Axillary strategies in breast cancer

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Axillary strategies in breast cancer: filling the gaps

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Chapter 1

General introduction and thesis outline

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General introduction

This thesis focuses on axillary staging and treatment strategies in invasive breast cancer. The aim is to address some of the current knowledge gaps, to further improve axillary management for both clinically node-negative (cN0) and node-positive (cN+) breast cancer. In this introduction, background information is provided, followed by an outline of this thesis.

In the Netherlands, approximately 15,000 women are diagnosed with invasive breast cancer each year.[1] This means that one in seven women will develop invasive breast cancer.[1] When breast cancer is diagnosed, part of the diagnostic work-up is to assess whether regional lymph nodes are involved. In the Netherlands, besides physical examination, an axillary ultrasound is routinely performed, with fine needle aspiration or core needle biopsy in case of suspicious lymph nodes.[2] Based on the results of this work-up, and if indicated, additional imaging such as PET-CT, patients are classified as having either cN0 (i.e., no metastatic lymph nodes) or cN+ (i.e., metastatic lymph node(s)) breast cancer. Until the 1990s, regardless of having cN0 or cN+ disease, patients underwent surgical removal of all axillary lymph nodes (i.e., axillary lymph node dissection, ALND), which is associated with substantial post-surgical morbidity such as lymphedema and limb paraesthesia.[3,4] Therefore, a trend was initiated towards less invasive axillary staging and treatment strategies, with the aim to improve post-surgical outcomes, including quality of life (QoL), while maintaining oncologic safety. As a result, over the past decades, standard ALND is increasingly being omitted in both cN0 and cN+ disease. With regard to timing of surgery, in current practice, cN0 as well as cN+ disease can be treated with primary surgery, or with neoadjuvant systemic therapy (NST), in which systemic therapy is applied before surgery. In this thesis, cN0 breast cancer treated with primary surgery, and both cN0 and cN+ breast cancer treated with NST will be further discussed.

cN0 breast cancer

In cN0 breast cancer, the sentinel lymph node biopsy (SLNB) has long replaced standard ALND following landmark trials such as NSABP B-32.[5-7] In case of no sentinel lymph node (SLN) involvement, SLNB without completion ALND provides comparable survival and regional control, with less morbidity.[5-7] In addition, completion ALND can even be safely omitted in case of limited SLN involvement in patients treated with breast-conserving therapy (BCT) (i.e., breast-conserving surgery (BCS) followed by whole-breast radiotherapy (WBRT)).[8-11] It is likely that due to an incidental radiotherapy (RT) dose to the axilla, WBRT contributes to improved regional control,[12-14] and thus to a low number of axillary recurrences.[8-11] Therefore, it is questioned whether performing an SLNB is of added value in these patients. Trials such as INSEMA, SOUND, and BOOG 2013-08 are

currently investigating whether the SLNB can be safely omitted in patients with cN0 breast cancer treated with BCT.[15-17] Recently published results of the SOUND trial support this de-escalation strategy.[18]

Meanwhile, the optimal axillary management for patients treated with mastectomy remains uncertain. This is due to the fact that these patients do not routinely receive chest wall RT, and the abovementioned trials did not included many, if any, patients treated with mastectomy.[8-11] The same uncertainty applies for patients with cN0 disease treated with NST, as they were not represented in these trials.[8-11]

cN+ breast cancer treated with neoadjuvant systemic therapy

Nowadays, patients with cN+ breast cancer are often treated with NST. It enables assessment of in vivo tumour response to systemic therapy, and has the benefit of downsizing the primary tumour, thereby making BCS more often feasible.[19,20] NST can also downstage nodal disease and can even result in a pathological complete response (pCR). In patients with cN+ breast cancer, pCR rates of the axilla vary depending on breast cancer molecular subtype and can be as high as 74% in human epidermal growth factor receptor 2 (HER2)-positive disease.[21-25] The ability to reduce both the size of the primary tumour and the extent of lymph node involvement, has resulted in adjuvant locoregional RT indications being challenged, since locoregional RT guidelines were originally based on studies in which patients were treated with primary surgery. Moreover, as pCR is associated with improved prognosis compared to residual disease,[26-29] patients with a pCR of the axilla are not expected to benefit from ALND. On that account, less invasive axillary staging procedures have been proposed to establish response-guided treatment, by identifying pCR in order to omit ALND in these patients.

Less invasive axillary staging procedures for cN+ breast cancer

Less invasive axillary staging procedure are the SLNB, excision of a targeted lymph node (TLN) (e.g., Marking Axillary lymph nodes with Radioactive Iodine seeds: MARI-procedure), and Targeted Axillary Dissection (TAD), in which the SLNB and excision of a TLN are combined. While these procedures are expected to diminish post-surgical morbidity compared to ALND, they all risk leaving behind (chemotherapy-resistant) disease. Trials such as SENTINA, ACOZOG Z1071, and SN FNAC have shown that performing an SLNB after NST results in false negative rates (FNRs) of 14.2%, 12.6%, and 13.3%, respectively, and a negative predictive value (NPV) that does not exceed 86%.[23,30-32] This indicates that potentially chemotherapy-resistant residual disease is missed in one out of six patients with a negative SLNB. Suggested methods to improve the FNR are the use of dual tracer, excision of ≥3 SLNs, and immunohistochemistry.[23] In a meta-analysis including six studies on SLNB, excision of ≥3 SLNs was associated with improved FNR.[22] However, as the median

number of detected SLNs is two,[6] in clinical practice it is often not feasible to excise ≥3 SLNs. Hence, although successful in cN0 patients, the SLNB does not seem to be accurate enough as stand-alone procedure in cN+ disease treated with NST. An alternative would be to specifically target a metastatic axillary lymph node by placing a marker inside this lymph node before NST, and to localise and subsequently excise this TLN after NST. In 2010, the MARI-procedure was introduced, in which a metastatic lymph node is marked with a radioactive iodine seed before NST, and excised after NST with the use of a hand-held gamma probe.[33,34] The MARI-procedure achieved an FNR of 7%, and an NPV of 83% (if isolated tumour cells were counted as residual disease), which is comparable to the NPV of the SLNB. It was hypothesized that combining SLNB with the excision of a TLN (i.e., performing TAD) would improve diagnostic accuracy, since the TLN appears not to be the SLN in 23.0-35.2% of cases.[35-37] Three small prospective single centre studies reported improved FNRs ranging from 2-4%.[35-37] In 2022, the Dutch prospective multicentre trial investigating the RISAS-procedure (Radioactive Iodine Seed localisation in the Axilla with the Sentinel node procedure) corroborated these findings with an FNR of 3.5%, and an NPV of 92.8% in a cohort of 212 patients, confirming the superior diagnostic accuracy of TAD.[38,39] In clinical practice, several TAD-procedures are now being investigated and performed, which differ with regard to the type of definitive marker used (e.g., radioactive iodine seed, black ink, wire) and timing of definitive marker placement (i.e., before or after NST). Meanwhile, it is unclear to what extent the different types of less invasive axillary staging procedures (and their diagnostic accuracy) affect response-guided treatment outcomes, including long-term oncologic outcomes and impact on QoL.[40]

Response-guided axillary treatment and long-term prognosis

The implementation of less invasive axillary staging procedures for cN+ disease has led to a decrease in (completion) ALND, not only in the Netherlands (99% in 2006, to 53% in 2016),[41] but also in other countries,[42-44] a trend which seems to coincide with an increased use of adjuvant axillary RT.[41] Interestingly, ALND is also being omitted (or replaced by axillary RT) in selected patients with residual disease.[41,45] Limited but increasing evidence is available regarding the oncologic outcomes of response-guided treatment based on less invasive axillary staging procedures.[45] In 2022, Van Loevezijn et al. published 3-year follow-up results of response-guided treatment according to the MARI-protocol,[45] in which the ALND was omitted in 217 (80.0%) of 272 patients (and replaced by axillary RT in 161 (74.2%) of 217 patients) in a single centre study. The 3-year axillary recurrence-free survival achieved in this study was 98.0% (95%-CI 96.0-100.0). Although these results are promising, more evidence is needed with regard to long-term oncologic safety (i.e., survival, recurrence) and impact on QoL, hereby also taking into account prognostic factors such as response to systemic therapy and breast cancer molecular subtype. Ongoing randomised controlled trials are assessing the value of ALND and/or locoregional RT in cN+ disease treated

with NST, in either patients with an axillary-pCR (NSABP-B51/RTOG 1304 and ATNEC, respectively NCT01872975 and NCT04109079), or in patients with axillary residual disease (Alliance A011202 and TAXIS, respectively NCT01901094 and NCT03513614).

In conclusion, de-escalation of axillary staging and treatment strategies in breast cancer is an ongoing trend. While aiming to find the most optimal strategy, oncologic safety as well as impact on QoL has to be taken into consideration. This thesis aims to provide insight into current practice variation, various TAD-procedures, and long-term oncologic safety outcomes in both cN0 and cN+ disease, all to further optimise axillary staging and treatment. Considering the large variety of axillary staging and treatment strategies currently being applied in clinical practice, it is of utmost importance that (more) consensus is reached, preferably in the near future.

Thesis outline

In the first part of this thesis, **Chapter 2** presents the 5-year follow-up results of the BOOG 2013-07, a registry study conducted to provide insight into oncologic safety when axillary treatment is omitted in patients with cN0 breast cancer, who are treated with mastectomy and have limited SLN involvement.

The second part of this thesis focuses on patients with cN+ breast cancer. In **Chapter 3**, an overview of studies describing TAD in cN+ breast cancer treated with NST is provided, hereby especially focusing on types of definitive markers used for TLN excision, the timing of marker placement, and the ability to identify the TLN. In **Chapter 4,** the 5-year follow-up results of the RAPCHEM study are presented, a registry study performed to evaluate the oncologic safety of de-escalated locoregional RT in patients with cT1-2N1 breast cancer treated with NST, according to a predefined consensus-based study guideline. In **Chapter 5**, the 5-year follow-up results of a cohort study are provided, conducted to determine the prognostic effect of the nodal status before and after NST in a Dutch population-based cohort. In **Chapter 6**, the study protocol of the MINIMAX study is presented, a registry study conducted to provide insight into the oncologic safety and impact on QoL of response guided-treatment based on both the less and more invasive axillary staging procedures in cN+ disease treated with NST. In **Chapter 7**, the current practice variation with regard to axillary staging and treatment strategies in the Netherlands is explored, by means of a survey that was conducted among the 35 hospitals participating in the MINIMAX study.

In the third part of this thesis, **Chapter 8** provides a descriptive systematic review of the relationship between personality and QoL in women with non-metastatic breast cancer.

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Part I

Node-negative breast cancer treated with mastectomy in the primary setting

Chapter 2

De-escalation of axillary treatment in case of a positive sentinel lymph node biopsy in cT1-2N0 breast cancer treated with mastectomy: a nationwide registry study to provide insight into oncologic safety (BOOG 2013-07)

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Abstract

Background: Trials have demonstrated the safety of omitting completion axillary lymph node dissection (ALND) in cT1-2N0 breast cancer patients who undergo breast-conserving therapy and have limited sentinel lymph node (SLN) involvement. The aim of this registry study was to provide insight into oncologic safety of omitting completion axillary treatment in mastectomy patients with SLN involvement.

Methods: Women diagnosed in 2013-2014 with unilateral cT1-2N0 breast cancer treated with mastectomy, with 1-3 SLN metastases (pN1mi-pN1a), were identified from the Netherlands Cancer Registry, and classified by axillary treatment-strategy: no completion axillary treatment, completion ALND, regional RT, or completion ALND followed by regional RT. Five-year regional recurrence (RR) rate was the primary endpoint. Recurrence-free interval (RFi) and overall survival (OS) were among secondary endpoints.

Results: In total, 1,090 patients were included: 219 (20.1%) in the no completion axillary treatment-group, 437 (40.1%) in the completion ALND-group, 327 (30.0%) in the regional RT-group, and 107 (9.8%) in the completion ALND and regional RT-group. The no completion axillary treatment-group had more patients with favorable tumor characteristics and an older age. The overall 5-year RR rate was 1.3% (2.5% for the no completion axillary treatment-group) and did not statistically significant differ between groups. RFi was also comparable among groups. The no completion axillary treatment-group had a statistically significant worse 5-year OS, due to a higher percentage of non-cancer deaths.

Conclusion: In this registry study of patients with cT1-2N0 breast cancer treated with mastectomy, who had limited SLN involvement, the 5-year RR rate was low and comparable between patients with and without completion axillary treatment.

Introduction

In clinically node-negative (cN0) breast cancer, standard axillary lymph node dissection (ALND) has long been replaced by sentinel lymph node biopsy (SLNB) as a result of landmark trials such as NSABP B-32.[1-4] In case of absence of sentinel lymph node (SLN) involvement, SLNB without completion ALND provides comparable survival and regional control, and less morbidity.[1-3] In addition, in case of limited SLN involvement, completion ALND can be safely omitted in patients who undergo breast-conserving therapy (BCT) (i.e., breast-conserving surgery (BCS) and whole breast radiotherapy (WBRT)).[5-9] Therefore, the added value of SLNB itself is investigated in trials such as INSEMA, SOUND, BOOG 2013-08, SOAPET, AND NAUTILUS.[10-14] Recently published results of the SOUND trial support this de-escalation strategy in patients treated with BCT.[15]

It is hypothesized that WBRT after BCS improves regional control, as a result of incidental irradiation of the axilla.[16-18] Thus, it is not possible to simply extrapolate results from trials such as Z0011 to patients treated with mastectomy, who do not routinely receive chest wall RT.[7,8] Moreover, the beneficial effect of adjuvant systemic therapy on regional control should also be considered. Furthermore, trials such as the IBCSG 23-01 did include patients treated with mastectomy, yet a limited number.[5,6,19] Therefore, the Dutch BOOG 2013-07 randomized controlled trial (RCT) was designed and initiated (NCT02112682).[20] Due to a lack of accrual the RCT was ended in 2017. In an effort to still provide insight into oncologic safety, a nationwide registry study was conducted. The 5-year results are now presented with regard to oncologic safety of omitting completion axillary treatment in mastectomy patients with limited SLN involvement.

Methods

Study design and participants

In- and exclusion criteria for this registry study were similar to those of the BOOG 2013-07 RCT.[20] Women aged ≥18 years, with unilateral cT1-2N0 invasive breast cancer treated with mastectomy, with a maximum of three SLN metastases (i.e., pN1mi-pN1a), and diagnosed between January 1, 2013, and December 31, 2014, were identified from the Netherlands Cancer Registry (NCR). A cN0 status was defined as the absence of lymph node metastases at time of diagnosis. This was based on ultrasound, and if indicated, confirmed with a negative fine needle aspiration or core needle biopsy in case of suspicious lymph nodes, all part of the recommended method to assess axillary nodal status in the Netherlands since 2008. Exclusion criteria were distant metastases, neoadjuvant systemic therapy, positive surgical margins after mastectomy, previous surgery or RT of the ipsilateral axilla,

history of invasive breast cancer, and other malignancies (except successfully treated malignancies >5 years before invasive breast cancer diagnosis, basal cell or squamous cell skin cancer, and carcinoma in situ of the breast or cervix).

The NCR is a nationwide registry that is managed by the Netherlands Comprehensive Cancer Organization (IKNL).[21] Patients are included in this registry via an opt-out approach. Specially trained registration clerks of IKNL gather clinical data from the patients' medical files. The collected data can be used for research after approval by the Privacy Review Board of the NCR, as was done for this study. Written informed consent was not required.

For each patient the following variables were gathered: year of diagnosis, age, histomorphological subtype, breast cancer molecular subtype, tumor grade, (lymph-) vascular-invasion (LVI), multifocality, TNM status at diagnosis and after surgery,[22] number of (positive) lymph nodes identified at axillary surgery, type of axillary treatment, type of systemic therapy, details regarding RT (e.g., target volumes, dose, and the number of fractions), and follow-up in terms of recurrence and survival.
The overall mortality data in the NCR were derived from the municipality registry (GBA), and were last updated on January 31, 2023. Cause of death was derived from the Statistics Netherlands (CBS).

Patients were retrospectively assigned to one of four groups based on axillary treatment: no completion axillary treatment, completion ALND, regional RT, or completion ALND followed by regional RT. In this study, regional RT was defined as RT to axillary levels I-II and/or levels III-IV (i.e., periclavicular region) (with or without RT of the internal mammary nodes).[23]

In the study period, treatments were based on the Dutch breast cancer treatment guideline of 2012, and definitive treatment choices were left to the discretion of the multidisciplinary team of each hospital. If no completion ALND was performed, and regional RT was applied, this consisted of RT to axillary levels I-II. In case of high risk disease (i.e., ≤2 macrometastases with risk factors such as age <40 or triple negative disease, or >2 metastases), RT was extended to the periclavicular region and chest wall. If a completion ALND was performed, locoregional RT was indicated in case of risk factors such as a total of ≥4 positive lymph nodes, or lymph node involvement at the medio-cranial border of the dissected axilla. This consisted of RT of the chest wall and the periclavicular lymph nodes, including the undissected part of the axilla, however, could exceptionally also include (part of) the dissected axilla. RT of the internal mammary nodes was applied if considered indicated (e.g., extensive lymph node involvement, primary tumor located medially). An RT dose of 42.56 Gy given in 16 fractions or another dose biologically equivalent to 25x2 Gy was applied.

Outcomes

Five-year RR rate was the primary endpoint. Five-year local recurrence (LR) rate, locoregional recurrence (LRR) rate, distant metastases (DM) rate, recurrence-free interval (RFi),[24] overall survival (OS), the occurrence of contralateral breast cancer, and the number of delayed ALNDs were secondary endpoints. RR rate included recurrences in ipsilateral axillary levels I-II, periclavicular region, internal mammary, and intramammary lymph nodes.[23] LR rate comprised chest wall recurrences (invasive or in situ carcinoma), and DM rate comprised recurrences in any other location, all in accordance with the Maastricht Delphi Consensus on Event Definition by Moosdorff et al.[25] In this study, if DM occurred as first event, no further data were collected with regard to other recurrences that occurred at a later time. RR rate, LR rate, LRR rate, and DM rate were based on events occurring between primary breast cancer diagnosis and 5-year follow-up. Patients were censored if they were lost to follow-up or were still alive at 5-year follow-up without a recurrence. Contralateral breast cancer was defined as an invasive tumor in the contralateral breast. RFi was based on the time interval between primary breast cancer diagnosis and occurrence of an RR, LR, DM, or death from breast cancer, whichever came first, measured in days. Patients were censored if they died from a non-breast cancer cause as first event, or if they were lost to follow-up or still alive at 5-year follow-up without an event. OS was based on the time interval between primary breast cancer diagnosis until death from any cause, measured in days. Patients were censored if they were lost to follow-up or were still alive at 5-year follow-up. Delayed ALND was defined as an ALND performed in case of recurrent axillary disease.

Statistical analyses

Categorical variables were summarized as frequencies and percentages, and Pearson's Chi^2-test or Fisher's exact test were conducted to compare groups. Five-year follow-up analyses were performed for RR rate, LR rate, LRR rate, DM rate, RFi, and OS, in the whole cohort and subsequently stratified per axillary treatment-group. In addition, supplementary 5-year follow-up analyses were performed for patients with macrometastatic disease identified in the SLNB. Cumulative incidence function was used to estimate RR rate, LR rate, LRR, and DM rate. In case of RR rate, LR rate, and LRR rate, distant metastases as first event and death were treated as competing risks, and in case of DM rate, death was treated as competing risk. Cox proportional hazards regression analyses were used to compare groups. Results were reported as hazard ratios (HRs) with 95%-confidence interval (CI). Kaplan Meier survival analyses were performed to assess RFi, and OS, and log-rank tests were used to compare groups. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. All analyses were conducted in STATA SE16.1 (ref: StataCorp. In: College Station TSL, editor. Stata statistical software: release, vol. 16; 2020).

Results

Patient, tumor, and treatment characteristics

As shown in Figure 1, 1,142 patients were identified from the NCR, of whom 1,090 were eligible for analyses. Fifty-two patients were excluded, since they did not match the inclusion criteria. Median age was 60.0 years [interquartile range (IQR) 49.0-71.0]. Characteristics of the study population are summarized in Table 1.

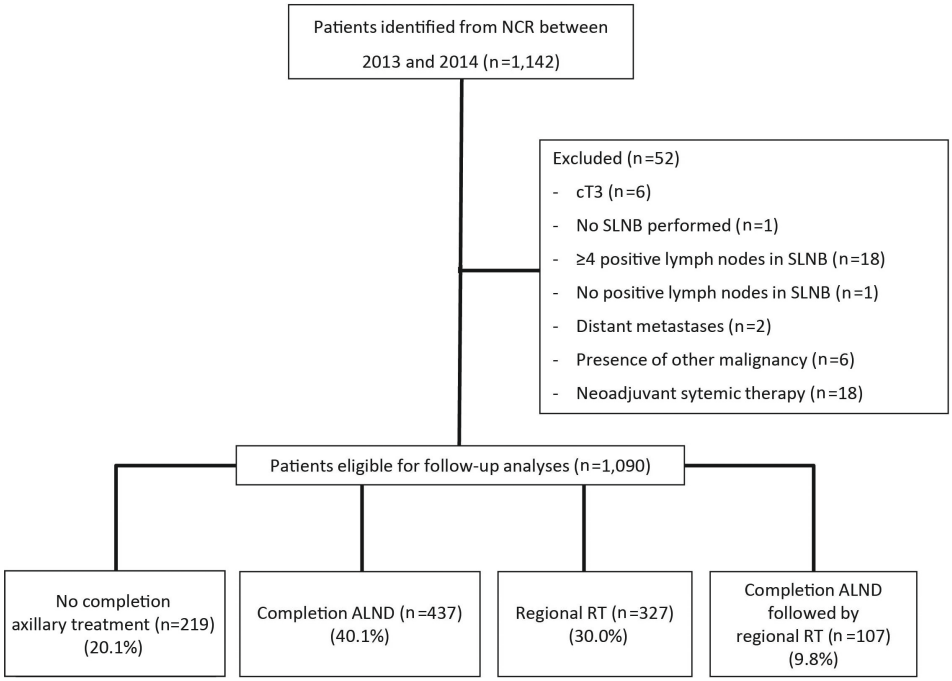


Figure 1. Consort diagram

Most tumors were hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative (81.3%), grade 2 (56.0%), and/or cT2 at diagnosis (52.5%). Median number of excised SLNs was two [IQR 1-3]. After SLNB, 73.6% of patients had pN1a(sn) disease, and 26.4% of patients had pN1mi(sn) disease. Most patients had only one SLN with metastatic disease (80.0%). Adjuvant chemotherapy was administered in 633 (58.1%) patients, hormonal therapy in 925 (84.9%) patients, and adjuvant RT of the chest wall in 434 (39.8%) of 1,090 patients.

Table 1. Patient, tumor, and treatment characteristics

	Whole cohort n=1,090	No completion axillary treatment n=219	Completion ALND n=437	Regional RT n=327	Completion ALND and regional RT n=107	Chi² *p*-value
Age, years#						
<40	54 (5.0)	4 (1.8)	23 (5.3)	21 (6.4)	6 (5.3)	**<0.001**
40-59	473 (43.4)	67 (30.6)	228 (52.2)	134 (41.0)	44 (41.1)	
60-74	357 (32.8)	61 (27.9)	142 (32.5)	110 (33.6)	44 (41.1)	
≥75	206 (18.9)	87 (39.7)	44 (10.1)	62 (19.0)	13 (12.2)	
Molecular subtype						
HR+, HER2-	886 (81.3)	193 (88.1)	356 (81.5)	252 (77.1)	85 (79.4)	0.137
HR+, HER2+	109 (10.0)	18 (8.2)	42 (9.6)	38 (11.6)	11 (10.3)	
HR-, HER2+	42 (3.9)	3 (1.4)	17 (3.9)	16 (4.9)	6 (5.6)	
Triple negative	53 (4.9)	5 (2.3)	22 (5.0)	21 (6.4)	5 (4.7)	
Grade						
1	188 (17.7)	55 (24.4)	75 (17.7)	51 (15.9)	9 (8.7)	**<0.001**
2	596 (56.0)	132 (60.8)	239 (56.2)	164 (51.3)	61 (59.2)	
3	281 (26.4)	32 (14.8)	111 (26.1)	105 (32.8)	33 (32.0)	
Unknown	25	2	12	7	4	
(Lymph-)vascular-invasion						
No	651 (71.6)	151 (81.2)	252 (70.8)	195 (70.9)	53 (57.6)	**0.001**
Yes	258 (28.4)	35 (18.8)	104 (29.2)	80 (29.1)	39 (42.4)	
Unknown	181	25	82	55	16	
cT-status						
cT1	518 (47.5)	110 (50.2)	219 (50.1)	148 (45.3)	41 (38.3)	0.106
cT2	572 (52.5)	109 (49.8)	218 (49.9)	179 (54.7)	66 (61.7)	
Multifocality						
No	741 (68.0)	166 (75.8)	290 (66.4)	214 (65.4)	71 (66.4)	0.051
Yes	349 (32.0)	53 (24.2)	147 (33.6)	113 (34.6)	36 (33.6)	
pT-status						
pT1	445 (40.8)	101 (46.1)	186 (42.6)	132 (40.4)	26 (24.3)	**<0.001**
pT2	585 (53.7)	115 (52.5)	226 (51.7)	175 (53.5)	69 (64.5)	
pT3	56 (5.1)	2 (0.9)	25 (5.7)	17 (5.2)	12 (11.2)	
pT4	4 (0.4)	1 (0.5)	0 (0.0)	3 (0.9)	0 (0.0)	
pN-status after SLNB						
pN1mi	288 (26.4)	164 (74.9)	45 (10.3)	75 (22.9)	4 (3.7)	**<0.001**
pN1a	802 (73.6)	55 (25.1)	392 (89.7)	252 (77.1)	103 (96.3)	
Number of positive SLNs						
1	872 (80.0)	204 (93.2)	335 (76.7)	266 (81.4)	67 (62.6)	**<0.001**
2	183 (16.8)	13 (5.9)	93 (21.3)	52 (15.9)	25 (23.4)	
3	35 (3.2)	2 (0.9)	9 (2.1)	9 (2.8)	15 (14.0)	

Table 1. Continued.

	Whole cohort n=1,090	No completion axillary treatment n=219	Completion ALND n=437	Regional RT n=327	Completion ALND and regional RT n=107	Chi² *p*-value
Chemotherapy						
No	457 (41.9)	153 (69.9)	136 (31.1)	143 (43.7)	25 (23.4)	**<0.001**
Yes	633 (58.1)	66 (30.1)	301 (68.9)	192 (56.3)	82 (76.6)	
Targeted therapy						
No	965 (88.5)	206 (94.1)	382 (87.4)	285 (87.2)	92 (86.0)	**0.038**
Yes	125 (11.5)	13 (5.9)	55 (12.6)	42 (12.8)	15 (14.0)	
Hormonal therapy						
No	165 (15.1)	30 (13.7)	60 (13.7)	62 (19.0)	13 (12.2)	0.139
Yes	925 (84.9)	189 (86.3)	377 (86.3)	265 (81.0)	94 (87.9)	
RT of the chest wall[$]						
No	656 (60.2)	210 (95.9)	368 (84.2)	78 (23.9)	0 (0.0)	**<0.001**
Yes	434 (39.8)	9 (4.1)	69 (15.8)	249 (76.2)	107 (100.0)	

Values are n(%).

[#] Median age [IQR] was 68 [52-81], 56 [48-66], 60 [50-70], and 61 [50-78], respectively, in the no completion axillary treatment-group, completion ALND-group, regional RT-group, and completion ALND followed by regional RT-group.

[$] Fifteen patients received RT of the internal mammary chain: one, one, five, and eight, respectively, in the no completion axillary treatment-group, completion ALND-group, regional RT-group, and completion ALND followed by regional RT-group.

Eventually, 219 (20.1%) patients were included in the no completion axillary treatment-group, 437 (40.1%) patients in the completion ALND-group, 327 (30.0%) patients in the regional RT-group, and 107 (9.8%) patients in the completion ALND and regional RT-group. Patients in the no completion axillary treatment-group were more often ≥75 years of age, more often had grade 1 tumors, pN1mi(sn), and a maximum of one positive SLN. Furthermore, LVI was less often present, and fewer patients were treated with chemotherapy or RT of the chest wall. Compared to the completion ALND-group, the regional RT-group consisted of more patients with pN1mi(sn), and more patients received RT of the chest wall. In the completion ALND and regional RT-group, most patients had grade 2 or 3 tumors, and they more often presented with LVI, as well as with more extensive axillary disease and larger tumors at surgery. Furthermore, more of these patients were treated with chemotherapy, and chest wall RT was always administered.

Follow-up results

Median follow-up for recurrence was 6.0 years [IQR 5.1-6.7][range 0.1-8.8]. Median follow-up with regard to vital status was 8.8 years [IQR 8.1-9.4][range 0.3-10.1]. All recurrences (i.e., RR, LR, and DM), contralateral breast cancers, and data regarding vital status (including cause of death) at 5-year follow-up are summarized in Table 2.

The overall 5-year RR rate was 1.3% [95%-CI 0.8-2.2]. The 5-year RR rate per axillary treatment-group is listed in Table 3. The 5-year RR rates of the no completion axillary treatment-group, completion ALND-group, and regional RT-group were 2.5% [95%-CI 0.9-5.4], 1.4% [0.6-2.9], and 1.0% [0.3-2.6], respectively. There were no statistically significant differences between groups. No RR occurred in the completion ALND and regional RT-group. In the whole cohort, one delayed ALND was performed due to an RR (solitary axillary metastasis) that occurred 2.1 years after primary cancer diagnosis.

Table 2. All recurrences, contralateral breast cancers, and data regarding vital status at 5-year follow-up

	Whole cohort n=1,090	No completion axillary treatment n=219	Completion ALND n=437	Regional RT n=327	Completion ALND and regional RT n=107
Regional recurrence	9* (0.8)	3 (1.4)	4 (0.9)	2 (0.6)	0 (0.0)
Synchronous distant metastases	6	1	3	2	0
Local recurrence[$]	12** (1.1)	2 (0.9)	7 (1.6)	2 (0.6)	1 (0.9)
Synchronous distant metastases	3	0	3	0	0
Both regional and local recurrence[#,$]	5 (0.5)	2 (0.9)	2 (0.5)	1 (0.3)	0 (0.0)
Synchronous distant metastases	4	2	1	1	0
Distant metastases as first event	63 (5.8)	9 (4.1)	27 (6.2)	16 (4.9)	11 (10.2)
Contralateral breast cancer	12 (1.1)	2 (0.9)	6 (1.4)	2 (0.6)	2 (1.9)
Vital status					
Alive	944 (86.6)	173 (79.0)	392 (89.7)	285 (87.2)	94 (87.9)
Deceased	146 (13.4)	46 (21.0)	45 (10.3)	42 (12.8)	13 (12.1)
Cause of death					
Breast cancer	57 (5.2)	14 (6.4)	21 (4.8)	15 (4.6)	7 (6.5)
Other or unknown type of cancer	<25 (NR)	<5 (NR)	<10 (NR)	<10 (NR)	<5 (NR)
Other than cancer	63 (5.8)	27 (12.3)	16 (3.7)	17 (5.2)	5 (4.7)
Unknown	<5 (NR)	<5 (NR)	<5 (NR)	<5 (NR)	<5 (NR)

Values are n (%). NR, not reported.

* In one patient, a local recurrence and distant metastases occurred at a later time.

** In three patients, distant metastases (and a regional recurrence in one patient) occurred at a later time.

[$] All local recurrences were invasive breast cancer.

[#] Regional and local recurrence occurred synchronously. These patients were not included in rows "regional recurrence" and "local recurrence".

In analyses for which data was used from Statistics Netherlands, adjustments were made (e.g., <5 was reported in case of less than five patients in one cell) to avoid risk of revealing the identity of individual patients.

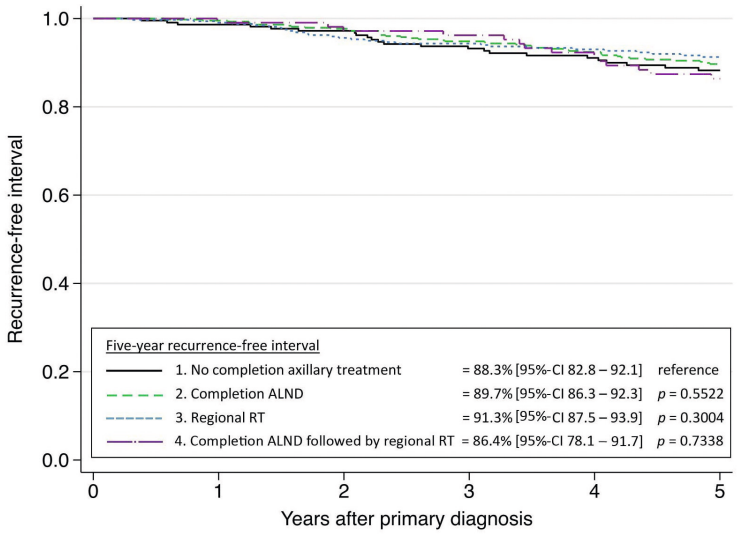
Table 3. Five-year regional recurrence rate

	No. of events	Regional recurrence rate [95%-CI]	HR [95%-CI]	*p*-value
Whole cohort (n=1,090)	14	1.3% [0.8-2.2]	-	-
No completion axillary treatment (n=219)	5	2.5% [0.9-5.4]	Reference	-
Completion ALND (n=437)	6	1.4% [0.6-2.9]	0.5 [0.1-1.7]	0.299
Regional RT (n=327)	3	1.0% [0.3-2.6]	0.4 [0.1-1.5]	0.170
Completion ALND followed by regional RT (n=107)	0	-	-	-

p-values of the other group comparisons were also not significant (not reported).

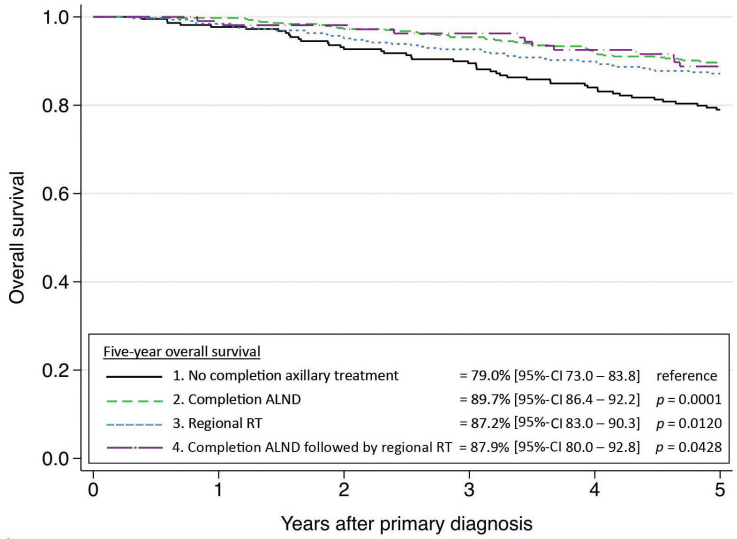
The overall 5-year LR rate, LRR rate, and DM rate were 1.7% [95%-CI 1.0-2.6], 2.5% [95%-CI 1.7-3.5], and 7.2% [95%-CI 5.7-8.8], respectively. The 5-year RR, LR, LRR, and DM rates per axillary treatment-group are listed in Table S1. There were no statistically significant differences between groups. In the whole cohort, 12 (1.1%) patients developed contralateral invasive breast cancer: two (0.9%) in the no completion axillary treatment-group, six (1.4%) in de completion ALND-group, two (0.6%) in the regional RT-group, and two (1.9%) in the completion and regional RT-group, as provided in Table 2. The overall 5-year RFi and OS were 89.5% [95%-CI 87.5-91.3] and 86.6% [95%-CI 84.4-88.5], respectively. The 5-year RFi and OS per axillary treatment-group are presented in Figure 2. Five-year RFi did not significantly differ between groups. Five-year OS of the no completion axillary treatment-group (79.0%) was significantly worse compared to the completion ALND-group (89.7%, p=0.0001), the regional RT-group (87.2%, p=0.0120), and the completion ALND and regional RT-group (87.9%, p=0.0428). Of the 146 patients who died, the percentage of non-cancer deaths was 58.7%, 35.6%, 40.4%, and 38.5%, in the no completion axillary treatment-group, completion ALND-group, regional RT-group, and completion ALND and regional RT-group, respectively.

In Table S2 and S3, as well as Figure S1, follow-up results are provided specifically for patients with macrometastatic disease identified in the SLNB. Once again, no statistically significant differences were observed in terms of RR, LR, LRR, and DM rate, and RFi. The no completion axillary treatment-group (n=55) had a statistically significant worse 5-year OS. The median age in this group was 83.0 years [IQR 69.0-88.0].



Number at risk

Group 1	219	214	196	182	168	143
Group 2	437	430	414	397	377	350
Group 3	327	320	299	289	277	258
Group 4	107	105	103	100	93	83



Number at risk

Group 1	219	214	203	196	184	173
Group 2	437	435	424	416	400	389
Group 3	327	322	311	303	294	285
Group 4	107	105	105	103	99	94

Figure 2. Five-year recurrence-free interval and overall survival per axillary treatment-group
p-values of the other group comparisons were also not significant (not reported).

Discussion

This nationwide registry study presents a low 5-year RR rate of 1.3% in a cohort of 1,090 patients with cT1-2N0 breast cancer treated with mastectomy, and with limited SLN involvement. The group of patients in whom completion axillary treatment was omitted was older and had more favorable tumor characteristics. These patients had a 5-year RR rate of 2.5%, which did not statistically significant differ from that of the completion ALND-group (1.4%), or regional RT-group (1.0%). The 5-year LR rate, LRR rate, DM rate, and RFi endpoints also did not statistically significant differ between groups. The no completion axillary treatment-group did have a statistically significant worse 5-year OS, due to a higher percentage of non-cancer deaths.

A similar but smaller study was previously reported by FitzSullivan et al. who performed a retrospective single center study of 525 patients who were treated with mastectomy between 1994 and 2010, and had a limited number of SLN metastases (median 1, range 1-4).[26] With a median follow-up of 5.5 years, the no completion axillary treatment-group (n=58) had an extrapolated 10-year RR rate of 3.8%. Forty-seven (81.0%) of 58 patients had pN1mi(sn). No statistically significant differences were demonstrated between groups (no further axillary treatment compared to ALND and/or RT) with regard to RR rate, recurrence-free survival, and OS. Zaveri et al. identified 548 patients diagnosed between 2006 and 2015, who were treated with mastectomy, and had up to two positive SLNs.[27] With a median follow-up of 5.4 year, the 5-year LRR rate in the no completion axillary treatment-group (n=126) was 1.8%. Sixty-seven (53.2%) of 126 patients had pN1mi(sn), and 36 (28.6%) received RT. No statistically significant differences were demonstrated between groups (no ALND or ALND (with or without RT)) with regard to LRR rate, DM rate, and OS. In the present study, the 5-year OS of the no completion axillary treatment-group was statistically significant worse compared to that of the other groups, despite having a comparable number of breast cancer-related events. This may be largely explained by the fact that these patients were more often ≥75 years of age (39.7% versus 18.9% in the whole cohort), thus more often died of causes other than cancer (58.7% versus 44.4% in the whole cohort).

In this study, patients in the no completion axillary treatment-group had more favorable tumor characteristics (e.g., pN1mi(sn) in 74.9% of cases), and less often received adjuvant treatment such as chemotherapy and chest wall RT, when compared to the other groups. This was also found in an American population-based study on axillary management patterns of 12,190 patients with cT1-2N0 breast cancer treated with mastectomy, and with 1-2 SLN metastases.[28] In addition, in their study, patients in the no axillary treatment-group more often had comorbidities. Hence, patients are likely already being selected for

omission of (axillary) treatment not only based on tumor characteristics, but also based on other important factors such as age and comorbidities. In the present study, it is likely that some patients in the no completion axillary treatment-group already had a lower life expectancy (since 58.7% of patients died of another cause than cancer), which may have contributed to opting for omission of (axillary) treatment.

Despite limited evidence regarding oncologic safety, completion ALND is being omitted or replaced by regional RT in case of limited SLN involvement in cT1-2N0 breast cancer treated with mastectomy in daily practice.[28-32] RCTs that included mastectomy patients with micrometastatic SLNs and compared ALND with no further axillary treatment were the IBCSG 23-01 and AATRM 048/13/2000.[5,6,19] In both trials no benefit was found for completion ALND regarding disease-free survival. Unfortunately, the percentage of included patients treated with mastectomy was small in both trials (7% and 9%, respectively). Ongoing non-inferiority RCTs on this topic are the SINODAR ONE, POSNOC, and SENOMAC trial, which are all assessing oncologic safety of omitting completion axillary treatment in case of macrometastatic SLNs.[33-35] In the SINODAR ONE trial, patients with cT1-2N0 breast cancer and 1-2 macrometastatic SLNs were randomized between SLNB only and ALND.[33] In a subanalysis of only mastectomy patients (n=218), with a median follow-up of 33 months, SLNB only was not inferior to ALND in terms of 5-year recurrence-free survival (94.1% versus 95.7%) and OS (98.7% versus 97.8%).[36] RT (27% versus 8%) and chemotherapy (56.8% versus 49.5%) were more often administered in the ALND-group. Currently, mastectomy patients are still being enrolled in the study to increase power. In the POSNOC trial, 1,900 patients with cT1-2N0 breast cancer and 1-2 macrometastatic SLNs are randomized between adjuvant systemic therapy and adjuvant systemic therapy with either ALND or axillary RT, with 5-year axillary recurrence rate as primary endpoint.[34] The first results are expected in 2026. In the SENOMAC trial, 3,500 patients with cT1-3N0 breast cancer and 1-2 macrometastastic SLNs are randomized between SLNB only and ALND.[35] One-year quality of life outcomes have been published in 2022.[37] The results regarding the primary endpoint 5-year breast cancer-specific survival are awaited. Interestingly, in an interim analysis on generalizability, the authors concluded that older patients were underrepresented in their study.[38] In all three RCTs, either patients aged ≥75 or patients deemed unfit for adjuvant systemic therapy were not included. This is in accordance with studies evaluating the generalizability of RCTs, indicating that older patients are underrepresented in RCTs.[39,40] With 206 (18.9%) of 1,090 patients being ≥75 years of age, the current study provides highly relevant results to help guide axillary treatment strategies, also in the elderly patient population.

