and size of the area, in the same way as on MRI.[43, 53, 54]

In conclusion, breast MRI and CEM show potential in the evaluation of a DCIS component in invasive breast cancer. In both the neoadjuvant setting and before primary surgery, it is particularly important to use imaging to detect a DCIS component outside the invasive component, as this has implications for surgical management. The results of **Chapter 5**, as well as the study by Kuhl et al., demonstrate that the detection of DCIS increases with larger size and presence outside the invasive tumor.[40]

Part III Surgery and prognosis

Summary

The last two chapters of this thesis, **Chapter 6 and 7**, concern studies investigating the surgical and prognostic outcomes of IBC patients with a DCIS component. The aim of **Chapter 6** was to evaluate the trend of surgical treatment over 10 years in a nationwide cohort of 5289 patients with HER2+ IBC, treated with NST. Overall, a decline in mastectomy rates and a consequent increase of breast-conserving surgery (BCS) was found. In the analysis, patients were divided between patients with a DCIS component and patients with IBC only in the pre-NST biopsy. Patients with a DCIS component were significantly more often treated with mastectomy, with 48.4% compared to 30.0% in IBC only in 2019. After adjusting for confounders in multivariable logistic regression analysis, the presence of DCIS remained independently associated with a higher likelihood of mastectomy. Other important factors associated with mastectomy were clinical T3-4 disease and multifocal disease. Moreover, the analyses revealed that patients with a DCIS component significantly less often achieved ypT0. This lower chance of pCR might explain the higher rate of mastectomy, although 38.7% of IBC+DCIS did achieve

ypT0. Interestingly, patients with clinical T3-4 or node-positive disease had a similar likelihood of achieving ypT0 compared to clinical T1-2 and node-negative disease, yet a significant higher mastectomy rate. Unfortunately, the extent of the DCIS lesion and imaging characteristics such as widespread suspicious calcifications on mammography were unknown in this database. More importantly, patients may choose mastectomy despite the fact that BCS is possible for various reasons, with literature showing that fear of recurrence is very important. In this nationwide retrospective database it was not possible to evaluate patient preferences.

Another factor influencing the decision to opt for mastectomy is the risk of positive surgical margins following BCS. In **Chapter 7**, the surgical outcomes of 3056 patients with HER2+ IBC were reported after treatment with NST and BCS. Overall, 8.1% had positive surgical margins, but the rate was significantly higher in patients with a DCIS component compared to patients without (12.8% versus 4.9%). The positive margins in the patients with IBC+DCIS were caused in 47.8% by DCIS, and in 37.6% by IBC. In addition, the prognostic outcomes of these patients with regard to locoregional recurrence rate and overall survival were compared between patients with and without a DCIS component. Patients with a DCIS component had a significant higher rate of locoregional recurrence within 5 years after diagnosis. However, in multivariable Cox regression analysis, the presence of DCIS was not associated with a higher risk of locoregional recurrence. The most important predictor for locoregional recurrence was residual disease in the breast (ypT+/is). Overall survival did not significantly differ between patients with and without a DCIS component.

Literature review and discussion

Since the first surgical treatment for breast cancer, which involved extensive surgery including removal of the pectoral muscles[55], significant advances have been made in breast surgery. Nowadays, BCS followed by radiation therapy is an oncologically safe option, when free surgical margins are achieved.[56] Eligibility for BCS after NST depends on the tumor's response, which is estimated based on tumor characteristics and imaging during NST. Therefore, one might expect that the probability of achieving pCR (ypT0), based on tumor characteristics, is linked to the final surgical treatment. In **Chapter 6**, this correlation was evident among patients with a DCIS component, where the likelihood of achieving ypT0 was lower, resulting in a higher probability of mastectomy in multivariable logistic regression analysis. Conversely, it was observed that patients receiving dual anti-HER2 therapy had a significantly higher probability of ypT0 and a correspondingly lower likelihood of undergoing mastectomy. However, it is interesting to note that the relationship between ypT0 and mastectomy was not consistent for all variables. For example, the odds ratio for mastectomy was highest in clinical T3-4 patients, but the rate of ypT0 was similar in patients with clinical T1-2 disease. Reasons for opting mastectomy in these patients may be the concern about local recurrence in extensive T4 disease, or that imaging did not accurately reflect the complete response.[57]

With the increasing survival outcomes in breast cancer, focus shifts more and more towards improving quality of life. In literature, quality of life, especially with regard to physical health and body image, seems to be better after BCS than mastectomy.[58] However, we should not forget that a proportion of women actively choose mastectomy.[59] Reasons include fear of recurrence, no desire for radiation therapy and that it feels more like definitive surgery.[60, 61] An important factor in evaluating quality of life is personality. A systematic review by Wintraecken et al. shows that personality is either positively or negatively associated with quality of life, and particularly the personality traits 'optimism' and 'trait anxiety' influence quality of life evaluation.[62] More optimistic women may be more likely to opt for breast-conserving surgery, due to their positive view of the future, whereas women with high trait anxiety may fear potential adverse effects and would rather undergo mastectomy. Another reason why breast-conserving surgery is not the ultimate goal is because more and more options for direct reconstruction after mastectomy have become possible.[63] Oncoplastic surgeons have the most innovative ways to ensure cosmetic results after mastectomy, for instance using tissue from the abdomen or thighs for autologous reconstruction, increasing quality of life compared to mastectomy without reconstruction.[58, 64, 65] Oncoplastic reconstruction is also feasible after breast-conserving surgery, and in these patients, achieving tumor-free surgical margins is crucial, as reoperation can compromise the reconstruction.