In Western countries, almost a third of breast cancers occur in patients older than 65 years, with the greatest incidence between 75-79 years.[41] These patients tend to have

more comorbidities, and lower life expectancy regardless of breast cancer. Therefore, especially in these patients, it is of utmost importance to keep these factors in mind when deciding on (axillary) treatment. Taking it one step further, one of the recommendations of the Choosing Wisely campaign is to not routinely perform the SLNB in patients older than 70 years with HR+HER2- disease.[42] This was based on two RCTs in which most patients received BCT, and all were treated with adjuvant tamoxifen, and omission of SLNB did not compromise long-term survival outcomes.[43-45] In a Canadian population-based cohort study, 17,370 woman aged 65-95 years diagnosed with stage I-II breast cancer between 2010-2016 were identified.[46] Of these patients, 1,771 (10.2%) did not undergo axillary surgery. These patients were older, had more comorbidities, and were less likely to receive adjuvant treatment. After performing propensity score weighting, patients not undergoing axillary surgery had comparable breast cancer-specific survival (HR 0.98), yet worse OS (HR 1.14). Similar results were found in patients older than 70 years with HR+HER2- disease. The authors suggested that the worse OS was probably due to competing risks of death from causes other than breast cancer. These findings are similar to the findings in the current study, which confirmed a higher percentage of non-cancer deaths in the no axillary treatment-group. With the aim to predict 5-year survival and recurrence and to subsequently optimize treatment in older patients (≥65 years), in 2021 the PORTRET tool was developed.[47] In this tool, age, tumor characteristics, comorbidities according to the ICD-10 classification, and geriatric predictors such as walking difficulties, dementia or cognitive impairment, polypharmacy, and sensory deficits were included. This tool may help guide (axillary) treatment strategies specifically for the older patient.

A strength of the present study was the availability of detailed recurrence and survival data (including cause of death, which was known in >95% if patients) for all axillary treatment-groups, including data on cause of death. Due to its population-based design, this study provides an overview of real-world clinical practice in Dutch breast cancer care. However, this study is also accompanied by heterogeneity between groups regarding baseline characteristics. The heterogeneity between groups, and not having comorbidity data, prevents us from drawing firm conclusions. Nonetheless, the results demonstrate comparable outcomes when all available data is taken into account, and emphasize the importance of also considering factors such as age and overall health when deciding on treatment strategies. Another limitation is the median follow-up time of 6.0 years for recurrence, considering 91.3% of patients had HR+ breast cancer, which tends to develop recurrences after a longer follow-up time.[48] Lastly, no data was available on factors that played a role in decision-making regarding axillary treatment strategies, which would be helpful for clinicians and patients to guide treatment strategies in daily practice.

To conclude, in this registry study with patients with cT1-2N0 invasive breast cancer treated with mastectomy, with limited SLN involvement, the overall 5-year RR rate was low. Patients in whom completion axillary treatment was omitted were often older and had more often favorable tumor characteristics. Their 5-year RR rate was comparable to that of the other axillary treatment-groups, yet patients in whom completion axillary treatment was omitted did have a worse 5-year OS due to a higher percentage of non-cancer deaths. These results show that there is room for refraining from completion axillary treatment in selected patients. In the decision-making process, not only tumor characteristics should be taken into account, but also patient-related factors such as age and comorbidities. Future studies will have to provide more evidence to enable optimization of patient selection for de-escalation of axillary treatment, in an effort to prevent both under and overtreatment, while also keeping in mind the importance of maintaining quality of life.

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Supplementary Table 1. Five-year LR rate, LRR rate, and DM rate

	No. of events	LR rate [95%-CI]	HR [95%-CI]	*p*-value	No. of events	LRR rate [95%-CI]	HR [95%-CI]	*p*-value	No. of events	DM rate [95%-CI]	HR [95%-CI]	*p*-value
Whole cohort (n=1,090)	18	1.7% [1.0-2.6]	-	-	26	2.5% [1.7-3.5]	-	-	78	7.2% [5.7-8.8]	-	-
No completion axillary treatment (n=219)	5	2.5% [0.9-5.4]	reference	-	7	3.4% [1.5-6.6]	reference	-	13	5.9% [3.3-9.6]	reference	-
Completion ALND (n=437)	9	2.1% [1.0-3.8]	0.8 [0.3-2.4]	0.707	13	3.0% [1.7-5.0]	0.8 [0.3-2.1]	0.700	35	8.0% [5.7-10.8]	1.3 [0.7-2.6]	0.356
Regional RT (n=327)	3	1.0% [0.3-2.6]	0.4 [0.1-1.5]	0.173	5	1.6% [0.6-3.5]	0.4 [0.1-1.4]	0.161	19	5.8% [3.6-8.7]	1.0 [0.5-2.0]	0.953
Completion ALND followed by regional RT (n=107)	1	1.0% [0.1-4.7]	0.4 [0.04-3.1]	0.360	1	1.0% [0.1-4.7]	0.3 [0.03-2.1]	0.209	11	10.3% [5.5-16.9]	1.7 [0.8-3.9]	0.180

p-values of the other group comparisons were also not significant (not reported).

Supplementary Table 2. Five-year RR rate in case of macrometastatic disease in the SLNB

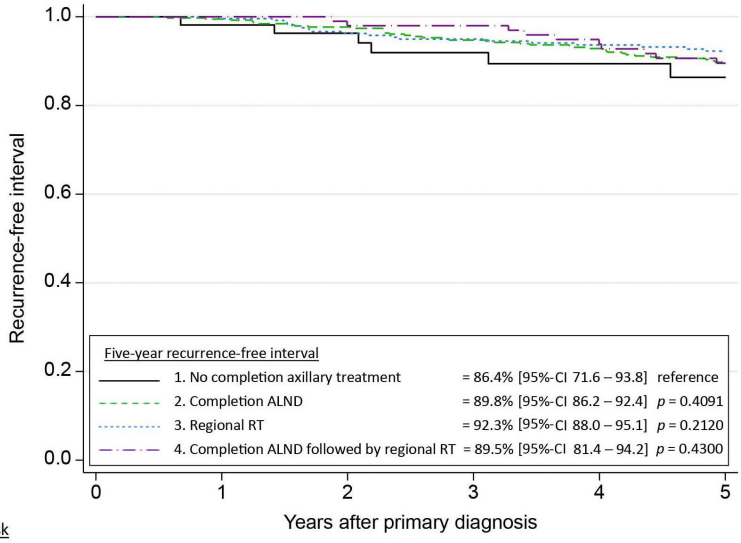
	No. of events	Regional recurrence rate [95%-CI]	HR [95%-CI]	*p*-value
Whole cohort (n=802)	10	1.3% [0.7-2.3]	-	-
No completion axillary treatment (n=55)	2	4.0% [0.7-12.2]	reference	-
Completion ALND (n=392)	6	1.6% [0.7-3.2]	0.3 [0.1-1.6]	0.166
Regional RT (n=252)	2	0.8% [0.2-2.7]	0.2 [0.02-1.2]	0.079
Completion ALND followed by regional RT (n=103)	0	-	-	-

p-values of the other group comparisons were also not significant (not reported).

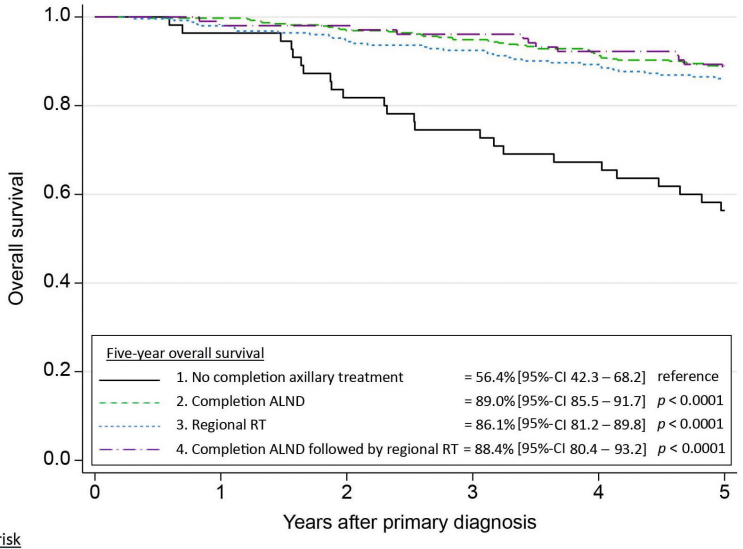
Supplementary Table 3. Five-year LR, LRR, and DM rate in case of macrometastatic disease in the SLNB

	No. of events	LR rate [95%-CI]	HR [95%-CI]	*p*-value	No. of events	LRR rate [95%-CI]	HR [95%-CI]	*p*-value	No. of events	DM rate [95%-CI]	HR [95%-CI]	*p*-value
Whole cohort (n=802)	13	1.7% [1.0-2.8]	-	-	19	2.4% [1.5-3.7]	-	-	63	7.9% [6.1-9.9]	-	-
No completion axillary treatment (n=55)	2	4.0% [0.7-12.2]	reference	-	3	5.9% [1.5-14.7]	reference	-	4	7.3% [2.3-16.1]	reference	-
Completion ALND (n=392)	8	2.1% [1.0-3.9]	0.4 [0.1-2.1]	0.310	12	3.1% [1.7-5.2]	0.4 [0.1-1.6]	0.205	33	8.4% [5.9-11.4]	1.2 [0.4-3.3]	0.782
Regional RT (n=252)	2	1.0% [0.2-2.7]	0.2 [0.03-1.3]	0.086	3	1.2% [0.3-3.3]	0.2 [0.04-0.9]	0.034	17	6.8% [4.1-10.3]	0.9 [0.3-2.8]	0.892
Completion ALND followed by regional RT (n=103)	1	1.0% [0.1-4.9]	0.2 [0.02-2.3]	0.204	1	1.0% [0.1-4.9]	0.1 [0.01-1.3]	0.087	9	8.7% [4.3-15.2]	1.2 [0.4-3.9]	0.760

p-values of the other group comparisons were also not significant (not reported).



Number at risk						
Group 1	55	53	44	38	34	23
Group 2	392	385	370	354	336	307
Group 3	252	245	226	219	209	195
Group 4	103	101	98	96	89	79



Number at risk						
Group 1	55	53	45	41	37	31
Group 2	392	390	379	371	356	347
Group 3	252	247	238	233	225	217
Group 4	103	101	101	99	95	91

Supplementary Figure 1. Five-year recurrence-free interval and overall survival in case of macro-metastatic disease in the SLNB

p-values of the other group comparisons were also not significant (not reported).

Part II

Node-positive breast cancer treated with neoadjuvant systemic therapy: from staging the axilla to response-guided treatment

Chapter 3

A systematic review on targeted axillary dissection in node-positive breast cancer treated with neoadjuvant systemic therapy: variation in type of marker, and timing of placement

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Abstract

Background: In node-positive (cN+) breast cancer treated with neoadjuvant systemic therapy (NST), combining sentinel lymph node biopsy (SLNB) and targeted lymph node (TLN) excision (i.e., Targeted Axillary Dissection; TAD) increases accuracy. TAD-procedures differ in terms of the TLN excision technique. This systematic review aimed to provide an overview of TAD-procedures regarding definitive marker type, and timing of placement (before (one-step procedure) or after NST adjacent to a pre-NST placed clip (two-step procedure)).

Methods: PudMed and Embase were searched until 04/07/2023, for randomised controlled trials, cohort, and case-control studies, with ≥25 patients. Studies on TLN excision only (without SLNB) or where intra-operative localisation of the TLN was not attempted were excluded. For qualitative synthesis, studies were grouped by definitive marker, and timing of placement. The TLN identification rate (IR) was reported. Study quality was assessed with an NIH Quality Assessment Tool.

Results: Of 277 unique records, 51 studies (4,512 patients) were included, and six definitive markers identified: wire, radioactive iodine seed, ^{99m}Technetium, (electro) magnetic/radiofrequency markers, black ink, and a clip. Eighteen studies evaluated one-step procedures; the IR of the TLN at surgery varied from 61.5%-100%. Forty-one studies evaluated two-step procedures; IR of the clipped TLN on imaging after NST varied from 48.8%-100%, and the IR of the TLN at surgery from 70.8%-100%. Most (40/51) studies were rated as fair quality.

Conclusion: Various TAD-procedures are used in clinical practice. Due to study heterogeneity, the most optimal TLN excision technique concerning IR and feasibility could not be determined. However, two-step procedures risk not identifying the clipped TLN on imaging after NST. High-quality prospective studies reporting all relevant aspects are needed.

Introduction

In clinically node-positive (cN+) breast cancer, the axillary lymph node dissection (ALND), which is associated with substantial morbidity,[1,2] used to be standard of care. Nowadays, patients with cN+ disease are often treated with neoadjuvant systemic therapy (NST). Following NST, approximately a third of patients achieve an axillary pathological complete response (axillary-pCR),[3-6] which is associated with improved prognosis compared to residual disease.[7-10] Less invasive axillary staging procedures were therefore proposed in an effort to enable response-guided treatment, by identifying axillary-pCR in order to omit ALND in these patients. Currently, several less invasive axillary staging procedures are being performed worldwide.

Several studies assessed the diagnostic accuracy of these less invasive axillary staging procedures compared to ALND in cN+ patients. Trials such as SENTINA, SN FNAC, and ACOZOG Z1071 have shown that performing the sentinel lymph node biopsy (SLNB) after NST results in false negative rates (FNRs) of 14.2%, 13.3%, and 12.6%, respectively, and a negative predictive value (NPV) that does not exceed 86%.[6,11-13] Use of dual tracer, immunohistochemistry (IHC), and excising ≥3 sentinel lymph nodes (SLNs) can improve the FNR.[6] However, as the median number of detected SLNs is two,[14] recommending to remove ≥3 SLNs may result in node-picking in which also non-SLNs are removed. An alternative to SLNB is to specifically target a metastatic axillary lymph node by placing a marker inside this lymph node before NST. After NST, this targeted lymph node (TLN) is localised using visual, imaging, or probe-guided methods (dependent on the type of marker that is used), and subsequently excised. For example, when performing the MARI-procedure (Marking the Axilla with Radioactive Iodine)[15] a radioactive iodine (^{125}I) seed is placed before NST, followed by excision of the TLN after NST under the guidance of a hand-held gamma probe. The MARI-procedure, first described in 2010, has an FNR of 7%, and an NPV of 83.3% (if isolated tumour cells are counted as residual disease).[16] This is comparable to the NPV of the SLNB. Lastly, the SLNB and excision of a TLN can be combined (i.e., Targeted Axillary Dissection, TAD).[17] In a sub-analysis of the Z1071 trial, which was published in 2016, a clip was placed in a metastatic axillary lymph node before NST in 170 patients.[18] Intra-operative localisation of the clipped lymph node was not attempted, yet it was encouraged to report whether it was located in either the SLNB or ALND specimen. In 29 (24.1%) of 170 patients, the clipped lymph node was reported to be found in the ALND specimen, suggesting that performing TAD improves diagnostic accuracy by removing additional relevant lymph nodes.[18] Three studies assessing TAD in 35 to 85 patients reported an FNR that varied from 2% to 4%, and an NPV that varied from 92% to 97%.[17,19,20] In 2022, the Dutch prospective multicentre trial investigating the RISAS-procedure (Radioactive Iodine Seed localisation in the Axilla with the Sentinel node

procedure) presented an FNR of 3.5%, and an NPV of 92.8% in 212 patients, confirming the superior diagnostic accuracy of TAD.[21] Studies on oncologic outcomes and especially on impact on quality of life of response-guided axillary treatment based on less invasive axillary staging techniques are still limited.[22-24]

Meanwhile, a wide variety of different TAD-procedures are being incorporated in clinical practice, in which the type of definitive marker varies (e.g., magnetic marker, black ink, wire, clip),[20,25-27] as does the timing of definitive marker placement (i.e., before or after NST). The technique used may affect the ability to identify the TLN. Therefore, the aim of this systematic review was to provide an overview of studies reporting on TAD in cN+ breast cancer treated with NST, focusing on types of markers for TLN excision, timing of marker placement, and the ability to identify the TLN.

Methods

Criteria for Considering Studies for This Review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for this systematic review.[28] A systematic literature search was performed for randomized controlled trials, cohort studies, and case-control studies with a minimum of 25 included patients describing their experience with TAD in cN+ breast cancer treated with NST. Study protocols, conference abstracts, case reports, editorials, commentaries, and reviews were excluded, as were studies of which the full text was not available in English. Pathological confirmation of nodal positivity was not required, as the focus was on the surgical technique and the identification rate (IR) of the TLN, rather than on diagnostic accuracy. Studies in which the suspicious or pathologically proven metastatic axillary lymph node was marked only after NST (without clip placement before NST), were excluded as this was not in agreement with the definition of TAD.[17] Studies that only evaluated excision of a TLN (without SLNB) were also excluded, as were studies in which intra-operative localisation of the TLN was not attempted (e.g., only an x-ray to check whether the TLN was present in the surgical specimen). If studies also included patients with clinically node-negative breast cancer or patients treated with primary surgery, these studies were excluded if it was not possible to identify the results specifically of the patients with cN+ disease treated with NST. Lastly, if more than one study reported on (part of) the same cohort, the study describing the largest cohort was solely included. For qualitative synthesis, studies were grouped by the type of definitive marker used and by timing of definitive marker placement. If the definitive marker was placed before NST, followed by excision of the TLN during surgery, this was considered a one-step procedure. If first a clip was placed before NST, followed by placement of a

definitive marker adjacent to the clip to enable subsequent excision of the TLN during surgery, this was considered a two-step procedure. In clinical practice, a wide variety of clips is used. When assessing the included studies, the specific type of clip used was not taken into account.

Search methods for Identification of Studies

PubMed and Embase were searched until July 4, 2023, without restriction on language or date of publication. The search strategies of both databases were checked by a librarian specialized in health sciences. Details of the search strategies are provided in Appendix S1. The reference lists of included studies were checked for additional relevant studies, as were existing reviews.

Selection of Studies

Reference management software (Endnote version 20.5) was used to identify and remove duplicate references. Title and abstract of all remaining references, and subsequently the full text articles of potentially eligible studies, were evaluated independently by SdW and JMS. Disagreements regarding eligibility of studies were resolved in a consensus meeting between SdW and JMS.

Data Extraction and Analysis

The following variables were extracted from each included study by SdW: first author, year of publication, study design, sample size, percentage of patients with cN+ disease in whom nodal positivity at diagnosis was pathologically proven, type of tracer used for the SLNB, type of definitive marker used for intra-operative excision of the TLN, whether this marker was placed before or after NST, the IR of the clipped TLN on imaging after NST (if applicable), the IR of the TLN during surgery, percentage of patients that underwent ALND, SLN and TLN being the same node (concordance), the number of excised lymph nodes (mean or median), and whether immunohistochemistry was used for assessment of the excised lymph nodes. JMS was consulted in case of uncertainties.

The random-effects model for meta-analysis in the 'metaprop' command in STATA SE16.1 (ref: StataCorp. In: College Station TSL, editor. Stata statistical software: release, vol. 16; 2020) was employed to calculate the overall pooled estimate of the IR of the TLN during surgery for both one-step and two-step procedures. Effect sizes with 95%-confidence interval (CI) and weights were provided in forest plots visualised per type of marker and for the whole group. The variability of IR estimates due to heterogeneity among included studies was quantified using the I^2 index. The Chi^2-test was used to assess statistical heterogeneity. The test was two-sided, and a *p*-value of <0.05 was considered statistically significant.

Quality Assessment

SdW assessed the quality of the included studies, including the risk of bias, with the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which consists of 14 questions.[29] All questions could be answered with yes (Y), no (N), cannot determine (CD), not applicable (NA), or not reported (NR). Based on these answers, studies were rated as having good, fair, or poor quality. JMS was consulted in case of uncertainties.

Results

Study Selection

The literature search resulted in 460 articles. After deduplication, 277 titles and abstracts were screened, followed by full-text evaluation of 89 articles. Eventually, 51 studies with a total of 4,512 patients were included for qualitative synthesis, as illustrated in Figure 1.

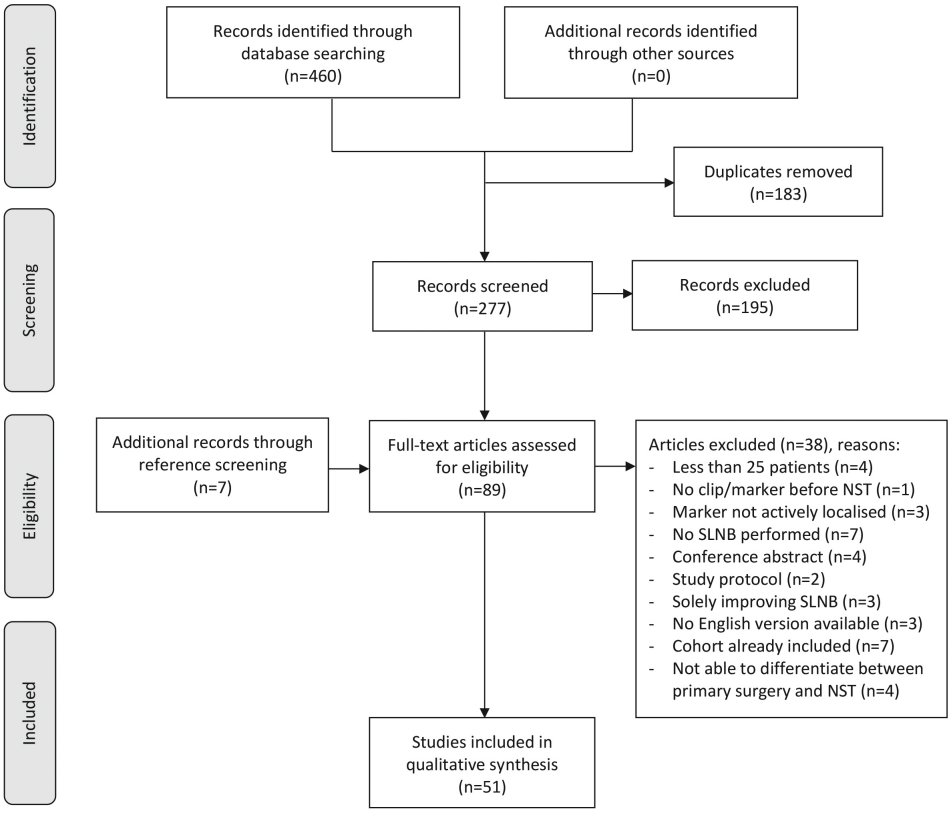

Figure 1. Flowchart of the Study Selection Process

Study Characteristics

The characteristics of the included studies, sorted by type of definitive marker, are listed in Table S1. In 42 (82.4%) of 51 studies, nodal positivity at diagnosis was pathologically proven in all patients. In 18 (35.3%) of 51 studies, dual tracer (consisting of blue dye and radioisotope) was routinely used when performing the SLNB. In 42 (82.4%) of 51 studies, the percentage of patients that underwent ALND was available, and varied from 22.2% to 100%. In eight (19.0%) of 42 studies, all patients underwent an ALND.

Type of definitive marker

Six definitive markers were identified that were used to mark the TLN to enable intra-operative localisation for excision of the TLN, all combined with SLNB. In 17 studies, a wire was placed after NST in the clipped TLN on the day of surgery.[17,19,27,30-43] In twelve studies, the (clipped) TLN was marked with a ^{125}I seed, either before or after NST,[17,21,41,42,44-51] and in five studies, a form of ^{99m}Tc was used to localise and excise the clipped TLN.[52-56] In three of five studies, the clipped TLN was injected with ^{99m}Tc-labeled macroaggregated albumin (^{99m}Tc-MAA) under ultrasound (US)-guidance one day before surgery.[52-54] In the other two studies, either ^{99m}Tc- Nanoscan tracer or ^{99m}Tc-nanocolloid was injected (peritumorally or periareolarly) to localise the SLN on SPECT/CT the day of surgery or one day before, and to determine whether the clipped TLN was an SLN.[55,56] If not, either ^{99m}Tc-Nanoscan tracer was injected into the clipped TLN, or a wire was placed under US-guidance to enable excision of the clipped TLN. In both ^{125}I and ^{99m}Tc marking, a hand-held gamma probe was used to localise and subsequently excise the TLN during surgery. In ten studies, the (clipped) TLN was marked with a magnetic marker,[25,57-61] radiofrequency identification (RFID) tag,[57] or electromagnetic reflector,[43,57,62-64] either before or after NST. At surgery, the TLN was localised with a hand-held probe based on magnetic fields, radio wave signalling, or radar/infrared technology, respectively. In nine studies, the (clipped) TLN was tattooed with black ink (i.e., carbon, charcoal, or 4% carbon microparticle suspension),[26,65-72] either before or after NST. Subsequently, it was excised under visual guidance during surgery. Lastly, in two studies, the clipped TLN was localised and excised under guidance of intra-operative US (IOUS).[73,74]

Timing of marker placement

Five studies assessed both a one-step and a two-step procedure, the remaining studies assessed either a one-step or two-step procedure. Tables 1 and 2 show detailed information for respectively one-step (15 studies) and two-step (41 studies) procedures.

One-step procedure studies

Fifteen studies described a one-step procedure, with a total of 1,321 patients. In all studies, the definitive marker was placed in the metastatic or suspicious TLN before NST,

followed by surgical excision after NST. The marking technique comprised the use of either a ^{125}I seed (four studies), magnetic marker (three studies), black ink (seven studies), or clip combined IOUS-guided localisation (two studies). Overall, the IR of the TLN at surgery varied from 61.5% to 100%. When grouped per type of definitive marker, the IR varied from 93.0%-99.3%, 98.1%-100%, 61.5%-100%, and 84.4%-96.2%, respectively, for ^{125}I seed, magnetic marker, black ink, and clip with IOUS-guided localisation. The overall pooled IR at surgery was 96% (95%-CI 93%-98%), as provided in Figure S1. Between studies, statistically significant heterogeneity was present (I^2=73.17%, p<0.001). The concordance rate between the TLN and SLN ranged between 47.9% and 100%.

Table 1. Studies describing a one-step procedure

First author (publication year)	Sample size	Type of definitive marker	IR at surgery (%)
Simons (2019)	68	^{125}I seed	93.0
Rebollo Aguirre (2022)	6#	^{125}I seed	97.2*
Simons (2022)	238	^{125}I seed	94.1
Munck (2023)	142	^{125}I seed	99.3
Martínez (2022)	44	Magnetic marker	100
Barry (2023)	54	Magnetic marker	98.1
Patel (2019)	47	Carbon ink	100
Natsiopoulos (2019)	75	Carbon ink	94.6
Allweis (2020)	63	Carbon ink	95.2
Dostalek (2021)	27	Carbon ink	81.5
de Boniface (2022)	149	Carbon ink	94.6
Pinto (2022)	13#	Carbon ink	61.5
Spautz (2020)	123	4% CMS	98.3
Pinto (2022)	37	Clip (IOUS)	81.1
Siso (2023)	235	Clip (IOUS)	96.2

CMS, carbon microparticle suspension.
* Study in which both a one-step and a two-step procedure was assessed. An overall outcome was provided.
# These studies were included since the total study comprised ≥25 patients.

Two-step procedure studies

Forty-one studies described a two-step procedure, with a total of 3,191 patients. In all studies, a clip was placed in the metastatic or suspicious TLN before NST. After NST, the clipped TLN was localised with imaging (in the vast majority with US), and was subsequently marked with either a wire (17 studies), ^{125}I seed (ten studies), ^{99m}Tc (five studies), (electro)magnetic/radiofrequency marker (11 studies), or black ink (three studies). The IR of the clipped TLN on imaging was reported in 23 (56.1%) of 41 studies, ranging from 48.8% to 100%. In 18 (43.9%) of 41 studies, the IR of the clipped TLN on imaging could not be determined (in three studies, e.g., only an overall IR was provided),

or it was not reported (in 15 studies, in the vast majority due to patients being excluded from analyses in case of unsuccessful localisation of the clipped TLN on imaging). Overall, the IR of the TLN at surgery varied from 70.8% to 100%. When grouped per type of marker, the IR at surgery varied from 70.8%-100%, 92.0%-100%, 90.0%-98.1%, 76.0%-100%, and 84.4%-100%, respectively, for wire, ^{125}I seed, ^{99m}Tc, (electro)magnetic/radiofrequency markers, and black ink. In six studies the IR at surgery could either not be determined, or was not reported. The overall pooled IR was 97% (95%-CI 95%-98%). Between studies, statistically significant heterogeneity was present (I^2=69,27%, p<0.001), as provided in Figure S2. The concordance rate between the TLN and SLN was reported in 28 studies and ranged between 35.7% and 91.0%.

Table 2. Studies describing a two-step procedure

First author (publication year)	Sample size	Type of definitive marker	IR on imaging after NST (%)	IR at surgery (%)
Plecha (2015)	73	Wire	NR	97.0
Dashevsky (2018)	28	Wire	100	92.9
Hartmann (2018)	30	Wire	80.0	70.8
Balasubramanian (2020)	25	Wire	100	92.0
Alarcón (2021)	28	Wire	100	100
Flores-Funes (2021)	60	Wire	96.7	96.6
García-Novoa (2021)	42	Wire	100	100
Gurleyik (2021)	64	Wire	98.4	100
Sierra (2021)	51	Wire	NR	96.1
Kuemmel (2022)	423	Wire	CD	77.8*
Acea-Figueira (2023)	81	Wire	100	98.8
Sargent (2023)	62	Wire	NR	NR
Wu (2023)	239	Wire	CD	94.1*
Munck (2023)	543	Wire (263); ^{125}I seed (103); ink on skin (62); magnetic marker (3)	79.4**	90.1; 96.1; 82.3; 100
Caudle (2016)	96	^{125}I seed (94); wire (2)	NR	NR
Diego (2016)	30	^{125}I seed	96.7	100
Nguyen (2017)	25	^{125}I seed	80.0	100
Beniey (2021)	35	^{125}I seed	97.1	97.1
Simons (2019)	70	^{125}I seed (12); wire (58)	NR	92.0; 95.0
Aragón-Sánchez (2022)	32	^{125}I seed	91.6	96.9***
Rebollo Aguirre (2022)	44	^{125}I seed	NR	97.2****
Weiss (2022)	78	^{125}I seed	CD	CD
Clark (2023)	77	^{125}I seed	NR	97.4
Fuertes Manuel (2022)	30	^{99m}Tc	100	90.0
del Castillo (2023)	54	^{99m}Tc	NR	98.1
Rella (2023)	77	^{99m}Tc	93.5	97.2

Table 2. Continued

First author (publication year)	Sample size	Type of definitive marker	IR on imaging after NST (%)	IR at surgery (%)
Winder (2022)	38	^{99m}Tc	NR	97.4
Dilege (2023)	61	^{99m}Tc	93.4	96.5
Laws (2020)	56	RFID tag (43); magnetic marker (12); electromagnetic reflector (1)	94.6**	92.5**
Sun (2020)	45	Electromagnetic reflector	NR	100
Balija (2021)	99	Electromagnetic reflector (57)[@]; wire (42)	84.2; 83.3	100[@], 79.2**
Weinfurtner (2022)	105	Electromagnetic reflector	NR	100
Taj (2023)	80	Electromagnetic reflector	48.8	NR
Mariscal Martínez (2021)	30	Magnetic marker	100	100
Reitsamer (2021)	40[&]	Magnetic marker	100	100
Simons (2021)	51	Magnetic marker	98.0	100
Martínez (2022)	37	Magnetic marker	NR	100
Barry (2023)	74	Magnetic marker	98.0	76.0
Kim (2019)	28	Charcoal	NR	96.0
Pinto (2022)	18[#]	Carbon ink	NR	94.4
Porpiglia (2023)	32	Carbon ink	NR	84.4

CD, cannot determine; NR, not reported.
* An overall IR was provided (i.e., on imaging and during surgery combined).
** Study in which more than one marking technique was assessed. An overall outcome was provided.
*** Three of 32 patients underwent stereotactic wire-localisation with mammography to enable excision.
**** Study in which both a one-step and a two-step procedure was assessed. An overall outcome was provided.
[#] This study was included since the total study comprised ≥25 patients.
[@] In 22 patients, the marker was placed in the clipped targeted lymph node before or during NST.
[&] In two patients, the marker was directly placed before NST.

Quality Assessment

With the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, eight studies were rated as good quality, 40 as fair quality, and three as poor quality. Details are reported in Table S2.

Discussion

Worldwide, several different surgical procedures are used in clinical practice for axillary staging after NST in cN+ breast cancer. Most institutions now prefer less invasive staging procedures such as the SLNB, excision of a TLN, or TAD, with the aim to enable response-guided treatment, and thus to potentially omit ALND in case of an axillary-pCR.[75-78] In

this systematic review, 51 studies on TAD with a total of 4,512 patients were included, and a vast variety of TLN excision techniques was identified. Six definitive markers were recognized: wire, ^{125}I seed, ^{99m}Tc, (electro)magnetic/radiofrequency markers, black ink, and clip (with IOUS-guided localisation and excision). Apart from this, variations in timing of definitive marker placement were assessed. The current systematic review underlines the scarcity of high-quality studies, rendering it impossible to determine the most optimal procedure in terms of IR and feasibility. However, each TLN excision technique has its own benefits and drawbacks that are relevant to take in consideration when performing TAD in clinical practice.

The use of wire-guided localisation is accessible and inexpensive.[79] However, the wire needs to be placed on the day before or the day of surgery, which requires adequate planning and placement of a clip before NST. Furthermore, in case of patient movement or manipulation during surgery, the wire may dislocate, which can complicate retrieval of the clipped TLN.[32] Apart from this, the wire may be uncomfortable for the patient. The ^{125}I seed does not have to be placed on the day of surgery (and can even be placed before start of NST due to its long half-life of 60 days), and the use of a hand-held gamma probe facilitates the identification of the TLN.[16] A downside is, however, that the use of ^{125}I seeds is strictly regulated, and widespread use is not possible since in many countries it is either not allowed for diagnostic purposes, or only if the ^{125}I seed is placed after NST.[79] An alternative would be to mark the TLN with ^{99m}Tc, which is inexpensive, already widely applied for diagnostic purposes, and the use of a hand-held gamma probe facilitates localisation of the TLN during surgery.[52-54] A downside is its short half-life of six hours, therefore it has to be injected just before surgery.[52-54] If ^{99m}Tc is not injected in the TLN itself but peritumorally or periareolarly (as is already part of routine SLNB) and the clipped TLN is an SLN on SPECT/CT, an additional procedure (e.g., injecting ^{99m}Tc-Nanoscan tracer in the clipped non-SLN to enable excision) is not needed. Magnetic markers, RFID tags, and electromagnetic reflectors are promising non-radioactive alternatives, which can all be placed before start of NST, and are localised with a hand-held probe to facilitate intra-operative excision of the TLN.[25,43,58-64,80] In case of the RFID tag and electromagnetic reflector, the probe also displays the distance from the tip of the probe to the marker.[81] As all three markers are not radioactive, there are no regulatory issues. However, these procedures are more expensive and require purchase of additional instruments, such as the localisation device.[79] In addition, the magnetic marker and RFID tag both create an artefact on MRI,[25,82] complicating response evaluation with MRI (especially when the primary tumour is located in the lateral upper quadrant) if placed before start of NST, and use of the magnetic marker also requires use of non-magnetic equipment during surgery. The electromagnetic marker may also create (minimal) artefacts.[82] Currently, the magnetic marker is being updated, in an effort to reduce MRI artefacts and to avoid the

need for non-magnetic equipment.[83] Another non-radioactive and inexpensive technique is tattooing the TLN with black ink. However, as this technique lacks a detection probe and can also not be visualised on imaging, it is more difficult to localise the TLN intra-operatively (the IR for this type of marker was reported to be as low as 61.5%). Moreover, studies have described spontaneous migration of black ink,[26,79] but also deliberate distribution of black ink around the TLN to increase the IR.[65,66] In both cases, this can result in unnecessary excision of additional lymph nodes,[26,66] hereby increasing the risk of post-surgical morbidity. Finally, IOUS-guided excision of the clipped TLN can be performed, which is again inexpensive and does not require additional markers or the purchase of new instruments. It does require an US on the operating room, and a specialist qualified to perform IOUS.[79]

As a result of the abovementioned benefits and drawbacks of the different techniques, each institution and/or specialist has its own preference with regard to performing TAD, resulting in a wide variety of techniques used in daily practice. Since the included studies are very heterogeneous with a broad range of reported IRs, it was not possible to conclude which technique is superior in identifying the TLN. However, this systematic review does show an important draw-back of two-step procedures that breast cancer specialists should be aware of: the TLN needs to be localised twice, not only at surgery, but already previously, i.e., after NST to place the definitive marker. As provided in Table 2, the ability to localise the clipped TLN on imaging after NST varied from 48.8% to 100%. Importantly, 19 (47.5%) of 40 studies did not report any data regarding this aspect of the procedure. The wide variation in the ability to localise the clipped TLN on imaging may be explained by the diverse range of clips used in clinical practice. In addition, it may be influenced by the level of experience of the specialist performing the localisation and whether or not this is performed by a dedicated breast cancer specialist. Furthermore, the inability to identify the TLN on imaging after NST is possibly due to the fact that the visibility of clips decreases in time.[84] When the hyperechogenic clip is placed in the hypoechogenic cortex, regression of the cortex in case of response to NST can also affect the visibility of the clip or cause the clip to dislocate.[85] This is in accordance with the multivariable analyses of Kuemmel et al., in which an axillary-pCR on imaging was also associated with the inability to identify the TLN at surgery.[19] Hence, it is important that a clip is used which has good visibility on US. If the clip cannot be identified after NST and thus the definitive marker cannot be placed to enable intra-operative localisation of the TLN, this may result in the need to proceed to ALND, while a patient may have axillary-pCR.

In this systematic review, a large number of studies describing experiences with marking techniques for TLN excision have been identified. While it is of great importance that these studies are performed to share experiences, there were also some limitations of the

included studies. First, most studies had a relatively small sample size. Study populations ranged from 25 to 543 patients. Twenty-four studies (about half of included studies) comprised <60 patients. For example, the study of Pinto et al., which assessed both a one-step and a two-step procedure with carbon ink in a prospective cohort, the IR of the TLN at surgery was 61.5% for the one-step procedure.[70] However, this was based on the results of a small subgroup of the study population (13 patients). Another limitation was an often retrospective study design (45.1% of studies) or single-centre study design (80.3% of studies). Moreover, the definition of the IR was not always clearly defined, and, in case of two-step procedures, in 18 (43.9%) of 41 studies, the IR of the clipped TLN on imaging was not provided. Due to these limitations and study heterogeneity, results of random-effects model should be interpreted with caution. Lastly, it was not considered whether, at time of primary diagnosis, the definitive marker (in case of a one-step procedure) or clip (in case of a two-step procedure) was placed directly after fine needle aspiration cytology or core needle biopsy of the suspicious axillary lymph node, or if this was done after the lymph node was pathologically proven to be metastatic. Along this line, the assessment did not include the different types of clips used for marking the TLN pre-NST, which also vary between and even within institutions. Currently, there are no data available for comparing different clips. High-quality prospective studies are needed, that evaluate both one-step and two-step procedures, provide a clear definition of the IR, and take into account the results of clip identification on imaging in case of a two-step procedure. Currently, the Magellan trial is recruiting patients in a prospective study evaluating the magnetic marker in a one-step procedure (NCT03796559). In addition, Hartmann et al. recently published results regarding the applicability of the magnetic marker as one-step procedure in a multicentre cohort of 151 patients. In 146 patients, the TLN was successfully removed, which resulted in an IR of 96.0%. Response assessment with MRI was reported to be compromised in 15 (9.9%) of 151 patients.[86] Furthermore, in the prospective IMTAD study in which 189 patients were included, marking with ^{125}I seed (after NST in pre-NST clipped TLN) (135 patients), magnetic marker (30 patients), and carbon suspension (24 patients) are compared. Recently published results demonstrated comparable complication rates regarding marker placement and localisation, and marker dislodgement.[87]

In the meantime, while TAD and other less invasive axillary staging procedures are being performed in daily practice worldwide, limited but increasing evidence is available regarding the oncologic outcomes of response-guided treatment based on less invasive axillary staging procedures. Interestingly, while these procedures were initially introduced to omit ALND in case of an axillary-pCR, ALND is now also being omitted in selected patients with residual disease.[75] Van Loevezijn et al. recently published 3-year follow-up results of the MARI-protocol, in which axillary treatment decisions were made based on

findings on the 18F-FDG PET/CT in combination with the outcome of the MARI-procedure, in which the ALND was omitted in 217 (80.0%) of 272 patients (and replaced by axillary radiotherapy (RT) in 161 (74.2%) of 217 patients) in a single centre study, with a 3-year axillary recurrence-free survival of 98.0% (95%-CI 96.0-100.0).[23] Ongoing randomised controlled trials evaluating the value of ALND and/or locoregional RT in patients with cN+ breast cancer with NST are the NSABP-B51/RTOG 1304 and ATNEC (respectively NCT01872975 and NCT04109079), in which patients with ypN0 disease are included, and the Alliance A011202 and TAXIS (respectively NCT01901094 and NCT03513614), in which patients with ypN+ disease are included. Together with registry studies such as MINIMAX and AXSANA,[84,88] these trials will provide more evidence about appropriate locoregional treatment strategies for cN+ disease in terms of long-term prognosis, in order to prevent overtreatment as well as undertreatment. In addition, these trials may help determine the most optimal less invasive procedure for axillary staging in these patients, not only in terms of IR and feasibility but also in terms of oncologic safety and QoL. With regard to QoL, the number of excised lymph nodes should also be taken into account, as this can affect arm morbidity. For instance, excising ≥3 SLNs may be required when performing an SLNB (to improve the FNR), while TAD may involve the removal of a single lymph node.

In conclusion, nowadays, several TAD-procedures are being performed, each having its own benefits and drawbacks regarding TLN excision techniques. Due to the heterogeneity of the included studies, it was not possible to conclude which technique is superior in identifying the TLN. However, this systematic review does show that the two-step procedure has an important draw-back as the TLN has to be localised not only at surgery, but also on imaging after NST (when the definitive marker has to be placed). More high-quality prospective studies are needed to determine the most optimal TAD technique, taking into account IR and feasibility of TLN excision techniques, but also long-term outcomes regarding oncologic safety and quality of life.

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Supplementary Appendix 1. Search strategy

PubMed

(((((Breast neoplasms[MeSH] OR ((Breast[MeSH] OR breast[tiab] OR mamma*[tiab]) AND (Neoplasms[MeSH] OR carcinom*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR malign*[tiab])))) AND (Lymphatic Metastasis[MeSH] OR ((Axilla[MeSH] OR axilla*[tiab] OR Lymphatic system[MeSH] OR lymph node*[tiab] OR lymphatic node*[tiab] OR nodal[tiab] OR node*[tiab]) AND (positive[tiab] OR disease[tiab] OR metasta*[tiab])))) AND (staging[tiab] OR excision[tiab] OR axillary surgery[tiab] OR axillary evaluation[tiab] OR axillary dissection[tiab] OR TAD[tiab] OR (combin*[tiab] AND procedure*[tiab]) OR Lymph Node Excision[MeSH])) AND (seed[tiab] OR reflector[tiab] OR mark*[tiab] OR clip*[tiab] OR wire[tiab] OR tattoo*[tiab] OR charcoal[tiab] OR carbon[tiab] OR radiofreq*[tiab] OR iodine[tiab] OR magnetic[tiab])) AND (Sentinel Lymph Node/surgery[MeSH] OR Sentinel Lymph Node Biopsy[MeSH] OR Sentinel*[tiab] OR SLN[tiab] OR SLNB[tiab])) AND (Neoadjuvant Therapy[MeSH] OR ((preoperative[tiab] OR primary[tiab] OR neoadjuvant[tiab] OR neo-adjuvant[tiab]) AND (therapy[tiab] OR chemotherap*[tiab] OR immunotherap*[tiab] OR targeted therap*[tiab] OR systemic therap*[tiab])))

EMBASE

1. exp breast tumor/ or ((breast/ or breast.ti,ab,kw. or mamma*.ti,ab,kw.) and (malignant neoplasm/ or carcinom*.ti,ab,kw. or cancer*.ti,ab,kw. or neoplasm*.ti,ab,kw. or malign*.ti,ab,kw.))
2. lymph node metastasis/ or ((axilla/ or axilla*.ti,ab,kw. or lymphatic system/ or lymph node*.ti,ab,kw. or lymphatic node*.ti,ab,kw. or nodal.ti,ab,kw. or node.ti,ab,kw.) and (positive or disease of metasta*).ti,ab,kw.)
3. (staging or excision or axillary surgery or axillary evaluation or axillary dissection or TAD or (combin* and procedure)).ti,ab,kw. or lymph node dissection/
4. (seed of reflector or mark* or clip* or wire or tattoo* of charcoal or carbon or radiofreq* or iodine or magnetic).ti,ab,kw.
5. sentinel lymph node biopsy/ or sentinel*.ti,ab,kw. or SLN.ti,ab,kw. or SLNB.ti,ab,kw.
6. exp neoadjuvant therapy/ or ((preoperative or primary or neoadjuvant or neo-adjuvant) and (therapy or chemotherap* or targeted therapy* of systemic therap*)).ti,ab,kw.
7. 1 and 2 and 3 and 4 and 5 and 6
8. limit 7 to conference abstract status
9. 7 not 8

Supplementary Table 1. Included articles and their characteristics sorted per type of marker

First author (publication year)	Study design	Sample size*	PA-proven cN+ (%)	Type of definitive marker	Tracer for SLNB	Lymph nodes excised (SLN/TLN/TAD) Mean ± SD (median, IQR), range	Concordance TLN=SLN (%)	IHC	ALND (%)
Plecha (2015)	R, S	73$	100	Wire	Tc ± blue	5.5 ± 2.5 SLNs	NR	NR	CD
Dashevsky (2018)	R, S	28$	100	Wire	Tc + blue	(4) SLNs	NR	NR	25.0
Hartmann (2018)	P, S	30$	83.3	Wire	Tc + blue	1.6, 1-5 SLNs	35.7	If indicated	100
Balasubramanian (2020)	R, S	25	100	Wire	Tc + blue	(3), 1-5 TAD	87.0	If indicated	NR
Alarcón (2021)	P, M	28	100	Wire	Tc	2.8 ± 1.2 SLNs	80.0	If indicated	100
Flores-Funes (2021)	P, S	60	100	Wire	Tc	(1, 1-2) SLNs	53.3	NR	100
García-Novoa (2021)	P, S	42	100	Wire	Tc + blue	2.7 ± 1.5 SLNs	80.0	If indicated	26.2
Gurleyik (2021)	P, S	64	100	Wire	Blue	4.6, 2-9 TAD	82.1	NR	53.1
Sierra (2021)	P, S	51	100	Wire	Tc	1.8 SLNs	CD	NR	100
Kuemmel (2022)	P, M	423$	100	Wire	Tc ± blue	(1), 0-2 TLNs; (2), 0-10 SLNs	NR	If indicated	65.7
Acea-Figueira (2023)	P, S	81	100	Wire	Tc and/or blue	2.6 ± 1.5 SLNs	78.9	NR	23.5
Sargent (2023)	R, S	62	100	Wire	Tc ± blue	NR	NR	NR	43.5
Wu (2023)	P, S	239	100	Wire	Tc and/or blue	NR	NR	If indicated	63.6
Munck (2023)	R, M	543	100	Wire (263), ^{125}I seed (103), ink on skin (62), magnetic marker (3)	Tc + blue	(2) SLNs	77.9	NR	NR
Caudle (2016)	P, S	96	100	^{125}I seed (94), wire (2)	Tc and/or blue	NR	NR	If indicated	88.5
Diego (2016)	R, S	30	100	^{125}I seed	Tc + blue	(4), 1-11 TAD	91.0	If indicated	23.3
Nguyen (2017)	R, S	25	100	^{125}I seed	NR	NR	NR	NR	NR
Beniey (2021)	R, S	35	100	^{125}I seed	Tc + blue	NR	NR	Routinely	51.4
Simons (2019)	R, M	138**	100	^{125}I seed (80), wire (58)	Tc ± blue	2.6 (2, 1-3), 1-9 TAD	65.0	If indicated	22.3
Aragón-Sánchez (2022)	P, S	32	100	^{125}I seed	Tc + blue	3.9 ± 2.2 (3 ,3-4) SLNs	74.2	If indicated	100

Supplementary Table 1. Continued

First author (publication year)	Study design	Sample size*	PA-proven cN+ (%)	Type of definitive marker	Tracer for SLNB	Lymph nodes excised (SLN/TLN/TAD) Mean ± SD (median, IQR), range	Concordance TLN=SLN (%)	IHC	ALND (%)
Rebollo Aguirre (2022)	R, S	50$^{\$,**}$	100	^{125}I seed	Tc	1.7 ± 0.8 SLNs	61.9	Routinely	64.0
Simons (2022)	P, M	238	100	^{125}I seed	Tc and/or blue	1.8 ± 1.1 (2), 1-8 TAD	71.3	If indicated	92.4
Weiss (2022)	P, S	78	100	^{125}I seed	Tc and/or blue	(4), 1-9 TAD	83.3	Routinely	CD
Clark (2023)	R, S	77$^{\$}$	100	^{125}I seed	NR	NR	NR	If indicated	40.3
Munck (2023)	R, M	142	100	^{125}I seed	Tc + blue	(2), 0-7 SLNs	72.3	NR	59.2
Fuertes Manuel (2022)	P, S	30	100	^{99m}Tc	Tc	2.0, 1-5 SLNs; 2.8, 1-5 TAD	50.0	NR	76.7
del Castillo (2023)	R, S	54	100	^{99m}Tc	Tc + blue	(2, 1-3), 0-4 SLNs	NR	NR	36.3
Rella (2023)	P, S	77	100	^{99m}Tc	Blue	2.6, 1-7 SLNs	77.3	If indicated	84.4
Winder (2022)	R, S	38	100	^{99m}Tc	Tc + blue	(5), 1-14 TAD	55.3	Routinely	52.6
Dilege (2023)	P, S	61	100	^{99m}Tc	Tc and/or blue	2.5, 1-6 SLNs	88.5	Routinely	67.2
Laws (2020)	R, S	56	100	RFID tag (43), magnetic marker (12), electromagnetic reflector (1)	Tc + blue	(3), 1-11 TAD	NR	NR	37.5
Sun (2020)	R, S	45	100	Electromagnetic reflector	Tc + blue	(1), 1-4 TLNs; (2.5), 0-9 SLNs	80.0	NR	22.2
Balija (2021)	R, S	99$^{\$}$	97.0	Electromagnetic reflector (57), wire (42)	Tc + blue	(3 and 4, respectively) SLNs	NR	NR	52.5
Weinfurtner (2022)	R, S	105$^{\$}$	91.2	Electromagnetic reflector	NR	(3) TAD	83.5	NR	32.8
Taj (2023)	R, S	80	100	Electromagnetic reflector	Tc + blue	NR	NR	NR	NR
Mariscal Martínez (2021)	P, S	30	100	Magnetic marker	Tc	1.2, 0-2 SLNs	50.0	NR	100
Reitsamer (2021)	P, S	40	100	Magnetic marker	Tc	(1, 1-1) TLNs; (1, 1-2) SLNs	65.0	NR	NR

Supplementary Table 1. Continued

First author (publication year)	Study design	Sample size*	PA-proven cN+ (%)	Type of definitive marker	Tracer for SLNB	Lymph nodes excised (SLN/TLN/TAD) Mean ± SD (median, IQR), range	Concordance TLN=SLN (%)	IHC	ALND (%)
Simons (2021)	P, S	50	100	Magnetic marker	Tc ± blue	1.3 (1), 1-6 TAD	80.0	NR	60.0
Martínez (2022)	P, M	81**	100	Magnetic marker	NR	1.5 ± 1.2 (1, 1-1) TAD	81.5	NR	92.6
Barry (2023)	R, S	128**	98.4	Magnetic marker	Tc and/or blue	(2, 2-3) SLNs	54.7	NR	28.9
Kim (2019)	P, S	28	100	Charcoal	Tc + blue	5, 2-14 TAD	62.5	NR	28.6
Patel (2019)	P, S	47	78.7	Carbon ink	Tc and/or blue	3.1, 1-7 SLNs; 1.0, 1-2 TLNs	100	NR	25.5
Natsiopoulos (2019)	R, S	75	85.3	Carbon ink	Tc + blue	(4), 1-10 SLNs; (4), 2-10 TAD	75.7	If indicated	38.6
Allweis (2020)	P, M	63[$]	100	Carbon ink	Tc	(4), 1-8 TAD	80.0	NR	NR
Dostalek (2021)	R, S	27	100	Carbon ink	Tc	4.1 ± 3.3 TAD	54.5	If indicated	44.4
de Boniface (2022)	P, M	149[$]	NR	Carbon ink	Tc and/or blue	NR	47.9	If indicated	100
Pinto (2022)	P, S	31**	100	Carbon ink	Tc + blue	3.2 TAD	88.9	NR	100
Porpiglia (2023)	R, S	32	98.1	Carbon ink	Tc and/or blue	4, 1-7 SLNs	71.8	NR	46.8
Spautz (2020)	P, M	123	60.1	4% CMS	Blue	2.3, 1-9 TAD	62.6	NR	CD
Pinto (2022)	P, S	37	100	Clip (IOUS)	ICG + blue	(3), 1-5 SLNs	100	NR	43.2
Siso (2023)	P, S	235	100	Clip (IOUS)	Tc ± blue	(3), 1-14 TAD	75.0	If indicated	71.9

ICG, indocyanine green; IQR, interquartile range; M, multicentre; P, prospective; PA, pathologically; R, retrospective; S, single centre; SD, standard deviation.
* The sample size was based on the number of patients in whom an attempt was made to localise the TLN.
** In these studies, both a one-step and a two-step procedure was assessed.
[$] If an ALND was performed directly after NST (with localisation of the TLN), the SLNB was omitted.

Supplementary Table 2. Quality assessment including risk of bias

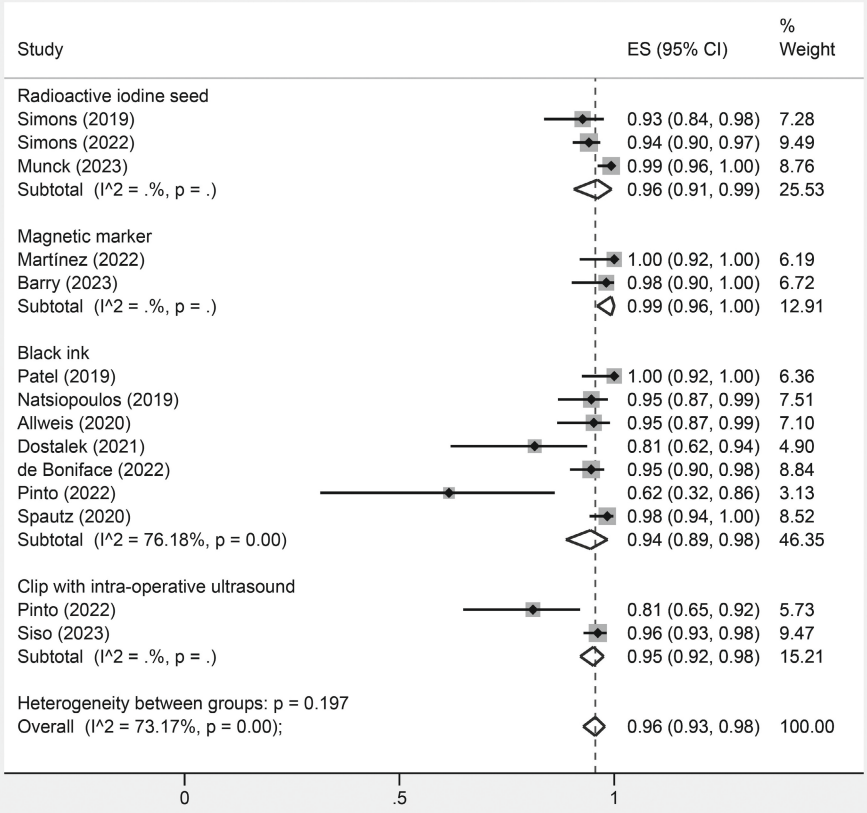
Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality rate
Acea-Figueira et al.[38]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	N	Fair
Alarcón et al.[33]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	N	Fair
Allweis et al.[81]	Y	Y	NR	CD	N	Y	NA	NA	Y	NA	N	NA	NA	N	Poor
Aragón-Sánchez et al.[47]	Y	Y	Y	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Good
Balasubramanian et al.[82]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	N	NA	NA	N	Fair
Balija et al.[43]	Y	Y	NA	Y	N	Y	NA	NA	N	NA	Y	NA	NA	N	Fair
Barry et al.[61]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Beniey et al.[46]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Caudle et al.[83]	Y	Y	NR	Y	N	Y	NA	NA	N	NA	Y	NA	NA	Y	Fair
Clark et al.[50]	Y	N	NA	Y	N	Y	NA	NA	N	NA	N	NA	NR	Y	Poor
Dashevsky et al.[31]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
de Boniface et al.[69]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
del Castillo et al.[53]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	N	NA	NA	N	Fair
Diego et al.[84]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Dilege et al.[56]	Y	Y	Y	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Good
Dostalek et al.[68]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Flores-Funes et al.[34]	Y	Y	NR	Y	Y	Y	NA	NA	Y	NA	Y	NA	NA	N	Good
Fuertes Manuel et al.[52]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
García-Novoa et al.[85]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	N	Fair
Gurleyik et al.[36]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Hartmann et al.[86]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Kim et al.[87]	Y	Y	NR	Y	N	Y	NA	NA	N	NA	N	NA	NA	N	Poor
Kuemmel et al.[19]	Y	Y	Y	Y	N	Y	NA	NA	N	NA	Y	NA	NA	Y	Good
Laws et al.[88]	Y	Y	NA	Y	N	Y	NA	NA	N	NA	Y	NA	NA	N	Fair
Mariscal Martínez et al.[58]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Martínez et al.[60]	Y	Y	Y	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	N	Good
Munck et al.[51]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Munck et al.[41]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Natsiopoulos et al.[89]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Nguyen et al.[90]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Patel et al.[66]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	N	NA	NA	N	Fair
Pinto et al.[70]	Y	Y	Y	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Good
Pinto et al.[73]	Y	Y	NR	Y	N	Y	NA	NA	N	NA	Y	NA	NA	N	Fair
Plecha et al.[91]	Y	Y	NA	Y	N	Y	NA	NA	N	NA	Y	NA	NA	N	Fair
Porpiglia et al.[71]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Rebollo Aguirre et al.[48]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	N	NA	NA	N	Fair

Supplementary Table 2. Continued

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality rate
Reitsamer et al.[25]	Y	Y	NR	N	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Rella et al.[54]	Y	N	Y	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Sargent et al.[39]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	N	Fair
Sierra et al.[37]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Simons et al.[6]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Simons et al.[21]	Y	Y	NR	Y	Y	Y	NA	NA	Y	NA	Y	NA	NA	N	Good
Simons et al.[59]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Siso et al.[74]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NR	Y	Good
Spautz et al.[92]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Sun et al.[93]	Y	Y	NA	Y	N	Y	NA	NA	N	NA	Y	NA	NR	N	Fair
Taj et al.[64]	Y	Y	NA	Y	N	Y	NA	NA	N	NA	Y	NA	NA	Y	Fair
Weinfurtner et al.[63]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Weiss et al.[49]	Y	Y	NR	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Winder et al.[55]	Y	Y	NA	Y	N	Y	NA	NA	Y	NA	Y	NA	NA	N	Fair
Wu et al. [40]	Y	Y	NR	Y	N	Y	NA	NA	N	NA	Y	NA	NR	N	Fair

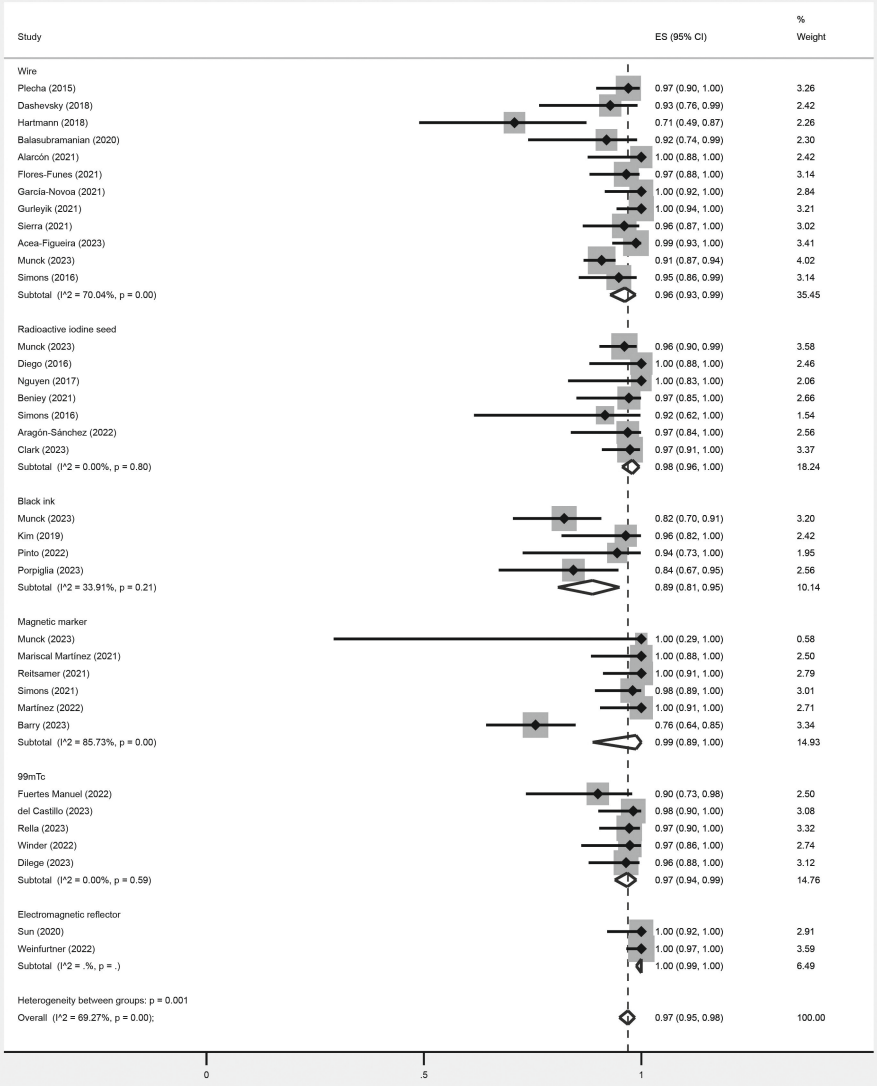
CD, cannot determine; NA, not applicable; NR, not reported; N, no; Y, yes.
The quality of the included studies was assessed with the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies.

Questions
Q1. Was the research question or objective in this paper clearly stated?
Q2. Was the study population clearly specified and defined?
Q3. Was the participation rate of eligible persons at least 50%?
Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5. Was a sample size justification, power description, or variance and effect estimates provided?
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10. Was the exposure(s) assessed more than once over time?
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12. Were the outcome assessors blinded to the exposure status of participants?
Q13. Was loss to follow-up after baseline 20% or less?
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?



Supplementary Figure 1. Forest plot of the IR for one-step procedures

ES, effect size.
Study by Rebollo Aguirre et al. was not included in the analysis, since only an overall IR (for both one- and two-step procedure) was provided.



Supplementary Figure 2. Forest plot of the IR for two-step procedures

ES, effect size.

Studies by Kuemmel et al, Wu et al, Laws et al, Sargent et al, Caudle et al, Taj et al, Rebollo Aguirre et al, Weiss et al, and Balija et al. were not included in the analysis, since no data regarding IR were provided, or only an overall IR (for both one- and two-step procedure, for multiple markers, or for both imaging and surgery).

Chapter 4

De-escalation of radiotherapy after primary chemotherapy in cT1-2N1 breast cancer (RAPCHEM; BOOG 2010-03): 5-year follow-up results of a Dutch, prospective, registry study

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Abstract

Background: Primary chemotherapy in breast cancer poses a dilemma with regard to adjuvant locoregional radiotherapy, as guidelines for locoregional radiotherapy were originally based on pathology results of primary surgery. We aimed to evaluate the oncological safety of de-escalated locoregional radiotherapy in patients with cT1-2N1 breast cancer treated with primary chemotherapy, according to a predefined, consensus-based study guideline.

Methods: In this prospective registry study (RAPCHEM, BOOG 2010-03), patients referred to one of 17 participating radiation oncology centres in the Netherlands between Jan 1, 2011, and Jan 1, 2015, with cT1-2N1 breast cancer (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one had been pathologically confirmed), and who were treated with primary chemotherapy and surgery of the breast and axilla were included in the study. The study guideline comprised three risk groups for locoregional recurrence, with corresponding locoregional radiotherapy recommendations: no chest wall radiotherapy and no regional radiotherapy in the low-risk group, only local radiotherapy in the intermediate-risk group, and locoregional radiotherapy in the high-risk group. Radiotherapy consisted of a biologically equivalent dose of 25 fractions of 2 Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was forward-planned or inverse-planned intensity modulated radiotherapy. 5-year follow-up was assessed, taking into account adherence to the study guideline, with locoregional recurrence rate as primary endpoint. We hypothesised that 5-year locoregional recurrence rate would be less than 4% (upper-limit 95%-CI 7.8%). This study was registered at ClinicalTrials.gov, NCT01279304, and is completed.

Findings: 838 patients were eligible for 5-year follow-up analyses: 291 in the low-risk group, 370 in the intermediate-risk group, and 177 in the high-risk group. The 5-year locoregional recurrence rate in all patients was 2.2% (95%-CI 1.4-3.4). The 5-year locoregional recurrence rate was 2.1% (0.9-4.3) in the low-risk group, 2.2% (1.0-4.1) in the intermediate-risk group, and 2.3% (0.8-5.5) in the high-risk group. If the study guideline was followed, the locoregional recurrence rate was 2.3% (0.8-5.3) for the low-risk group, 1.0% (0.2-3.4) for the intermediate-risk group, and 1.4% (0.3-4.5) for the high-risk group.

Interpretation: In this study, the 5-year locoregional recurrence rate was less than 4%, which supports our hypothesis that it is oncologically safe to de-escalate locoregional radiotherapy based on locoregional recurrence risk, in selected patients with cT1-2N1 breast cancer treated with primary chemotherapy, according to this predefined, consensus-based study guideline.

Introduction

Primary chemotherapy is increasingly used in patients with breast cancer. This practice challenges defining indications for adjuvant locoregional radiotherapy, as locoregional radiotherapy guidelines were originally based on studies in which patients were treated with primary surgery. Several retrospective studies have identified tumour biology,[1-6] and tumour stage before and after primary chemotherapy,[6-11] as important factors related to locoregional recurrence in patients treated with primary chemotherapy. Most guidelines now state that patients with stage III disease benefit from locoregional radiotherapy, regardless of their response to primary chemotherapy,[12-14] and that patients with cT1-2N0 disease who have a good response to primary chemotherapy do not benefit from locoregional radiotherapy.[13-15] In cT1-2N1 disease (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one has been pathologically confirmed), it is less clear when locoregional radiotherapy is indicated.[13-15] Studies have shown that locoregional radiotherapy in case of pT1-2N1a lowers locoregional recurrence rate and improves survival,[15,16] yet results also suggested that locoregional radiotherapy could be omitted in patients with an estimated low risk of locoregional recurrence. A study concluded that in case of axillary pathological complete response after primary chemotherapy (i.e., ypN0), only whole breast radiotherapy after breast conserving therapy, and no locoregional radiotherapy after mastectomy, resulted in 10-year locoregional recurrence rates of 0-12.4%, depending on age, tumour size, and primary tumour response.[11] Hence, more evidence is needed to reach a consensus about the most optimal strategy for locoregional radiotherapy in cT1-2N1 disease treated with primary chemotherapy.

We hypothesised that adjuvant locoregional radiotherapy could be de-escalated in patients with cT1-2N1 breast cancer (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one has been pathologically confirmed) treated with primary chemotherapy. Therefore, a Dutch, prospective, registry study (RAPCHEM, BOOG 2010-03) was developed to evaluate the oncological safety of de-escalated locoregional radiotherapy, according to a predefined consensus-based study guideline. Adherence to the study guideline was evaluated in a previous paper by comparing the volumes irradiated to the study guideline, along with possible explanations for observed practice variation of the participating radiation oncology centres.[17] We found that presence or absence of known risk factors was not associated with deviation from the study guideline. The aim of this study was to assess 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival, taking into account adherence to the study guideline. We hypothesised that the 5-year locoregional recurrence rate would be less than 4% if the study guideline was followed.

Methods

Study design and participants

In this prospective registry study, patients with cT1-2N1 invasive breast cancer treated with at least three cycles of primary chemotherapy and surgery of the breast and axilla were eligible if referred to one of 17 participating radiation oncology centres in the Netherlands between Jan 1, 2011, and Jan 1, 2015 (appendix 1).[17] At least one axillary lymph node had to contain a confirmed metastasis, based on a core needle biopsy or fine needle aspiration, or a sentinel lymph node biopsy (SLNB) before primary chemotherapy. Exclusion criteria were four or more suspicious lymph nodes on imaging before primary chemotherapy, distant metastases, or irradical surgery of the primary tumour. Patients were identified from the Netherlands Cancer Registry (NCR), in which they were included via an opt-out recruitment approach, and clinical data were collected from their medical files by specially trained registration clerks of the Netherlands Comprehensive Cancer Organisation. Therefore, written, informed consent was not required. The Institutional Review Board (IRB) of Maastro performed an ethics review, and both the IRB of Maastro and the Privacy Review Board of the NCR approved the study.

Procedures

Treatment was planned according to the Dutch guidelines, which consisted of 6-8 cycles of primary chemotherapy, followed by surgery of the breast and axilla. The study guideline for locoregional radiotherapy was based on the existing literature at the time of protocol development, and endorsed by the Dutch Breast Cancer Research Group. In the study guideline, based on ypN-status, patients were assigned to one of three predefined risk groups: low (i.e., ypN0), intermediate (i.e., ypN1, one to three positive nodes in surgical specimen after primary chemotherapy), or high (i.e., ypN2-3, four or more positive nodes in surgical specimen after primary chemotherapy) risk of developing a locoregional recurrence. Each risk group had its own locoregional radiotherapy recommendations (table 1). In each risk group, radiotherapy consisted of a biologically equivalent dose of 25 fractions of 2 Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was forward-planned or inverse-planned intensity modulated radiotherapy.

Until mid-2013, the vast majority of patients with node-positive (cN+) disease underwent an axillary lymph node dissection (ALND). The outcomes of ACOSOG Z0011[18] resulted in a protocol amendment on March 5, 2013, in which less invasive axillary staging procedures (i.e., SLNB before primary chemotherapy, or SLNB or MARI-procedure [marking the axilla with radioactive iodine seed],[19] or both, after primary chemotherapy) were also allowed. Decisions on type of axillary surgery were left to the discretion of the multidisciplinary team.

Table 1. Study guideline with risk groups based on locoregional recurrence risk, and locoregional radiotherapy recommendations

Risk group	Description	Radiotherapy after breast conserving surgery	Radiotherapy after mastectomy
Low	ypN0 (ALND)	Whole breast radiotherapy	-
	If SLNB before primary chemotherapy and no ALND: cN1mi (SLNB), no risk factor*; or if SLNB after primary chemotherapy and no ALND: ypN0 (SLNB)	Whole breast radiotherapy	-
Intermediate	ypN1 (ALND)	Whole breast radiotherapy	
	If SLNB before primary chemotherapy and no ALND[$]: cN1mi (SLNB), ≥1 risk factor*, or cN1 (SLNB), ≤2 macrometastases, no risk factor*; or if SLNB after primary chemotherapy and no ALND[$]: ypN1mi (SLNB), no risk factor*	Whole breast radiotherapy Axilla level I and II[$]	Chest wall radiotherapy Axilla level I and II[$]
High	ypN2-3 (ALND)	Whole breast radiotherapy Axilla level III and IV	Chest wall radiotherapy Axilla level III and IV
	If SLNB before primary chemotherapy and no ALND[$]: cN1 (SLNB), with ≤2 macrometastases and ≥1 risk factor*, or ≥3 macrometastases; or if SLNB after primary chemotherapy and no ALND[$]: ypN1mi (SLNB), ≥1 risk factor*, or ypN1 (SLNB)	Whole breast radiotherapy Axilla level III and IV Axilla level I and II[$]	Chest wall radiotherapy Axilla level III and IV Axilla level I and II[$]

* Risk factor: grade 3, lymphvascular invasion, tumour size more than 3 cm.
[$] If ALND was omitted in the intermediate or high-risk group, radiotherapy of the axilla (level I and II) was recommended. Radiotherapy of the axilla (level I and II) after ALND, and radiotherapy of the internal mammary chain were optional.

If ALND was omitted, patients were assigned to the risk groups based on the pathology outcomes of the less invasive staging procedure and other factors related to locoregional recurrence. Radiotherapy of the axilla (level I-II) was recommended if ALND was omitted in the intermediate-risk or high-risk group. Intervals between treatment modalities (i.e., primary chemotherapy, surgery, radiotherapy) were aimed to be less than 5 weeks. Follow-up was performed by physical examination and mammography, and was carried out according to the Dutch guideline (i.e., at least yearly). The primary endpoint was not centrally reviewed.

Outcomes

The primary endpoint was 5-year locoregional recurrence rate. Secondary endpoints were 10-year locoregional recurrence rate; 5-year, 10-year, and 15-year recurrence-free interval; and 5-year, 10-year, and 15-year overall survival. Since the 10-year and 15-year follow-up timepoints were not yet reached at the time of this primary analysis, these endpoints are not reported here, and only 5-year results are presented in this Article. Locoregional recurrence events comprised ipsilateral in-breast and chest wall recurrence (i.e., invasive or ductal carcinoma in situ), and ipsilateral regional recurrence (i.e., axillary, internal mammary, or periclavicular metastases). Locoregional recurrence rate was defined as time interval between primary breast cancer diagnosis and occurrence of a (pathologically confirmed) locoregional recurrence as first event, measured in days. If distant metastases occurred first, or within 90 days of the locoregional recurrence (i.e., synchronous distant metastases), the locoregional recurrence was not included in the locoregional recurrence rate. Patients were censored if they were still alive without a recurrence at last date of follow-up. Recurrence-free interval was defined as time interval between primary breast cancer diagnosis and occurrence of locoregional recurrence, distant metastases, or death from breast cancer, whichever came first, measured in days.[20] Patients were censored if death from another or unknown cause occurred as first event, or if they were still alive without an event at last date of follow-up. Overall survival was defined as time interval between primary breast cancer diagnosis until death from any cause, measured in days. Patients were censored if they were still alive at last date of follow-up.

Statistical analyses

To show with a *Z*-test that the study guideline resulted in a 5-year locoregional recurrence rate of less than 4%, with 7.8% as upper-limit of 95%-CI, 237 patients per risk group were required (one-sided α of 5%, and 80% power; n=711). Enrolment was continued until a total sample size of 848 patients was reached, as previously described.[17]

Categorical variables (e.g., age, grade, and breast cancer molecular subtype) were summarised as frequencies and percentages, and Chi^2 test or Fisher's exact test was conducted to compare the risk groups. 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival were assessed for the whole group and per risk group. Post hoc analyses were performed to take into account adherence to the study guideline. Locoregional recurrence rate was estimated with the cumulative incidence function, treating distant metastases and death as competing risks, and Kaplan-Meier survival analyses were performed to assess recurrence-free interval and overall survival including 95%-CIs of these outcomes. Cox proportional hazards regression analyses and log-rank tests were used to compare the outcomes. To examine whether prognosis differed between patients who underwent ALND (ie, ALND group), and patients in whom ALND was omitted (i.e., no ALND group), stratified analyses of 5-year locoregional recurrence rate, 5-year recurrence-free interval, and 5-year overall survival were performed post hoc. Finally, to investigate which patient and tumour characteristics were related to recurrence-free interval (i.e., chance of developing any recurrence), post hoc multivariable analyses were performed in the ALND group. If the *p*-value was 0.2 or less in univariable analysis, variables were included in the multivariable Cox proportional hazards regression analyses. Results were reported as hazard ratios (HRs) with 95%-confidence interval (CI). In case of missing data in the patient and tumour characteristics, we first applied multiple imputation in STATA. We considered these missing values as missing at random. Multivariable analyses for locoregional recurrence rate was not performed, due to a low number of locoregional recurrences.
All tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant. All analyses were conducted in STATA (16.1). The study is registered at ClinicalTrials.gov, NCT01279304.

Results

838 patients were eligible for 5-year follow-up analyses: 291 in the low-risk group, 370 in the intermediate-risk group, and 177 in the high-risk group (figure 1). Ten patients were excluded from the 5-year follow-up analyses because their medical files were not available. Characteristics of the study population are summarised in table 2. Median age of the whole group was 49 years (interquartile range (IQR) 43-57). All patients were women. We did not collect data on race or ethnicity.

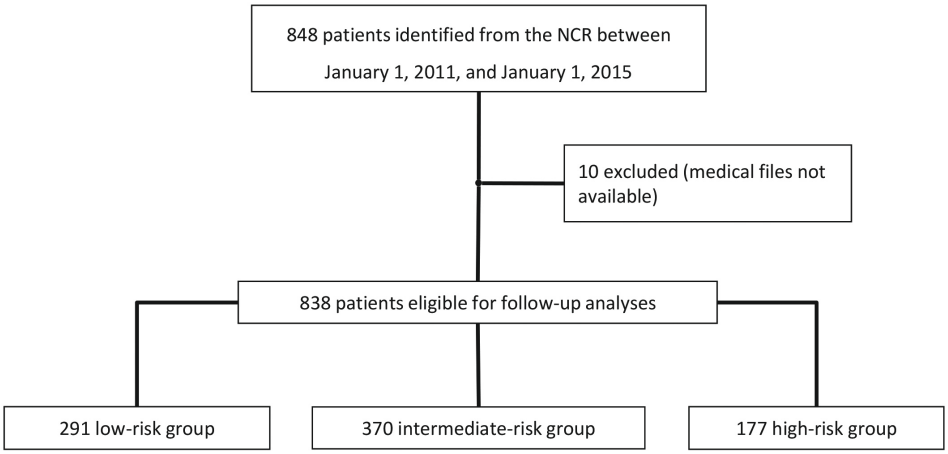

Figure 1. Study profile

In agreement with the Dutch guidelines, all patients underwent mammography and ultrasound of the breast and axilla. 732 (87%) of 838 patients also underwent breast MRI. Regarding primary chemotherapy regimens, of 838 patients, 137 (16%) were treated with anthracyclines, 59 (7%) with taxanes, and 634 (76%) with both anthracyclines and taxanes.[17] All patients received at least three cycles of primary chemotherapy, and 759 (91%) of 838 patients received at least six cycles of primary chemotherapy. 699 (83%) of 838 patients were irradiated. Radiotherapy dose was biologically equivalent to 25 fractions of 2 Gy, with or without a boost of eight fractions of 2 Gy: 90 (13%) of 699 patients received a 2 Gy fraction schedule, and all other patients (87%) received a 2.66 Gy schedule. A boost to the tumour bed was applied in 377 (54%) patients, in 50 (7%) patients a boost was delivered to the chest wall, and in 41 (6%) of 699 patients to the nodal regions. The irradiated volumes are listed in table 1. Internal mammary chain radiotherapy was given to 40 (6%) of 699 patients (ten in the low-risk group, 18 in the intermediate-risk group, and 12 in the high-risk group).

Median follow-up for disease recurrence was 5.8 years (IQR 5.2-6.4). Median follow-up with regard to vital status was 6.8 years (IQR 6.1-7.9). 43 (5%) of 838 patients were lost to follow-up before reaching 5-year follow-up, without an event reported. Of the 838 patients, 18 patients had a locoregional recurrence as first event (2%), 25 patients had a locoregional recurrence with synchronous distant metastases (3%), and 70 patients had distant metastases as first event (8%; appendix 2). 65 (8%) of 838 patients died, of whom 26 patients died of breast cancer (40%), and four patients died of another cause (6%). In 35 (54%) of 65 patients the cause of death was not recorded: 33 (94%) of these 35 patients had distant metastases (with or without locoregional recurrence), and one patient had a locoregional recurrence.

Table 2. Baseline characteristics

	Whole group n=838	Low-risk n=291	Intermediate-risk n=370	High-risk n=177	Chi² *p*-value
Age, years					
<40	101 (12%)	45 (15%)	45 (12%)	11 (6%)	**0.0053**
40-59	585 (70%)	206 (71%)	256 (69%)	123 (69%)	
≥60	152 (18%)	40 (14%)	69 (19%)	43 (24%)	
Molecular subtype					
HR+, HER2-	534 (64%)	128 (44%)	276 (75%)	139 (80%)	**<0.0001**
HR+, HER2+	108 (13%)	58 (20%)	38 (10%)	12 (7%)	
HR-, HER2+	57 (7%)	35 (12%)	18 (5%)	4 (2%)	
Triple negative	123 (15%)	69 (24%)	35 (9%)	19 (11%)	
Hormone receptor missing	7	1	3	3	
Grade					
1	123 (19%)	36 (17%)	57 (19%)	30 (20%)	**0.0035**
2	348 (53%)	92 (44%)	174 (58%)	82 (55%)	
3	185 (28%)	79 (38%)	68 (23%)	38 (25%)	
Unknown	182	84	71	27	
Lymphvascular invasion					
No	441 (81%)	145 (86%)	208 (82%)	88 (70%)	**0.0013**
Yes	106 (19%)	23 (14%)	45 (18%)	38 (30%)	
Unknown	291	123	117	51	
Initial tumour size, cm					
≤2.0	165 (20%)	46 (16%)	84 (23%)	35 (20%)	0.064
2.1-5.0	657 (80%)	242 (84%)	275 (77%)	140 (80%)	
Exact size unknown (≤5.0)	16	3	11	2	
Type of breast surgery					
Breast conserving surgery	475 (57%)	175 (60%)	214 (58%)	86 (49%)	**0.042**
Mastectomy	363 (43%)	116 (40%)	156 (42%)	91 (51%)	
Tumour size after primary chemotherapy, cm					
≤2.0	580 (72%)	229 (81%)	252 (70%)	99 (59%)	**<0.0001**
2.1-5.0	208 (26%)	47 (17%)	100 (28%)	61 (36%)	
>5.0	20 (2%)	5 (2%)	6 (2%)	9 (5%)	
Unknown	30	10	12	8	
Response of primary tumour					
No pathological complete response	542 (74%)	142 (54%)	259 (82%)	141 (91%)	**<0.0001**
Pathological complete response	191 (26%)	122 (46%)	55 (18%)	14 (9%)	
Unknown	105	27	56	22	

Table 2. Continued

	Whole group n=838	Low-risk n=291	Intermediate-risk n=370	High-risk n=177	Chi² *p*-value
Axillary surgery					
ALND	681 (81%)	234 (80%)	319 (86%)	128 (72%)	**<0.0001**
SLNB before primary chemotherapy, no ALND	90 (11%)	16 (5%)	49 (13%)	25 (14%)	
SLNB or MARI after primary chemotherapy, no ALND	67 (8%)	41 (14%)	2 (1%)	24 (14%)	
Radiotherapy					
According to study guideline	533 (64%)	181 (62%)	200 (54%)	152 (86%)	**<0.0001**[#]
Less than study guideline	90 (11%)	2 (1%)	63 (17%)	25 (14%)	
More than study guideline	214 (26%)	108 (37%)	106 (29%)	0	
Less or more than study guideline	1 (0%)	0	1 (0%)	0	

Data are n (%). All patients were women.
[#] Fisher's exact test was conducted if the expected frequency count was less than 5 for more than 20% of cells.

For the whole group (n=838), 5-year locoregional recurrence rate was 2.2% (95%-CI 1.4-3.4). 5-year locoregional recurrence rate did not significantly differ between risk groups: low-risk versus intermediate-risk group: HR 1.08 (95%-CI 0.37-3.10), *p*=0.89; low-risk versus high-risk group: 1.23 (0.35-4.36), *p*=0.75; and intermediate-risk versus high-risk group: 1.14 (0.34-3.80), *p*=0.83 (figure 2). Table 3 shows the outcomes of the performed post hoc analyses per risk group considering adherence to the study guideline. If the study guideline was followed, locoregional recurrence rate was 2.3% (95%-CI 0.8-5.3) for the low-risk group, 1.0% (0.2-3.4) for the intermediate-risk group, and 1.4% (0.3-4.5) for the high-risk group. In each risk group, less or more locoregional radiotherapy than prescribed by the study guideline did not result in significantly altered locoregional recurrence rate. 5-year locoregional recurrence rate if locoregional recurrences with synchronous distant metastases were included are shown in appendix 3.

For the whole group (n=838), 5-year recurrence-free interval was 86.4% (95%-CI 83.9-88.6), and 5-year overall survival was 92.2% (90.2-93.8). Outcomes of recurrence-free interval and overall survival per risk group are presented in figure 2, and table 3 shows the outcomes when adherence to the study guideline is considered.