As the survival outcomes of **Chapter 7** show, achieving a pathologic complete response (pCR) is widely recognized in literature as the most important predictor of improved survival outcomes.[66] The pCR rate based on the ypT0 definition in the studies in this dissertation ranged between 28.5% and 47.3%. However, the definition used for pCR of the breast differs amongst studies, especially with regard to the presence of residual DCIS (ypTis). Previous studies on HER2+ invasive breast cancer almost exclusively use the ypT0/is definition, with a rate ranging between 27.4-80.0% in a meta-analysis including 15 HER2+ NST trials.[67] Despite Cortazar et al. demonstrating no significant difference in prognosis between ypT0 and ypT0/is[68], residual DCIS (ypTis) should not be considered as a pathological complete response. This thesis demonstrates that DCIS can completely disappear after NST, in the same way as the invasive tumor. Moreover, ongoing trials are investigating the possibility of omitting surgery in cases of pCR, and if residual DCIS remains in the breast, it could serve as a nidus for recurrent invasive disease.

Prior to studies that actually omit surgery, several studies have been performed on tumor bed biopsy after NST.[69] Their aim was to investigate whether it is possible to use these tumor bed biopsies to detect a pCR of the breast, in patients with a complete response on imaging. Patients underwent biopsies after NST followed by definitive surgery. False negative rates (FNR), i.e. residual tumor present in the postoperative specimen when biopsies revealed complete response, ranged between 0-60.9% in studies including all patients with a radiological complete response.[70-74] The FNR

decreased to 0-10% in better selection of patients including only cT1-2, HER2+ or triple negative breast cancer, with use of multimodality imaging and improved vacuum-assisted core biopsy procedures.[75-77]

Two trials have subsequently investigated the possibility to omit breast surgery. Kuerer et al. performed a multicenter trial in patients with cT1-2N0-1M0 triple negative or HER2+ breast cancer, with a residual lesion smaller than 2cm on imaging. If the 9G image-guided vacuum-assisted biopsy identified no invasive or in situ disease, breast surgery was omitted. At a median follow-up of 26.4 months, no ipsilateral breast recurrences occurred in the 31 patients with pCR of the biopsy.[78] The OPTIMIST trial is currently enrolling patients in 17 Korean hospitals with complete response on MRI in which breast surgery will be omitted when vacuum-assisted biopsy shows no residual tumor.[79] In these two clinical trials, the presence of DCIS was not an exclusion criterium, however, residual suspicious calcifications >2cm were. As **Chapter 4** and the second part of this discussion highlighted, calcifications pre-NST are often related to DCIS, yet can remain post-NST in the necrotic tumor bed without DCIS present. This would therefore mean that these patients are wrongfully excluded, but it is understandable that these strict exclusion criteria are maintained in such novel trials. Moreover, Koelbel et al. showed that the presence of an accompanying DCIS component in the pre-NST biopsy was associated with a false-negative vacuum-assisted biopsy, which even more validates that these patients should not be considered for omitting surgery.[80] Given the few studies to date on complete response of DCIS, it is not yet safe to include these patients in omitting surgery trials, yet they should not be overlooked when future studies could more accurately predict DCIS response.

Conclusion

This thesis presents six studies investigating invasive breast cancer patients with a DCIS component, highlighting the current challenges in diagnosis and treatment.

Part I demonstrates that the DCIS component accompanying invasive breast cancer can achieve a complete response after NST. This response often coincides with complete response of the invasive tumor, and is associated with specific invasive tumor characteristics (e.g. ER-negativity). Future studies should investigate whether characteristics of the DCIS component, such as grade and receptor status, can improve prediction of DCIS response.

Part II highlights the potential of breast MRI and CEM for detecting and monitoring DCIS in invasive breast cancer patients. Both modalities improve identification of the DCIS component outside the invasive tumor, which is important for surgical decision-

making. However, challenges remain in evaluating residual DCIS after NST and future studies should further investigate diagnostic performance.

Lastly, Part III demonstrates that the presence of a DCIS component itself does not influence prognosis. However, it does increase the risk of positive surgical margins in patients treated with breast-conserving surgery. On the other hand, the rate of mastectomy is significantly higher in invasive breast cancer patients with a DCIS component, even in patients that achieve a pCR. This suggests that the selection of surgical treatment in these patients should be optimized, to improve surgical and quality of life outcomes.