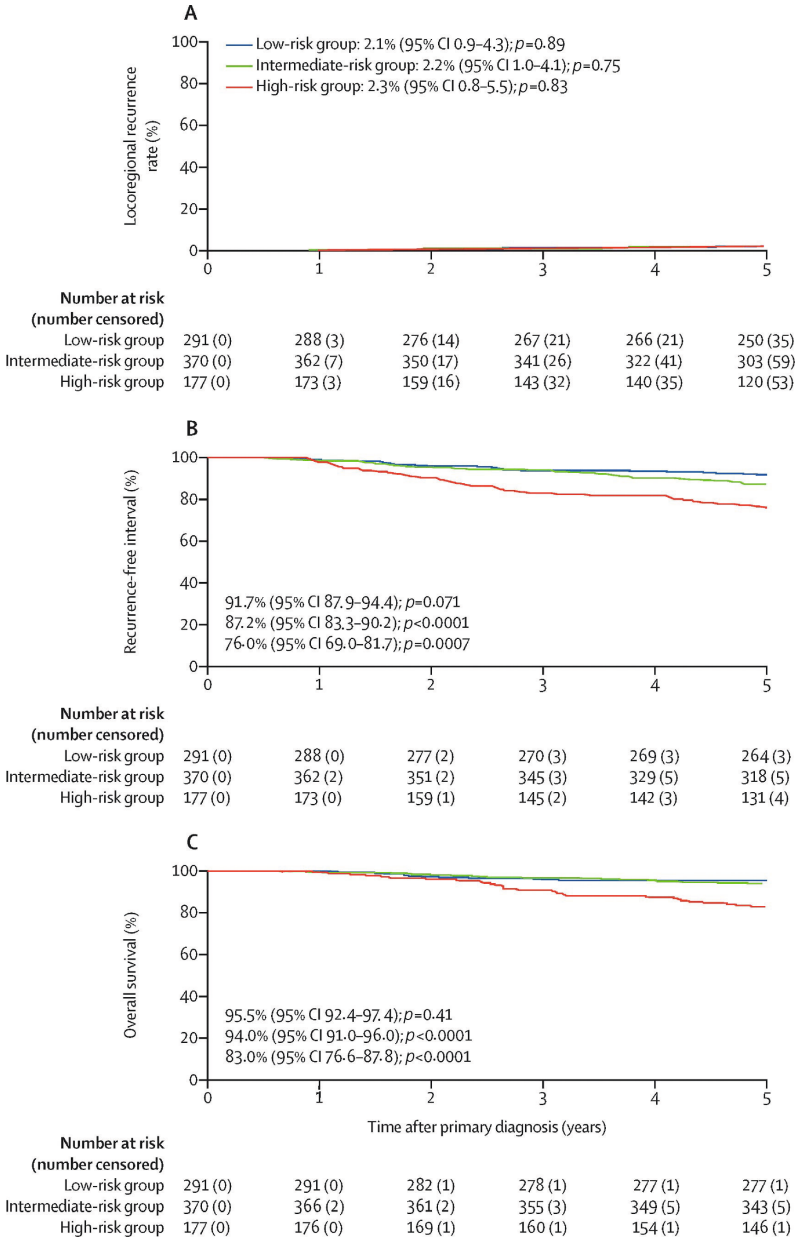

Figure 2. 5-year follow-up results per risk group

(A) 5-year locoregional recurrence (without synchronous distant metastases). (B) 5-year recurrence-free interval. (C) 5-year overall survival.

p-values at (A) were derived from Cox proportional hazards regression analyses: low-risk vs. intermediate-risk group: HR 1.08 [95%-CI 0.37-3.10], low-risk vs. high-risk group: HR 1.23 [95%-CI 0.35-4.36], and intermediate-risk vs. high-risk group: HR 1.14 [95%-CI 0.34-3.80]. *p*-values at (B) and (C) were derived from log-rank tests.

Table 3. 5-year results per risk group, taking into account adherence to the study guideline

	Locoregional recurrence rate*		Recurrence-free interval		Overall survival	
	Number of events	5-year locoregional recurrence rate (% [95%-CI])	Number of events	5-year recurrence-free interval (% [95%-CI])	Number of events	5-year overall survival (% [95%-CI])
Low-risk (n=291)	**6**	**2.1 [0.9 - 4.3]**	**24**	**91.7 [87.9 - 94.4]**	**13**	**95.5 [92.4 - 97.4]**
1. According to study guideline (n=181)	4	2.3 [0.8 - 5.3]	11	93.9 [89.2 - 96.6]	7	96.1 [92.0 - 98.1]
2. Less radiotherapy than study guideline (n=2)	0	NR	0	NR	0	NR
3. More radiotherapy than study guideline (n=108)	2	1.9 [0.4 - 6.0]	13	88.0 [80.2 - 92.8]	6	94.4 [88.1 - 97.5]
p-value						
1 vs. 3		0.86 (HR 0.9 [0.2 - 4.7])		0.076		0.50
Intermediate-risk (n=370)	**8**	**2.2 [1.0 - 4.1]**	**47**	**87.2 [83.3 - 90.2]**	**22**	**94.0 [91.0 - 96.0]**
1. According to study guideline (n=200)	2	1.0 [0.2 - 3.4]	19	90.4 [85.4 - 93.8]	10	95.0 [90.8 - 97.3]
2. Less radiotherapy than study guideline (n=63)	2	3.2 [0.6 - 9.8]	11	82.5 [70.7 - 89.9]	3	95.2 [86.0 - 98.4]
3. More radiotherapy than study guideline (n=106)	4	3.8 [1.3 - 8.8]	17	83.8 [75.2 - 89.6]	9	91.4 [84.1 - 95.4]
4. More or less radiotherapy than study guideline (n=1)	0	NR	0	NR	0	NR
p-value						
1 vs. 2		0.24 (HR 3.3 [0.5 - 23.2])		0.082		0.92
1 vs. 3		0.11 (HR 4.0 [0.7 - 21.6])		0.079		0.22
2 vs. 3		0.83 (HR 1.2 [0.2 - 6.6])		0.86		0.35
High-risk (n=177)	**4**	**2.3 [0.8 - 5.5]**	**42**	**76.0 [69.0 - 81.7]**	**30**	**83.0 [76.6 - 87.8]**
1. According to study guideline (n=152)	2	1.4 [0.3 - 4.5]	37	75.4 [67.7 - 81.5]	27	82.1 [75.0 - 87.4]
2. Less radiotherapy than study guideline (n=25)	2	8.4 [1.5 - 23.5]	5	80.0 [58.4 - 91.2]	3	88.0 [67.3 - 96.0]
p-value						
1 vs. 2		0.073 (HR 6.0 [0.9 - 42.6])		0.62		0.49

NR, not reported (due to limited data).

* Without synchronous distant metastases.

p-values were either derived from Cox proportional hazards regression analyses in case of 5-year locoregional recurrence rate, or from log-rank test in case of 5-year recurrence-free interval and overall survival.

Regarding the extent of axillary surgery, post hoc analyses were performed. 5-year locoregional recurrence rate did not differ between the ALND group and the no ALND group (appendix 4). Figure 3 illustrates the 5-year recurrence-free interval of the ALND group and the no ALND group. Overall, the ALND group had a worse recurrence-free interval (85.2%, 95%-CI 82.3-87.7) than the no ALND group (91.7%, 86.1-95.1; *p*=0.032). In the low-risk and intermediate-risk group, there was no significant difference between groups. In the high-risk group, the ALND group had a significantly worse recurrence-free interval (69.3%, 60.1-76.5) compared with the no ALND group (93.8%, 82.0-98.0; *p*=0.0010). Similar results were found for 5-year overall survival (appendix 5). Patient and tumour characteristics of patients in the high-risk group are listed in appendix 6.

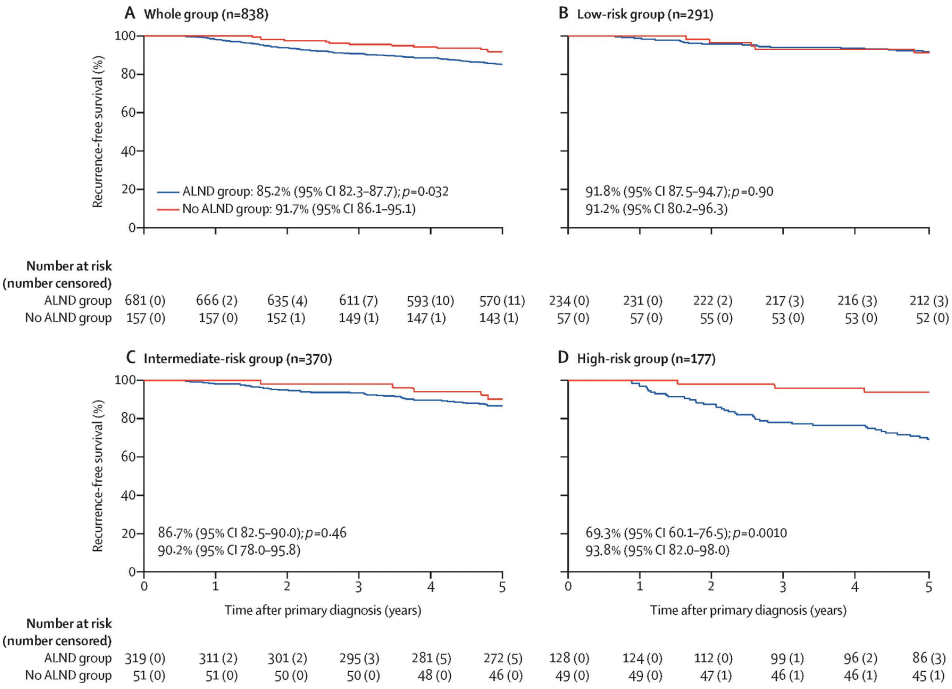

Figure 3. 5-year recurrence-free interval of ALND group versus no ALND group (post hoc analysis)
(A) All patients. (B) Low-risk group. (C) Intermediate-risk group. (D) High-risk group.
p-values were derived from log-rank tests.

The outcomes of the post hoc univariable and multivariable analyses for predictors of recurrence-free interval in the ALND group are shown in appendix 7. In multivariable analyses, risk group, triple negative disease, and grade 3 disease were significantly associated with worse recurrence-free interval. A pathological complete response of the primary tumour was significantly associated with improved recurrence-free interval. All other factors analysed were not significantly associated with worse or improved recurrence-free interval.

Discussion

In this prospective registry study of patients with cT1-2N1 breast cancer treated with primary chemotherapy, locoregional recurrence rates were less than 4% for the whole group and for each risk group, with the upper-limit of the 95%-CI not exceeding 7.8%, which is in accordance with our hypothesis.

A similar analysis was performed by Haffty and colleagues in 701 patients with cT1-4N1-2 breast cancer, who received primary chemotherapy followed by ALND and locoregional radiotherapy if indicated.[21] In their study with median follow-up of 5.9 years, 43 patients (6%) had a locoregional recurrence, which was a higher risk than we found in our study (2%). However, Haffty and colleagues also included patients with more advanced breast cancer, whereas we also included those with cN1 disease based on a positive SLNB. Moreover, locoregional recurrences with synchronous distant metastases were not included in our locoregional recurrence rate. When locoregional recurrences with synchronous distant metastases were included, locoregional recurrence rates were between 4.9% and 5.8%. Regardless of the differences between studies, Haffty and colleagues concluded that omission of locoregional radiotherapy after mastectomy, and omission of regional radiotherapy after breast conserving therapy, was not associated with worse locoregional recurrence outcomes in ypN0 disease. This is identical to our conclusions about locoregional radiotherapy in the low-risk group.

681 (81%) of 838 patients in our study population underwent ALND, providing an accurate ypN-status. When only a less invasive axillary staging procedure was performed, it became more complex to assign patients to the risk groups, as these procedures are less accurate. Therefore, in these patients, we also considered other factors related to locoregional recurrence. However, the criteria to assign patients to the risk groups might not have been entirely correct. For example, patients with ypN0 based on SLNB or MARI-procedure, or both, were assigned to the low-risk group, yet some of these patients might have had residual disease, which would have been detected by ALND; therefore, they should have been assigned to the intermediate-risk or high-risk group. Conversely, patients with limited nodal disease based on the SLNB or MARI-procedure, or both, after primary chemotherapy (i.e., ypN1mi with one or fewer risk factors, or ypN1), were assigned to the high-risk group, whereas if ALND would have been performed resulting in the same ypN-status, patients would have been assigned to the intermediate-risk group. In the high-risk group, the ALND group had a significantly worse 5-year recurrence-free interval compared with the no ALND group. This finding could be explained by the fact that the ALND group represented fewer patients achieving pathological complete response of the primary tumour, and represented patients with extensive residual axillary

disease (i.e., ypN2 or ypN3). In the no ALND group, 25 (51%) of 49 patients had no axillary surgery performed after primary chemotherapy (i.e., cN1 based on SLNB before primary chemotherapy), and 24 (49%) of 49 patients had ypN1mi or ypN1 disease after primary chemotherapy. These findings suggest that a proportion of the no ALND group had a more favourable ypN-status compared with the ALND group, which might have positively affected prognosis. Therefore, these findings must be interpreted with caution.

In patients who underwent ALND, this study guideline did not consider other factors related to locoregional recurrence, besides ypN-status. As a result, the low-risk group (ypN0) contained more patients with less favourable triple negative and HER2-positive subtypes, which is counterintuitive, but could have been expected as these subtypes are more often associated with axillary pathological complete response. The intermediate-risk group (ypN1) and high-risk group (ypN2-3) were significantly associated with worse recurrence-free interval in the multivariable analyses. Therefore, dividing patients into risk groups based on ypN-status appears a good foundation for estimating locoregional recurrence rate. However, even in multivariable analysis, triple negative disease, and grade 3 tumours were still significantly associated with worse recurrence-free interval. Therefore, these factors should also be considered when deciding if locoregional radiotherapy is indicated.

30-70% of patients with cN+ disease achieve axillary pathological complete response after primary chemotherapy.[22,23] It is hypothesised that ALND can be omitted in these patients, as axillary pathological complete response is associated with improved prognosis when compared with residual axillary disease.[24,25] Therefore, less invasive axillary surgery procedures are being implemented, in an effort to establish response-guided treatment. This approach has resulted in a decreased use of ALND,[26,27] and an increased use of axillary radiotherapy,[26] also in patients with residual axillary disease.[26] However, as data are scarce,[28] it is unclear whether omitting ALND in cN+ breast cancer is safe with regard to long-term prognosis. In a review on currently available data derived mainly from retrospective patient series,[29] an overview was provided on de-escalating axillary treatment after primary chemotherapy. The reviewed studies showed that if an ALND was omitted, very few axillary recurrences occurred in patients with cN+ disease who converted to ypN0 (based on less invasive surgery). However, the extent of radiotherapy in these studies was not clearly stated. Thus, it is unclear whether the axilla was irradiated or not. It was suggested that local radiotherapy might be omitted in selected patients with ypN0; however, while we await results from ongoing randomised controlled trials and registry-based studies, decisions on de-escalating axillary treatment should be taken with caution, especially when an ALND is omitted. Several ongoing randomised controlled trials are assessing the value of ALND and locoregional

radiotherapy in cN+ breast cancer treated with primary chemotherapy. NSABP-B51/RTOG-1304 and ATNEC include patients with axillary pathological complete response (NCT01872975 and NCT04109079), and Alliance A011202 and TAXIS include patients with residual disease (NCT01901094 and NCT03513614). All have disease-free survival as primary endpoint. In addition, MINIMAX (NCT04486495)[30] and AXSANA (NCT04373655) are registry studies that include both patients with axillary pathological complete response and those with residual disease. Together, these trials and registry studies will provide more information regarding appropriate locoregional treatment strategies for cN+ disease in terms of long-term prognosis and will help to create guidelines for patients in whom ALND is omitted.

A strength of this study was the availability of detailed data regarding locoregional radiotherapy and disease recurrences. Although radiotherapy practices vary widely in cT1-2N1 disease, and adherence to the study guideline was not mandatory, 533 (64%) of 838 patients were treated according to the study guideline. As practice variation is inherent to studies using real-world data, 108 (37%) of 291 patients in the low-risk group and 106 (29%) of 370 patients in the intermediate-risk group received more radiotherapy than prescribed by the study guideline. Remarkably, this did not seem to affect locoregional recurrence rate, recurrence-free interval, and overall survival in a statistically significant or clinically relevant way. Limitations of our study include the fact that, in each risk group, the actual sample size treated according to the study guideline was smaller than required based on the power calculation. Nevertheless, when performing the analyses in the subset of patients treated according to the study guideline, the upper limit of 95%-CI of 5-year locoregional recurrence rate did not exceed 7.8%. These findings support the oncological safety of the study guideline and will likely contribute to more uniform radiotherapy practices. Finally, since we adapted the study based on extrapolation from ACOSOG Z0011,[18] we also included patients in whom ALND was omitted, which made the study population more heterogeneous. However, as the size of the no ALND group was small, we cannot draw any conclusions regarding these patients. Nevertheless, this study population reflects the population of daily practice, and by taking into account other factors related to locoregional recurrence if ALND is omitted, this study guideline might pave the way to safely de-escalate locoregional radiotherapy in these patients as well.

To conclude, based on the results of this study with cT1-2N1 patients treated with primary chemotherapy, it seems oncologically safe to de-escalate locoregional radiotherapy based on ypN-status following ALND. This study supports the hypothesis that locoregional radiotherapy can be omitted in selected patients in whom ALND is performed (i.e., no chest wall radiotherapy and no regional radiotherapy in case of ypN0, and no regional radiotherapy in case of ypN1). Randomised controlled trials are needed to further

evaluate the effect of de-escalation on disease-free survival and overall survival, both for patients in whom ALND is performed, and for patients in whom ALND is omitted. In the future, this approach based on response to primary chemotherapy and type of surgery might lead to locoregional radiotherapy being more often omitted, and might therefore result in less morbidity and better quality of life for patients with breast cancer who are treated with primary chemotherapy.

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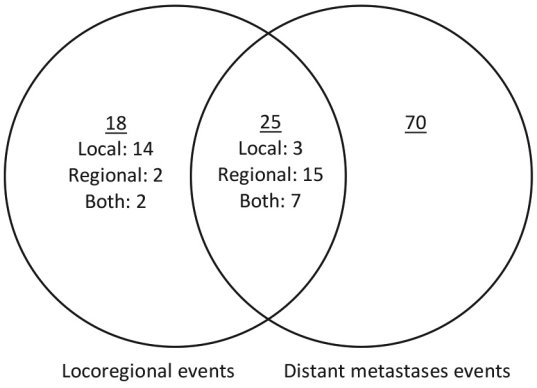
Appendix 1. Recruitment sites, the Principal Investigators, and the number of patients recruited per site

Recruitment site	Principal Investigator	Number of patients
The Netherlands Cancer Institute	P.H.M. Elkhuizen	167
Catharina Hospital	M.J.C. van der Sangen	137
Instituut Verbeeten	L.J.E.E. Scheijmans	92
Amsterdam University Medical Centres	D.H.F. Rietveld	53
Maastro	L.J. Boersma	52
Utrecht University Medical Centre	H.J.G.D. van den Bongard	43
Isala Hospital	E.M.A. Roeloffzen	40
Leiden University Medical Centre	M. van Hezewijk	36
Erasmus Medical Centre	M.H.A. Baaijens	35
Medisch Spectrum Twente	A. Jonkman	34
Radboud university medical centre	D.A.X. Schinagl	34
Radiotherapy group, Deventer	M. Stenfert Kroese	34
Radiotherapy group, Arnhem	M.R. Stam	26
Zeeland Radiotherapy Institute	B.V.A. Wachters	19
Radiation Institute Friesland	W.G.J.M. Smit	14
Haaglanden Medical Centre	M.E. Mast	13
University Medical Centre Groningen	J.H. Maduro	9



Appendix 2. Localisation of first recurrences

Appendix 3. Five-year locoregional recurrence rate, including locoregional recurrences that occurred synchronously with distant metastases

	Number of events	5-year locoregional recurrence rate (% [95%-CI])
Whole group (n=838)	**43**	**5.2 [4.9 - 6.9]**
Low-risk (n=291)	**14**	**4.9 [2.8 - 7.8]**
1. According to study guideline (n=181)	8	4.5 [2.1 - 8.3]
2. Less radiotherapy than study guideline (n=2)	0	NR
3. More radiotherapy than study guideline (n=108)	6	5.6 [2.3 - 11.1]
p-value		
1 vs. 3		0.643 (HR 1.3 [0.5 - 3.7])
Intermediate-risk (n=370)	**19**	**5.3 [3.3 - 7.9]**
1. According to study guideline (n=200)	7	3.6 [1.6 - 7.0]
2. Less radiotherapy than study guideline (n=63)	6	9.5 [3.9 - 18.3]
3. More radiotherapy than study guideline (n=106)	6	5.8 [2.4 - 11.4]
4. More or less radiotherapy than radiotherapy (n=1)	0	NR
p-value		
1 vs. 2		0.065 (HR 2.8 [0.9 - 8.3])
1 vs. 3		0.338 (HR 1.7 [0.6 – 5.1])
2 vs. 3		0.392 (HR 0.6 [0.2 – 1.9])
High-risk (n=177)	**10**	**5.8 [3.0 - 9.9]**
1. According to study guideline (n=152)	7	4.7 [2.1 - 8.9]
2. Less radiotherapy than study guideline (n=25)	3	12.6 [3.2 - 28.9]
p-value		
1 vs. 2		0.168 (HR 2.6 [0.7 - 10.0])

NR, not reported (due to limited data).
p-values were derived from Cox proportional hazards regression analyses.

Appendix 4. Five-year locoregional recurrence rate of ALND group versus no ALND group

	Number of events	5-year locoregional recurrence rate* (% [95%-CI])
Whole group (n=838)	**18**	**2.2 [1.4 - 3.4]**
1. ALND (n=681)	15	2.3 [1.3 - 3.6]
2. No ALND (n=157)	3	1.9 [0.5 - 5.0]
p-value		0.752 (HR 0.8 [0.2 - 2.8])
Low-risk (n=291)	**6**	**2.1 [0.9 - 4.3]**
1. ALND (n=234)	4	1.8 [0.6 - 4.2]
2. No ALND (n=57)	2	3.5 [0.7 - 10.7]
p-value		0.419 (HR 2.0 [0.4 - 11.0])
Intermediate-risk (n=370)	**8**	**2.2 [1.0 - 4.1]**
1. ALND (n=319)	7	2.9 [1.4 - 5.2]
2. No ALND (n=51)	1	3.9 [0.7 - 11.9]
p-value		0.865 (HR 0.8 [0.1 - 6.8])
High-risk (n=177)	**4**	**2.3 [0.8 - 5.5]**
1. ALND (n=128)	4	3.2 [1.1 - 7.4]
2. No ALND (n=49)	0	NR
p-value		NA

NA, not applicable.
* Without synchronous distant metastases.
p-values were derived from Cox proportional hazards regression analyses.

Appendix 5. Five-year overall survival of ALND-group versus no ALND-group

	Number of events	5-year overall survival (% [95%-CI])
Whole group (n=838)	**65**	**92.2 [90.2 - 93.8]**
1. ALND (n=681)	61	91.0 [88.6 - 92.9]
2. No ALND (n=157)	4	97.4 [93.3 - 99.0]
p-value		**0.0076**
Low-risk (n=291)	**13**	**95.5 [92.4 - 97.4]**
1. ALND (n=234)	12	94.9 [91.1 - 97.0]
2. No ALND (n=57)	1	98.3 [88.2 - 99.8]
p-value		0.2711
Intermediate-risk (n=370)	**22**	**94.0 [91.0 - 96.0]**
1. ALND (n=319)	21	93.4 [90.0 - 95.6]
2. No ALND (n=51)	1	98.0 [86.9 - 99.7]
p-value		0.1952
High-risk (n=177)	**30**	**83.0 [76.6 - 87.8]**
1. ALND (n=128)	28	78.1 [69.9 - 84.3]
2. No ALND (n=49)	2	95.9 [84.5 - 99.0]
p-value		**0.0068**

p-values were derived from log-rank test.

Appendix 6. Patient and tumour characteristics of the high-risk group

	ALND n=128	No ALND n=49	Chi² *p*-value
Age, years			
<40	7 (5.5%)	4 (8.2%)	0.647
40-59	88 (68.8%)	35 (71.4%)	
≥60	33 (25.8%)	10 (20.4%)	
Molecular subtype			
HR+, HER2-	108 (85.0%)	31 (66.0%)	**0.019**[#]
HR+, HER2+	5 (3.9%)	7 (14.9%)	
HR-, HER2+	2 (1.6%)	2 (4.3%)	
Triple negative	12 (9.5%)	7 (14.9%)	
Hormone receptor missing	1	2	
Grade			
1	23 (20.9%)	7 (17.5%)	0.117
2	64 (58.2%)	18 (45.0%)	
3	23 (20.9%)	15 (37.5%)	
Unknown	18	9	
Lymphvascular invasion			
No	60 (64.5%)	28 (84.9%)	**0.029**
Yes	33 (35.5%)	5 (15.5%)	
Unknown	35	16	
Initial tumour size, cm			
≤2.0	29 (22.8%)	6 (12.5%)	0.127
2.1-5.0	98 (77.2%)	42 (87.5%)	
Exact size unknown (≤5.0)	1	1	
Type of surgery			
Breast-conserving surgery	50 (39.1%)	36 (73.5%)	**<0.001**
Mastectomy	78 (60.9%)	13 (26.5%)	
Tumour size after primary chemotherapy, cm			
≤2.0	71 (57.3%)	28 (62.2%)	0.534
2.1-5.0	45 (36.3%)	16 (35.6%)	
>5.0	8 (6.5%)	1 (2.2%)	
Unknown	4	1	
Response of primary tumour			
No pathological complete response	106 (96.4%)	35 (77.8%)	**0.001**[#]
Pathological complete response	4 (3.6%)	10 (22.2%)	
Unknown	18	4	

Appendix 6. Continued

	ALND n=128	No ALND n=49	Chi² *p*-value
Response of the axilla**			
ypN1	0	24 (49.0%)	NR
ypN2	114 (89.1%)	0	
ypN3	14 (10.9%)	0	
Unknown[$]	0	25 (51.0%)	
Radiotherapy			
According to study guideline	121 (94.5%)	31 (63.3%)	**<0.001**
Less than study guideline	7 (5.5%)	18 (36.7%)	

Data are n (%). NR, not reported.
[#] Fisher's exact test was conducted if the expected frequency count was less than 5 for more than 20% of cells.
** ypN0 is not mentioned, as these patients were not included in the high-risk group.
[$] If no axillary surgery was performed after primary chemotherapy, ypN-status was unknown (i.e., sentinel lymph node biopsy before primary chemotherapy).

Appendix 7. Univariable and multivariable analyses: association of patient and tumour characteristics with recurrence-free interval in the ALND group

	Univariable analyses		**Multivariable analyses**	
	Hazard ratio [95%-CI]	*p*-value	Hazard ratio [95%-CI]	*p*-value
Risk group				
Low-risk (reference)				
Intermediate-risk	1.7 [1.0 - 2.9]	0.067	2.1 [1.1 - 3.7]	**0.016**
High-risk	4.3 [2.5 - 7.4]	<0.001	4.4 [2.1 - 9.4]	**<0.001**
Age, years				
<40 (reference)				
40-59	1.0 [0.6 - 1.8]	0.99		
≥60	0.8 [0.4 - 1.7]	0.56		
Molecular subtype				
HR+, HER2- (reference)				
HR+, HER2+	0.5 [0.2 - 1.2]	0.10	0.7 [0.3 - 1.9]	0.50
HR-, HER2+	1.2 [0.6 - 2.7]	0.63	1.9 [0.8 - 4.6]	0.14
Triple negative	3.0 [1.9 - 4.6]	<0.001	3.8 [2.1 - 6.7]	**<0.001**
Grade				
1 (reference)				
2	1.5 [0.7 - 3.0]	0.31	1.4 [0.7 - 2.9]	0.36
3	3.0 [1.4 - 6.0]	0.004	2.5 [1.1 - 5.7]	**0.023**
Lymphvascular invasion				
No (reference)				
Yes	1.6 [0.9 - 2.7]	0.10	1.0 [0.6 - 2.8]	0.98
Initial tumour size, cm				
≤2.0 (reference)				
2.1-5.0	1.1 [0.7 - 1.8]	0.71		
Type of surgery				
Breast-conserving surgery (reference)				
Mastectomy	1.0 [0.7 - 1.5]	0.82		
Response of primary tumour				
No pathological complete response (reference)				
Pathological complete response	0.5 [0.3 - 1.0]	0.040	0.5 [0.2 - 1.0]	**0.038**
Whole breast or chest wall radiotherapy				
No (reference)				
Yes	1.8 [1.0 - 3.3]	0.055	0.9 [0.4 - 1.7]	0.66
Radiotherapy axilla level I and II				
No (reference)				
Yes	1.9 [1.2 - 2.9]	0.004	1.0 [0.6 - 1.6]	0.85
Radiotherapy axilla level III and IV				
No (reference)				
Yes	2.2 [1.5 - 3.3]	<0.001	1.5 [0.8 - 2.6]	0.18

Chapter 5

Prognostic effect of nodal status before and after neoadjuvant chemotherapy in breast cancer: a Dutch population-based study

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Abstract

Purpose: In breast cancer, neoadjuvant chemotherapy (NAC) can downstage the nodal status, and can even result in a pathological complete response, which is associated with improved prognosis. This study aimed to determine the prognostic effect of nodal status before and after NAC.

Methods: Women with breast cancer treated with NAC were selected from the Netherlands Cancer Registry if diagnosed between 2005 and 2019, and classified based on nodal status before NAC: node-negative (cN0), or node-positive based on fine needle aspiration cytology or core needle biopsy (cN+). Subgroups were based on nodal status after NAC: absence (ypN0) or presence (ypN+) of nodal disease. Five-year overall survival (OS) was assessed with Kaplan-Meier survival analyses, also per breast cancer molecular subtype. To adjust for potential confounders, multivariable analyses were performed.

Results: A total of 6,580 patients were included in the cN0 group, and 11,878 in the cN+ group. The 5-year OS of the cN0ypN0-subgroup was statistically significant better than that of the cN+ypN0-subgroup (94.4% versus 90.1%, $p<0.0001$). In cN0 as well as cN+ disease, ypN+ had a statistically significant worse 5-year OS compared to ypN0. For hormone receptor (HR)+ human epidermal growth factor receptor 2 (HER2)-, HR+HER2+, HR-HER2+, and triple negative disease, respectively, 5-year OS in the cN0ypN+-subgroup was 89.7%, 90.4%, 73.7%, and 53.6%, and in the cN+ypN+-subgroup 84.7%, 83.2%, 61.4%, and 48.8%. In multivariable analyses, cN+ and ypN+ disease were both associated with worse OS.

Conclusion: This study suggests that both cN-status and ypN-status, and molecular subtype should be considered to further improve prognostication.

Introduction

Neoadjuvant chemotherapy (NAC) is increasingly applied in breast cancer. It enables assessment of in vivo disease response to chemotherapy, and can downsize the primary tumor, which makes breast-conserving surgery (BCS) more often feasible.[1,2] Moreover, NAC can downstage the nodal status, and can even result in a pathological complete response (pCR). In node-positive (cN+) disease, the pCR rates of the axilla vary per breast cancer molecular subtype, and can reach 74% in patients with human epidermal growth factor receptor 2 (HER2)+ breast cancer.[3-6] Traditionally, nodal status is considered an important prognostic factor. Studies have shown that this also applies for disease response to chemotherapy,[7,8] which challenges staging and treatment strategies in patients treated with NAC. Both breast pCR and nodal pCR are associated with improved survival.[7-10] Nodal-only pCR has a greater effect on survival than breast-only pCR,[9,11,12] and patients with a combined breast and nodal pCR have the most favorable prognosis.[7,8,10] Two previous studies took into account nodal status before (i.e., cN-status) as well as after (i.e., ypN-status) NAC.[10,13] Both studies concluded that ypN-status was associated with prognosis, yet only one of these studies suggested that cN-status also affected prognosis.[10] The present study was conducted to determine the prognostic effect of the cN-status and ypN-status in a Dutch population-based cohort, in terms of 5-year overall survival (OS). In addition, it was assessed whether breast cancer molecular subtype affects the prognostic significance of the nodal status.

Methods

Study design and participants

Women with invasive breast cancer treated with NAC, diagnosed between January 1, 2005, and December 31, 2019, were selected from the Netherlands Cancer Registry (NCR). Exclusion criteria were an unknown cN-status, distant metastases, no surgery of the breast or axilla, unknown timing of the sentinel lymph node biopsy (SLNB) if performed, radiotherapy (RT) before NAC, no RT after BCS, unknown ypN-status (ypNX) if axillary surgery was performed after NAC, and discrepancies within the registry with regard to the number of metastatic lymph nodes found at surgery and the nodal status (e.g., no metastases were found in the SLNB after NAC, yet the ypN-status was ypN1a(sn), suggesting residual disease).

In the study period, treatments were based on the Dutch Guidelines, with definitive treatment choices being left to the discretion of the multidisciplinary team of each institution. Indications for NAC were for example human epidermal growth factor

receptor 2 (HER2) positivity, triple negative (TN) disease, an inoperable primary tumor, an operable primary tumor yet unsuitable for BCS, and/or cN+ disease (regardless of histological subtype (e.g., lobular breast cancer)).

The NCR is a nationwide registry, hosted by the Netherlands Comprehensive Cancer Organization (IKNL),[14] in which patients are included via an opt-out approach. The NCR registers data based on notification from the Dutch Nationwide Pathology Databank (PALGA). Clinical data are gathered from the patients' medical files by specially trained registration clerks of IKNL. After approval of the Privacy Review Board of the NCR, the collected data can be used for research, as was done for this study. Written informed consent was not required.

We received the following data for each patient: year of diagnosis, age, morphological subtype, hormone receptor (HR) status, HER2 status, tumor grade, TNM status before and after NAC, type of surgery of the breast (i.e., BCS, or mastectomy), type of axillary surgery (i.e., SLNB, MARI-procedure (Marking the Axillary lymph nodes with Radioactive Iodine seeds),[15,16] Targeted Axillary Dissection (e.g., RISAS-procedure: Radioactive Iodine Seed localization in the Axilla combined with the Sentinel node procedure[17]), and/or axillary lymph node dissection (ALND)), timing of axillary surgery in case of SLNB (i.e., SLNB before or after NAC), number of (positive) lymph nodes identified at axillary surgery, adjuvant treatment (i.e., RT, and systemic therapy), and follow-up in terms of survival.

Since the Dutch Guideline of 2008, axillary ultrasound is recommended as part of the standard diagnostic work-up (in patients diagnosed prior to 2008, cN-status may have been based on physical examination alone).[18] In this study, patients were classified based on cN-status before NAC: node-negative (cN0), or cN+. A cN0 status was defined as the absence of suspicious lymph nodes on ultrasound, or a negative fine needle aspiration (FNA) or core needle biopsy (CNB). If suspicious lymph nodes were present on imaging before NAC, and axillary metastases were confirmed with FNA or CNB, this was defined as cN+.

Within these two groups, subgroups were made based on ypN-status: absence (ypN0) or presence (ypN+) of nodal disease after NAC. The presence of solely isolated tumor cells was considered ypN0. This resulted in four cNypN-subgroups: cN0ypN0, cN0ypN+, cN+ypN0, and cN+ypN+. Patients with cN0 disease in whom an SLNB was performed before NAC were not included in the analyses.

With regard to the primary tumor, a breast pCR was defined as the absence of invasive primary tumor after NAC, irrespective of whether or carcinoma in situ was present (ypT0/is).

Additionally, in the cN+ group, six subgroups were made: cN1ypN0, cN1ypN+, cN2ypN0, cN2ypN+, cN3ypN0, and cN3ypN+. Data regarding cN+ status were copied from the patients' medical files. Generally, cN+ status was defined in accordance with the AJCC staging system.[19] In more recent years, some institutions also include the number of suspicious lymph nodes when reporting cN+ status (e.g., cN1 according to the formal AJCC staging system may have been reported as cN2 in case of four or more suspicious axillary lymph nodes on imaging at diagnosis).

Outcome

The primary endpoint was 5-year OS, which was defined as time interval between primary breast cancer diagnosis and death from any cause, measured in days. To assess 5-year OS, patients were censored if they were lost to follow-up before reaching 5-year follow-up, or if they were alive at 5-year follow-up. The mortality data in the NCR were derived from the municipality registry (GBA), and were last updated on January 31, 2023.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, and Pearson's Chi^2-tests were conducted to compare the cN0 group and cN+ group. Kaplan-Meier survival analyses were performed to assess 5-year OS for the whole cohort, for the four cNypN-subgroups, and for the six cN+-subgroups. For the cNypN-subgroups, 5-year OS was additionally calculated for the breast cancer molecular subtypes (i.e., HR+HER2-, HR+HER2+, HR-HER2+, and TN disease). Log-rank tests were used to compare the survival outcomes of all subgroups. To adjust for potential confounders, multivariable analyses were performed. Clinicopathological variables were included in the multivariable Cox proportional hazards regression analyses if the *p*-value was ≤0.2 in the univariable analysis. Results were reported as hazard ratios with 95%-confidence interval (CI). In case of missing data, multiple imputation was applied. We considered these missing values as missing at random. Supplementary 5-year OS analyses were performed for the four cNypN-subgroups in patients with and without breast pCR. All tests were two-sided, and a *p*-value of <0.05 was considered statistically significant. All analyses were conducted in STATA SE16.1 (ref: StataCorp. In: College Station TSL, editor. Stata statistical software: release, vol. 16; 2020).

Results

Patient, tumor, and treatment characteristics

As shown in Figure 1, 26,322 patients were treated with NAC between January 1, 2005 and December 31, 2019, of whom 18,458 were included in the study. Median age was

50.0 years [interquartile range (IQR) 44.0-59.0]. Characteristics of the study population are summarized in Table 1.

Of the 18,458 included patients, 6,580 patients were included in the cN0 group, and 11,878 patients were included in the cN+ group. Patient, tumor and treatment characteristics of these two groups are compared in Table 1. In the cN0 group 5,337 (81.1%) patients had ypN0, and 1,243 (18.9%) patients had ypN+. In the cN+ group, 4,346 (36.6%) patients had ypN0, and 7,532 (63.4%) patients had ypN+.

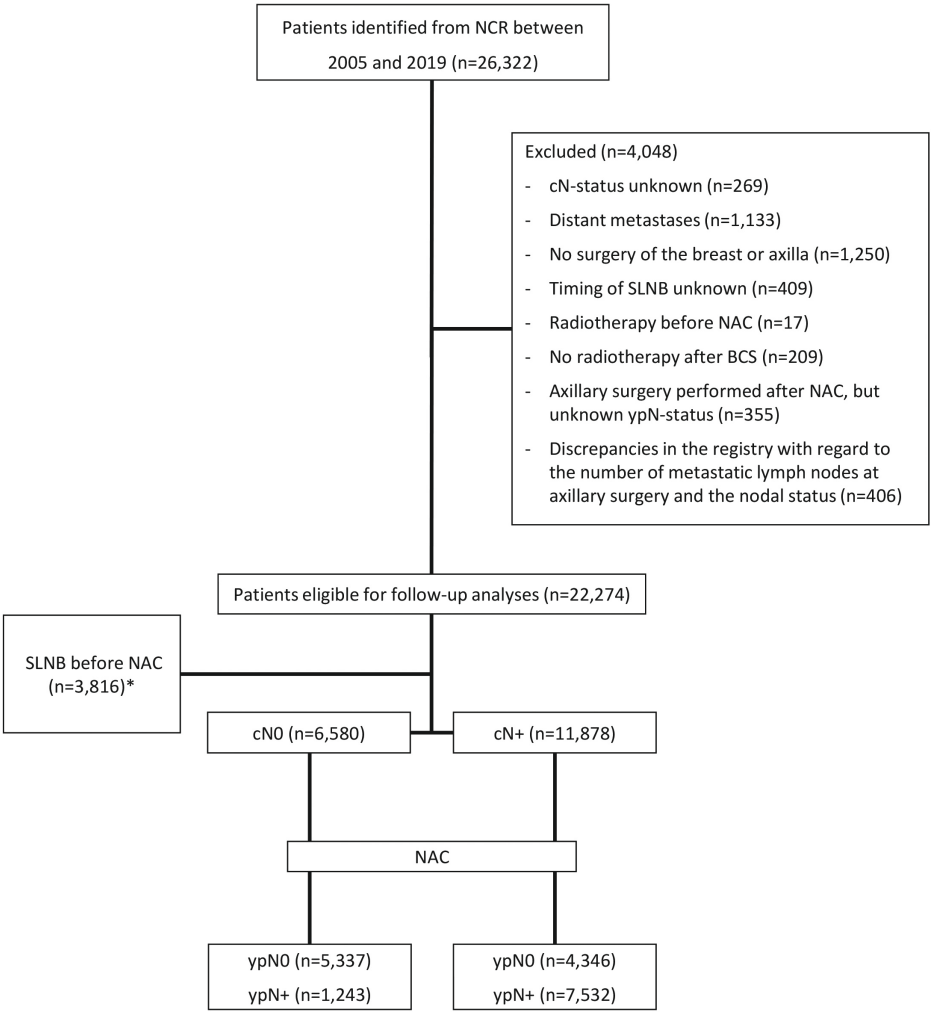


Figure 1. Consort diagram

* The percentage of patients that underwent SLNB before NAC increased from 15.8% in 2005 to 79.0% in 2012, followed by a decrease to 8.3% in 2019.