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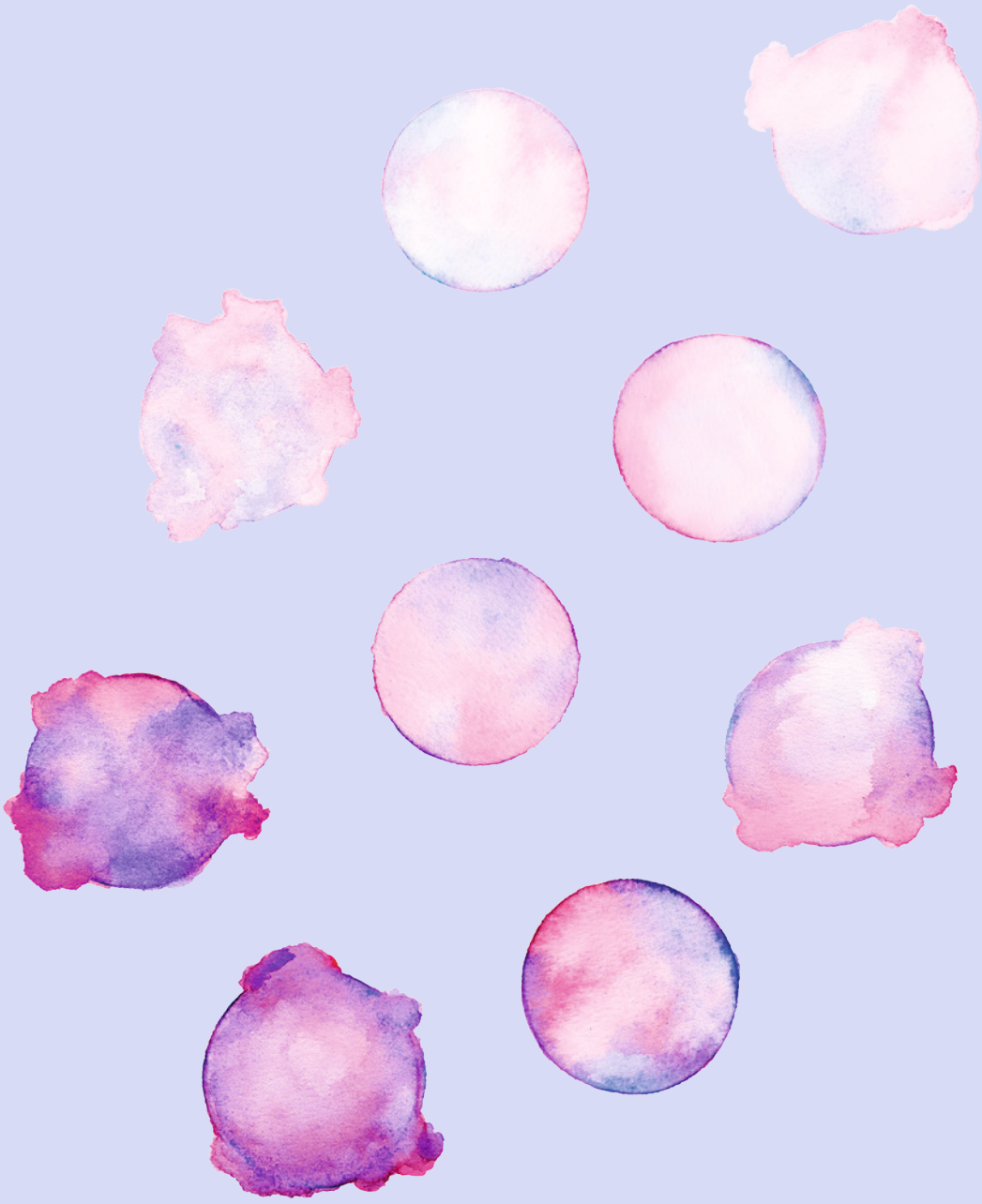

CHAPTER 9

Future perspectives

The aim of this thesis was to examine the current diagnosis and treatment of invasive breast cancer patients with a DCIS component. Another subsequent aim was to use these studies to raise awareness for this specific population. As this thesis assembles some of the first studies on this subject, several objectives and goals remain unexplored, which are important to improve treatment options and outcomes for these patients.

Part I Pathology

In the Netherlands, pathologists use the PALGA system to report histopathology exams following a national protocol, ensuring standardized and accessible reports. However, the presence of a DCIS component is not a mandatory field in case of reporting on the primary invasive tumor. Moreover, even when it is recorded, details on grade and extent are often left out, as the focus is on the invasive tumor. As a result, in **Chapter 3**, various histopathological characteristics of the DCIS component contained missing data. Consequently, only the relationship between DCIS grade and a complete response of the DCIS component could be evaluated. Unfortunately, receptor status of the DCIS component is not routinely assessed in the Netherlands, and therefore the receptor status of the invasive tumor was used for the analyses. Although there is a strong correlation between the ER and HER2 receptor status of the invasive tumor and the accompanying DCIS component, it is more objective and beneficial to assess the receptors of the DCIS directly.[1, 2] As noted by van Bockstal et al., this approach could also improve the grading of the DCIS component, especially considering the significant interobserver and inter-laboratory variability reported in previous studies.[3-5] The staining and immunohistochemistry for receptor analysis are routinely performed, requiring no additional materials or tests. However, it does take extra time for the pathologist to evaluate the DCIS component as well. Given the significance of these features, as proposed by this thesis, it would be beneficial for future practice to mandate the inclusion of DCIS grade and receptor status through consultation with the Dutch Society for Pathology and the Dutch Nationwide Pathology Databank.

Part II Imaging

The detection of the DCIS component accompanying invasive breast cancer on imaging still needs improvement. It is especially important to detect the DCIS component extending beyond the invasive tumor, as this influences surgical management. **Chapter 5** comprises the first study on imaging findings of a DCIS component on contrast-enhanced mammography (CEM), in a retrospective single center cohort. For a future study, it would be interesting to conduct a prospective, multi-center study, to include more patients, both with and without a DCIS component. In this way, the diagnostic performance, particularly the sensitivity, specificity, positive predictive value and

negative predictive value of CEM can be examined. Preferably, patients should undergo both CEM and MRI to objectively compare these modalities; however, these studies are usually not combined in clinical practice.

The next step in evaluating response of the DCIS component is a prospective imaging study using breast MRI or CEM, including patients with (HER2+) invasive breast cancer with a DCIS component in the biopsy. Before NST, it would be required to perform an additional biopsy of the region that is suspected to be the DCIS component and leave a marker. In this way, before, during and after NST, this region can be specifically evaluated with regard to changes in enhancement and calcifications.

An emerging field in breast cancer imaging is the use of radiomics and artificial intelligence.[6-8] Radiomics is a technique that extracts extensive quantitative data from standard medical images, providing insights into a specific region of interest.[9, 10] It would be interesting to investigate whether quantitative data could improve the detection and monitoring of a DCIS component on imaging. Artificial intelligence is a broad term that includes various components and training methods, such as artificial neural networks, machine learning, and deep learning.[11] Currently, it is applied in select areas of radiology, such as breast cancer screening, to assist radiologists in detecting suspicious findings on mammography.[12, 13] However, only a few imaging studies have focused on invasive breast cancer with a DCIS component, and no consensus has been reached on specific diagnostic characteristics. Therefore, the implementation of radiomics and artificial intelligence in the diagnosis or response evaluation of these patients may still be premature.

Part III Surgery and prognosis

As demonstrated in **Chapter 7**, patients with a DCIS component who undergo breast-conserving surgery are more likely to achieve positive surgical margins. Conversely, **Chapter 6** reveals that nearly half of the patients who achieved a pathological complete response (38.8%) were treated with mastectomy. This indicates that the selection criteria for breast-conserving surgery in this patient population have not yet been fully optimized. Ideally, a predictive model should be developed based on histopathology and imaging characteristics to assess the likelihood of a complete response in both the invasive tumor and DCIS component. Such a model would enable surgeons to discuss with the patient the potential of achieving a complete response, and the subsequent success rates of breast-conserving surgery. Involving patients in treatment decisions, by the use of shared decision-making or patient-decision aids, has been shown to improve patient outcomes.[14, 15] Future studies should include patient questionnaires or interviews, to compare the benefits and risks of opting for breast-conserving surgery to their preferences.

Another way to improve surgical outcomes after breast-conserving surgery is by intra-operative margin assessment, for instance with the use of fluorescence-guided imaging. While studies on patients with invasive breast cancer or DCIS in the primary setting show promising results, this technique has been less explored in the neoadjuvant setting.[16, 17]

This thesis specifically focused on the HER2+ subtype due to its high prevalence of accompanying DCIS and the significant rates of pathological complete response observed in these patients. As a result, evaluating the DCIS component and its potential response in this population could improve surgical outcomes. Given that these studies have shown that approximately 50% of patients with a DCIS component achieve a complete response, it would also be valuable to explore the DCIS component in other breast cancer subtypes. Although DCIS is less common in triple-negative breast cancer, these patients also achieve high rates of pathological complete response, in approximately 50% of patients, following treatment with neoadjuvant systemic therapy.[18] It would be interesting to compare the rates of complete response of the DCIS components between HER2+, triple negative and ER+ subtypes.

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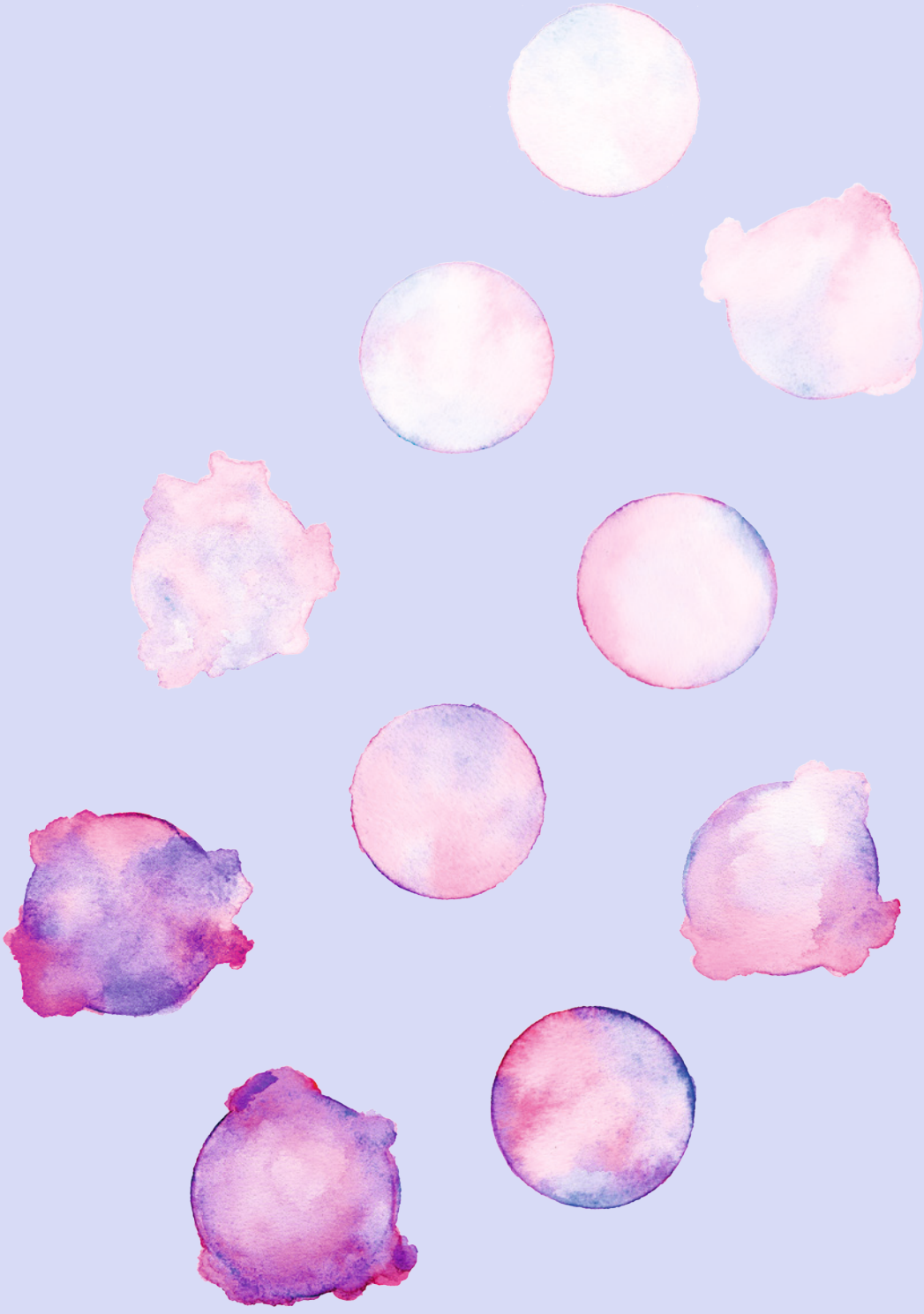