Table 1. Patient, tumor, and treatment characteristics

	Whole cohort n=18,458	cN0 group n=6,580	cN+ group n=11,878	Chi² *p*-value
Age (years), no. (%)				
<40	2,591 (14.0)	1,019 (15.6)	1,572 (13.2)	**<0.001**
40-59	11,455 (62.1)	4,110 (62.5)	7,345 (61.8)	
≥60	4,412 (23.9)	1,451 (22.1)	2,961 (24.9)	
Morphological subtype, no. (%)				
Ductal	16,055 (87.0)	5,558 (84.5)	10,497 (88.4)	**<0.001**
Lobular	1,723 (9.3)	761 (11.6)	962 (8.1)	
Mixed	414 (2.2)	154 (2.3)	260 (2.2)	
Other	266 (1.4)	107 (1.6)	159 (1.3)	
Molecular subtype, no. (%)				
HR+, HER2-	8,866 (48.8)	2,868 (44.1)	5,998 (51.4)	**<0.001**
HR+, HER2+	3,275 (18.0)	1,295 (19.9)	1,980 (17.0)	
HR-, HER2+	2,027 (11.1)	554 (8.5)	1,473 (12.6)	
Triple negative	4,012 (22.1)	1,787 (27.5)	2,225 (19.1)	
HR missing	278	76	202	
Grade, no. (%)				
1	1,061 (8.3)	435 (8.5)	626 (8.2)	**0.002**
2	6,191 (48.3)	2,379 (46.4)	3,812 (49.6)	
3	5,557 (43.4)	2,311 (45.1)	3,246 (42.2)	
Unknown	5,649	1,455	4,194	
cT-status, no. (%)				
cTX[$]	154 (0.8)	28 (0.4)	126 (1.1)	**<0.001**
cTis	17 (0.1)	2 (0.03)	15 (0.1)	
cT1	3,048 (16.5)	1,352 (20.6)	1,696 (14.3)	
cT2	9,457 (51.2)	3,819 (58.0)	5,638 (47.5)	
cT3	3,794 (20.6)	1,026 (15.6)	2,768 (23.3)	
cT4	1,988 (10.8)	353 (5.4)	1,635 (13.8)	
Breast surgery, no. (%)				
Breast-conserving surgery	8,294 (44.9)	3,569 (54.2)	4,725 (39.8)	**<0.001**
Mastectomy	10,164 (55.1)	3,011 (45.8)	7,153 (60.2)	
ypT-status, no. (%)				
ypTis	739 (4.2)	267 (4.2)	472 (4.2)	**<0.001**
ypT0	4,870 (27.4)	1,911 (30.0)	2,959 (26.0)	
ypT1	6,832 (38.5)	2,559 (40.1)	4,264 (37.5)	
ypT2	3,725 (21.0)	1,231 (19.3)	2,494 (21.9)	
ypT3	1,268 (7.1)	343 (5.3)	925 (8.1)	
ypT4	325 (1.8)	69 (0.01)	256 (2.3)	
Unknown	708	200	508	

Table 1. Continued

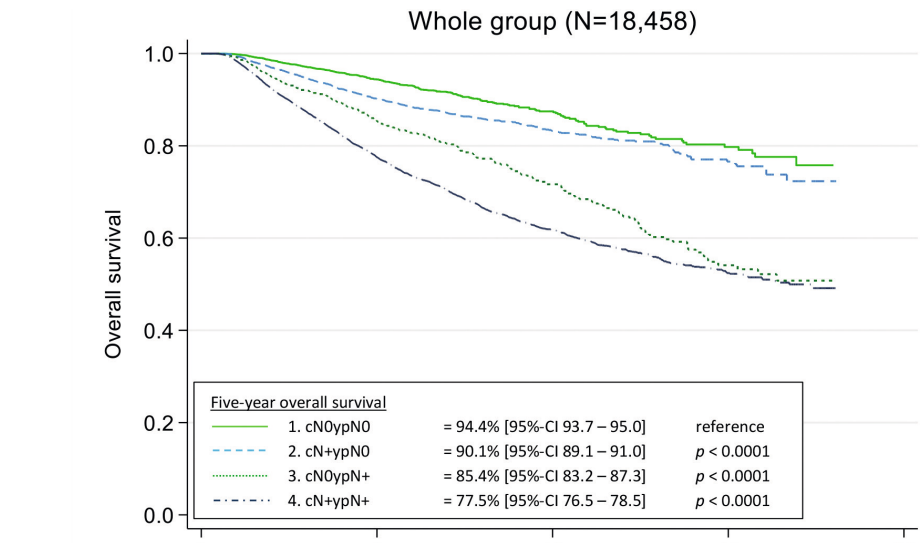
	Whole cohort n=18,458	cN0 group n=6,580	cN+ group n=11,878	Chi² *p*-value
Axillary lymph node dissection, no. (%)				
No	9,531 (51.6)	5,613 (85.3)	3,792 (31.9)	**<0.001**
Yes#	8,927 (48.4)	967 (14.7)	8,086 (68.1)	
ypN-status, no. (%)				
ypN0	9,683 (52.5)	5,337 (81.1)	4,346 (36.6)	**<0.001**
ypN+	8,775 (47.5)	1,243 (18.9)	7,532 (63.4)	
Targeted therapy, no. (%)				
No	12,975 (70.3)	4,637 (70.5)	8,338 (70.2)	0.696
Yes	5,483 (29.7)	1,943 (29.5)	3,540 (29.8)	
Hormonal therapy, no. (%)				
No	6,833 (37.0)	2,654 (40.3)	4,179 (35.2)	**<0.001**
Yes	11,625 (63.0)	3,926 (59.7)	7,699 (64.8)	
Radiotherapy, no. (%)				
No	2,702 (14.6)	1,655 (25.2)	1,047 (8.8)	**<0.001**
Yes	15,756 (85.4)	4,925 (74.9)	10,831 (91.2)	

$ Primary tumor size could not be assessed, or no evidence of primary tumor (i.e., occult breast cancer).
# Of whom 126 patients did not undergo formal axillary lymph node dissection: 15 and 111 patients, respectively, in the cN0 and cN+ group.

Five-year follow-up results in the whole cohort

Median follow-up was 5.6 years [IQR 4.0-8.2; range 0.4-18.1]. Of the 18,458 patients, 5,302 patients (28.7%) did not reach 5-year follow-up, without an event reported. Of these 5,302 patients, 5,224 patients (98.5%) were diagnosed in 2018-2019.

In total, 3,658 (19.8%) of 18,458 patients died, of whom 2,438 within five year after diagnosis. For the whole cohort, 5-year OS was 87.2% [95%-CI 85.2-86.2]. Five-year OS was 92.6% [95%-CI 91.9-93.2] for cN0 disease, and 82.1% [95%-CI 81.4-82.8] for cN+ disease, irrespective of ypN-status. Five-year OS was 92.4% [95%-CI 91.8-93.0] for ypN0, and 78.6% [95%-CI 77.7-79.5] for ypN+, irrespective of cN-status. Five-year OS per cNypN-subgroup is presented in Figure 2, and *p*-values for all subgroup comparisons are provided in Online Resource 1.



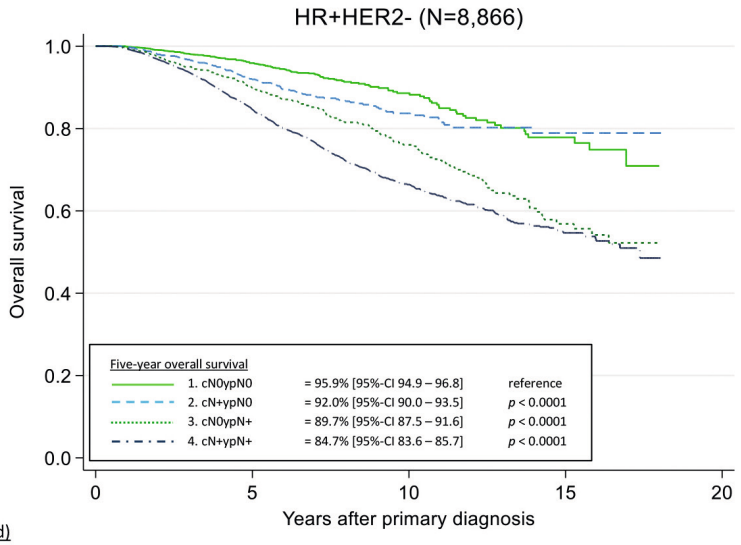
Number at risk (number censored)				
cN0ypN0	5,337 (0)	2 768 (2,304)	455 (4,517)	139 (4,804)
cN+ypN0	4,346 (0)	2 752 (1,193)	793 (3,023)	164 (3,620)
cN0ypN+	1,243 (0)	769 (305)	257 (739)	68 (886)
cN+ypN+	7,532 (0)	4 429 (1,500)	1 499 (3,792)	338 (4,804)

Figure 2. Overall survival per cNypN-subgroup

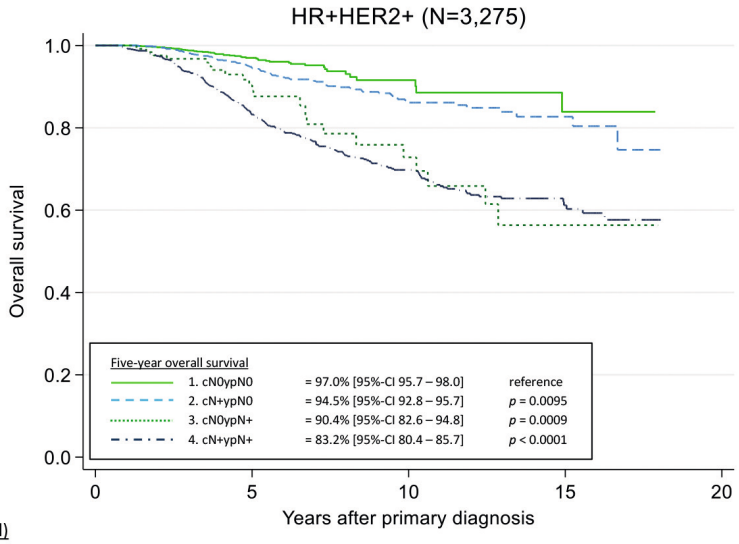
p-values for all subgroup comparisons are provided in Online Resource 1.

The cN0ypN0-subgroup had a statistically significant better 5-year OS compared to the other subgroups. Within each cN-group, ypN+ disease resulted in a statistically significant worse 5-year OS compared to ypN0. When taking into account breast cancer molecular subtype, findings were consistent, as illustrated in Figure 3. Online Resource 1 provides *p*-values for all subgroup comparisons. For HR+HER2-, HR+HER2+, HR-HER2+, and TN disease, respectively, 5-year OS in the cN0ypN0-subgroup was 95.9%, 97.0%, 95.7%, and 90.6%; in the cN+ypN0-subgroup 92.0%, 94.5%, 89.7%, and 84.4%; in the cN0ypN+-subgroup 89.7%, 90.4%, 73.7%, and 53.6%; and in the cN+ypN+-subgroup 84.7%, 83.2%, 61.4%, and 48.8%.

When specified for patients with and without breast pCR, findings were consistent, as illustrated in Online Resource 2. Patients with breast pCR had a better 5-year OS compared to those who did not achieve breast pCR. Online Resource 1 provides *p*-values for all subgroup comparisons.

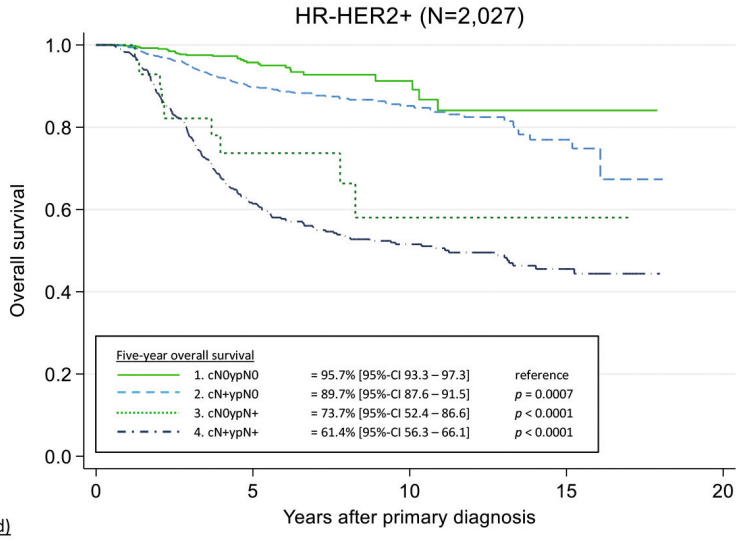


Number at risk (number censored)				
cN0ypN0	1,929 (0)	1,178 (681)	237 (1,573)	67 (1,722)
cN+ypN0	1,051 (0)	703 (271)	183 (751)	46 (881)
cN0ypN+	939 (0)	627 (223)	206 (584)	51 (705)
cN+ypN+	4,947 (0)	3,134 (1,112)	928 (2,856)	163 (3,521)

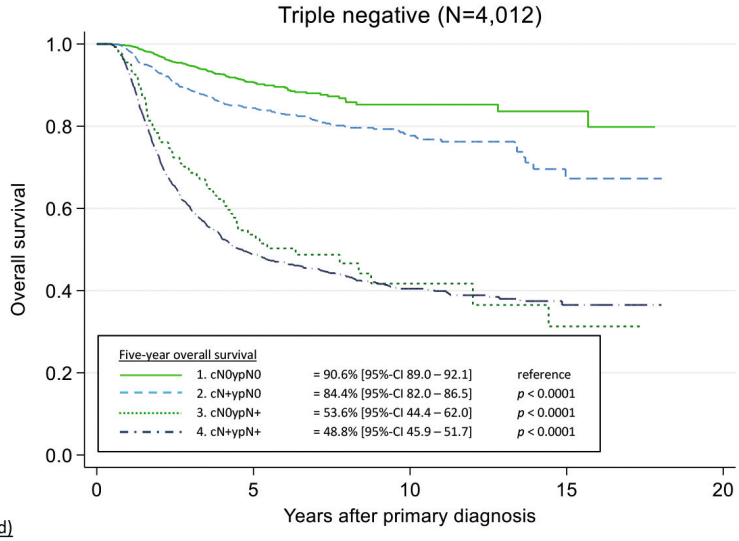


Number at risk (number censored)				
cN0ypN0	1,171 (0)	582 (559)	64 (1,063)	16 (1,108)
cN+ypN0	1,115 (0)	731 (329)	205 (817)	39 (979)
cN0ypN+	124 (0)	66 (48)	22 (84)	6 (96)
cN+ypN+	865 (0)	545 (187)	246 (279)	71 (431)

Figure 3. Overall survival per cNypN-subgroup, specified per breast cancer molecular subtype
p-values for all subgroup comparisons are provided in Online Resource 1.



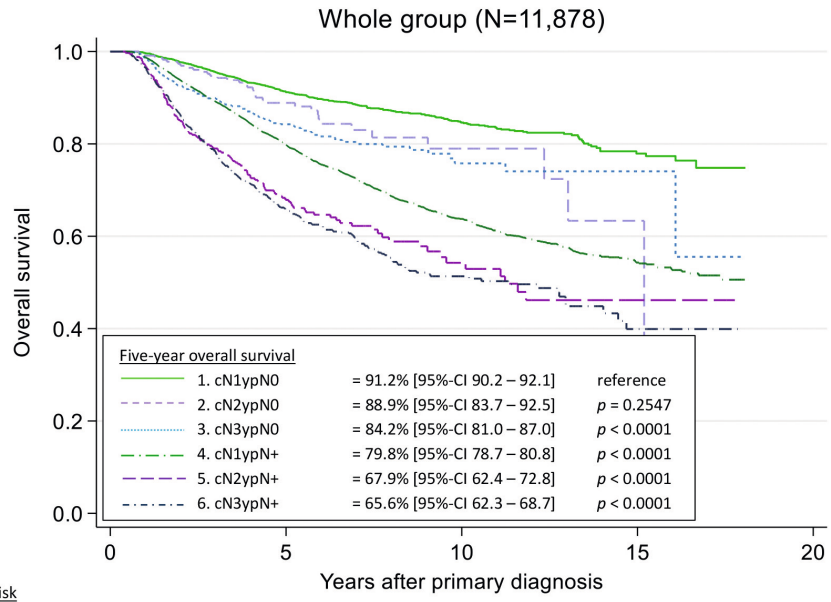
Number at risk (number censored)				
cN0ypN0	526 (0)	281 (226)	43 (457)	17 (480)
cN+ypN0	1,075 (0)	679 (293)	188 (764)	36 (906)
cN0ypN+	28 (0)	13 (8)	7 (12)	4 (15)
cN+ypN+	398 (0)	210 (39)	112 (108)	44 (166)



Number at risk (number censored)				
cN0ypN0	1,653 (0)	691 (825)	96 (1 400)	31 (1,464)
cN+ypN0	1,042 (0)	589 (297)	179 (678)	29 (819)
cN0ypN+	134 (0)	50 (25)	13 (55)	5 (61)
cN+ypN+	1,183 (0)	436 (155)	153 (385)	36 (493)

Five-year follow-up results in cN+-subgroups

In the cN1 group, 3,516 (35.9%) patients had ypN0, and 6,281 (64.1%) of 9,797 patients had ypN+; in the cN2 group, 227 (40.1%) patients had ypN0, and 339 (59.9%) of 566 patients had ypN+; in the cN3 group, 603 (39.8%) patients had ypN0, and 912 (60.2%) of 1,515 patients had ypN+. Figure 4 shows the 5-year OS per cN+-subgroup, and *p*-values for all subgroup comparisons are listed in Online Resource 3. The cN1ypN0-subgroup had a statistically significant better 5-year OS (91.2%, 95%-CI 90.2-92.1) compared to the cN3ypN0-subgroup (84.2%, 95%-CI 81.0-87.0, $p<0.0001$). All ypN0-subgroups had better 5-year OS compared to those with ypN+. The cN1ypN+-subgroup had a statistically significant better 5-year OS (79.8%, 95%-CI 78.7-80.8) compared to the cN2ypN+ and cN3ypN+-subgroup (67.9%, 95%-CI 62.4-72.8, and 65.6%, 95%-CI 62.3-68.7, respectively, both $p<0.0001$).



Number at risk
(number censored)

cN1ypN0	3,516 (0)	2,297 (931)	708 (2,417)	156 (2,940)
cN2ypN0	227 (0)	124 (80)	23 (173)	2 (192)
cN3ypN0	603 (0)	331 (182)	62 (433)	6 (488)
cN1ypN+	6,281 (0)	3,840 (1,240)	1,355 (3,169)	306 (4,085)
cN2ypN+	339 (0)	158 (78)	42 (175)	13 (199)
cN3ypN+	912 (0)	431 (182)	102 (448)	19 (520)

Figure 4. Overall survival per cN+-subgroup

p-values for all subgroup comparisons are provided in Online Resource 3.

Clinicopathological variables associated with OS

Multiple imputation was performed for tumor grade and breast cancer molecular subtype. All variables were included in the multivariable Cox proportional hazards regression analyses. The outcomes of the univariable and multivariable analyses in the whole cohort are listed in Table 2. Regarding nodal status, both cN+ (cN1, cN2 and cN3) and ypN+ disease were associated with worse OS. Apart from this, age>60, HR-HER2+ and TN disease, grade 2 and 3 disease, cT3-4 disease, presence of invasive primary tumor after NAC (i.e., ypT+ disease), and mastectomy were associated with worse OS.

Table 2. Univariable and multivariable analyses: association of patient, tumor, and treatment characteristics with overall survival

	Univariable analyses		**Multivariable analyses**	
	Hazard ratio [95%-CI]	*p*-value	Hazard ratio [95%-CI]	*p*-value
Age (years)				
<40 (reference)				
40-59	0.9 [0.8 - 1.0]	0.085	1.0 [0.9 - 1.1]	0.659
≥60	1.4 [1.2 - 1.6]	<0.001	1.3 [1.1 - 1.5]	**<0.001**
Molecular subtype				
HR+, HER2- (reference)				
HR+, HER2+	0.7 [0.6 - 0.8]	<0.001	1.0 [0.9 - 1.2]	0.935
HR-, HER2+	1.4 [1.2 - 1.6]	<0.001	2.0 [1.7 - 2.4]	**<0.001**
Triple negative	2.6 [2.4 - 2.8]	<0.001	3.4 [3.0 - 3.8]	**<0.001**
Grade				
1 (reference)				
2	1.5 [1.1 - 1.9]	0.003	1.5 [1.1 - 1.9]	**0.005**
3	3.1 [2.4 - 4.1]	<0.001	2.7 [2.0 - 3.6]	**<0.001**
cT-status				
cT1-2 (reference)				
cT3-4	2.4 [2.2 - 2.6]	<0.001	1.6 [1.4 - 1.8]	**<0.001**
cN-status				
cN0 (reference)				
cN1	2.3 [2.1 - 2.6]	<0.001	1.4 [1.3 - 1.6]	**<0.001**
cN2	3.7 [3.0 - 4.5]	<0.001	2.0 [1.6 - 2.5]	**<0.001**
cN3	4.3 [3.7 - 4.9]	<0.001	2.1 [1.8 - 2.5]	**<0.001**
Breast surgery				
Breast-conserving surgery (reference)				
Mastectomy	2.5 [2.2 - 2.7]	<0.001	1.7 [1.8 - 2.5]	**<0.001**
ypT-status				
ypT0/is (reference)				
ypT+	2.3 [2.0 - 2.6]	<0.001	2.2 [1.9 - 2.5]	**<0.001**

Table 2. Continued

	Univariable analyses		Multivariable analyses	
	Hazard ratio [95%-CI]	*p*-value	Hazard ratio [95%-CI]	*p*-value
ypN-status				
ypN0 (reference)				
ypN+	3.0 [2.8 - 3.3]	<0.001	2.6 [2.3 - 2.9]	**<0.001**

ypT0/is (or breast pCR), absence of invasive primary tumor, irrespective of whether or not in situ carcinoma was present; ypT+ (or no breast pCR), presence of invasive primary tumour.
One hundred and seventy-one patients were excluded from these analyses since they had cTX or cTis disease at diagnosis, and 683 patients were excluded since they had an unknown ypT-status.

Discussion

In this Dutch population-based cohort study of 18,458 patients with invasive breast cancer and a median follow-up of 5.6 years, the nodal status before as well as after NAC was associated with OS. The cN0ypN0-subgroup had a statistically significant better 5-year OS than the cN+ypN0-subgroup, and in cN0 as well as cN+ disease, ypN+ resulted in a statistically significant worse 5-year OS compared to ypN0. These findings were consistent across all breast cancer molecular subtypes. This study suggests that, to further improve prognostication, both cN-status and ypN-status, and molecular subtype should be taken into account.

A similar analysis was performed by Zetterlund et al. in 417 patients treated with NAC, and a median follow-up of 4.0 years.[13] Patients were divided by cN-status: cN0 disease (with or without a positive SLNB before NAC), or cN+ disease. Five-year OS was 87.8% for the whole cohort, which is similar to the 5-year OS of 87.2% in our study. They presented a 5-year OS of 90.0% for cN0, and 85.5% for cN+ disease, yet the cN-status was not associated with OS. Having ypN+ disease did result in a statistically significant worse 5-year OS compared to ypN0 (83.3% versus 91.0%, p=0.0017). In a study performed by Fayanju et al. in 20,265 patients treated with NAC, and a median follow-up of 3.0 years, having ypN+ disease also resulted in a statistically significant worse 5-year OS compared to ypN0 in both patients with cN0 disease (86.0% versus 95.0%, p<0.0001), and those with cN1 disease (80.0% versus 94.0%, p<0.0001).[10] Patients with cN0 disease had a comparable prognosis to those who had cN1 disease and achieved ypT0N0. In their multivariable analyses, cN1 disease was associated with worse OS (hazard ratio of 1.5, p<0.001). In our multivariable analyses, after adjusting for ypN-status, cN+ disease was also associated with worse OS (hazard ratio of 1.4, 2.0, and 2.1 for cN1, cN2, and cN3, respectively). These results indicate that cN-status should be kept in mind, even when a patient achieves ypN0. Interestingly, in our study, the cN0ypN+-subgroup had a worse 5-year OS than the cN+ypN0-subgroup (85.4% versus

90.1%, respectively, $p<0.0001$). In cN0 disease treated with NAC, ypN+ may indicate therapy-resistant or even progressive disease. Therefore, future studies must indicate whether the Z0011 approach provides similar results when performed in the NAC setting.[20] Interestingly, ALND is also being omitted in patients with ypN+ disease.[21] However, with limited data available, it is unclear whether ALND can be safely omitted in cN+ breast cancer.

When taking into account breast cancer molecular subtype, differences between cNypN-subgroups remained. The negative effect of ypN+ on prognosis was most apparent in HR-HER2+ and TN disease, suggesting that especially in these subtypes, achieving ypN0 is of great importance to improve OS, in both cN0 and cN+ disease. Cortazar et al. also concluded that the prognostic value of ypN0 was greatest in HR-HER2+ and TN disease,[7] and in a study by Boughey et al. in 701 patients with cN+ disease treated with NAC,[22] the statistically significant effect of TN disease on OS in case of ypN+ was also present. These results indicate that patients with HR-HER2+ or TN ypN+ disease are in need for a more extensive treatment. Von Minckwitz et al. and Masuda et al. demonstrated that in case of residual invasive disease in patients with HR-HER2+ disease or TN disease, the addition of adjuvant TDM-1 or capecitabine, respectively, increased both disease-free survival and OS.[23,24] This has led to the implementation of TDM-1 and capecitabine in recent years. Since our database includes patients diagnosed until December 31, 2019, we could not evaluate the effect of TDM-1 and capecitabine in our patient cohort.
When subanalyses were performed for patients with or without breast pCR, patients with breast pCR had a better 5-year OS compared to those who did not have breast pCR, which is in accordance with previous studies.[7-10]
In the multivariable analyses, mastectomy was associated with worse OS. In a study by Lagendijk et al., the association between type of breast surgery and prognosis was already assessed thoroughly, by adjusting for several potential confounders.[25] In their cohort of patients with cT1-2N0-2 disease treated with primary surgery, BCS with whole breast RT had superior prognosis in most subgroups. However, confounding by severity and residual confounding could not be ruled out.

In patients with cN+ disease, 30%-70% achieves an ypN0,[3-6] which is associated with better prognosis when compared to ypN+.[7] Our study supports this association, since all cN+ypN0-subgroups had a better 5-year OS than the cN+ypN+-subgroups. In clinical practice, the hypothesis that patients with cN+ypN0 disease do not benefit from ALND, has resulted in the implementation of less invasive staging strategies such as the MARI-procedure and RISAS-procedure.[15-17] In the Netherlands, and also in other countries, this had led to a decreased use of ALND,[21,26-28] and a trend towards increased use of adjuvant RT.[21] Interestingly, ALND is also being omitted in patients with ypN+ disease. However, with limited data available, it is unclear whether ALND can be safely omitted in

cN+ breast cancer. Van Loevezijn et al. recently published 3-year follow-up results of the MARI-protocol, in which the ALND was omitted in 217 of 272 (80.0%) patients in a single center study, with a 3-year axillary recurrence-free survival of 98.0% (95%-CI 96.0-100.0).[29] More evidence is needed with regard to factors important for selecting patients in whom ALND can be omitted. For example, some studies suggest that the extent of residual nodal disease and its effect on OS varies per breast cancer molecular subtype.[30,31] The value of locoregional treatment with regard to improving prognosis should be investigated, especially in relation to aggressive tumor biology. Ongoing randomized controlled trials are assessing the value of ALND and/or locoregional RT in cN+ disease treated with NAC, in either patients with ypN0 disease (NSABP-B51/RTOG 1304 and ATNEC, respectively NCT01872975 and NCT04109079), or patients with ypN+ disease (Alliance A011202 and TAXIS, respectively NCT01901094 and NCT03513614). Together with registry studies such as MINIMAX and AXSANA,[32,33] these trials will provide more information with regard to appropriate locoregional treatment strategies for cN+ disease in terms of long-term prognosis, to prevent overtreatment as well as undertreatment.

Strengths of this study were its nationwide and population-based design, large sample size, and the availability of stratified survival data for all cNypN-subgroups. Limitations of our study were that various treatment strategies were used over time, and that there was no data available with regard to lymph-vascular-invasion, or the number of suspicious lymph nodes before NAC. Nowadays, the latter is sometimes used to define the cN-status (e.g., 1-3, or ≥4 suspicious lymph nodes before NAC). In some patients values were missing. Regarding grade, this constituted a substantial number of patients (approximately 30%). Therefore, in order to not discard any patient with a missing value from multivariable analysis we performed multiple imputation. Another limitation was that we did not have detailed data with regard to RT, and therefore in patients treated with RT, we could not determine whether local RT was given, or regional RT, or both. Moreover, as axillary ultrasound was not a part of the recommendations of the Dutch guidelines in the first years of this study,[18] this may have led to nodal understaging in the cN0 group, since performing physical examination alone has a sensitivity of only 30-40%.[34,35] Finally, limited data was available with regard to disease recurrence. Therefore, we could not analyze recurrence-related outcomes.

To conclude, based on the results of this Dutch population-based study with patients with invasive breast cancer treated with NAC, both the cN-status and ypN-status, as well as breast cancer molecular subtype should be considered, to allow for more precise prognostication. In cN0 as well as cN+ disease, ypN+ resulted in a statistically significant worse 5-year OS compared to ypN0. These results may help guide locoregional treatment strategies in future studies.

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Online resource 1. *p*-values of cNypN-subgroups

Groups	Figure 2	Figure 3				Online resource 2	
		HR+HER2-	HR+HER2+	HR-HER2+	TN	Breast pCR	No breast pCR
1 vs 2	<0.0001	<0.0001	0.0095	0.0001	<0.0001	<0.0001	<0.0001
1 vs 3	<0.0001	<0.0001	0.0009	<0.0001	<0.0001	<0.0001	<0.0001
1 vs 4	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
2 vs 3	<0.0001	0.0882	0.0897	0.0031	<0.0001	0.2733	0.1836
2 vs 4	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
3 vs 4	<0.0001	0.0001	0.0552	0.2829	0.1366	0.2861	<0.0001

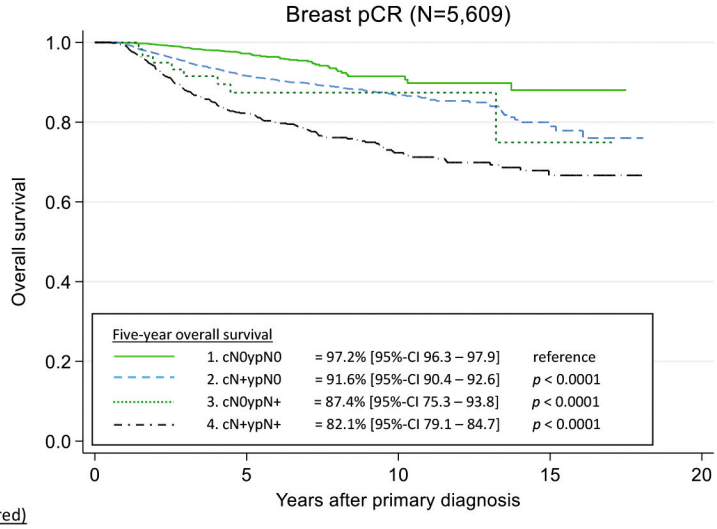
Groups: 1=cN0ypN0; 2=cN+ypN0; 3=cN0ypN+; 4=cN+ypN+

Online resource 2. Next page

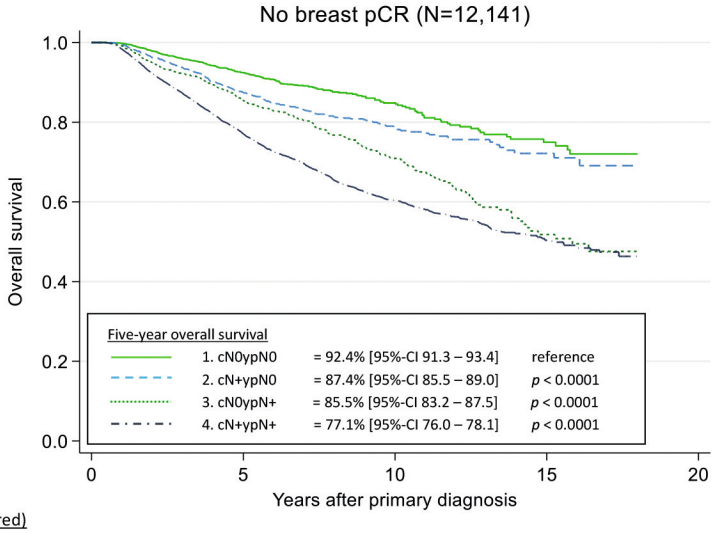
Online Resource 3. *p*-values of cN+-subgroups

Groups	Fig. 4
1 vs 2	0.2547
1 vs 3	<0.0001
1 vs 4	<0.0001
1 vs 5	<0.0001
1 vs 6	<0.0001
2 vs 3	0.0688
2 vs 4	0.0016
2 vs 5	<0.0001
2 vs 6	<0.0001
3 vs 4	0.0352
3 vs 5	<0.0001
3 vs 6	<0.0001
4 vs 5	<0.0001
4 vs 6	<0.0001
5 vs 6	0.4888

Groups: 1=cN1ypN0; 2=cN2ypN0; 3=cN3ypN0; 4=cN1ypN+; 5=cN2ypN+; 6=cN3ypN+



Number at risk (number censored)				
cN0ypN0	2,119 (0)	1,032 (1,036)	133 (1,929)	31 (2,028)
cN+ypN0	2,682 (0)	1,657 (814)	447 (1,160)	78 (1,512)
cN0ypN+	59 (0)	36 (16)	11 (41)	4 (46)
cN+ypN+	749 (0)	454 (166)	203 (378)	54 (517)



Number at risk (number censored)				
cN0ypN0	3,069 (0)	1,641 (1,219)	300 (2,489)	93 (2,671)
cN+ypN0	1,493 (0)	961 (356)	281 (972)	72 (1,168)
cN0ypN+	1,133 (0)	694 (287)	220 (688)	55 (815)
cN+ypN+	6,446 (0)	3,731 (1,319)	1,138 (2,032)	234 (2,820)

Online Resource 2. Overall survival per cNypN-subgroup, specified for breast pCR and no breast pCR

Seven hundred and eight patients were excluded from these analyses since it was unknown whether these patiens had breast pCR or no breast pCR (i.e., unknown ypT-status). Breast pCR was defined as ypT0/is. All *p*-values are provided in Online Resource 1.

Chapter 6

Minimal versus maximal invasive axillary staging and treatment after neoadjuvant systemic therapy in node-positive breast cancer: protocol of a Dutch multicenter registry study (MINIMAX)

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Clinical Breast Cancer 2022.

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Abstract

Background: Node-positive breast cancer (cN+) patients with an axillary pathologic complete response after neoadjuvant systemic therapy (NST) are not expected to benefit from axillary lymph node dissection (ALND). Therefore, less invasive axillary staging procedures have been introduced to establish response-guided treatment. However, evidence is lacking with regard to their oncologic safety and impact on quality of life (QoL). We hypothesize that if response-guided treatment is given, less invasive staging procedures are non-inferior to standard ALND in terms of oncologic safety, and superior to standard ALND in terms of QoL.

Patients and methods: MINIMAX is a Dutch multicenter registry study that includes patients with cN1-3M0 unilateral invasive breast cancer, who receive NST, followed by axillary staging and treatment according to local protocols. In a retrospective registry of ±4000 patients, the primary endpoint is oncologic safety at 5 and 10 years (disease-free, breast cancer-specific and overall survival, and axillary recurrence rate). In a prospective multicenter registry, the primary endpoints are QoL at 1 and 5 years, and we aim to verify the 5-year oncologic safety. With an estimated 5-year disease-free survival of 72.5% and anticipated loss to follow-up of 10%, a sample size of 549 is needed to have 80% power to detect non-inferiority (with a 10% margin) of less invasive staging procedures.

Conclusion: In cN+ patients treated with NST, less invasive axillary staging procedures are already implemented globally. Evidence is needed to support the assumed oncologic safety and superior QoL of such procedures. This study will contribute to evidence-based guidelines.

Introduction

In the past decades, there has been a trend towards de-escalating axillary surgery in breast cancer patients who undergo primary surgery. Following landmark trials such as NSABP B-32, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in node-negative (cN0) patients, on account of their equivalent survival and regional control, and the superiority of SLNB in terms of post-surgical morbidity outcomes.[1-3] Even in the case of a positive SLNB (limited to two positive nodes), it is safe to omit ALND when breast-conserving therapy is performed and adjuvant treatment is given.[4-8]

In node-positive (cN+) patients who receive neoadjuvant systemic therapy (NST), staging and treatment of the axilla remains an area of controversy. NST results in an axillary pathologic complete response (axillary-pCR) in at least a third of cN+ patients[9-12]; depending on breast cancer molecular subtype, axillary-pCR rates can be as high as 74%.[13] It is hypothesized that patients with an axillary-pCR do not benefit from ALND, since axillary-pCR is associated with an improved survival.[14,15] As a result, less invasive axillary staging procedures have been introduced to enable response-guided treatment, thereby omitting standard ALND. Examples of these less invasive staging procedures are SLNB, Marking Axillary lymph nodes with Radioactive Iodine seeds (MARI-procedure), and Targeted Axillary Dissection (TAD, a combination of SNLB and excision of a marked metastatic lymph node).[16-20] While these less invasive staging procedures are expected to diminish morbidity, each procedure risks leaving behind chemotherapy-resistant disease. Several studies have shown that SLNB is associated with unacceptably high false negative rates (FNRs), and a negative predictive value (NPV) that does not exceed 86%. This means that residual disease resistant to systemic therapy is missed in 1 in 6 patients with tumor-free SLNs.[9,17,18,20,21] Donker et al. developed the MARI-procedure, which resulted in an FNR of 7%, and a comparable NPV of 83%.[16, 22] The accuracy of TAD appears higher, yet evidence is limited to a few small cohort studies.[19,23-25] Preliminary results of the RISAS trial (combining MARI-procedure and SLNB) presented at SABCS 2020 seem to confirm the accuracy of TAD in a large multicenter cohort.[26] Final results of the RISAS trial and trials such as GANEA3 (NCT03630913) have to be awaited to determine the most accurate procedure.[27]

While the less invasive axillary staging procedures are being implemented in daily practice, ALND is more frequently replaced by axillary radiotherapy.[28-30] However, there is only little evidence that it is safe to omit standard ALND in cN+ patients undergoing NST, in terms of survival and recurrence rates.[31] Furthermore, it is unknown how this trend affects quality of life (QoL), the importance of which has grown as the survival and recurrence

rates of breast cancer improve. Hence, studies are urgently required that adequately compare the less and more invasive axillary staging and treatment procedures in terms of oncologic safety and impact on QoL. Four randomized controlled trials are currently comparing axillary treatment strategies in cN+ patients undergoing NST, with disease-free survival as primary endpoint (ATNEC: NCT04109079; NASBP-B51: NCT01872975; TAXIS: NCT03513614; Alliance A011202: NCT01901094). These trials have some limitations. It will be some years before the first trial results are expected, while prompt assessment of oncologic safety is required. With the ongoing trend towards less invasive strategies, it may also become progressively difficult to motivate patients to participate in these trials. Furthermore, three of four trials only include patients with cN1 disease. Patients with cN2-3 disease can also achieve an axillary-pCR, which implies that an ALND may not be necessary. Moreover, they have an indication for locoregional radiotherapy and thus an increased risk of developing morbidity when this is combined with ALND.[4,32]

In the Netherlands, axillary staging and treatment strategies in cN+ patients treated with NST vary widely between institutions.[28] Consequently, a retro- and prospective registry of cN1-3M0 patients can be assembled, that allows for comparison between less and more invasive strategies. The observational MINIMAX study will offer insight into the oncologic safety and impact on QoL of response guided-treatment based on the outcome of less versus more invasive axillary staging procedures in cN+ patients treated with NST, and therefore will contribute to evidence-based practice. In the event that less invasive strategies and standard ALND both have benefits and drawbacks, the study results will be most valuable for shared decision-making and personalized treatment.

Main study objectives

The primary objectives are 1) to compare the oncologic safety at 5 and 10 years, in terms of disease-free survival (DFS), breast cancer-specific survival (BCSS), overall survival (OS), and axillary recurrence rate (ARR), and 2) to assess the impact on QoL at 1 and 5 years, of the less and more invasive axillary staging and treatment procedures in cN+ breast cancer patients treated with NST.

Patients and methods

Study design

MINIMAX is a Dutch multicenter registry study that includes cN1-3M0 unilateral invasive breast cancer patients, who receive NST, followed by axillary staging and treatment according to local protocols. It comprises a retrospective registry, and a prospective multicenter registry. In both parts of the study, clinical data will be collected from patients'

medical files by specially trained datamanagers of the Netherlands Comprehensive Cancer Organization (IKNL), and databases will be based on the Netherlands Cancer Registry (NCR). They will partly consist of regular NCR data, such as patient characteristics, baseline tumor characteristics (based on pathology and imaging), data on systemic therapy, and type of surgery of the breast and axilla (i.e., SLNB, excision of a marked metastatic lymph node, TAD, and/or ALND). In addition, data will be collected on imaging strategies (i.e., ultrasound, MRI and/or PET-CT) to evaluate nodal status (before, during, and after NST), specifications of axillary surgery (e.g., number of lymph nodes excised) and pathology outcomes, radiotherapy target volumes, doses and fractionation, and follow-up in terms of survival and recurrence.

In the retrospective registry, clinical data will be analyzed of approximately 4,000 patients, who were diagnosed with cN+ breast cancer between 2014 and 2017, to determine oncologic safety at 5 and 10 years. Five-year oncologic safety will be available in 2023.

In the prospective multicenter registry, to evaluate impact on QoL, Patient Reported Outcome Measurements (PROMs) will be provided at baseline (i.e., time of diagnosis), and 1 and 5 years after diagnosis. Therefore, written informed consent will be obtained. Moreover, we aim to verify the 5-year oncologic safety. The first results will be available by the end of 2023. Thirty-five centers will participate in this study. A list of participating centers and their local principal investigators is provided in Appendix A. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute – Antoni van Leeuwenhoek (IRB 20-003) and by the local ethics committees of the participating centers. The MINIMAX study is registered at ClinicalTrials.gov (NCT04486495).

Study population

Women are eligible for this study if they are ≥ 18 years with unilateral invasive breast cancer and cN1-3 with at least one pathologically proven axillary lymph node metastasis, who are treated with NST (chemotherapy ± immunotherapy), followed by surgery of the breast and the axilla. Exclusion criteria are neoadjuvant endocrine therapy, distant metastases (also in case of oligometastatic disease), previous surgery (including SLNB prior to NST) or radiotherapy of the ipsilateral axilla, history of invasive breast cancer, and other malignancies except for basal/squamous cell skin cancer and in situ carcinoma of the cervix or breast (unless surgery or radiotherapy of the ipsilateral axilla has been performed).

Quality of life – prospective multicenter study

Patient Reported Outcome Measures (PROMs)

PROMs can be used to quantify QoL at several time points, with the purpose of giving feedback to the individual patient at the outpatient clinic, improving individual health care as well as shared decision-making.[33,34] Therefore, PROMs have a leading role in the Standard Set for Breast Cancer, which was developed by a multidisciplinary international working group in collaboration with the International Consortium for Health Outcomes Measurement (ICHOM). For this study, a validated Dutch version of the generic EORTC QLQ-C30, and the breast cancer specific EORTC QLQ-BR23 and BREAST-Q will be used, as proposed by ICHOM,[35] along with the generic EQ-5D-5L. Together, these PROMs will evaluate various domains of the patients' QoL, such as global health status, physical functioning, treatment-related morbidity (e.g., pain or other complaints of the breast and arm), body image, and psychosocial and sexual wellbeing. The PROMs will be provided at baseline (i.e., time of diagnosis), and 1 and 5 years after diagnosis. To attain a proper baseline, the first PROMs need to be completed before NST starts. The coordinating investigator will send and then collect the PROMS, a process facilitated by a secure platform built by two software programs, LimeSurvey and GemsTracker. PROMs will be available both online and paper-based.

Spielberger State-Trait Anxiety Inventory (STAI-trait) & Neuroticism Extraversion Openness Five Factor Inventory (NEO-FFI)

Studies have shown that personality traits, such as anxiety, can affect QoL.[36,37] A Dutch validated short version of the STAI-trait and NEO-FFI will be used to assess whether personality traits influence the QoL outcome.[38] These questionnaires will be provided at baseline (i.e., time of diagnosis).

Statistics

Endpoints

In the retrospective study, DFS, BCSS, OS, and ARR will be assessed at 5 and 10 years for various invasive axillary staging and treatment procedures separately using the Kaplan-Meier method. DFS is defined as the time interval between the date of diagnosis and the date of any invasive locoregional or distant recurrence, contralateral breast cancer, second primary invasive non-breast cancer, or death from any cause, whichever comes first, measured in days. Patients who are still alive without an event are censored at the date of last follow-up. BCSS and OS are defined as the time interval between the date of diagnosis and the date of death from the disease or from any cause, respectively,

measured in days. Patients who are still alive are censored at the date of last follow-up. ARR is defined as tumor recurrence or as a residual tumor that becomes clinically apparent in the ipsilateral axilla (pathologically proven).
In the prospective multicenter study, 5-year oncologic safety will be defined in the same manner. Impact on QoL will be assessed at 1 and 5 years.