CHAPTER 10

Appendix

Impact
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List of publications
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Impact

This thesis explores the challenges of a DCIS component accompanying invasive breast cancer from different perspectives. While the primary focus is on the patient diagnosed with breast cancer, the findings also affect other key audiences. This impact paragraph summarizes the overall influence of the research presented in this thesis.

Patients

The research presented in this thesis was made possible by the breast cancer patients involved in these studies and nationwide databases. As described in the introduction of this thesis, breast cancer is the most common malignancy amongst women in the Netherlands, with one in seven women diagnosed during their lifetime. While this thesis focuses primarily on HER2+ invasive breast cancer, future studies could extend the insights of this research to other patient populations. For instance, patients with triple-negative breast cancer, that often show high response rates to systemic therapy, could also benefit from investigating how a DCIS component may influence treatment outcomes.

Because of all previous research in the field of breast cancer screening, diagnostics and treatment, survival rates have significantly improved over the past decades. As a result, quality of life has become increasingly important. While many studies, including those in this thesis, tend to focus on objective outcomes such as complete tumor response, mastectomy rates, recurrences, etcetera, it is essential to consider how these results translate into the patient's daily life. This thesis highlights several opportunities to enhance patients' quality of life, such as suggesting the possibility for more personalized choices regarding breast surgery in specific patient populations. Therefore, the ultimate goal is not to eliminate the use of mastectomy, but to ensure that patients are able to make an informed choice about surgical treatment. Involving patients in surgical decision-making enhances their autonomy by allowing them to express preferences aligned with their body image and future goals.

Despite these insights, the findings from the current studies are still too preliminary to alter the standard treatment protocols and assess the impact on quality of life. In the future, it is important to identify patient preferences and considerations when evaluating changes in treatments. A patient advisory board can participate in developing such questionnaires to ensure patient-centered research.

Moreover, research on the impact of an accompanying DCIS component remains limited, leading to uncertainties in clinical practice, especially regarding imaging findings and treatment choices. For example, there is ambiguity regarding the necessity of removing residual mammographic calcifications following neoadjuvant systemic therapy. These inconsistencies not only create uncertainty among caregivers, but also lead to stress and

concern for patients, especially when additional procedures like biopsies are required. Conducting further prospective research could help clarify these issues, ultimately providing patients with greater reassurance and confidence.

Health care professionals

As discussed in the General Discussion and Future Perspectives of this thesis, raising awareness among clinicians about this specific group of patients is crucial. The multidisciplinary breast cancer teams in the Netherlands consist of all clinicians involved in the diagnosis and treatment of breast cancer patients. This thesis addresses several areas of expertise relevant to these teams.

In Part I, pathologists received insights into key factors related to the complete response of DCIS, emphasizing the need for further research into the grade and receptor status of the DCIS component. Part II summarized the radiological features of a DCIS component, highlighting the significance of suspicious calcifications and non-mass enhancement. While the current focus in clinical care is primarily on evaluating response of the invasive tumor, radiologists can use these findings to provide more comprehensive information about the DCIS component. Part III examined the surgical treatment and outcomes in patients with a DCIS component, highlighting that patient selection for either breast-conserving surgery or mastectomy could be improved.

In addition to the pathologist, radiologist and surgeon addressed in these specific thesis parts, others can benefit from the results of this thesis. For instance, Chapters 3 and 7 provide oncologists with data on the likelihood of complete response of a DCIS component and patient prognosis. Radiation oncologists could explore ways to adjust radiation therapy in patients with a DCIS component in case of positive surgical margins, or in case of a pathological complete response. Plastic surgeons should be involved in multidisciplinary decision-making to enhance cosmetic outcomes for those eligible for breast-conserving surgery. Additionally, breast cancer nurses and nurse specialists should be actively involved in future prospective studies to ensure high-quality care, as they are often the first point of contact for patient concerns. Ultimately, effective breast cancer care relies on a multidisciplinary approach that integrates the expertise of various specialists in close consultation with the patient.

Research networks

The Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank facilitated a significant part of the research in this thesis. By collecting information from the hospital's electronic patient files and pathology laboratories, these organizations facilitate research into nationwide patient data. Throughout our studies, we encountered certain challenges with these retrospective databases. For instance, the Netherlands Cancer Registry did not separate the presence of DCIS in invasive breast cancer by biopsy or postoperative pathology, which hindered our ability to assess the rate of

complete response of DCIS. In addition, several variables of interest in the evaluation of a DCIS component, such as presence of microcalcifications and comedonecrosis, were poorly reported in the pathology reports. Moreover, determining the receptor status of the DCIS component is not routinely performed and therefore not included in the nationwide databases. By sharing our results with these organizations and discussing potential solutions, we could improve the nationwide registration system to enhance future national research. This would allow us to better understand this specific patient population. Ultimately, when future prospective studies confirm our results, the Dutch breast cancer guideline can be updated on the related topics, in collaboration with regional and national organizations.

In addition to the collaboration with national organizations, the results of the studies in this thesis were brought to attention to international research networks. We presented our studies at several prominent conferences, including the European Breast Cancer Conference, the European Congres of Radiology, the Congress of the European Society of Surgical Oncology, and the San Antonio Breast Cancer Symposium in the USA. All studies were published in, or submitted to, renowned international journals with a focus on breast cancer research. This creates a worldwide awareness for the topic, with the aim of stimulating more future research and eventually leading to improved outcomes in these breast cancer patients.

Nederlandse samenvatting

Achtergrond

Per jaar krijgen ongeveer 16000 vrouwen in Nederland de diagnose borstkanker. Dit betekent dat één op de zeven vrouwen in Nederland gedurende haar leven de diagnose krijgt, wat het de meest voorkomende vorm van kanker bij vrouwen maakt. Borstkanker ontstaat veelal in de melkkliergangen van de borst, de ducti genoemd, waar kwaadaardige cellen zich kunnen vermenigvuldigen. Wanneer deze kwaardaardige cellen beperkt blijven tot de ducti, spreekt men van ductaal carcinoma in situ (DCIS), wat wordt beschouwd als een voorstadium van borstkanker. Dringen de kwaadaardige cellen door in het omliggende weefsel, dan wordt dit invasieve borstkanker genoemd. Bij een deel van de patiënten komt invasieve borstkanker voor samen met een gebied van DCIS. De diagnose borstkanker wordt gesteld middels beeldvorming (radiologie) en weefselonderzoek (pathologie). Er worden verschillende beeldvormende technieken gebruikt, zoals mammografie (bekend van het bevolkingsonderzoek), echografie, en MRI van de borst. Wanneer er een verdachte afwijking op beeldvorming wordt gezien, wordt hiervan weefsel afgenomen middels een biopt en naar de patholoog gestuurd voor verder onderzoek. De stadiëring van borstkanker is gebaseerd op de tumorgrootte en de aanwezigheid van uitzaaiingen in de oksel of elders in het lichaam (TNM-classificatie). Daarnaast wordt bij het weefselonderzoek de graad en de receptorstatus van de tumor vastgesteld. De graad geeft inzicht in de agressiviteit van de tumor, en de oestrogeenreceptor (ER) en HER2-receptor worden gebruikt om diverse subtypen te onderscheiden.

Er zijn verschillende soorten behandeling van borstkanker. De chirurgische behandeling omvat ofwel het verwijderen van alleen de tumor (borstsparende chirurgie), of het verwijderen van de gehele borst (borstamputatie). Welke operatie de patiënt moet ondergaan hangt van verschillende factoren af, zoals de grootte van de tumor in verhouding tot de grootte van de borst, maar ook de wens van de patiënt zelf. Wanneer een patiënt kiest voor borstsparende chirurgie, wordt dit in de huidige behandeling vaak gecombineerd met bestraling (radiotherapie) van de borst. Naast chirurgie en radiotherapie is er in veel gevallen ook een indicatie voor systemische therapie, zoals chemotherapie, doelgerichte therapie en antihormonale therapie, gebaseerd op het borstkanker subtype. Aanvankelijk werd systemische therapie na de operatie gegeven, maar tegenwoordig wordt het steeds vaker vooraf aan de operatie gegeven. Dit wordt neoadjuvante systemische therapie genoemd (NST). Het voordeel hiervan is onder andere dat de tumor kan krimpen, waardoor er in een deel van de gevallen een kleinere operatie nodig is.

Bij patiënten die worden behandeld met NST is het essentieel om te evalueren hoe de tumor op de therapie reageert, oftewel de respons. Hiervoor wordt de tumor vóór, tijdens en na de NST beoordeeld met beeldvorming, waarbij de voorkeur uitgaat

naar MRI of contrast-versterkte mammografie. Dit laatste is een relatief nieuwe beeldvormingstechniek, waarbij een mammogram wordt gecombineerd met de toediening van contrastmiddel. Het beoordelen van de tumorrespons met beeldvorming is belangrijk voor de chirurgische besluitvorming na NST. Bij een deel van de patiënten kan de tumor volledig verdwijnen na NST; dit wordt een pathologische complete respons (pCR) genoemd. Het bereiken van een pCR is bovendien prognostisch gunstig, want uit eerder onderzoek blijkt dat deze patiënten betere (ziektevrije) overlevingskansen hebben. Omdat beeldvorming op dit moment nog niet in staat is om de complete respons met voldoende zekerheid vast te stellen, ondergaan deze patiënten na NST alsnog een operatie van de borst.

Zoals in het begin vermeld heeft een deel van de patiënten met invasieve borstkanker ook een gebied van DCIS aanwezig in de borst. Er is tot op heden nog weinig onderzoek verricht welke invloed dit gebied van DCIS heeft, vooral ten tijde van behandeling met NST. In dit proefschrift worden de behandeling en uitkomsten van deze patiënten vanuit drie verschillende perspectieven onderzocht. Deze samenvatting beschrijft de belangrijkste resultaten per hoofdstuk binnen deze drie delen.

Deel I: Pathologie
In het eerste deel worden de pathologische uitkomsten onderzocht van patiënten met invasieve borstkanker en een gebied van DCIS, die zijn behandeld met NST.