Sample size

In the retrospective study, the estimated sample size is 4000 patients, who were diagnosed with cN+ breast cancer between 2014 and 2017. Preliminary analyses have shown that in the Netherlands the ratio of women who received less invasive axillary staging compared to standard ALND is about 1 to 1. In the prospective multicenter study, to test the hypothesis that less invasive axillary staging is non-inferior to standard ALND in terms of oncologic safety, we aim to analyze the data of 494 women. When assuming a 5-year DFS of 72.5%,[39] we should have 80% power to exclude a non-inferiority margin of 10%, and thus the lower bound of the 95%-confidence interval of DFS should not be less than 62.5%. In our registry, the anticipated loss to follow-up rate is 10%, and therefore we intend to include 549 patients. Based on analysis of NCR data, we expect to reach our calculated sample size within two years.
Regarding our second important outcome measure, impact on QoL, we expect a loss to follow-up rate of 20-30%, which would be in line with other QoL-studies. With 30% loss to follow-up, we would still have 80% power to detect a standardized mean difference in impact on QoL with Cohen's *d* of 0.3.

Planned analysis

In both studies, to assess oncologic safety with cohort data, we will compare Kaplan-Meier estimates derived using propensity score weighting. The propensity score is the probability of an individual to receive ALND conditional on observed baseline covariates. Conditional on this score, both groups' baseline characteristics are expected to be similar, as would be expected in a randomized clinical trial. To enable an individual's propensity score to be calculated if baseline data is missing, we will use stochastic regression imputation to complete the data before estimating the propensity score. This process will be performed for DFS, BCSS, OS, and ARR. The difference will be compared to the predefined non-inferiority limit of 10% using the upper bound of the 95%-confidence interval of the difference. If necessary, a competing risk model will be used. Using Kaplan-Meier estimates and both univariable and multivariable Cox proportional hazards regression, we will evaluate the influence of nodal status (cN1-3 and ypN0-3) and breast cancer subtype on the oncologic safety outcomes. Finally, univariable and multivariable Cox proportional hazards regression will be used to identify risk factors for regional recurrence.

In the prospective multicenter study, the one-way ANOVA will be used to compare parametric continuous variables (PROMs) between less and more invasive axillary surgery groups, all in relation to baseline levels. In case of evidence of differences, we will perform post hoc between-group testing adjusted for multiple testing using the bonferonni correction. To evaluate possible differences adequately both statistical significance and clinical significance need to be addressed.

Discussion

Nowadays, substantial axillary-pCR rates are achieved in cN+ patients treated with NST. It is hypothesized that ALND can be safely omitted in cN+ patients who achieve an axillary-pCR. As a result, less invasive axillary staging procedures are being implemented globally to establish response-guided treatment. This has led to a decrease in (completion) ALND, not only in the Netherlands (99% in 2006, to 53% in 2016),[28] but also in other countries,[40-42] and this trend seems to coincide with an increased use of adjuvant axillary radiotherapy.[28] Interestingly, ALND is being omitted in both patients with axillary-pCR, and those with residual disease.[28,29] However, it is unclear whether omitting ALND or replacing ALND by radiotherapy in cN+ patients treated with NST is safe with regard to long-term prognosis.[31]

Since omitting standard ALND is accompanied by the risk of leaving behind chemotherapy-resistant residual disease, this may result in undertreatment of the axilla. Moreover, adjuvant systemic treatment in case of residual disease can result in improved prognosis (e.g., capecitabine in HER2-negative patients, and TDM-1 in HER2-positive patients).[43,44] Therefore, it is of great importance that residual axillary disease is detected, and thus, in order to provide appropriate adjuvant treatment, the less invasive axillary staging procedure that replaces standard ALND has to be highly accurate.

While there is a search for the most accurate staging procedure, other issues need to be addressed. The question remains whether less invasive axillary staging is appropriate for all cN+ patients treated with NST, or if standard ALND should be applied in selected cN+ patients. This has resulted in differences regarding patient selection in accuracy studies. For instance, all cN+ patients were included in the MARI trial,[16] yet the RISAS trial did not include cN3a and cN3c patients,[27] and the trials Z1071, SN-FNAC and SENTINA did not include cN3 patients at all.[10,14,15] However, patients with extensive axillary involvement can achieve an axillary-pCR as well, in which case standard ALND is debatable. Moreover, cN3 patients already have an indication for locoregional radiotherapy, which can be an extra argument for omitting ALND.

Pathology outcomes of the less invasive staging procedures serve to guide adjuvant axillary treatment plans (i.e., no further treatment versus completion ALND and/or radiotherapy). In case of an axillary pCR, identified by less invasive staging procedures, completion ALND or radiotherapy may not be deemed necessary. In the event that less invasive staging procedures identify residual disease, adjuvant axillary treatment is indicated. In these cases, it is unclear whether completion ALND with or without radiotherapy is required, or if radiotherapy alone is sufficient. The AMAROS trial showed no significant difference in survival and recurrence rates between ALND or radiotherapy in cN0 patients with a positive SLNB who were treated with primary surgery and adjuvant systemic therapy.[4] However, these results cannot be extrapolated to cN+ patients treated in the neoadjuvant setting, with potentially chemotherapy-resistant residual disease. Moreover, it is unclear if decision-making with regard to adjuvant axillary treatment plans can be based solely on the pathology outcomes of the less invasive axillary staging procedures, since the impact of a false negative result is unknown. Furthermore, tumor biology (i.e., grade, lympho-vascular invasion, molecular subtype) may be a reason to apply adjuvant axillary treatment regardless of an axillary-pCR. Other factors such as the extent of lymph node involvement prior to NST (e.g., cN1-3, according to the AJCC staging system, or having <4 or ≥4 suspicious nodes, as proposed in the MARI protocol[26]), response on imaging after NST, and the extent of residual disease (isolated tumor cells versus micro- or macrometastases) are also taken into account to determine the extent of axillary staging and treatment strategies.[29]

All these uncertainties have resulted in an undesired variety of axillary staging and treatment strategies depending on local preferences. Some centers already have adopted less invasive axillary staging procedures, while other centers still perform standard ALND. Evidence in terms of oncologic safety is needed to determine the appropriate strategy for patients with axillary-pCR, as well as for patients with residual axillary disease. Since QoL is of utmost importance for shared decision-making, as it can affect patient preferences for specific strategies, this also has to be taken into account. The MINIMAX study is designed to answer both of these needs. Since a randomized controlled trial is no longer feasible in the Netherlands, due to less invasive strategies being the preferred policy in many hospitals, an observational study design is the favored option. The MINIMAX study is expected to offer insight into the oncologic safety and impact on QoL of the various invasive axillary staging and treatment procedures in cN1-3M0 breast cancer patients treated with NST. The retrospective cohort study will focus on oncologic safety, while the prospective multicenter study will assess impact on QoL, and validate the oncologic safety analysis. The results will contribute to developing uniform evidence-based guidelines. If less and more invasive strategies appear to have both risks and benefits, then these findings will be highly valuable for shared decision-making and personalized treatment.

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Appendix A. Participating centers and their local principal investigators

Participating center	Local principal investigator
Albert Schweitzer Hospital	M.B.E. Menke-Pluijmers
Alexander Monro Hospital	L.M. Veenendaal
Alrijne Hospital	C.C. van der Pol
Amphia Hospital	L.F.C. Dols
Canisius Wilhelmina Hospital	L.J.A. Strobbe
Catharina Hospital	R.J. Schipper
Diakonessenhuis	T. van Dalen
Dijklander Hospital	L.M. de Widt-Levert
Erasmus Medical Center	L.B. Koppert
Franciscus Vlietland	M.M.F. Aubuchon
Gelderse Vallei Hospital	M.L. Hoven-Gondrie
Gelre Hospital	M.J. Bolster-van Eenennaam
Haaglanden Medical Center	M.E. Straver
Ikazia Hospital	J. Nonner
Isala Hospital	A.B. Francken
Jeroen Bosch Hospital	M. Bessems
Leiden University Medical Center	W.J. van der Made
Maastricht University Medical Center+	M.L. Smidt
Maasstad Hospital	C.M.E. Contant
Martini Hospital	J.P. Deroose
Máxima Medical Center	A.J.G. Maaskant-Braat
Medical Center Leeuwarden	S.H. Estourgie
Medisch Spectrum Twente	A.E. Dassen
Netherlands Cancer Institute	M.T.F.D. Vrancken Peeters
Noordwest Ziekenhuis	G.A. Gooiker
Red Cross Hospital	L.M. Stengs
Rijnstate Hospital	R.R.J.P. van Eekeren
Saxenburgh Medical Center	D.J. Evers
Slingeland Hospital	K. Reijnders
Spaarne Gasthuis	K.M. Blaauwendraat
Tergooi Hospital	E.J.C. Vriens-Nieuwenhuis
Van Weel-Bethesda Hospital	R.P.M. Carstens-Brosens
Ziekenhuisgroep Twente	D.J. Evers
Zorgsaam Hospital	E. van Dessel

Chapter 7

Patients with node-positive breast cancer treated with neoadjuvant systemic therapy: nationwide practice variation

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Translated from Dutch.
NTvO 2022.

Summary

Neoadjuvant systemic therapy (NST) is increasingly applied in patients with breast cancer. Not only does NST enable downsizing the primary tumour, making breast conserving therapy more often feasible, in node-positive (cN+) breast cancer, it can also downsize axillary disease and result in a pathological complete response of the axilla (ax-pCR). It is hypothesized that patients who achieve an ax-pCR do not benefit from axillary lymph node dissection (ALND). Therefore, in cN+ disease, several less invasive staging procedures have been introduced to assess axillary disease response after NST. However, it is unclear whether it is safe to omit an ALND, or to replace it by radiotherapy. A lack of evidence and consensus has resulted in a large variety of axillary staging and treatment strategies worldwide. In order to assess practice variation in the Netherlands, we conducted a survey among the 35 hospitals participating in the MINIMAX study (a prospective registry study of patients with cN+ breast cancer treated with NST, ClinicalTrials.gov Identifier: NCT04486495). The results of the survey show variation with regard to the use of the TNM-classification, types of less invasive staging procedures, reasons to directly conduct an ALND after NST, and whether or not the number of positive lymph nodes before NST and the response to NST on imaging are taken into account when considering axillary staging and treatment strategies. Apart from the importance to have insight into current practice variation in the Netherlands, these results show the value of studies such as the MINIMAX study, which are needed to achieve (more) consensus, and promote shared decision-making and patient tailored treatment.

Introduction

Traditionally, patients with node-positive (cN+) breast cancer underwent axillary lymph node dissection (ALND), a procedure associated with the risk of (severe) morbidity.[1,2] Neoadjuvant systemic therapy (NST) is now increasingly applied in these patients, allowing for in vivo response assessment to systemic therapy. Moreover, breast-conserving surgery is more often feasible, and efforts are made to de-escalate axillary surgery.[3-5] One of the benefits of NST is that an axillary pathological complete response (ax-pCR) can be achieved.[6-10] It is expected that patients who achieve an ax-pCR do not benefit from an ALND. Therefore, over the years, various less invasive procedures have been introduced to stage the axilla: sentinel lymph node biopsy (SLNB), the MARI-procedure (where a pathologically proven metastatic lymph node is marked with a radioactive iodine seed), and the targeted axillary dissection (TAD). TAD involves combining SLNB with the MARI-procedure (i.e., RISAS-procedure) or a MARI-like procedure.[11-16] These procedures enable axillary response assessment after NST, allowing for response-guided treatment decisions (e.g., no axillary treatment in case of ax-pCR, or completion ALND and/or regional radiotherapy in case of residual disease). However, it remains unclear whether it is oncologically safe to omit ALND (or to replace it with radiotherapy) in patients with cN+ breast cancer treated with NST. A lack of evidence and consensus has led to a wide variety of axillary staging and treatment strategies for these patients, not only in the Netherlands but also worldwide.

To gain insights into oncologic safety and quality of life associated with the various axillary strategies, the Dutch nationwide registry study 'MINIMAX' was conducted and started patient enrolment in 2020.[17] The goal is to achieve (more) consensus based on the results, promote shared decision-making, and strive for patient-tailored treatment. In order to assess current practice variation concerning axillary staging and treatment strategies in the Netherlands, a survey was conducted among the 35 hospitals participating in the MINIMAX study.

Methods

The survey consisted of 14 questions: five open-ended questions, five closed-ended questions, and four partially closed questions. These questions covered topics such as imaging, pathology, response assessment, axillary surgery (including less invasive staging procedures and ALND), and regional treatment strategies. The questions are provided in Table 1.

Table 1. Survey

1. *General question*: What is the anticipated annual patient inclusion rate for your hospital?
2. Which imaging modalities does your hospital utilize for the staging of regional lymph nodes and distant metastases? (before, during, and after NST)
3. How is the axillary lymph node metastasis pathologically confirmed before NST? (in the majority of patients)
4. Is one of the metastatic lymph nodes marked before NST? If so, how?
5. Which surgical staging procedure(s) is (or are) performed in your hospital after NST?
6. Are there patients for whom an ALND is performed regardless after NST? If so, in whom?
7. Do the following patients qualify for less invasive axillary staging in your hospital? (cN3a, cN3b, cN3c, oligometastastic disease)
8. Does the radiological response of the axilla affect the choice of surgical staging procedure? If yes, in what way?
9. Does the total number of suspicious lymph nodes before NST affect axillary staging and treatment strategies after NST? If so, in what way?
10. Does your hospital consider an axillary lymph node that solely contains isolated tumour cells either as a positive or as a negative axillary lymph node?
11. *In case of ax-pCR*: Are there patients who do not undergo (further) axillary treatment? If so, which patients?
12. *In case of ax-pCR*: Are there patients who do undergo (further) axillary treatment? If so, which patients and what does it consist of?
13. *In case of residual disease*: Are there patients who do not undergo (further) axillary treatment? If so, which patients?
14. *In case of residual disease*: Are there patients who do undergo (further) axillary treatment? If so, which patients and what does it consist of?

Results

Response to survey

Thirty-two out of the 35 participating hospitals completed the survey: two academic hospitals, 15 topclinical hospitals, two specialized hospitals, and 13 general hospitals. Together, these 32 hospitals represented ten out of the 12 provinces, as shown in Figure 1.

Use of cTNM-classification

In the majority of hospitals, in addition to an ultrasound, a PET-CT is routinely performed before NST for axillary staging in all patients with cN+ breast cancer. In some hospitals, the number of positive lymph nodes (1-3 versus ≥4) on imaging before NST influences the cTNM-classification at diagnosis. In case of 1-3 positive lymph nodes before NST, this is defined as cN1 disease, and in case of ≥4 positive lymph nodes, this is defined as cN2 disease.

Figure 1. Respondents

Less invasive staging procedures after NST

In all 32 hospitals, less invasive axillary staging procedures are used, as illustrated in Figure 2. In 26 (81.3%) out of 32 hospitals, patients with oligometastases are also eligible for these procedures. Four out of 32 hospitals perform both TAD and the MARI-procedure. The remaining hospitals use either TAD (n=23), the MARI(-like)-procedure (n=4), or the SLNB (n=1). In the 27 hospitals where TAD is performed, 24 hospitals combine the SLNB with the MARI-procedure (i.e., RISAS-procedure), two hospitals combine the SLNB with wire localization of a clipped node, and one hospital combines the SLNB with iodine seed localization of a clipped node. Among the eight hospitals that perform the MARI(-like)-procedure, seven hospitals use iodine seed localization before NST, and one hospital uses wire localization of a clipped node after NST.

In cases where the less invasive staging procedure shows ax-pCR, 24 (75.0%) out of 32 hospitals refrain from adjuvant regional radiotherapy in selected patients (e.g., in patients with 1-3 positive lymph nodes before NST). In the remaining hospitals, adjuvant regional radiotherapy is still administered if the less invasive staging procedure indicates ax-pCR.

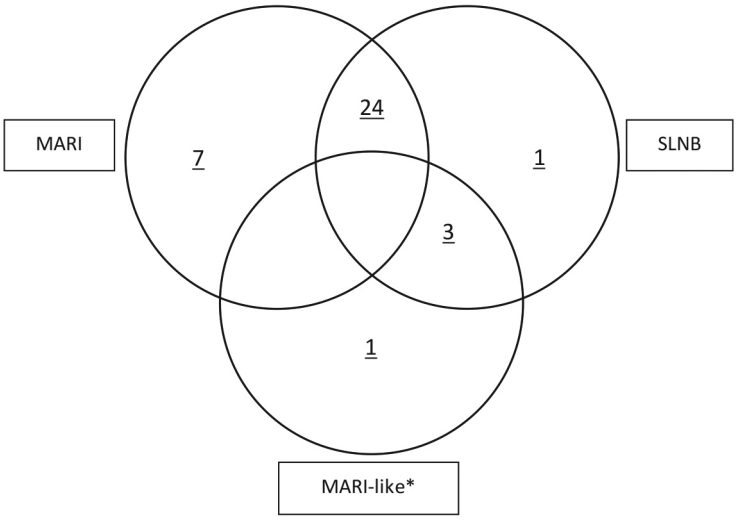

Figure 2. Performed less invasive procedures for axillary staging after NST

* Wire or iodine seed localisation after NST of a lymph node that was clipped before NST. Please note: some hospitals perform both the RISAS and the MARI-procedure, therefore the total sum is higher than the total number of respondents.

Reasons for ALND

In 19 (59.4%) out of 32 hospitals, if indicated, patients can undergo an ALND instead of a less invasive staging procedure. The most mentioned indication is having ≥4 positive lymph nodes before NST. The anatomical extent is also mentioned as an indication, distinguishing between cN3a, cN3b, and cN3c disease, corresponding with infraclavicular, parasternal, or supraclavicular involvement, respectively. Other indications to directly perform an ALND include no complete response on imaging and/or pathologically proven residual disease after NST (based on cytology or histology), and perioperative presence of "bulky disease". Some hospitals note that the breast cancer molecular subtype and patient's preferences are also included in the decision-making process.

Reasons to perform a completion ALND, after performing a less invasive staging procedure, vary between hospitals. The presence of residual disease in the MARI- and/or sentinel lymph node is not an independent reason for a completion ALND in any of the hospitals. Important factors for determining whether a completion ALND and/or regional radiotherapy should be performed, are the number of positive lymph nodes before NST (1-3 versus ≥4) and/or the presence of risk factors (e.g., triple negative disease, or ypT4) in combination with presence of residual disease.

Definition of isolated tumour cells after NST

In 18 (56.3%) out of 32 hospitals, isolated tumour cells (ITCs) are classified as negative (meaning ax-pCR), in 11 hospitals as positive, and in three hospitals this is evaluated per patient, where the number of lymph nodes containing ITCs can also have an effect.

Discussion

The results of this survey on current practice variation regarding axillary staging and treatment strategies in cN+ breast cancer treated with NST revealed several important points that need to be addressed. There is a difference in use of the cTNM-classification based on the number of positive lymph nodes before NST. We suggest using the formal cTNM-classification, and additionally providing the number of positive lymph nodes in parentheses (e.g., cN1(4)). Furthermore, factors such as the number of positive lymph nodes before NST, and the response to NST on imaging affect decision-making in one hospital, while not being of any influence in others. Moreover, besides various less invasive staging procedures being performed (with corresponding false negative rates), there are also several reasons to perform an ALND, the definition of ax-pCR varies with regard to ITCs, and if a less invasive staging procedure shows an ax-pCR, in some hospitals adjuvant regional radiotherapy is omitted in selected patients, while in others it is always performed. Aside from the importance for clinicians to have insight in and be aware of current practice variation in the Netherlands, these results indicate that it is important to include patients in registry studies such as MINIMAX. In daily practice, axillary staging and treatment strategies in cN+ breast cancer treated with NST are often based on studies involving patients with cN0 breast cancer who are primarily treated with surgery and have a positive SLNB, which represents a different patient population. While awaiting results of ongoing randomised controlled trials about cN+ breast cancer treated with NST (NSABP-B51/RTOG 1304, ATNEC, Alliance A011202, and TAXIS), patients can be included in registry studies such as MINIMAX and AXSANA.[18] By doing so, we can gain insight into the benefits and drawbacks of various axillary strategies in a relatively short term, leading to (more) consensus and a more uniform approach. In addition, patients can be better informed about the various strategies (and corresponding benefits and drawbacks), in order to promote shared decision-making and strive for patient-tailored treatment.

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Part III

Quality of life, and the impact of personality on patient-reported outcomes

Chapter 8

A descriptive systematic review of the relationship between personality traits and quality of life of women with non-metastatic breast cancer

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Abstract

Background**:** Quality of life (QoL) is an important patient-reported outcome that has been studied extensively as an endpoint. There is a growing interest in factors that may influence QoL, such as personality. This descriptive systematic review examined the relationship between personality and QoL in women with non-metastatic breast cancer.

Methods: On November 24th, 2020, with an update on March 7th, 2022, PubMed, PsycINFO, CINAHL, Web of Science and Embase were systematically searched for studies that assessed the direct relationship between personality traits and QoL among adult women diagnosed with non-metastatic breast cancer. The National Institutes of Health Study Quality Assessment Tool was used to assess the quality and risk of bias of the included studies. Three reviewers independently extracted data regarding objectives, population, setting, design, method, outcome measurements and key results. The results are descriptively reported.

Results: Twelve studies (6 cohort studies and 6 cross-sectional studies) were included. Three studies were rated as poor, one study was rated as good, and the remaining studies were rated as moderate. There was a small to moderate effect of personality on QoL as correlation coefficients ranged from 0.10 to 0.77, and the explained variance ranged from 4% to 43%. The (strength of the) relationship depended on the personality trait and QoL domain that was measured and was most apparent for the personality traits 'optimism' and 'trait anxiety' on psychosocial QoL domains. The results for the personality traits (unmitigated) agency, agreeableness, conscientiousness, novelty seeking, and self-efficacy indicated a smaller but statistically significant correlation between these personality traits and QoL.

Conclusion: The results confirm that personality affects QoL in women with non-metastatic breast cancer and thus provides evidence that personality traits are indeed important influential factors of QoL. It is therefore strongly recommended for all future QoL research to measure personality traits and use these variables as predictive factors, as they are needed to accurately interpret QoL. Information regarding personality traits provide physicians and patients with an interpretation of low or deterioration of QoL, which could guide physicians to improve their patients' health outcomes and subsequently QoL using psycho-oncological support or treatment.

Background

Quality of life (QoL) is an important patient-reported outcome (PRO) in oncology that has been studied extensively as an endpoint in breast cancer patients.[1,2] There is a growing interest in factors that may influence QoL, such as personality.[1-5]

The relationship between personality traits and health-related QoL (HRQOL) in the general population has been systematically reviewed by Huang and colleagues.[6] The overall conclusion stated that personality traits are indeed related to HRQOL. The review included 76 studies that were published up to 2009. The included populations consisted of individuals across several age groups and with various health states, such as cancer, chronic conditions, and healthy individuals. An important limitation of this specific review is the absence of quality and risk of bias assessment of the included studies. In combination with the considerable variance in included populations, and as only three of the included studies examined the relationship between personality traits and HRQOL in breast cancer patients, it is unclear if the results also apply to breast cancer patients in general.

The aim of this systematic review was to provide a descriptive overview of evidence from studies that investigated the direct relationship between personality and QoL in women with non-metastatic breast cancer. The results will not only provide a greater and more accurate understanding of the direct relationship between personality and QoL in these patients, but it can also provide physicians and patients with an explanation of a lower QoL.

Methods

Registration and protocol

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for transparent reporting of systematic reviews.[7] Objectives, methods of analysis, and inclusion criteria were specified in advance and documented in a protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO). Registration number: CRD42020215164.

Search strategy

In this review the theory of the Five Factor Model (FFM) was used to conceptualize and measure personality and its traits (i.e., aspects of personality that are relatively stable over time and influence behaviour).[8-10] The FFM measures personality traits at

a superordinate level (i.e., five dimensions: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience) and regard these dimensions as orthogonal (not correlated).[6,8,11] Each dimension comprises six facets, indicating that each domain contains different personality traits.[8] Another way to describe and measure personality is to focus on individual traits rather than personality dimensions. Individual traits have their own specific focus but can also be incorporated into one of the FFM dimensions (see Figure 1).[6] On November 24th, 2020, PubMed, PsycINFO, CINAHL, Web of Science and Embase were searched, using the keywords personality, QoL, and breast neoplasms (Appendix B provides details regarding the search strategy). These general keywords are most frequently used and led to an extensive search. For all three keywords multiple synonyms were used. To ensure comprehensiveness, individual personality traits were added to the search of personality. This systematic review included observational studies and randomized controlled trials (RCTs) to observe the relationship between personality and QoL. RCTs were not included to observe treatment effect, but to capture the abovementioned relationship if measured. Studies were considered eligible if: 1) the studies assessed the direct relationship between personality traits and QoL; 2) study population consisted of female non-metastatic breast cancer patients, ≥18 years; 3) personality traits and QoL were assessed with appropriate and validated questionnaires; 4) published in peer-reviewed scientific journals. Due to the heterogeneity in indirect, moderating or mediating effects, it was expected to lead to difficulties when comparing study results or conducting analysis. Therefore, indirect, mediating and moderating effects were excluded. Studies were excluded if: 1) an indirect relationship, mediating or moderating effect between personality traits and QoL was assessed; 2) published in a language other than English or Dutch. There were no restrictions regarding the time of publication or the length of follow-up. On March 7th, 2022, the search was updated with the same search strategy limiting the time of publication from December 2020 up to January 2022.

Study selection

Endnote was used as a reference management tool. After deduplication, three reviewers (VW, SV, and SdW) independently screened title and abstract of the retrieved articles using the in- and exclusion criteria, followed by full-text evaluation of potentially eligible studies. Disagreements regarding inclusion were resolved by consensus.

Data abstraction

The Cochrane data extraction template was used to develop a data extraction sheet. The following data were extracted: objectives, population, setting, design, method, outcome measurements and key results. The data extraction was individually conducted by all reviewers. Disagreements were resolved by consensus. The results are reported using correlation coefficient (r), Odds Ratio (OR) or explained variance (R^2).

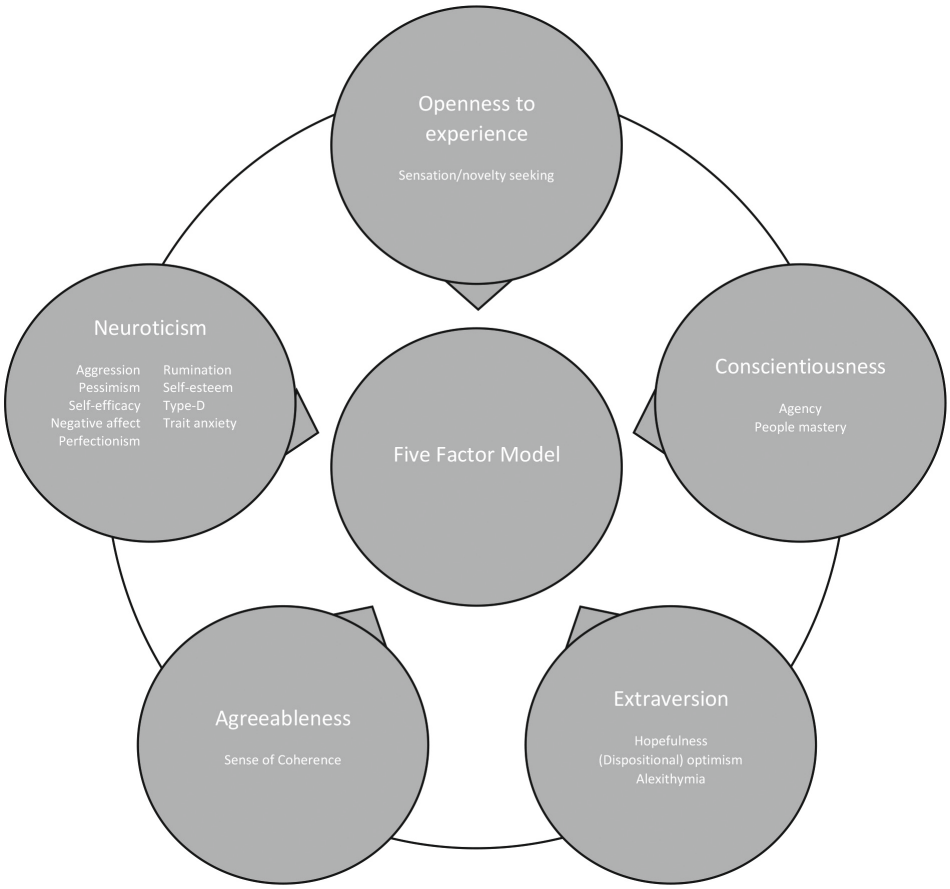

Figure 1. Schematic overview personality dimensions according the Five Factor Model and the subdivision of single personality traits

Risk of bias assessment

The risk of bias was independently assessed by all three reviewers using the Study Quality Assessment Tool from National Institutes of Health (NIH) for observational and cross-sectional studies.[12] Each question was answered with yes (Y), no (N), cannot be determined (CD), not applicable (NA), or not reported (NR). Based on these answers, a final quality rate was given (i.e., poor, fair, or good), as shown in Appendix C. Disagreements were resolved by consensus.

Results

Study selection

The first database search yielded 1980 articles. Twenty-four records were identified through screening the reference lists of the included studies. After deduplication, 1458 records were screened on title and abstract. Of these, 1383 were excluded. Of the remaining 75 articles, 63 articles were excluded after full-text screening. Eventually, 12 studies were included in this systematic review (6 cohort studies and 6 cross-sectional studies). Details are provided in Figure 2a. An updated search did not lead to new included studies, as provided in Figure 2b.

Risk of bias within studies

The detailed assessment of the risk of bias within the studies using the NIH assessment tool is summarized in Appendix C. Three of the included studies were rated as poor, one study was rated as good, and the remaining studies were rated as moderate.

Study characteristics and results of individual studies

The characteristics and results of individual studies are summarized in Tables 1 and 2, respectively. In the included studies there was heterogeneity in methods, personality trait(s) measured, QoL instruments, and outcomes. Therefore, no statistical method could be used to pool the retrieved data. Results of the included studies are descriptively presented and grouped per personality dimension and the corresponding individual personality traits. Appendix A holds information regarding the definition of each personality trait and the corresponding characteristics and individual personality traits.

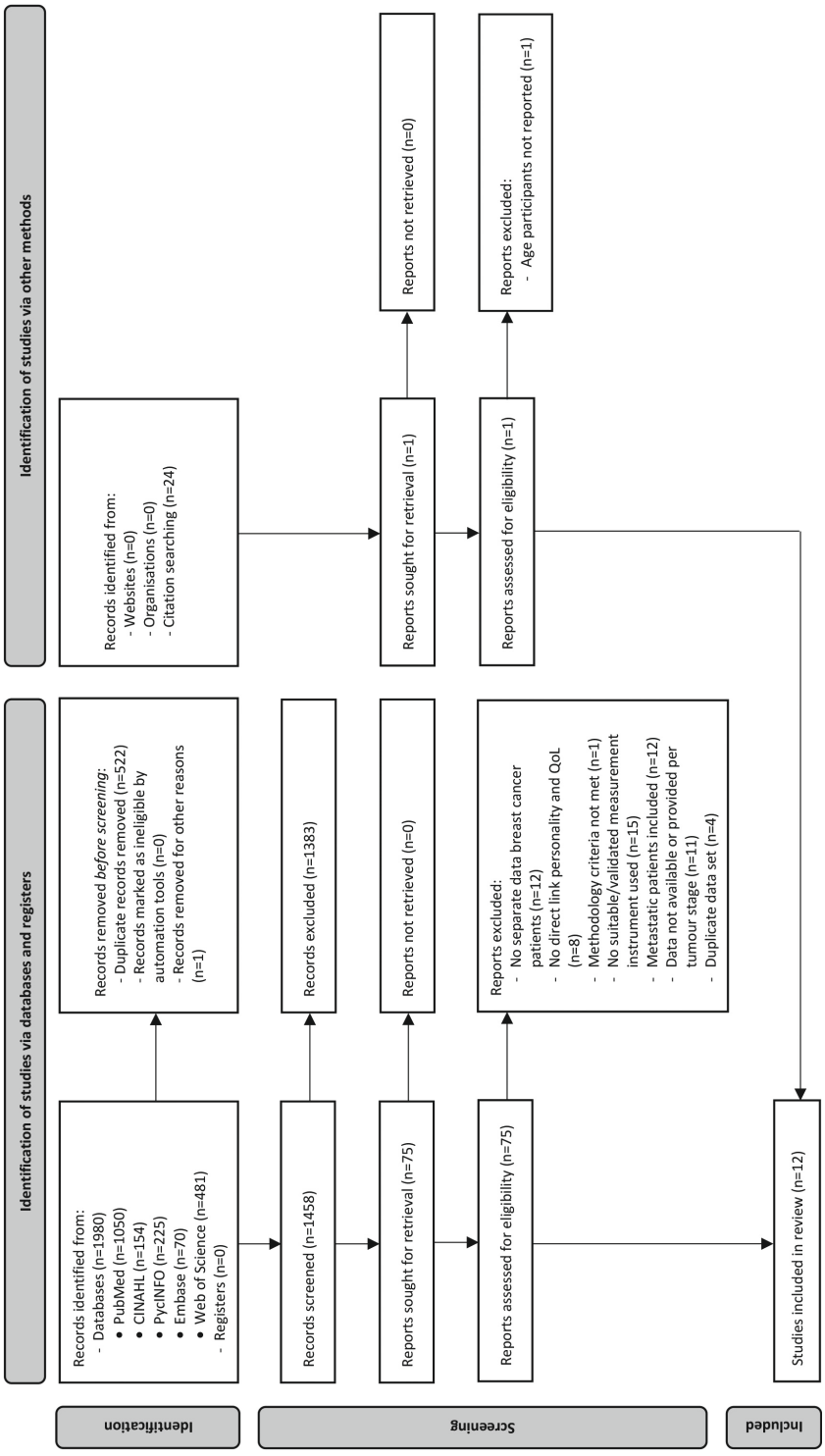

Figure 2a. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

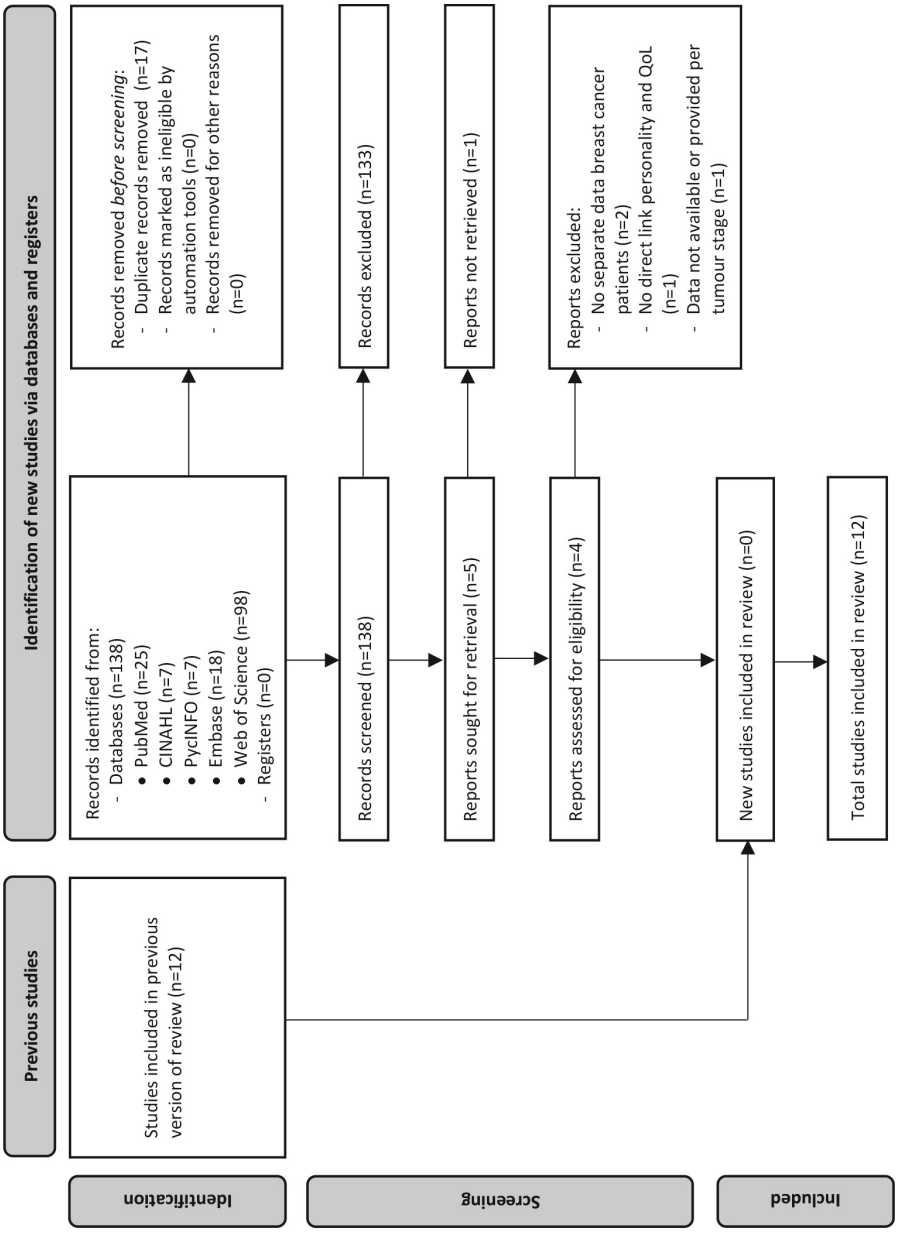

Figure 2b. PRISMA 2020 flow diagram updated search

Table 1. Study characteristics

Author, Year (Country) of study	Study design	Sample size	Personality trait	Personality measure	QoL domain	QoL measure	Statistical analyses	Quality rate
Bellino et al, 2011 (Italy)[13]	CO	57	NS	TCI	PF; RP; BP; GH; VT; SF; IE; MH	SF-36	Univariate regression	Fair
Carver et al, 2006 (USA)[14]	CS	163	O	LOT, LOT-R	NF; PFE; CP; SP; PP; F; SA; BCS	QLACS	Multivariate regression	Fair
Durá-Ferrandis et al, 2016 (USA)[15]	CO	1280	DO	LOT	PF; RF; EF; CF; SF	EORTC QLQ-C30	Multivariate regression	Fair
Härtl et al, 2010 (Germany)[16]	CO	203	DO; N	FPI-R, LOT	PF; RF; EF; CF; SF	EORTC QLQ-C30	Multivariate regression	Fair
Petersen et al, 2008 (USA)[17]	CS	268	O; P	MMPI	PH; MH	SF-36, SF-12	T-test and Kruskal-Wallis test	Fair
Popović-Petrović et al, 2018 (Serbia)[18]	CS	64	S	GSES	PWB; SWB; EWB; FWB	FACT-B+4	Hierarchical regression	Poor
Piro et al, 2001 (USA)[19]	CS	74	A; UA	M-EPAQ	EWB	FACT-B	Hierarchical regression	Poor
Schreier et al, 2004 (USA)[20]	CO	48	TA	STAI	HF; SEC; PS; FA	QLI	Multivariate regression	Fair
Shen et al, 2020 (China)[21]	CS	121	S	GSES	PWB; SWB; EWB; FWB; BCS	FACT-B	Multivariate regression	Fair
van der Steeg et al, 2010 (Netherlands)[1]	CO	222	N; E; OP; AG; C; TA	NEO-FFI, STAI	PH; PSH; LI; SR; EV; SPI	WHOQOL-100	Multivariate regression	Good
Tomich et al, 2006 (USA)[22]	CO	70	O; SE	RSES, LOT	PF; RP; BP; GH; VT; SF; IE; MH	SF-36	Hierarchical regression	Fair
You et al, 2018 (USA)[23]	CS	159	TA	STAI-T	PWB; SWB; EWB; FWB	FACT-B	Hierarchical regression	Poor

CO, Prospective Cohort study; CS, Cross-sectional study.

Personality traits: NS, Novelty Seeking; O, Optimism; DO, Dispositional Optimism; N, Neuroticism; P, Pessimism; S, Self-efficacy; A, Agency; UA, Unmitigated Agency; TA, Trait Anxiety; E, Extraversion; OP, Openness to Experience; AG, Agreeableness; C, Conscientiousness; SE, Self-esteem

Personality measures: TCI, The Temperament and Character Inventory; LOT(-R), Life Orientation Test(-Revised); FPI-R, Freiburg Personality Inventory-Revised; MMPI, Minnesota Multiphasic Personality Inventory; GSES, General Self-Efficacy Scale; M-EPAQ, Modifed-Extended Personal Attributes Questionnaire; STAI(-T), State-Trait Anxiety Inventory(-Trait); NEO-FFI, NEO Five-Factor Inventory; RSES, Rosenberg Self-Esteem Scale

QoL domain: PF, Physical Functioning; RP Role function Physical; BP, Bodily pain; GH, General Health perceptions; VT, Vitality; SF, Social Functioning; IE, Impact of Emotional problems or daily activities; MH, Mental health; NF, Negative feelings; PFE, Positive Feelings; CP, Cognitive Problems; SP, Sexual Problems; PP, Physical Pain; F, Fatigue; SA, Social Avoidance; BCS, Breast Cancer-specific Concerns; RF, Role Functioning; EF, Emotional Functioning; CF, Cognitive functioning; PH, Physical Health; PWB, Physical Well-Being; SWB, Social/Family Well-Being; EWB, Emotional Well-Being; FWB, Functional Well-Being; HF, Health/Functioning; SEC, Socioeconomics; PS, Psychological/Spiritual; FA, Family; PSH, Psychological Health; LI, Level of Independence; SR, Social Relationships; EV, Environment; SPI, Spirituality

QoL measures: SF-36, Short Form Health Survey-36 items; SF-12, Short Form Health Survey-12 items; QLACS, Quality of Life in Adult Cancer Survivors; EORTC QLQ-C30, European Organization for Research and Treatment for Cancer Quality of Life Questionnaire (version 3); FACT-B+4, Functional Assessment of Cancer Therapy-Lymphedema; FACT-B, Functional Assessment of Cancer Therapy-Breast; QLI, Quality of Life Index; WOQOL-100, World Health Organization Quality of Life assessment instrument.