- **Hoofdstuk 2** beschrijft hoe vaak er na behandeling met NST alleen nog DCIS in de borst overblijft, zonder een invasieve tumor. Dit wordt volgens de richtlijn geclassificeerd als ypTis. In een onderzoek met gegevens uit de Nederlandse Kankerregistratie (NKR) van 20495 patiënten bleek dat 28,5% van de patiënten na behandeling geen invasieve tumor of DCIS meer in de borst had (pCR, ypT0). Bij 4,3% bleef alleen DCIS achter (ypTis). Dit kwam vooral voor bij patiënten met HER2+ borstkanker en tumoren met een hogere graad. Eerder onderzoek toont aan dat een gebied van DCIS vaker voorkomt bij HER2+ tumoren. Tegelijkertijd hebben patiënten met HER2+ tumoren en een hogere graad de grootste kans op het verdwijnen van de tumor, wat mogelijk verklaart waarom deze groep vaker alleen DCIS overhoudt. Helaas bevatte deze database geen informatie over de aanwezigheid van een gebied van DCIS in het biopt bij de diagnose. Hierdoor kon niet worden vastgesteld of DCIS ook volledig kan verdwijnen tijdens NST.

- **Hoofdstuk 3** richt zich specifiek op het HER2+ subtype borstkanker en onderzoekt of een gebied van DCIS ook kan reageren tijdens behandeling met NST. Door de database met HER2+ subtype borstkankerpatiënten uit de Nederlandse Kankerregistratie te combineren met de pathologieverslagen van het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (Palga), werd het mogelijk de aanwezigheid van DCIS te vergelijken tussen het biopt en het postoperatieve weefsel. In de database van 5598

patiënten werd er bij 1403 patiënten een gebied van DCIS gevonden in het biopt. In 52% van deze patiënten verdween het gebied van DCIS volledig na behandeling. Dit gebeurde vooral bij patiënten met een complete respons van de invasieve tumor, tumoren van het ER-negatieve subtype, en patiënten die in recentere jaren werden gediagnosticeerd. Deze bevindingen wijzen mogelijk op verbeterde behandelingen, zoals de introductie van nieuwe systemische anti-HER2-therapie sinds 2017.

Deel II: Beeldvorming

In het tweede deel van dit proefschrift is onderzocht hoe beeldvormingstechnieken, zoals (contrast-versterkte) mammografie en MRI, kunnen bijdragen aan het beoordelen van DCIS bij patiënten met invasieve borstkanker.

- **Hoofdstuk 4** bevat een overzicht van 31 studies over beeldvorming van een gebied van DCIS bij patiënten met invasieve borstkanker tijdens NST. Deze systematische analyse van literatuur richt zich specifiek op mammografie, MRI en contrast-versterkte mammografie. Op mammografie bij diagnose (vóór start van NST) kunnen kalkspatjes een aanwijzing zijn voor een gebied van DCIS. Echter, na behandeling met NST is het merendeel van deze kalkspatjes gerelateerd aan goedaardige bevindingen, omdat de tumor en het gebied van DCIS bijvoorbeeld volledig verdwenen zijn door de behandeling. MRI wordt veelvuldig gebruikt om de respons van invasieve borstkanker te beoordelen, maar blijkt minder nauwkeurig in het bepalen van respons van het gebied van DCIS. Als na NST alleen rest DCIS aanwezig is, wordt dit slechts in 57% van de gevallen gedetecteerd met MRI. Contrast-versterkte mammografie biedt de mogelijkheid om zowel kalkspatjes als contrast aankleuring te beoordelen, wat deze techniek veelbelovend maakt voor toekomstige studies naar de detectie van DCIS. Tot nu toe zijn er echter nog te weinig onderzoeken uitgevoerd naar het gebruik van contrast-versterkte mammografie bij een gebied van DCIS.

- **Hoofdstuk 5** bespreekt hoe het gebied van DCIS eruitziet bij 62 patiënten met HER2+ invasieve borstkanker op contrast-versterkte mammografie (CEM). Bij 71% van de patiënten toonde CEM verdachte kalkspatjes of contrast aankleuring kenmerkend voor een gebied van DCIS. Bij patiënten die direct geopereerd werden, kon CEM in 77% van de gevallen een gebied van DCIS buiten de tumor identificeren. Dit is belangrijk voor de chirurgische behandeling, zodat zowel de invasieve tumor als het gebied van DCIS volledig wordt verwijderd. Contrast aankleuring op CEM blijkt een meer nauwkeurige inschatting te kunnen geven dan kalkspatjes voor het inschatten van de daadwerkelijke grootte van DCIS in weefselonderzoek. Toch blijkt dat beeldvorming regelmatig de grootte van het gebied van DCIS in het weefselonderzoek onderschat.

Deel III: Chirurgie en prognose
Het laatste deel van dit proefschrift richt zich op de invloed van een gebied van DCIS op de keuze voor chirurgische behandeling en de prognose van patiënten.

- **Hoofdstuk 6** beschrijft de trends in chirurgische behandelingen bij 5289 patiënten met HER2+ invasieve borstkanker over een periode van 10 jaar. Tussen 2010 en 2019 is het percentage patiënten dat een borstamputatie onderging aanzienlijk gedaald, van 62,6% naar 35,1%. Patiënten met een gebied van DCIS ondergaan echter vaker een borstamputatie dan patiënten zonder DCIS, zelfs wanneer zowel de invasieve tumor als het gebied van DCIS volledig verdwenen zijn na NST. Dit is deels te verklaren doordat patiënten met een gebied van DCIS minder vaak een pathologische complete respons bereiken. Bovendien kunnen patiënten om verschillende redenen een voorkeur hebben voor een borstamputatie, bijvoorbeeld vanwege zorgen over terugkeer van ziekte. Helaas was het in deze nationale database niet mogelijk om de patiëntvoorkeuren te onderzoeken en mee te nemen in de analyses.

- **Hoofdstuk 7** onderzoekt de chirurgische uitkomsten van 3056 patiënten met HER2+ borstkanker die een borstsparende operatie hebben ondergaan na NST. Bij patiënten met een gebied van DCIS werden vaker positieve snijvlakken gevonden, wat betekent dat tijdens de operatie niet alle tumorcellen zijn verwijderd uit de borst. Deze positieve snijvlakken werden het vaakst veroorzaakt door het gebied van DCIS. Daarnaast werden de overleving en het optreden van recidieven binnen deze groep onderzocht. Patiënten met een gebied van DCIS hadden een hogere kans op recidief in de borst of oksel binnen 5 jaar na diagnose (6,8%) vergeleken met patiënten zonder DCIS (3,6%). Uit verdere analyses bleek echter dat deze verhoogde kans niet direct gerelateerd was aan het gebied van DCIS zelf, maar eerder aan de eigenschappen van de aanwezige invasieve tumor. De algemene overleving was vergelijkbaar tussen patiënten met en zonder een gebied van DCIS: 95% van de patiënten leefde nog 5 jaar na diagnose. De aanwezigheid van restziekte (invasieve tumor of DCIS) in de borst na NST bleek de belangrijkste voorspeller van een slechtere prognose.

Conclusie
Dit proefschrift benadrukt het belang van onderzoek naar een gebied van DCIS bij patiënten met invasieve borstkanker. Deel I laat zien dat na behandeling met NST het gebied van DCIS volledig kan verdwijnen, wat zou kunnen leiden tot meer patiënten die in aanmerking komen voor een borstsparende operatie. De onderzoeken in deel II beschrijven de kenmerken van het gebied van DCIS op verschillende beeldvormende technieken. Deel III van dit proefschrift toont aan dat de keuze voor de operatie in deze groep patiënten vaak nog complex is. In het geval van borstsparende chirurgie is er in een deel van de patiënten sprake van invasieve tumor of DCIS in de snijvlakken, en ondanks het bereiken van een pathologische complete respons wordt er nog vaak een borstamputatie uitgevoerd. Verder onderzoek naar specifieke kenmerken van DCIS

in weefselonderzoek en verbetering van de nauwkeurigheid van de beeldvormende technieken is noodzakelijk voor het optimaliseren van de behandeling van toekomstige patiënten.

List of publications

This thesis

Ploumen RAW, Keymeulen KBMI, Kooreman LFS, van Kuijk SMJ, Siesling S, Smidt ML, van Nijnatten TJA. The percentage of residual DCIS in patients diagnosed with primary invasive breast cancer treated with neoadjuvant systemic therapy: A nationwide retrospective study. Eur J Surg Oncol. 2022;48(1):60-66.

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Curriculum vitae

Roxanne Alicia Wilhelmina Ploumen was born on April 21, 1995, in Heerlen, the Netherlands. She spent the first nine years of her life in Schimmert. Afterwards, she moved with her parents, Jan and Marion, and her younger sister, Evie, to Heijenrath, into the ancestral home of her mother, renovated by her father. Roxanne attended secondary school at Sophianum, Gulpen, where she pursued the Nature and Health track, graduating cum laude in 2013. After her graduation, she was admitted to the Medicine program at Maastricht University.

During her clinical rotations, Roxanne developed a strong interest in surgery, which led her to follow an international internship at the pediatric surgery department in Padova, Italy. This experience strengthened her interest and motivated her to complete her final internship at the pediatric surgery department of Maastricht UMC+. After earning her medical degree, she worked as a resident not in training (ANIOS) at the surgery department of Maastricht UMC+. During this year, her interest in oncological surgery grew, and she decided to start her PhD in breast cancer, under the supervision of Prof. Marjolein Smidt and Dr. Thiemo van Nijnatten. Later, Prof. Sabine Siesling, a clinical epidemiologist at the Netherlands Comprehensive Cancer Institute, joined her promotion team. During her PhD, Roxanne presented her research at various national and international conferences, including the European Breast Cancer Conference in Barcelona and the European Society of Surgical Oncology Congress in Florence. In addition to her research, Roxanne joined the board of the Pélerin symposium for two years, and enjoyed contributing to education, serving as a tutor for the abdomen course for third-year medical students. After completing her PhD, she started working as a resident not in training at the surgery department of Zuyderland Medical Center in Heerlen and Sittard-Geleen in February 2025.

Outside of work, Roxanne enjoys spending time renovating her home in Heugem, together with her partner Casper. She finds joy in hosting dinners for friends and family, combining her love for food and ambiance with good company. Roxanne has a passion for coffee and Italian culture, which she loves to combine during her holidays.

Cover

The cover of this thesis was designed by Roxanne herself, and the effort and thought behind it merit a brief explanation.

The front cover features 10 distinct circles, each representing one of the 10 main chapters of this thesis. The perfectly round circles symbolize DCIS, while the rough, undefined circles represent the invasive tumor. The diagonal line of ascending circles illustrates a gradual decrease in color and clarity, reflecting the response the tumor may undergo during neoadjuvant systemic therapy. The circles were created using an espresso cup, a nod to the countless cups of coffee that supported this thesis.

The title of the thesis is rendered in neon pink, the same color as the HER2 fluoresence in situ hybridization (FISH) test used in pathology, reflecting the significance of HER2+ breast cancer in this work.

The back cover features four irregular circles, representing the four parts of this thesis, as well as the four family members who played an essential role throughout the author's life. These circles were created with the base of a wine glass, subtly referencing the moments of relaxation and reflection during the PhD process. The splashes suggest spilled wine, offering a playful nod to the author's clumsy side, and how she learned to explore creativity and embrace imperfections.

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