Table 2. The relationship between personality traits and QoL

Personality traits	Correlation coefficient (r)		Variance in QoL explained by personality traits (%)		Odds ratio (CI)	
Openness to Experience						
Novelty seeking[11]			Overall QoL	8%*		
Conscientiousness[1]			Overall QoL T3/BCT	9%**		
Agency[19]	EWB	0.25*				
	IWB	0.10				
Unmitigated agency[19]	EWB	-0.21	IWB	35%**		
	IWB	-0.38***				
Extraversion						
Optimism[14,15]	NF	0.36***			EF (AD vs. MHI)	0.43 (0.30-0.65)***
	PFE	0.37***			EF (AD vs. MHI)	0.69 (0.56-0.86)***
	CF	0.15				
	SP	0.36***				
	SA	0.20*				
	F	0.22**				
Agreeableness[1]			Overall QoL T3/BCT	4%*		
			Overall QoL T4/BCT	6%*		
Neuroticism[1]			Overall QoL T2/MCT+	19%***		
			Overall QoL T3/MTC+	21%***		
			Overall QoL T4/MTC+	20%***		
			Overall QoL T5/MTC+	26%***		
			Overall QoL T5/BCT	34%***		
Self-efficacy[18,21]	Overall QoL	0.34*-0.49**				
	PWB	0.21-0.39**				
	SWB	0.24-0.27**				
	EWB	0.42**				
	FWB	0.27*-0.35**				

Table 2. Continued

Personality traits	Correlation coefficient (r)		Variance in QoL explained by personality traits (%)		Odds ratio (CI)	
Trait anxiety[1,20,23]	Overall QoL	-0.77**--0.32*	Overall QoL T2/BCT	29%***	Overall QoL	7.81 (2.42-25.72)***
	PWB	-0.63**	Overall QoL T3/BCT	37%***		
	SWB	-0.50**	Overall QoL T4/BCT	43%***		
	EWB	-0.73**				
	FWB	-0.62**				
	PS	-0.33*				

EWB, Emotional Well-Being; IWB, Interpersonal Well-Being; NF, Negative Feelings; PFE, Positive Feelings; CF, Cognitive functioning; SP, Sexual problems; SA, Social Avoidance; F, Fatigue; QoL, Quality of Life; PWB, Physical Well-Being; SWB, Social/family Well-Being; FWB, Functional Well-Being; PS, Psychological/Spiritual; EF, Emotional functioning; T2/3/4/5, Time measure point 2/3/4/5; BCT, Breast-Conserving Therapy; MTC+, Mastectomy and MTC after BCT; AD, Accelerated Decline; MHI, Maintained High; MD, Moderate Decline.

*p<0.05; **p<0.01; ***p<0.001.

Note: the included studies by Petersen et al., Tomich et al., and Härtl et al., did not have any specific data and therefore could not be included in the table.

Openness to experience

The results from the cohort study by Van der Steeg et al.[1,4,25,26] did not hold evidence that the personality trait openness to experience played a role in predicting patients' QoL six months post breast cancer diagnosis.

- Novelty seeking
  Bellino et al.,[13] assessed the effect of novelty seeking (i.e., sensation seeking) on QoL in a cohort study, and showed a clinically meaningful and a statistically significant difference in QoL between baseline and 3 months after surgical intervention (p=0.01) related to novelty seeking (p=0.02). The percentage of variance explained by the relationship between novelty seeking and the change of the QoL scores over time was 8%.

Conscientiousness

Van der Steeg et al.,[1,4,25,26] also examined the effect of conscientiousness on QoL. The results show an explained variance of 0.09 (p=0.004), one year post diagnosis.

- *Agency*
  Piro et al.[19] conducted a cross-sectional study and stated that there was a statistically significant correlation between agency and emotional well-being (r=0.25, p<0.05), and between unmitigated agency and interpersonal well-being (r=-0.38, p<0.001). There was no statistically significant correlation between agency and interpersonal well-being, and unmitigated agency with emotional well-being. Agency and unmitigated agency accounted for 35% (34% adjusted) of the variability in interpersonal well-being.

Extraversion

Van der Steeg et al.,[1,4,25,26] also examined the effect of extraversion on QoL. They found no evidence that QoL in breast cancer patients is significantly influenced by the personality trait extraversion.

- *Optimism*
  The effect of optimism on QoL was assessed in three studies. Analyses from a cohort study by Tomich et al.,[22] showed no significant association between optimism and QoL for disease-free participants. These findings were confirmed by the results of a hierarchical regression analysis, which revealed that the unstandardized Beta (B*)* of optimism on physical functioning (subscale of QoL) was 1.53 (β 0.14), while the B of optimism on mental functioning was 0.97 (β 0.10). None of these findings were statistically significant. In a cross-sectional study by Carver et al., analysis showed that there was a statistically significant relationship between most QoL domains and

optimism, except for the subscales cognitive impairment, pain or financial problems, with correlations ranging between 0.17 and 0.37 (p<0.001 - <0.05).[14]

Durá-Ferrandis et al.[15] performed a cohort study in which they created 3 groups based on QoL scores: 1) consisting of participants beginning with and maintaining near perfect QoL scores over time, 2) consisting of participants with the lowest baseline QoL scores and the steepest rate of decline, and 3) consisting of participants with QoL baseline scores slightly below and only slightly lower declines over time in parallel to group 1. Analysis for emotional functioning showed that the adjusted OR of being in group 2 (accelerated decline group) was 0.43 less for survivors with higher optimism, compared to group 1 (maintained high group). The OR of being in group 3 (phase shift group) was 0.69 less for survivors with higher optimism compared to group 1. Both ORs appeared to be statistically significant (p<0.001).

All three studies examining the relationship between optimism and QoL, found that optimistic women scored better on QoL compared to pessimistic women, especially on the QoL domains mental health, emotional functioning, negative feelings, (lack of) positive feelings, and sexual impairment.

Agreeableness

The explained variance of the personality trait agreeableness on QoL was 0.04 (p=0.037) one year after surgery, and 0.06 (p=0.015), 2 year post diagnosis (van der Steeg et al.,[1,4,25,26]).

Neuroticism

The results from a cohort study by Härtl et al.[16] showed that higher neuroticism scores at baseline predicted a poorer global health status (B=-0.25, p=0.001), role functioning (B=-0.15, p=0.043), emotional functioning (B=-0.18, p=0.015), and cognitive functioning (B=-0.16, p=0.013).

Van der Steeg et al.[1,4,25,26] (cohort study) stated that six months after surgery, neuroticism explained up to 26% of the variance in QoL scores in the mastectomy group (p<0.001), and up to 34% of the variance in QoL scores in the lumpectomy group (p<0.001). Irrespective of the type of surgery, high scores on neuroticism were associated with significantly lower overall QoL scores.

- *Self-esteem*

  Tomich et al.[22] also examined the relationship between self-esteem and QoL in their cohort study. The analyses showed no significant relation between self-esteem and physical and mental functioning.

- *Self-efficacy*

  Two studies investigated the relationship between the personality trait self-efficacy and QoL. A cross-sectional study by Popović-Petrović et al.[18] demonstrated that the r was 0.338 (p=0.006) for the total QoL, 0.418 (p=0.001) for emotional well-being, and 0.270 (p=0.031) for functional well-being, indicating significant correlations. When adding self-efficacy as a predictor for QoL in a hierarchical regression analysis, the personality trait self-efficacy was no longer significant.

  Results from a cross-sectional study by Shen et al.[21] showed a positive correlation between self-efficacy and the different QoL domains that were all statistically significant, ranging from 0.493 and 0.205 (p<0.0001 - 0.024). In a multiple stepwise regression model, hope, income, cancer stage, social support and self-efficacy appeared to be a statistically significant indicator for QoL.

  To recap, women with high self-efficacy levels assess their QoL higher/better compared to women who do not believe they possess the necessary capabilities.

- *Pessimism*

  Petersen et al.[17] conducted a cross-sectional study and showed that women with pessimistic scores, scored statistical significantly worse on the mental health QoL and Social Support subscale compared to optimistic women. Petersen et al. also assessed the clinical significance which corresponds with previous findings: pessimistic women scored lower on the mental health QoL (52 vs. 47, p=0.0001) but not on the Social Support subscale.

- *Trait anxiety*

  Three studies assessed the effect of trait anxiety on QoL. According to the results from a cross-sectional study by You et al.[23] Chinese patients had significantly higher trait anxiety levels compared to the US patients. For both the Chinese and the US patients, analyses revealed that there was a significant effect of trait anxiety on QoL, meaning that higher trait anxiety is associated with worse overall QoL (p<0.001). Trait anxiety was associated with all subscales of the FACT-B (physical-, social-, emotional- and functional well-being) with correlation coefficients ranging from 0.50 to 0.77 (all statistically significant, p<0.001).

  A cohort study by Van der Steeg et al.[1,4,25,26] demonstrated that at all measured QoL time points, patients with high trait anxiety at baseline had lower QoL scores, which was statistically significant. In this group, up to 43% of the variance in QoL scores was explained by trait anxiety (p<0.001).

  In a cohort study by Schreier and Williams,[20] results showed that trait anxiety was statistically significant correlated with total QoL (r=-0,32, p<0.05), and with psychological/spiritual QoL domain (r=-0,33, p<0.05).

The results show that all included studies examining the relationship between trait anxiety and QoL found a statistically significant correlation between trait anxiety and each of the QoL domains, as well as overall QoL.

Discussion

This systematic review demonstrates that all, except one, included studies show a small to moderate[27] statistically significant relation between personality traits and overall QoL or a specific QoL domain. All results showed a consistent direction of the relationship between personality traits and QoL. Depending on the personality trait and QoL domain, the correlation coefficients ranged from 0.20 to 0.77, and explained 4% up to 43% of variance in different domains of QoL. Two studies used OR, which varied between 0.43 and 7.81. The results indicate that the association of personality and QoL is most apparent for the personality traits optimism and trait anxiety, and psychosocial QoL domains, such as emotional- or social well-being. These specific associations can be partly explained by the fact that most of the included studies examined the relationship between trait anxiety or optimism and psychosocial QoL domains (5 and 12 studies, respectively). Only five of the included studies reported psychosocial *and* physical QoL scores, of which two found a statistically significant association between the personality traits self-efficacy and trait anxiety, and the QoL domain physical well-being.[21,23] Based on existing evidence, it was expected that the association between personality traits and QoL domains is the most apparent for psychosocial QoL domains.[6,28,29]

All included studies in this review examining the effect of trait anxiety on QoL have demonstrated that trait anxiety is negatively related to overall QoL and each QoL domain. This association is confirmed by other research groups.[24,28,30,31] Individuals with high trait anxiety often experience situations as more dangerous or threatening, are more susceptible to stress, and have more state anxiety reactions (a temporary emotional response about a particular situation or activity[32]) than individuals with low trait anxiety.[32-35] Trait anxiety is often seen as part of the personality dimension neuroticism, which is the tendency to experience negative emotions, such as anger and sadness.[36,37] The results from this review showed that up to 34% of variance in QoL domains can be explained by neuroticism. Individuals with high levels of neuroticism are more prone to stress, high levels of state anxiety, mental and physical health symptoms, and sleep difficulties, which ultimately affects an individual's short and long term QoL.[38-40]

Several studies indicated that the prevalence of anxiety and depression is much lower among optimistic individuals compared to pessimistic individuals.[41-44] This is confirmed

by the results of this review, which showed that the association between optimism and several QoL domains is positive, and that higher optimism is related to better QoL (i.e., less negative feelings, sexual problems, social avoidance, and fatigue). Optimistic individuals often have the generalized expectancy that the future holds positive outcomes. Pessimistic individuals have a more negative view on life.

The findings of this review are consistent with existing literature and the 2017 systematic review, which demonstrated that high scores on the personality traits agreeableness, openness to experience, extraversion, conscientiousness and optimism were associated with perception of good health and therefore higher overall QoL, while high level neuroticism was negatively associated with psychological functioning.[6,45-47]

The findings of the current review are also consistent with evidence from diverse groups of non-metastatic and metastatic cancer survivors. Several studies demonstrated that there is a consistent negative association between the personality traits neuroticism and trait anxiety, and QoL for patients with head and neck cancer, gynaecological cancer and colorectal cancer.[24,28,30,31] The association between the personality traits extraversion, dispositional optimism, self-esteem, conscientiousness and QoL is positive.[24,28,31,48-52]

Studies examining the relationship between personality traits and QoL in a sample with chronic conditions demonstrated similar results regarding the personality traits conscientiousness, optimism, self-efficacy and neuroticism.[53-55] There was no evidence found for an association between extraversion or agreeableness and QoL.

Based on the abovementioned evidence, high levels of trait anxiety or neuroticism have a negative effect on QoL, irrespective of being diagnosed with cancer, a chronic condition or being a healthy individual. High levels of optimism, self-esteem or self-efficacy have an opposite effect and are associated with better QoL.

Limitations

The first limitation regards the study quality of the included studies. Three studies were rated as to having poor quality, indicating an increase in the risk of bias (the results of the quality assessment are shown in Appendix C). An important cause of the relative low study quality can be found in the frugal methodological and statistical descriptions. Excluding the results from the studies rated as poor, does not impact the outcome.

The second limitation concerns reporting bias. Most of the included studies did not report non-significant results, which can distort the results from this review.

The third limitation concerns the lack of information regarding the personality traits of the non-responders in all included studies. Prior studies demonstrated that the personality traits from responders differ significantly from non-responders.[56,57] However, none of the included studies mentioned if they investigated whether the personality traits of the responders differed from the non-responders.

Another limitation concerns the generalizability of the studies. Several studies did not include relevant demographic information such as comorbidities or response rates, making it difficult to determine whether they had a representative group of breast cancer patients. This could have limited the ability to generalize the results from the study. Moreover, the vast amount of distinct questionnaires or subscales that were used to measure QoL (7 distinct questionnaires) or personality traits (10 distinct questionnaires), limited the ability to compare findings from different studies. Furthermore, we excluded articles that included patients with stage IV breast cancer because there is evidence that stage of disease has a direct effect on QoL.[2,58-60] However, there are studies reporting that the effect of personality on QoL outweigh the effects of demographic and medical characteristics.[1,13,61,62] This makes it difficult to determine whether the results from this review can be generalized to a representative group of breast cancer patients including stage IV patients.

Furthermore, personality traits are considered to be a part of someone's long term personality, which implicates that traits are stable over time. There are however critics of this theory, who believe that experiencing a traumatic event, such as cancer, can alter (to some degree) personality, both negatively as positively.[63,64]

Finally, most of the included studies in this review examined the relationship between trait anxiety or optimism, and QoL. The skewness of included articles that examined these particular relationships, increases the probability of finding significant associations.

The strengths of this current review include the systematic and comprehensive approach to identify studies published up to November 2020, and the quality assessment including reporting biases.

Clinical implications and recommendations

This review established that there is a statistically relevant relationship between an individual's personality traits and their QoL, following breast cancer diagnosis. This result validates the use of psychometric tests for all breast cancer patients to provide relevant information for physicians and patients regarding a potential cause of low or deterioration of QoL, and if desired, establish the patient's need for psycho-oncological support or treatment. The results also imply that measuring QoL without measuring personality traits is of limited value and may lead to inaccurate conclusions regarding QoL scores. All future QoL research should measure personality traits in order to accurately interpret QoL scores.

The strict in- and exclusion criteria that were used in this review, caused a particularly homogeneous group, as opposed to the systematic review conducted in 2017. Nevertheless, when comparing the results from this review with the 2017 review, the conclusions remain the same. This indicates that health state, disease stage or gender, does not affect the relationship between personality traits and QoL.

This review revealed that, although the evidence that personality traits are associated with QoL is strong and consistent, the amount of high-quality QoL studies that measure and stratify for personality traits in their study remains very limited. This review also showed that although there is a substantial variation in QoL and personality traits measurement instruments between studies, the results remain consistent. However, to facilitate the comparison of personality traits between studies, it is recommended to develop a standardized approach to measure these traits. Personality traits should (preferably) be measured as dimensions, to measure a whole range of personality traits along a continuum, to accurately interpret QoL results.

There is strong and consistent evidence that individuals with low levels of optimism, or high level of neuroticism or trait anxiety, are associated with more negative health perceptions, more symptoms, more treatment side effects, and consequently poorer QoL, regardless of their health status, disease stage, or gender.[45-47,65-67] Characteristics such as age, education, relationship status, and type of surgery are well-established factors influencing QoL. This review provides evidence that personality traits should be added as important influential factors.

Conclusion

This review has found evidence of a relationship between personality traits and QoL in non-metastatic breast cancer patients, especially for the personality traits 'trait anxiety' and 'optimism', and psychosocial QoL domains, such as emotional- or social well-being. Personality traits either have a negative or positive relationship, and the strength of the relationship depends on which personality trait and QoL domain(s) assessed. In order to interpret QoL data accurately, all future QoL research has to stratify for personality traits.

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Appendix A. Overview personality traits

Dimension	Individual personality trait (Superordinate factor)	Characteristics low score	Characteristics high score	Appropriate and validated measurement instrument
Openness to experience The open attitude towards other people, beliefs, and experiences.	Sensation/novelty seeking The need for varied, novel, and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experience. Individuals with high levels of novelty seeking are often more impulsive, extravagant, disorderly, and tend to have higher stress levels.	- Practical - Conventional - Prefers routine	- Curious - Wide range of interest - Independent	Openness to experience - NEO Personality Inventory (NEO-PI) - NEO Five Factor Inventory (NEO-FFI) - The Revised NEO Personality Inventory (NEO-PI-R) Sensation/novelty seeking - Sensation Seeking Scale (SSS-V)
Conscientiousness One's orientation towards experiences, goals, and interests of other people.	Agency An individual's striving to master the environment, to assert the self, to experience competence, achievement, and power. People mastery The feeling as the extent to which a person perceives himself or herself to be in control of events and ongoing situations.	- Impulsive - Careless - Disorganized	- Hardworking - Dependable - Organized	Conscientiousness - NEO Personality Inventory (NEO-PI) - NEO Five Factor Inventory (NEO-FFI) - The Revised NEO Personality Inventory (NEO-PI-R) Agency - Personal Attributes Questionnaire (PAQ) - The Sense of Agency Scale People mastery - The Pearlin Mastery Scale - DMQ-18
Extraversion The degree in which energy, orientation, and attention are focused on the outside world in contrast to the inner world.	Hopefulness A general tendency to construct and respond to the perceived future positively. (Dispositional) optimism A global expectation that good things will be plentiful in the future and bad things will be scarce. Alexithymia Individuals who experience difficulties in identifying and describing their feelings, their cognitive style is concrete and reality-based and they have impoverished inner emotional and fantasy lives.	- Quit - Reserved - Withdrawn	- Outgoing - Warm - Seeks adventure	Extraversion - NEO Personality Inventory (NEO-PI) - NEO Five Factor Inventory (NEO-FFI) - The Revised NEO Personality Inventory (NEO-PI-R) - Eysenck Personality Inventory (EPI) - Eysenck Personality Questionnaire (EPQ) Hopefulness - Hunter Opinions and Personal Expectations Scale (HOPES) Dispositional optimism - Life Orientation Test (LOT) - Attributional Style Questionnaire (ASQ) Alexithymia - Toronto Alexithymia Scale (TAS)

Appendix A. Continued

Dimension	Individual personality trait (Superordinate factor)	Characteristics low score	Characteristics high score	Appropriate and validated measurement instrument
Agreeableness One's orientation towards experiences, goals, and interests of other people.	Sense of coherence The extent to which one has a pervasive and enduring, though dynamic, feeling of confidence that (1) the stimuli derived from one's internal and external environments in the course of living are structured, predictable, and explicable (comprehensibility); (2) the resources are available to one to meet the demands posed by these stimuli (manageability); and (3) these demands are challenges that are worthy of investment and engagement (meaning)	- Critical - Uncooperative - Suspicious	- Helpful - Trusting - Empathetic	Agreeableness - NEO Personality Inventory (NEO-PI) - NEO Five Factor Inventory (NEO-FFI) - The Revised NEO Personality Inventory (NEO-PI-R) Sense of coherence - The Sense of Coherence (SOC) Scale
Neuroticism Weighing emotional instability against emotional stability, i.e., the tendency to experience distressing emotions, unrealistic ideas, excessive cravings or urges, and maladaptive coping responses	Aggression An intentional attempt to harm another person. Negative affect Common variance between anxiety, sadness, fear, anger, guilt and shame, irritability, and other unpleasant emotions. Perfectionism Demanding of oneself or others a higher quality of performance than is required by the situation. Pessimism Dimension of generalized expectancies about the occurrence of bad outcomes is one's future. Pessimism is related to more intense negative feelings such as anxiety, sadness, or despair. Pessimism is associated with health-damaging behaviours. Rumination An individuals' self-reflection as well as a repetitive and passive focus on one's negative emotions.	- Calm - Even-tempered - Secure	- Anxious - Unhappy - Prone to negative emotions	Neuroticism - NEO Personality Inventory (NEO-PI) - NEO Five Factor Inventory (NEO-FFI) - The Revised NEO Personality Inventory (NEO-PI-R) - Eysenck Personality Inventory (EPI) - Eysenck Personality Questionnaire (EPQ) - Dutch Personality Inventory (DPI) Aggression - Buss-Perry Aggression Questionnaire (BPA) Negative affect - The Positive and Negative Affect Schedule (PANAS) - The short form of Eysenck Personality Inventory Emotional Stability Scale (EPI-Q)

Appendix A. Continued

Dimension	Individual personality trait (Superordinate factor)	Characteristics low score	Characteristics high score	Appropriate and validated measurement instrument
Neuroticism Weighing emotional instability against emotional stability, i.e., the tendency to experience distressing emotions, unrealistic ideas, excessive cravings or urges, and maladaptive coping responses	Self-efficacy Beliefs in one's capabilities to mobilize motivation, cognitive resources and courses of action needed to meet given situational demands. Individuals with high levels of self-efficacy have trust in their own abilities to gain control over events affecting their life, to overcome obstacles, and to perform well. Self-esteem An individual's sense of his or her value or worth, or the extent to which a person values, approves of, appreciates, prizes, or likes him or herself. Patients with high levels of self-esteem tend to be more resilient, more likely to engage in healthy behaviours, and better QoL. Trait anxiety The existence of stable individual differences in the tendence to respond with state anxiety in the anticipation of threatening situations. Type D General propensity to psychological distress that is defined by elevated scores on two broad personality traits, negative affectivity, and social inhibition.			Perfectionism - Perfectionism Inventory (PI) - Frost Multidimensional Perfectionism Scale (FMPS) Pessimism - Life Orientation Test (LOT) Rumination - Ruminative Response Scale (RRS) Self-efficacy - General Self-Efficacy Scale (GSES) Self-esteem - Rosenberg Self-Esteem Scale (RSE) Trait anxiety - The State-Trait Anxiety Inventory (STAI) Type D - Type D Scale (DS)-14/16/24

Appendix B. PubMed Search Strategy

Search 1

"Five Factor Personality Model"[tiab] OR "five factor model"[tiab] " Big five personality traits"[tiab] OR "Big five model"[tiab] OR agreeableness[tiab] OR conscientiousness[tiab] OR extraversion[Mesh] OR neuroticism[Mesh] OR "openness to experience"[tiab] OR "Personality"[Mesh] OR personalit*[tiab] OR personality trait*[tiab] OR "NEO Personality Inventory"[tiab] OR "Eysenck's Three Factor model"[tiab] OR "Three Factor model"[tiab] OR psychoticism[tiab] OR "trait anxiety"[tiab] OR agency[tiab] OR aggression[tiab] OR Aggressiveness[tiab] OR alexithymia[tiab] OR "dispositional optimism"[tiab] OR optimism[tiab] OR hopefulness[tiab] OR "people mastery"[tiab] OR mastery[tiab] OR "negative affect*"[tiab] OR Negativism[tiab] OR "sense of coherence"[tiab] OR "self efficacy"[tiab] OR "self esteem"[tiab] OR "Type D"[tiab] OR "Type D personality"[tiab] OR "Type D behavior"[tiab] OR "novelty seeking"[tiab] OR "sensation seeking"[tiab] OR perfectionism[tiab] OR "rumination, cognitive"[Mesh] OR rumination, cognitive[tiab]

Search 2

"Quality of Life"[Mesh] OR quality of life[tiab] OR "Well being"[tiab] OR "Health related quality of life"[tiab] OR "life quality"[tiab] OR QOL[tiab] OR HRQOL[tiab]

Search 3

"Breast Neoplasm*"[Mesh] OR "breast neoplasm*"[tiab] OR "mammary neoplasm*"[tiab] OR "breast tumor*"[tiab] OR "mammary tumor*"[tiab] OR "breast tumour*"[tiab] OR "mammary tumour*"[tiab] OR "breast cancer"[tiab] OR "mammary cancer"[tiab] OR "breast carcinom*"[tiab] OR "mammary carcinom*"[tiab]

Search 4

("Five Factor Personality Model"[tiab] OR "five factor model"[tiab] " Big five personality traits"[tiab] OR "Big five model"[tiab] OR agreeableness[tiab] OR conscientiousness[tiab] OR extraversion[Mesh] OR neuroticism[Mesh] OR "openness to experience"[tiab] OR "Personality"[Mesh] OR personalit*[tiab] OR personality trait*[tiab] OR "NEO Personality Inventory"[tiab] OR "Eysenck's Three Factor model"[tiab] OR "Three Factor model"[tiab] OR psychoticism[tiab] OR "trait anxiety"[tiab] OR agency[tiab] OR aggression[tiab] OR Aggressiveness[tiab] OR alexithymia[tiab] OR "dispositional optimism"[tiab] OR optimism[tiab] OR hopefulness[tiab] OR "people mastery"[tiab] OR mastery[tiab] OR "negative affect*"[tiab] OR Negativism[tiab] OR "sense of coherence"[tiab] OR "self efficacy"[tiab] OR "self esteem"[tiab] OR "Type D"[tiab] OR "Type D personality"[tiab] OR "Type D behavior"[tiab] OR "novelty seeking"[tiab] OR "sensation seeking"[tiab] OR perfectionism[tiab] OR "rumination, cognitive"[Mesh] OR rumination, cognitive[tiab]) AND ("Quality of Life"[Mesh] OR quality of life[tiab] OR "Well being"[tiab] OR "Health related quality of life"[tiab] OR "life quality"[tiab] OR QOL[tiab] OR HRQOL[tiab]) AND ("Breast Neoplasm*"[Mesh] OR "breast neoplasm*"[tiab] OR "mammary neoplasm*"[tiab] OR "breast tumor*"[tiab] OR "mammary tumor*"[tiab] OR "breast tumour*"[tiab] OR "mammary tumour*"[tiab] OR "breast cancer"[tiab] OR "mammary cancer"[tiab] OR "breast carcinom*"[tiab] OR "mammary carcinom*"[tiab])

Restrictions

Population: Human

Language: Dutch and English

Methodology: Case reports; classical articles; clinical study; clinical trial; clinical trial phase 1; clinical trial phase 2; clinical trial phase 3; clinical trial phase 4; comparative study; controlled clinical trial; dataset; evaluation study; journal article; multicenter study; observational study; randomized controlled trial.

Table 1. Results PubMed search

	Without restrictions	**With restrictions**
Search 1	553,719	415,049
Search 2	408,226	293,135
Search 3	399,282	280,586
Search 4	1,194	1,050

Table 2. Results PubMed search (time of publication from December, 2020, up to January 2022)

	Without restrictions	**With restrictions**
Search 1	40,979	2,801
Search 2	59,024	7,156
Search 3	31,459	2,575
Search 4	108	25

Appendix C. Risk of bias assessment

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality rate
Bellino et al.[13]	Y	Y	NR	Y	NR	Y	N	N	Y	N	Y	NA	N	Y	Fair
Carver et al.[14]	Y	Y	NR	N	NR	NA	NA	N	Y	NA	Y	NA	NA	Y	Fair
Durá-Ferrandis et al.[15]	Y	Y	Y	Y	NR	Y	Y	N	Y	N	Y	NA	CD	Y	Fair
Härtl et al.[16]	Y	Y	NR	Y	NR	Y	Y	N	Y	N	Y	NA	NR	Y	Fair
Petersen et al.[17]	Y	Y	NR	Y	Y	NA	NA	Y	Y	NA	Y	NA	NA	N	Fair
Popović-Petrović et al.[18]	Y	Y	NR	Y	NR	NA	NA	N	Y	NA	Y	NA	NA	Y	Poor
Piro et al.[19]	Y	Y	NR	Y	NR	NA	NA	N	Y	NA	Y	NA	NA	Y	Poor
Schreier et al.[20]	Y	Y	NR	Y	NR	Y	Y	N	Y	N	Y	NA	N	N	Fair
Shen et al.[21]	Y	Y	Y	Y	NR	NA	NA	N	Y	NA	Y	NA	NA	Y	Fair
van der Steeg et al.[1]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y	Good
Tomich et al.[22]	Y	Y	NR	N	NR	Y	Y	N	Y	N	Y	NA	Y	N	Fair
You et al.[23]	Y	Y	Y	N	NR	NA	NA	N	CD	NA	CD	NA	NA	Y	Poor

CD, cannot be determined; NA, not applicable; NR, not reported; N, no; Y, yes.
Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies.

Questions
Q1. Was the research question or objective in this paper clearly stated?
Q2. Was the study population clearly specified and defined?
Q3. Was the participation rate of eligible persons at least 50%?
Q4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5. Was a sample size justification, power description, or variance and effect estimates provided?
Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10. Was the exposure(s) assessed more than once over time?
Q11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12. Were the outcome assessors blinded to the exposure status of participants?
Q13. Was loss to follow-up after baseline 20% or less?
Q14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Chapter 9

General discussion and future perspectives

Summary and general discussion

De-escalation of axillary staging and treatment strategies in breast cancer is ongoing in both node-negative (cN0) and node-positive (cN+) breast cancer. In this process, both oncologic safety and impact on quality of life (QoL) must be considered. The results of this thesis demonstrated the ongoing trend in de-escalation, a lack of consensus regarding appropriate axillary staging and treatment strategies especially in cN+ breast cancer, and it demonstrated long-term oncologic safety outcomes in cN0 as well as cN+ breast cancer. All research was performed with the aim to reach (more) consensus regarding axillary staging and treatment strategies. Furthermore, it provided some insights regarding personality traits and their effect on QoL, which may further aid in interpreting QoL endpoints.

Axillary staging and treatment strategies in cN0 breast cancer

In cN0 breast cancer treated with primary surgery, the sentinel lymph node biopsy (SLNB) has been the staging procedure of choice since the 1990s. As a result of trials such as the Z0011, indications to omit completion ALND in cN0 breast cancer were extended from a negative SLNB, to a positive SLNB (with up to two metastatic sentinel lymph nodes (SLNs)) in patients treated with breast-conserving surgery (BCS) followed by whole breast radiotherapy (RT).[1-4] As no or only few patients treated with mastectomy were included in these trials, and chest wall radiotherapy (RT) is not routinely performed after mastectomy, these results cannot be extrapolated to cN0 patients treated with mastectomy. Therefore, **Chapter 2** provided insight into the oncologic safety of omitting completion axillary treatment in patients with cT1-2N0 breast cancer and a positive SLNB (with up to three micro- and/or macrometastases) treated with mastectomy. In this nationwide registry study, patients were classified by axillary treatment-strategy. Of the 1,090 included patients, 219 (20.1%) were assigned to the no completion axillary treatment-group, 437 (40.1%) to the completion ALND-group, 327 (30.0%) to the regional RT-group, and 107 (9.8%) to the completion ALND followed by regional RT-group. With a median follow-up of 6.0 years, the overall 5-year regional recurrence (RR) rate was 1.3%. The 5-year RR rate of the no completion axillary treatment-group was 2.5%, which did not statistically significant differ from that of the completion ALND-group (1.4%) and regional RT-group (1.0%). Other 5-year recurrence outcomes (local, locoregional, and distant metastases rate, and recurrence-free interval (RFi), the latter including all recurrences and death from breast cancer) were also comparable among the different axillary treatment-groups. This was in accordance with other studies.[5,6] In our study, patients who did not receive completion axillary treatment were often older, had more favourable tumour characteristics (e.g., grade 1 disease, pN1mi(sn)), and less often received adjuvant treatment (chemotherapy 30.1% versus 58.1%, and chest wall RT 4.1%

versus 39.8% in the whole cohort). This trend was also found in an American population-based study on axillary management patterns in 12,190 patients with cT1-2N0 breast cancer treated with mastectomy, and with 1-2 metastatic SLNs.[7] In addition, in their study, data were collected regarding comorbidities, which were more often present in the no completion axillary treatment-group. In our study, the no completion axillary treatment-group did have a statistically significant worse 5-year overall survival (OS), which was due to a high percentage of non-cancer deaths (58.7% versus 44.4% in the whole cohort). In some patients, their estimated lower life expectancy at time of breast cancer diagnosis has likely contributed to omitting (axillary) treatment. Hence, in daily practice patients are being selected for omission of (axillary) treatment, not only based on tumour characteristics but also on other highly relevant factors such as age and overall health. This is also seen in trials such as TOP-1 and PRIME II, in which omission of RT after BCS is investigated in older patients with low-risk breast cancer, with local recurrence as primary endpoint. In the PRIME II trial, all patients were treated with adjuvant endocrine therapy. The authors reported a 10-year local recurrence rate of 9.5% if RT was omitted, compared to 0.9% in the RT-group.[8] Nonetheless, the groups had a comparable distant metastases rate and breast cancer-specific and OS at 10-year follow-up. The authors emphasized the importance of balancing the harms and benefits of RT, as omission did not increase the risk of death from breast cancer.

Ongoing non-inferiority randomised controlled trials (RCTs) regarding omitting axillary treatment following a positive SLNB are the SINODAR ONE, POSNOC, and SENOMAC trials, which all include patients treated with BCS or mastectomy, and who have 1-2 macrometastastic SLNs.[9-11] In the SINODAR ONE trial, a subanalysis was performed for 128 patients treated with mastectomy, who had been randomised between SLNB only and completion ALND.[12] With a median follow-up of 33 months, the SLNB was not inferior to ALND in terms of 5-year recurrence-free survival. Currently, more patients are being enrolled to increase power. In the POSNOC trial, 1,900 patients are randomised between adjuvant systemic therapy alone and adjuvant systemic therapy with ALND or axillary RT, with 5-year axillary recurrence rate as primary endpoint. The first results are expected in 2026. In the SENOMAC trial, 3,500 patients are randomised between SLNB only and ALND. The results regarding the primary endpoint 5-year breast cancer-specific survival are expected in 2029. Interestingly, in all three trials, either patients aged ≥75 or patients deemed unfit for adjuvant systemic therapy were not included. This was in line with studies evaluating generalisability of RCT's, and leaves questions specifically for this group of patients.[13,14]

As the Z0011 trial only included patients treated with primary surgery,[3,4] its outcomes do not apply to patients treated with neoadjuvant systemic therapy (NST). As a result of

NST, patients with cN0 disease more often have a negative SLNB as compared to patient treated with primary surgery. In a pooled analysis of five studies (n=3,834) assessing the nodal residual disease (i.e., ypN+) rate in best-responders (HER2+ and triple negative disease) with initially cN0 disease and with either a complete response on imaging or a pathological complete response (pCR) of the primary tumour, the pooled ypN+ rate was only 2.16% (95%-CI 1.70-2.63).[15] This could justify omission of axillary surgery in these patients. It will aid in predicting the chance of having either nodal pCR (i.e., ypN0) or ypN+, in order to prevent both under- and overtreatment as much as possible.

In patients with cN0 disease who do have metastatic SLNs after NST, this may indicate chemotherapy-resistant or even progressive disease. In **Chapter 5**, the prognostic significance of nodal status before and after NST was assessed in a nationwide cohort study consisting of 18,456 patients. In univariable analyses, patients with cN0 breast cancer and ypN+ after NST had a statistically significant worse 5-year OS when compared to patients with cN0 disease with ypN0 (85.4% versus 94.4%, respectively, p<0.0001). For HR+HER2- HR+HER2+, HR-HER2+, and triple negative disease, respectively, 5-year OS in the cN0ypN0-subgroup was 95.9%, 97.0%, 95.7%, and 90.6%; in the cN0ypN+-subgroup 89.7%, 90.4%, 73.7%, and 53.6%. These results suggest that treatment *escalation* instead of *de-escalation* may be indicated in case of ypN+, especially in patients with HR-HER2+ or triple negative disease, emphasizing the importance of axillary restaging after NST.

Axillary staging and treatment strategies in cN+ breast cancer

Patients with cN+ breast cancer are often treated with NST. As a result, approximately a third of these patients achieve ypN0.[16-19] As ypN0 is associated with improved prognosis, it was hypothesized that patients who achieve ypN0 do not benefit from an ALND.[20-23] To enable response-guided treatment, and thus to potentially omit ALND in case of ypN0, less invasive axillary staging procedures were implemented: SLNB, excision of a targeted lymph node (TLN) (e.g., MARI-procedure), and targeted axillary dissection (TAD), in which the former two procedures are combined. With its superior diagnostic accuracy, as confirmed by results of the RISAS trial in 2022,[19] TAD is the preferred option for axillary staging after NST, however, long-term oncologic outcomes are lacking.

Targeted axillary dissection

Nowadays, several TAD-procedures are being performed, which differ concerning the type of definitive marker used for excision of the TLN, and the timing of marker placement. In **Chapter 3**, we performed a systematic review of studies describing TAD, and included 51 studies with 4,512 patients. Six definitive markers were identified: wire, radioactive iodine (^{125}I) seed, ^{99m}Technetium, (electro)magnetic/radiofrequency markers, black ink, and a clip (with ultrasound-guided localisation and excision). Timing of definitive marker

placement was also evaluated. If the definitive marker was placed directly in the TLN before NST, followed by excision of the TLN after NST, this was considered a one-step procedure. If first a clip was placed before NST, and the definitive marker after NST, this was defined as a two-step procedure. The identification rate (IR) of the TLN at surgery varied from 61.5%-100% and from 70.8%-100%, for one-step and two-step procedures, respectively. Due to a lack of high-quality studies, and heterogeneity between studies, it was impossible to determine the most optimal TLN excision technique in terms of IR and feasibility. In **Chapter 3**, we discussed the benefits and drawbacks of each definitive marker, relevant to consider when performing TAD in clinical practice. Moreover, we emphasized an important drawback of the two-step procedure: as the TLN must be localised twice (on imaging after NST, to place the definitive marker, and at surgery), this can negatively affect the ability to identify the TLN. Interestingly, in this systematic review, only 19 (47.5%) of 40 included studies that reported on a two-step procedure, reported on the IR of the clipped TLN on imaging. In these 19 studies, the IR on imaging after NST varied from 48.8%-100%. This wide variation may be explained by the diverse range of clips used in clinical practice, by the level of experience of the specialist performing the localisation, and by decreased clip visibility over time. Furthermore, if the hyperechogenic clip is placed in the hypoechogenic cortex, cortex regression can also affect clip visibility, or cause dislocation. This is in accordance with the multivariable analyses of Kuemmel et al., in which nodal complete response on imaging was associated with the inability to identify the TLN at surgery.[24] Importantly, in clinical practice, if the clip is not identified after NST and thus the definitive marker cannot be placed to enable intra-operative localisation of the TLN, this may result in having to proceed to (potentially unnecessary) ALND. To determine the most optimal TAD procedure, both one-step and two-step procedures require further investigation in high quality prospective trials, in which both are preferably directly compared.

Response-guided axillary treatment

Nowadays, response-guided treatment is being performed worldwide, either following ALND or following one of the less invasive axillary staging procedures. The introduction of NST has not only affected surgical strategies, but also locoregional RT strategies, as locoregional RT guidelines were originally based on studies in the primary surgery setting. In patients with cT1-2N1 breast cancer (with 1-3 suspicious lymph nodes before NST), it was unclear if and to what extent locoregional RT was indicated after NST. In **Chapter 4**, 5-year oncologic safety outcomes of de-escalated locoregional RT according to a predefined consensus-based study guideline were presented. In the RAPCHEM registry study, 838 patients with cT1-2N1 disease were assigned to one of three risk groups for locoregional recurrence (LRR), with corresponding locoregional RT recommendations: no chest wall RT and no regional RT in the low-risk group (i.e., ypN0), only local RT in the

intermediate-risk group (i.e., ypN1), and locoregional RT in the high-risk group (i.e., ypN2-3). If the study guideline was followed (which was the case in 64% of the whole cohort), 5-year LRR-risks were 2.3%, 1.0%, and 1.4%, for the low-risk, intermediate-risk, and high-risk group, all in accordance with the hypothesis (LRR-risk <4%). Patients in whom less or more RT was given than prescribed did not have statistically significant altered LRR-risk, RFi, or OS. The study guideline therefore supported the hypothesis that locoregional RT can be omitted in selected patients in whom ALND is performed (i.e., no chest wall RT and no regional RT in case of ypN0, and no regional RT in case of ypN1). Haffty et al. performed a similar analysis in 701 patients with cT1-4N1-2 breast cancer treated with NST, followed by ALND, and locoregional RT if indicated.[25] They also concluded that omitting locoregional RT after mastectomy, and regional RT after BCS, was not associated with worse LRR outcomes in case of ypN0. In the RAPCHEM study, patients treated with ALND were assigned to the risk groups based solely on ypN-status, which resulted in patients with HER2+ or triple negative disease being more often assigned to the low-risk group. In the multivariable analyses for RFi, both intermediate- and high-risk (i.e., ypN1 and ypN2-3, respectively), and grade 3 and triple negative disease were associated with worse RFi. Therefore, assigning patients to a risk group based on ypN-status appears a good foundation, yet grade and breast cancer molecular subtype should also be taken into account when evaluating locoregional RT indications. In 157 (18.7%) of 838 included patients, no ALND was performed. Since less invasive axillary staging procedures are less accurate than the ALND, this complicated the study guideline, the analyses and the interpretation of the results. It also indicated the urge for more evidence regarding the value of locoregional RT and/or ALND in cN+ breast cancer treated with NST, especially when less invasive axillary staging procedures are used to determine treatment-response.

Initially, the aim of response-guided treatment was to omit ALND in case of ypN0. Yet, nowadays ALND is also being omitted (or is replaced by axillary RT) in case of ypN+.[26] Until more evidence is provided, resulting in (more) consensus, several staging and treatment strategies are being performed, also in the Netherlands. This enables a nationwide registry to evaluate these different strategies. Therefore, the Dutch MINIMAX registry study was conducted, of which the study protocol was described in **Chapter 6**. The MINIMAX study consists of a retrospective cohort and a prospective cohort, in which cN+ patients with ypN0 and those with ypN+ are both included. The outcomes are oncologic safety and impact on QoL. The 5-year oncologic safety results of the retrospective cohort (in terms of axillary recurrence rate, breast cancer-specific survival, disease-free survival, and OS) are expected in the near future. In the prospective cohort, besides oncologic safety, QoL is assessed through Patient Reported Outcome Measures at baseline (i.e., before NST), and one and five years after surgery. One-year QoL outcomes are expected to be published in 2024. In the meantime, to assess practice variation in the Netherlands in more detail,

a survey study was conducted among the 35 hospitals participating in the MINIMAX study. The results were presented in **Chapter 7**, and showed a wide variation regarding used less invasive axillary staging procedures, reasons to perform the ALND (directly after NST, or as completion axillary treatment), regional RT indications, and whether or not the number of suspicious lymph nodes before NST or radiological response to NST were included when deciding on axillary strategies. Interestingly, there was also variation with regard to the use of the clinical TNM classification. According to the AJCC staging system,[27] the cN-status is based on the anatomical extent of regional metastatic disease (e.g., cN1 in case of metastatic disease in level I-II of the axilla, not fixed). Nowadays, the number of suspicious lymph nodes is sometimes used to define the cN-status (e.g., 1-3, or ≥4 suspicious lymph nodes before NST, resulting in cN1 of cN2, respectively), as is done when evaluating the ypN-status. This requires attention in the multidisciplinary meeting as well as in research. A possible solution would be to describe the cN-status according to the AJCC, followed by the number of suspicious nodes in parentheses (e.g., cN1(4)).

While awaiting results of the MINIMAX study, limited yet increasing evidence is available regarding the oncologic safety of response-guided treatment based on less invasive axillary staging procedures. In the MARI-protocol,[28,29] axillary treatment decisions were made based on findings on the 18F-FDG PET/CT in combination with the results of the MARI-procedure. Three-year follow-up results of a single centre study demonstrated that the ALND was omitted in 217 (80.0%) of 272 patients (and replaced by axillary RT in 161 (74.2%) of 217 patients), with a 3-year axillary recurrence-free survival of 98.0% (95%-CI 96.0-100.0).[30] Of the five patients that had an axillary recurrence, four had triple negative breast cancer. This supports the idea that breast cancer molecular subtype should be taken into account when making treatment decisions. This was also suggested by studies in which the extent of residual nodal disease and its effect on OS varied per breast cancer molecular subtype.[31,32] The value of locoregional treatment with regard to improving prognosis should be investigated, especially in relation to aggressive tumour biology.

It is unclear if and to what extent the type of less invasive axillary staging procedure affects the oncologic outcomes and impact on QoL of response-guided treatment. Galimberti et al. suggested that performing TAD is not of added value if cN+ disease has converted to cN0 after NST,[33] based on mostly retrospective studies (with 58 to 234 patients) reporting limited axillary recurrences after performing SLNB alone.[34-38] Although these results are promising, it is important to realise that SLNB is less accurate compared to TAD, and thus has an increased risk of missing residual disease and thus the risk for patients of missing out on adjuvant systemic therapy. Coming back to **Chapter 5**, in cN+ disease the negative effect of residual nodal disease after NST on 5-year OS was also present in all breast cancer molecular subtypes, and most apparent in HR-HER2+

and triple negative disease. Cortazar et al. already had concluded that the prognostic value of nodal residual disease was greatest in HR-HER2+ and triple negative disease,[20] and in a study by Boughey et al. in 701 patients with cN+ disease treated with NAC the statistically significant effect of triple negative disease on OS in case of residual disease was also present.[16] Together with **Chapter 5**, the results indicate that these patients can be in need of more extensive treatment. Systemic therapies such as TDM-1 and capecitabine can improve prognosis, as was shown by Von Minckwitz et al. and Masuda et al., respectively.[39,40] More evidence is needed regarding the impact of the less invasive axillary procedures on oncologic safety, also in relation to the different subtypes.

Quality of life

With breast cancer survival improving, QoL has become more and more important. As ALND is associated with substantial morbidity,[41,42] its omission is expected to decrease post-surgical morbidity, also in patients with cN+ disease treated with NST. However, ALND is now often replaced by axillary RT.[26] Moreover, lymph drainage can be altered due to response to systemic therapy. It is unclear to what extent these aspects affect morbidity and QoL. Meanwhile, several other non-treatment related factors have already been identified as being associated with QoL.[43] After being investigated in the general population,[44] the relationship between personality and health-related QoL was examined in patients with breast cancer in the systematic review in **Chapter 8**. Twelve studies were included with 2,729 patients, and a small to moderate effect of personality on QoL was found, which varied depending on the type of personality trait and QoL domain being assessed. The effect was most apparent between the personality traits “optimism” and “trait anxiety”, and the psychosocial QoL domains. The results confirmed that personality is associated with QoL. Therefore, in future studies, personality should be taken into consideration when evaluating QoL. This was already done in the MINIMAX study, in order to optimize future analyses.

Main findings

- In cT1-2N0 breast cancer treated with primary mastectomy, and with a positive SLNB, it appears oncologically safe to omit axillary treatment in selected patients. In daily practice, axillary treatment is already being omitted, not only based on tumour characteristics, but also based on factors such as age and overall health.
- In patients with cN0 disease treated with NST, metastatic SLNs after NST may indicate chemotherapy-resistant or even progressive disease, and therefore may require treatment *escalation*, especially in HR-HER2+ and triple negative disease.

- In patients with cN+ disease treated with NST, several TAD-procedures are being performed. These differ concerning the type of definitive marker used for TLN excision, and the timing of marker placement. Due to a lack of high-quality studies, it is not possible to conclude which technique is most optimal. Each technique does have its own benefits and drawbacks, which are all important to consider when such procedures are used in clinical practice. In two-step procedures, the TLN must be localised twice, which can negatively affect the ability to identify the TLN and may thus increase the need for (unnecessary) ALND.
- In patients with cT1-2N1 breast cancer (with 1-3 suspicious lymph nodes before NST), who are treated with ALND, de-escalation of locoregional RT based on ypN-status appears feasible. Other factors such as triple negative and grade 3 disease are associated with worse RFi, and therefore need to be considered when deciding on locoregional RT strategies. The implementation of less invasive axillary staging procedures complicates response-based treatment choices.
- The MINIMAX study will provide more insight into oncologic safety and impact on QoL of currently used response-guided treatment strategies in the Netherlands. In the meantime, a wide variety of axillary staging and treatment strategies are being performed, important to realise while awaiting results of ongoing RCTs and registry studies.
- The negative effect of ypN+ on long-term oncologic outcomes is present in all breast cancer molecular subtypes, and most apparent in HR-HER2+ and triple negative disease. This indicates the importance of adequate restaging after NST, both in cN0 and cN+ disease.
- Personality is associated with QoL in patients with breast cancer. The effect is most apparent between personality traits “optimism” and “trait anxiety” and the psychosocial QoL domains.

Future perspectives

For cN0 breast cancer

1) Primary surgery

The SINODAR ONE, POSNOC, and SENOMAC trial will provide more evidence regarding the oncologic safety of omitting completion axillary treatment in patients treated with mastectomy, and who have 1-2 macrometastatic SLNs. In the meantime, studies should be conducted for patients of older age and/or decreased overall health. In Western countries, approximately a third of breast cancer patients are ≥65 of age, with the greatest incidence between 75-79 years.[45] As these patients more often have HR+HER2- breast cancer, tend to have reduced treatment tolerance, a lower life expectancy regardless of breast cancer,

and possibly also changed personal priorities, these factors should be taken into account when deciding on (axillary) treatment. The Choosing Wisely campaign recommends to not routinely perform SLNB in case of patients aged ≥70 with HR+HER2- breast cancer,[46] based on RCTs in which omission of SLNB did not result in worse long-term survival outcomes.[47-49] Most patients were treated with BCS, and all received adjuvant tamoxifen. In a recently published Canadian population-based cohort study, patients aged 65-95 years and diagnosed with stage I-II breast cancer between 2010-2016 were included.[50] In 1,771 (10.2%) of 17,370 patients, axillary surgery was omitted. These patients were older, with more comorbidities, and were less likely to receive adjuvant treatment. After applying propensity score weighting, they had comparable breast cancer-specific survival, yet worse OS. The authors suggested that the latter was probably due to other cause mortality, as we also found in our study. To predict 5-year survival and recurrence, including individualized risk estimations of adjuvant treatment benefits in older patients, the PORTRET tool was developed in 2021.[51] In this tool, age, tumour characteristics, comorbidities according to the ICD-10 classification, and geriatric predictors such as walking difficulties, dementia or cognitive impairment, polypharmacy, and sensory deficits were included. This may guide better individualized (axillary) treatment strategies specifically for the older patient.

2) Neoadjuvant systemic therapy

The ongoing POSNOC and SENOMAC trials also include patients treated with NST, and therefore will provide more evidence regarding the safety of omitting completion axillary treatment in case of ypN+. In the POSNOC trial, these patients are only included if the SLNB is performed before start of NST, which complicates response assessment after NST, and is less often used in clinical practice nowadays. Thus, the results may be of limited value.

In the meantime, the EUBREAST-01 and ASICS trials are assessing the oncologic safety of omitting axillary surgery based on primary tumour response in patients with cN0 disease with HER2+ or triple negative subtype, as these subtypes have the highest chance of achieving ypN0. In the EUBREAST-01 trial (NCT04101851), patients with a complete response of the primary tumour on imaging will undergo BCS, and in case of a pCR in the surgical specimen, no axillary surgery will be performed. The primary outcome is 3-year axillary recurrence-free survival. In the ASICS trial (NCT04225858), in which patients undergo BCS or mastectomy, axillary surgery is omitted based on a complete response of the primary tumour on MRI. The primary outcome is 5-year axillary recurrence-rate. The results will be very valuable especially in the light of studies on the omission of breast surgery in selected patients with HER2+ or triple negative disease (NCT02945579).[52] If for example image-guided vacuum-assisted core biopsy can adequately predict pCR of the primary tumour, this may make omission of both breast and axillary surgery feasible.

For cN+ breast cancer

1) Axillary staging after neoadjuvant systemic therapy

With regard to TAD, it would be of added value to investigate which clip remains best visible after a longer period of time, and if possible how to optimize the clipping technique (e.g., how to decrease the risk of dislodgement). Furthermore, in future studies a clear definition of the IR should be provided, and in case of a two-step procedure, the ability to identify the clipped TLN on imaging should also be taken into account. Together with information on costs, regulations, and logistics, this can enable institutions to decide which TAD-procedure is most appropriate. An ongoing prospective study is the Magellan trial, investigating the magnetic marker in a one-step procedure (NCT03796559). Results are expected in 2024. Furthermore, in the prospective IMTAD study, marking with ^{125}I seed (after NST) (n=135), magnetic marker (n=30), and carbon suspension (n=24) are being compared.[53] Recently published results described comparable complication rates regarding marker placement and localisation, and marker dislodgement. Lastly, Hartmann et al. recently published results regarding the magnetic marker as one-step procedure in a multicentre cohort (n=151). In 146 patients, the TLN was successfully removed, resulting in an IR of 96.0%.[54]

2) Response-guided treatment

Ongoing RCTs evaluating the value of ALND and/or locoregional RT in patients with cN+ breast cancer with NST are the NSABP-B51/RTOG 1304 and ATNEC (respectively NCT01872975 and NCT04109079), in which patients with ypN0 disease are included, and the Alliance A011202 and TAXIS (respectively NCT01901094 and NCT03513614), in which patients with ypN+ disease are included. Together with registry studies such as MARI, AXSANA, and MINIMAX, these trials will provide more evidence about appropriate locoregional treatment strategies for cN+ disease in terms of long-term prognosis, to prevent over- as well as undertreatment. To prevent potential undertreatment, the axillary staging procedure has to be highly accurate. It is therefore important to also take into account which less invasive axillary staging procedure is used, as is done in the AXSANA and MINIMAX study, to assess the effect of the less invasive procedure on the oncologic outcomes as well as on QoL. Apart from this, it is highly valuable to obtain detailed RT data (i.e., data regarding treated volumes and RT doses), which is often lacking.

Meanwhile, new systemic therapies are already being investigated. In the DESTINY 05 (NCT04622319), TDM-1 is compared to ENHERTU, and in case of HR+HER2- disease with residual disease, the monarchE RCT is investigating the prognostic significance of CDK4/6 inhibitor “abemaciclib” in case of residual disease.[55] In their prespecified analysis, abemaciclib combined with endocrine therapy demonstrated benefit with regard to

disease-free survival and distant relapse-free survival when compared to endocrine therapy alone. This emphasizes the importance of systemic therapy, and the role of axillary surgery as a staging procedure to identify residual disease rather than a treatment itself, enabling both treatment de-escalation and escalation.

4) Further optimizing response-guided treatment

It is being investigated whether imaging can accurately determine response after NST. For example, the diagnostic accuracy of the sequential [18F]FDG PET/MRI has been assessed.[56] The authors concluded that the PET/MRI can predict (area under the curve of 0.71) the response of the primary tumour on pathology, yet cannot predict the nodal response.

Another test is being assessed as potential predictor for pCR and risk of recurrence, namely circulating tumour DNA (ctDNA). In the I-SPY 2 trial, it was concluded that having ctDNA after NST was a significant predictor of poor response and associated with higher risk of recurrence, while not having ctDNA was associated with better prognosis, regardless of actually having a pCR at pathology.[57]

Lastly, artificial intelligence (AI) is increasingly applied, and in breast cancer it is assessed whether AI can predict a pCR based on response imaging and tumour characteristics.[58] If so, in the future it may be also used during NST. For example: if AI predicts that a pCR will not be achieved with current systemic treatment, a switch can be made to another systemic treatment.

Thus, several tests are being investigated that may eventually improve response-guided treatment. As always, it is important to also assess cost-effectiveness, especially with health care becoming increasingly expensive.

5) QoL

QoL should always be taken into account when evaluating new treatment strategies. Ideally, in the future, prediction models will be developed in which both oncologic safety outcomes and patient-reported QoL outcomes are incorporated. This will aid to shared decision making in daily practice. Ongoing RCT's and studies assessing response-guided treatment all have QoL endpoints. In addition, in the MINIMAX study, personality is also evaluated. This should be standard in future research due to its impact on QoL. It has to be determined which questionnaire is most suitable, for example the STAI-trait, which measures trait anxiety, or the NEO-FFI, which measures neuroticism. It has yet to be determined whether in the future evaluating personality will have a place in clinical practice.

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Addendum

Dutch summary | Nederlandse samenvatting

In Nederland krijgen jaarlijks ongeveer 15.000 vrouwen de diagnose invasieve borstkanker. Dit betekent dat één op de zeven vrouwen gedurende haar leven invasieve borstkanker zal ontwikkelen. Bij de diagnose borstkanker maakt het beoordelen van de regionale lymfeklieren deel uit van het diagnostisch onderzoek. Naast lichamelijk onderzoek wordt in Nederland standaard een echografie van de oksel verricht, met eventueel weefselafname middels een punctie of biopt bij verdachte okselklieren. Op basis van de resultaten van dit onderzoek wordt bepaald of een patiënt kliernegatieve (cN0) of klierpositieve (cN+) borstkanker heeft.

Over de afgelopen decennia heeft de behandeling van borstkanker grote ontwikkelingen doorgemaakt. Tot halverwege de vorige eeuw ondergingen patiënten gediagnosticeerd met borstkanker standaard een radicale mastectomie, waarin de gehele borst, borstspieren en alle okselklieren werden verwijderd. Na verloop van tijd werd deze ingrijpende procedure aangepast naar een mastectomie waarbij de borstspieren werden gespaard. In de jaren ’70 werd de borstsparende operatie geïntroduceerd, die dezelfde overlevingskansen bood als een mastectomie indien de borstsparende operatie gevolgd werd door borstbestraling. Tot de jaren ’90 bleef het de standaard om alle okselklieren te verwijderen om deze te beoordelen (stadiëren) op de aan- of afwezigheid van uitzaaiingen. Deze invasieve procedure, ook wel de okselklierdissectie (OKD) genoemd, kan aanzienlijke klachten geven aan de arm, zoals lymfoedeem en pijn, en zo de kwaliteit van leven van patiënten verminderen. Door de jaren heen zijn er minder invasieve procedures ontwikkeld om de okselklieren te stadiëren, om zo indien mogelijk de OKD achterwege te kunnen laten. Het doel hiervan was het verbeteren van de kwaliteit van leven met behoud van oncologische veiligheid. Als gevolg van deze ontwikkeling wordt de OKD de afgelopen decennia steeds vaker achterwege gelaten, een trend die ook wel “de-escalatie” wordt genoemd.

Naast lokale behandelingen middels chirurgie en bestraling, hebben systemische behandelingen zoals chemotherapie ook een belangrijke plaats in de behandeling van borstkanker. Waar patiënten vroeger primair geopereerd werden (direct na diagnose), eventueel gevolgd door systematische therapie, wordt systematische therapie sinds de jaren ’70 ook op voorhand gegeven, voorafgaand aan de operatie. Deze zogenaamde neoadjuvante systemische therapie (NST) heeft onder andere als voordeel dat het de tumor in de borst kan verkleinen, waardoor patiënten vaker borstsparende chirurgie kunnen ondergaan. Daarnaast kan ook de oksel vaker minder invasief geopereerd worden, omdat ook hier de ziekte kan afnemen of zelfs geheel kan verdwijnen. Dit proefschrift richt zich op okselstadiëring- en behandelstrategieën bij invasieve borstkanker, zowel in

patiënten die primair geopereerd worden als in patiënten die met NST worden behandeld. Het doel is om bij te dragen aan het oplossen van enkele van de huidige kennishiaten en zo okselstrategieën verder te verbeteren voor zowel cN0 als cN+ borstkanker.

Okselstadiëring- en behandelstrategieën bij cN0 borstkanker

In cN0 borstkanker behandeld met primaire chirurgie wordt sinds de jaren '90 de oksel gestadieerd met de schildwachtklier (SWK)-procedure. Hierbij worden niet alle okselklieren verwijderd, maar alleen de klieren waar tumorcellen zich als eerste naartoe verspreiden. Indien er geen uitzaaiingen in deze klieren worden gevonden, kan de OKD achterwege worden gelaten. In geval er maximaal twee uitzaaiingen worden gevonden, dan kan de OKD ook achterwege worden gelaten als patiënten behandeld zijn met borstsparende chirurgie gevolgd door borstbestraling. **Hoofdstuk 2** biedt inzicht in de oncologische veiligheid van het weglaten van OKD en/of okselbestraling bij patiënten met cT1-2N0 borstkanker met maximaal drie uitzaaiingen in de SWK-procedure die behandeld zijn met mastectomie. In deze landelijke registratiestudie werden patiënten ingedeeld op basis van de okselbehandelstrategie die volgde na de SWK-procedure. Van de 1.090 geïncludeerde patiënten werden 219 (20,1%) toegewezen aan de groep zonder aanvullende okselbehandeling (geen OKD en geen okselbestraling), 437 (40,1%) aan de groep met aanvullende OKD, 327 (30,0%) aan de groep met okselbestraling, en 107 (9,8%) aan de groep met aanvullende OKD gevolgd door okselbestraling. Het 5-jaars regionale recidief (RR) percentage was 1,3% in de gehele studiepopulatie. Het 5-jaars RR-percentage van de groep zonder aanvullende okselbehandeling was 2,5%, wat niet statistisch significant verschilde van de groep met aanvullende OKD (1,4%) en de groep met regionale bestraling (1,0%). Andere 5-jaars recidiefresultaten waren ook vergelijkbaar tussen de groepen. Patiënten die geen aanvullende okselbehandeling kregen waren vaak ouder, hadden gunstigere tumorkarakteristieken, en kregen minder vaak chemotherapie. Opvallend was dat zij een statistisch significant slechtere 5-jaars algehele overleving hadden, wat te wijten was aan een hoog percentage niet-kanker gerelateerde sterfgevallen. Bij sommige patiënten heeft hun geschatte lagere levensverwachting op het moment van de diagnose van borstkanker zeer waarschijnlijk bijgedragen aan het achterwege laten van okselbehandeling.

Patiënten met cN0 borstkanker kunnen in plaats van primaire chirurgie ook eerst behandeling met NST ondergaan. Na behandeling met NST worden er bij patiënten minder vaak uitzaaiingen in de SWK-procedure gevonden in vergelijking met patiënten die zijn behandeld met primaire chirurgie. Patiënten bij wie na NST geen uitzaaiingen in de okselklieren worden gevonden (ypN0) hebben een betere prognose dan patiënten bij wie na NST wel uitzaaiingen in de okselklieren worden gevonden (ypN+). Dit zou het weglaten van aanvullende okselbehandeling kunnen rechtvaardigen in geval van ypN0.

Bij patiënten met cN0-ziekte en ypN+ na NST, kan dit wijzen op chemotherapie-resistente of zelfs progressieve ziekte. Het is daarom belangrijk te kunnen voorspellen of er na NST sprake is van ypN0 of of ypN+, om zo onder- en overbehandeling zoveel mogelijk te voorkomen. In **Hoofdstuk 5** werd de prognostische waarde van de klierstatus voor en na NST beoordeeld in een landelijke cohortstudie bestaande uit 18.456 patiënten. In univariable analyses hadden patiënten met cN0 borstkanker en ypN+ een statistisch significant slechtere 5-jaars algehele overleving dan patiënten met ypN0 (85,4% versus 94,4%, respectievelijk, p<0,0001). Deze bevinding werd ook in de verschillende subtypen teruggevonden. De 5-jaars algehele overleving voor de verschillende borstkanker subtypen HR+HER2-, HR+HER2+, HR-HER2+ en triple negatief was respectievelijk in de cN0ypN0-subgroep 95,9%, 97,0%, 95,7% en 90,6% en in de cN0ypN+-subgroep 89,7%, 90,4%, 73,7% en 53,6%. Deze resultaten helpen bij het beter kunnen inschatten van de prognose van patiënten en kunnen mogelijk bijdragen aan het verder vormgeven van okselbehandelstrategieën.

Okselstadiëring- en behandelstrategieën bij cN+ borstkanker

Patiënten met cN+ borstkanker worden vaak behandeld met NST. Als gevolg van NST bereikt ongeveer een derde van deze patiënten een pathologisch complete respons van de oksel (ofwel ypN0, er is geen ziekte meer aanwezig in de oksel). Aangezien ypN0 geassocieerd is met een verbeterde prognose ten opzichte van ypN+, wordt gedacht dat patiënten die ypN0 bereiken geen baat hebben bij een OKD. Om behandeling op basis van respons op NST mogelijk te maken, en dus de OKD weg te laten in geval van ypN0, werden minder invasieve okselstadiëringsprocedures geïmplementeerd: de SWK-procedure, het chirurgisch verwijderen (excideren) van een gemarkeerde lymfeklier die ten tijde van diagnose een uitzaaiing bevatte (bijvoorbeeld de MARI-procedure), en ‘targeted axillary dissection’ (TAD), waarbij de eerste twee procedures worden gecombineerd. Met zijn superieure diagnostische nauwkeurigheid heeft TAD de minste kans op het missen van uitzaaiingen. Op dit moment ontbreken echter nog de resultaten om deze verschillende minder invasieve okselstadiëringsprocedures op lange termijn uitkomsten met elkaar te kunnen vergelijken.

Targeted axillary dissection

Tegenwoordig worden in de dagelijkse praktijk verschillende TAD-procedures uitgevoerd. Deze TAD-procedures verschillen wat betreft het type definitieve marker welke gebruikt wordt voor de excisie van de gemarkeerde klier, en het tijdstip van markerplaatsing. In **Hoofdstuk 3** hebben we een systematische review uitgevoerd naar studies waarin ervaringen met TAD worden beschreven. Hierbij hebben we 51 studies met in totaal 4.512 patiënten geïncludeerd. Zes definitieve markers werden geïdentificeerd. Ook werd het tijdstip van plaatsing van de definitieve marker geëvalueerd. Als de definitieve marker

direct in de klier werd geplaatst vóór NST, gevolgd door excisie van de klier na NST, werd dit beschouwd als een eenstapsprocedure. Als eerst een clip werd geplaatst vóór NST, en na NST de definitieve marker bij de clip werd geplaatst, werd dit gedefinieerd als een tweestapsprocedure. Het identificatiepercentage van de gemarkeerde klier tijdens de operatie varieerde van 61,5% tot 100% en van 70,8% tot 100%, voor respectievelijk de eenstaps- en tweestapsprocedures. Vanwege een gebrek aan studies van hoge kwaliteit, en door heterogeniteit tussen studies, was het niet mogelijk om de meest optimale procedure te bepalen. We bespraken de voor- en nadelen van de verschillende definitieve markers die relevant zijn om te overwegen bij het uitvoeren van TAD in de klinische praktijk. Bovendien benadrukten we een belangrijk nadeel van de tweestapsprocedure: aangezien de klier tweemaal moet worden gelokaliseerd (niet alleen tijdens de operatie zelf, maar ook voorafgaand aan de operatie om de definitieve marker te plaatsen), kan dit een negatieve invloed hebben op het vermogen om de klier te identificeren. Interessant genoeg rapporteerden slechts 19 (47,5%) van de 40 geïncludeerde studies die een tweestapsprocedure beschreven, het identificatiepercentage van de geclipte klier op beeldvorming. In deze 19 studies varieerde het identificatiepercentage op beeldvorming na NST van 48,8% tot 100%. Als in de klinische praktijk de clip niet wordt geïdentificeerd na NST en dus de definitieve marker niet kan worden geplaatst om lokalisatie van de klier tijdens de operatie mogelijk te maken, kan dit resulteren in het moeten overgaan tot (mogelijk onnodige) OKD. Om de meest optimale TAD-procedure te bepalen, moeten zowel eenstaps- als tweestapsprocedures verder worden onderzocht in kwalitatief goede prospectieve studies, waarin bij voorkeur beide direct met elkaar worden vergeleken.

Respons-gerichte behandeling

De introductie van NST heeft niet alleen de chirurgische behandelingen beïnvloed, maar ook de bestralingsbehandelingen van de borst en okselklieren (ofwel locoregionale bestraling). Dit komt onder andere doordat patiënten steeds vaker met NST worden behandeld, terwijl de richtlijnen voor bestraling oorspronkelijk gebaseerd waren op behandeling met primaire chirurgie. Bij patiënten met cT1-2N1 borstkanker (met 1-3 verdachte lymfeklieren vóór NST) was het onduidelijk of en in hoeverre bestraling geïndiceerd was na NST. In **Hoofdstuk 4** werd de oncologische veiligheid van een vooraf gedefinieerde consensus-gebaseerde bestralingsrichtlijn gepresenteerd (RAPCHEM studie). In de RAPCHEM studie werden 838 patiënten met cT1-2N1-ziekte toegewezen aan een van de drie risicogroepen voor locoregionaal recidief (LRR) op basis van ypN-status, met bijbehorende aanbevelingen voor bestraling: geen borstwandbestraling en geen regionale bestraling in de laag-risicogroep (ypN0), alleen borst(wand)bestraling in de middelhoog-risicogroep (ypN1), en locoregionale bestraling in de hoog-risicogroep (ypN2-3). Als de studierichtlijn werd gevolgd (wat het geval was bij 64% van de patiënten), was het 5-jaars locoregionaal recidiefpercentage respectievelijk 2,3%, 1,0% en 1,4%, voor

de laag-risico-, middelhoog-risico- en hoog-risicogroep, allemaal in overeenstemming met de hypothese die van te voren was opgesteld (locoregionaal recidiefpercentage <4%). Patiënten bij wie minder of meer bestraling werd gegeven dan voorgeschreven, hadden geen statistisch significant veranderd recidiefrisico of algehele overleving. De uitkomsten ondersteunden de hypothese dat locoregionale bestraling kan worden weggelaten bij geselecteerde patiënten bij wie een OKD is uitgevoerd: geen borstwand bestraling en geen regionale bestraling in geval van ypN0, en geen regionale bestraling in geval van ypN1. In de multivariabele analyses voor recidiefvrij interval waren zowel de middelhoog- als de hoog-risicogroep (ypN1 en ypN2-3, respectievelijk), graad 3 en triple negatieve ziekte geassocieerd met een slechtere uitkomst. Daarom lijkt het toewijzen van patiënten aan een risicogroep op basis van ypN-status een goede basis, maar moeten tumor graad en subtype ook worden meegenomen bij het evalueren van de indicaties voor locoregionale bestraling. Bij 157 (18,7%) van de 838 geïncludeerde patiënten werd geen OKD uitgevoerd. Aangezien minder invasieve okselstadiëringsprocedures minder nauwkeurig zijn dan de OKD (deze procedures kunnen immers uitzaaiingen missen), compliceerde dit de studierichtlijn, de analyses en de interpretatie van de resultaten. Het benadrukte ook de noodzaak voor meer bewijs betreffende de waarde van de OKD en locoregionale bestraling bij cN+ borstkanker behandeld met NST, vooral wanneer minder invasieve okselstadiëringsprocedures worden gebruikt om de aanvullende okselbehandelstrategieën te bepalen.

In eerste instantie was het doel van respons-gerichte behandeling om de OKD achterwege te kunnen laten in geval van ypN0. Echter, tegenwoordig wordt de OKD ook achterwege gelaten (of vervangen door bestraling) in geval van ypN+. Tot er meer bewijs wordt geleverd, wat leidt tot (meer) consensus, worden in de dagelijkse praktijk veel verschillende stadiëring- en behandelstrategieën uitgevoerd, ook in Nederland. Dit maakte het mogelijk deze verschillende strategieën te evalueren middels een landelijke observationele studie. Daarom werd de MINIMAX registratie studie opgezet, waarvan het studieprotocol wordt beschreven in **Hoofdstuk 6**. De MINIMAX studie bestaat uit een retrospectief en een prospectief cohort, waarin zowel cN+ patiënten met ypN0 als met ypN+ worden geïncludeerd. De eindpunten zijn oncologische veiligheid en impact op kwaliteit van leven. De 5-jaars oncologische veiligheidsresultaten van het retrospectieve cohort worden momenteel geanalyseerd. In het prospectieve cohort wordt naast oncologische veiligheid, ook gekeken naar kwaliteit van leven, waarvoor patiënten vragenlijsten invullen bij aanvang (vóór NST), en één en vijf jaar na de operatie. De kwaliteit van leven-resultaten van één jaar worden halverwege 2024 verwacht. Om de huidige praktijkvariatie in Nederland in kaart te brengen, werd een enquêteonderzoek uitgevoerd onder de 35 ziekenhuizen die deelnemen aan de MINIMAX studie. De resultaten werden gepresenteerd in **Hoofdstuk 7**, en toonden een grote variatie in de

toegepaste minder invasieve okselstadiëringsprocedures, redenen om een OKD uit te voeren (direct na NST, of n.a.v. uitkomsten van de minder invasieve procedure), indicaties voor bestraling van de klieren, en in of het aantal verdachte lymfeklieren vóór NST of radiologische respons op NST werd meegenomen bij het beslissen over okselstrategieën. Interessant genoeg was er ook variatie met betrekking tot het gebruik van de klinische TNM-classificatie. Volgens het AJCC-stadiëringssysteem is de cN-status gebaseerd op de anatomische uitgebreidheid van ziekte in de klieren. Echter wordt tegenwoordig soms het aantal verdachte lymfeklieren gebruikt om de cN-status te definiëren (bijv. 1-3, of ≥4 verdachte lymfeklieren vóór NST, resulterend in respectievelijk cN1 of cN2), zoals normaal gesproken wordt gedaan bij het evalueren van de (y)pN-status. Dit vereist aandacht in het multidisciplinair overleg en in toekomstige studies. Een mogelijke oplossing zou zijn om de cN-status volgens de AJCC te beschrijven, gevolgd door het aantal verdachte lymfeklieren tussen haakjes (bijv. cN1(4)).

In afwachting van de resultaten van de MINIMAX-studie, is er vooralsnog beperkt maar wel toenemend bewijs beschikbaar met betrekking tot de oncologische veiligheid van respons-gerichte behandeling op basis van minder invasieve okselstadiëringsprocedures. Studies hebben laten zien dat de omvang van restziekte in de klieren en het effect ervan op de algehele overleving varieert per subtype. De waarde van locoregionale behandeling met betrekking tot het verbeteren van de prognose moet verder worden onderzocht. Het is onduidelijk of en in hoeverre het type minder invasieve okselstadiëringsprocedure de oncologische uitkomsten en de impact op de kwaliteit van leven van respons-gerichte behandeling beïnvloedt. Terugkomend op **Hoofdstuk 5**, was het negatieve effect van restziekte op de 5-jaars algehele overleving ook in cN+ borstkanker aanwezig in alle subtypen, en eveneens het meest duidelijk bij HR-HER2+ en triple negatieve ziekte. Deze resultaten helpen ook in deze groep patiënten om de prognose beter in te kunnen schatten en kunnen bijdragen aan (onderzoek naar) het verder vormgeven van meest optimale okselbehandelstrategieën.

Kwaliteit van leven

Met de verbetering van de overleving van borstkanker is de kwaliteit van leven steeds belangrijker geworden. Het wordt verwacht dat ook in patiënten met cN+ ziekte behandeld met NST het weglaten van de OKD de postoperatieve morbiditeit zal doen verminderen. Echter, in deze patiënten wordt de OKD nu vaak vervangen door okselbestraling. Bovendien kan lymfedrainage veranderd zijn als gevolg van de respons op systemische therapie. Het is onduidelijk in hoeverre deze aspecten van invloed zijn op morbiditeit en kwaliteit van leven. Ondertussen zijn verschillende niet-behandeling gerelateerde factoren geïdentificeerd die geassocieerd zijn met kwaliteit van leven. Na eerder onderzoek bij de algemene bevolking, is de relatie tussen persoonlijkheid en

kwaliteit van leven onderzocht bij patiënten met borstkanker in de systematische review in **Hoofdstuk 8**. Twaalf studies met 2.729 patiënten werden geïncludeerd, en er werd een klein tot matig effect van persoonlijkheid op kwaliteit van leven gevonden, wat varieerde afhankelijk van het type persoonlijkheidstrek en het domein van kwaliteit van leven dat werd beoordeeld. Het effect was het meest duidelijk tussen de persoonlijkheidstrekken 'optimisme' en 'angst', en de psychosociale domeinen van kwaliteit van leven. De resultaten tonen het belang van het meenemen van persoonlijkheid in toekomstige studies omtrent kwaliteit van leven. Dit werd al gedaan in de MINIMAX studie, om zo toekomstige analyses te optimaliseren.

Impact paragraph

In the past decades, breast cancer treatment has evolved extensively. Until the mid-twentieth century, patients underwent a radical mastectomy according to the Halsted approach, which included the excision of the pectoral muscles and axillary lymph nodes. Through advancements in research, better understanding of breast cancer biology, and improved treatments, leading to improved survival, we have entered the current era. The primary aim now is to de-escalate treatment while maintaining oncologic safety and improving morbidity outcomes, thereby enhancing quality of life (QoL). In modern breast surgery, options include mastectomy (i.e., removal of the breast) and breast-conserving surgery (BCS), which can be complemented by reconstructive or oncoplastic surgery, respectively. Regarding the axilla, ongoing efforts are being made to de-escalate axillary staging and treatment strategies in both node-negative (cN0) and node-positive (cN+) breast cancer. The aim of this thesis was to pave the way for more consensus-based axillary strategies in both cN0 and cN+ breast cancer.

Axillary strategies in cN0 breast cancer - primary surgery

In cN0 disease, axillary lymph node dissection (ALND) has long been replaced by sentinel lymph node biopsy (SLNB). Even in case of limited sentinel lymph node (SLN) involvement, it is safe to omit completion axillary treatment in patients treated with BCS. It is expected that an incidental dose to the axilla provided by whole breast radiotherapy (RT) following BCS results in a low axillary recurrence rate. Since chest wall RT is not routinely performed after mastectomy, we evaluated the oncologic safety of omitting completion axillary treatment in mastectomy patients with limited SLN involvement.

The results showed a low number of regional recurrences, indicating that there is room for refraining from completion axillary treatment in selected patients. Patients were selected for omission of completion axillary treatment based not only on tumour characteristics (e.g., micrometastatic disease) but also based on factors such as age and overall health. While awaiting ongoing randomized controlled trials that include patients with macrometastatic SLN involvement, these results can already be used in clinical practice when deciding on axillary treatment. Moreover, it emphasizes the importance of considering overall health when making treatment decisions, with shared decision-making being an important part of the process. These results are of great importance for clinicians as well as patients and should be incorporated into breast cancer guidelines.

Neoadjuvant systemic therapy

Neoadjuvant systemic therapy (NST) has presented several opportunities. It allows for assessment of in vivo disease response to systemic therapy, and can downsize local disease. Initially inoperable local disease can become operable, and in cases of operable

local disease, BCS is more often feasible. NST can also downstage nodal disease. In both the primary tumour and in the lymph nodes, it can even lead to a pathological complete response (pCR), which is associated with improved prognosis. However, the use of NST has also introduced uncertainties regarding staging and treatment after NST.

Axillary strategies in cN0 breast cancer - neoadjuvant systemic therapy

In cN0 breast cancer, it was unclear whether results of trials investigating axillary strategies in patients with SLN involvement in the primary surgery setting could be extrapolated to patients with SLN involvement after NST (i.e., ypN+). We assessed the prognostic significance of ypN+ in cN0 disease.

The results revealed that patients with cN0ypN+ had a statistically significant worse 5-year overall survival compared to patients with cN0 with nodal pCR (i.e., ypN0). These results highlight the importance of studies evaluating axillary strategies in the NST setting, and will hopefully raise awareness during multidisciplinary meetings, as these patients can have chemotherapy-resistant or even progressive disease, and therefore may need additional treatment. These findings are of great importance for both clinicians and patients.

Axillary strategies in cN+ breast cancer

In patients with cN+ disease, NST also had implications for clinical practice. While the ALND was replaced by the SLNB in case of cN0 disease decades ago, it remained common practice in cN+ disease for quite some time. However, due to NST, it became possible to achieve ypN0. Therefore, less invasive axillary staging procedures were implemented to provide response-guided treatment, and to omit the ALND in case of ypN0: SLNB, excision of a marked lymph node (e.g., MARI-procedure), and targeted axillary dissection (TAD) (e.g., RISAS-procedure).

Targeted axillary dissection

Given its superior diagnostic accuracy, targeted axillary dissection (TAD) seems the preferred option for axillary staging. We performed a systematic review on TAD techniques.

We discussed the benefits and drawbacks of each definitive marker, and evaluated the timing of definitive marker placement. We emphasized that the two-step procedure can negatively affect the ability to identify the marked lymph node, and thus the importance of assessing the identification rate of the marked lymph node at imaging after NST, and not just at surgery. The findings are therefore very relevant for researchers when conducting future studies. In clinical practice, together with additional information (e.g., costs, logistics), these results are also relevant for clinicians, as they can help determine

the most appropriate TAD technique for their hospital. Furthermore, it enables clinicians to inform patients about the benefits and drawbacks of the TAD techniques.

Response-guided treatment

NST did not only affect surgical strategies, but also locoregional RT strategies, as locoregional RT guidelines were originally based on studies in the primary surgery setting. We investigated the oncologic safety of de-escalated locoregional RT according to a predefined consensus-based study guideline in patients with cT1-2N1 breast cancer.
The results suggested that locoregional RT can be omitted in selected patients in whom ALND is performed (i.e., no chest wall RT and no regional RT in case of ypN0, and no regional RT in case of ypN1 (1-3 positive nodes)). The study guideline has laid a good foundation for response-guided RT, and can thus contribute to treatment decisions in clinical practice. The results are relevant for clinicians, especially in countries where ALND is still often performed. As the study guideline requires fine-tuning, such as taking into account breast cancer molecular subtype, the results are also important for researchers. Moreover, since results were difficult to interpret when ALND was omitted, this highlighted the need for more evidence concerning response-guided treatment based on less invasive axillary staging procedure. It also emphasized the importance of informing patients about the current knowledge gaps.

Meanwhile, in clinical practice, ALND was being omitted (or replaced by RT), sometimes even in case of ypN+. With a wide variety of axillary staging and treatment strategies being performed in the Netherlands, it was made possible to conduct a nationwide registry study to assess these strategies. The Dutch multicentre MINIMAX study was therefore initiated. The 5-year oncologic safety outcomes of the retrospective cohort are yet to be analysed. The 1-year QoL outcomes are expected half 2024.
Hence, within a short period of time, this study will provide more insight into the outcomes of currently performed axillary strategies, for both ypN0 and ypN+ disease, also taking to account factors such as breast cancer molecular subtype and the extent of residual disease (if applicable). The results need to be awaited. In the future, if found clinically relevant, the results on oncologic safety and impact on QoL will be implemented into breast cancer guidelines, to be used for decision-making in multidisciplinary meetings. The results will be relevant for both the clinician and the patient, as it will enhance shared decision-making based on more evidence regarding oncologic safety and impact on QoL of the different axillary strategies. Lastly, the results can also be relevant for researchers, as they may aid to the development of prediction models in which both oncologic safety outcomes and patient-reported QoL outcomes are incorporated.

To gain insight into practice variation in the Netherlands, we conducted a survey among the local principal investigators of the hospitals participating in the MINIMAX study.
It has provided an overview of the nationwide variety in less invasive axillary staging procedures, reasons to directly perform an ALND after NST, and response-guided treatment strategies, including indications for completion ALND and/or RT. These results are important for raising awareness about these variations in clinical practice, not only among clinicians but also among patients. Furthermore, it emphasizes the importance of including patients in studies such as the MINIMAX. In addition, we found that some hospitals define the cN-status not based on anatomical extent (according to the AJCC), but on the number of suspicious lymph nodes before NST (e.g., 1-3 is cN1, and ≥4 is cN2). We hope that these results will lead to the cN-status primarily being defined according to the AJCC in all hospitals (with the number of suspicious nodes in parentheses if also wanting to provide this information, e.g., cN1(4)). Not doing so can particularly lead to unreliable data when conducting research. Therefore, outcomes of this survey are not only important in clinical practice, but also in research.

In both cN0 and cN+ disease, having ypN+ disease can be chemotherapy-resistant or even progressive disease. We assessed the prognostic significance of nodal status before and after NST.
We found that patients with ypN+ have decreased overall survival, most apparent in HR-HER2+ and triple negative disease. This indicates that especially these patients can benefit from additional treatment, such as TDM-1 or capecitabine, as was demonstrated by the KATHERINE and CREATE-X trials, respectively. Hence, restaging after NST is of utmost importance. It is especially relevant that clinicians consider these results when deciding on type of staging procedure.

Quality of life

When optimizing treatment, impact on QoL should be taken into account. We performed a systematic review to assess the relationship between personality traits and QoL in breast cancer patients.
We found that personality affects QoL, with the effect being most apparent between personality traits "optimism" and "trait anxiety" and the psychosocial QoL domains. These results are highly relevant for researchers, as personality should be considered when evaluating impact on QoL of breast cancer treatment. This is done in the MINIMAX study, and will help interpret the patient-reported QoL outcomes. Moreover, both clinicians and patients should be aware of these results, as personality can have a substantial impact on patient's well-being during and after treatment.

Acknowledgements | Dankwoord

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Ik heb mijn promotietraject als pittig ervaren. Ik miste het ziekenhuis; de patiëntenzorg, de routine, de dynamiek, het dokter zijn. Toch ben ik blij dat ik het maar mooi heb afgemaakt. Dit avontuur heeft me veel moois gebracht, waaronder fijne collega's, fantastische vrienden en veel kennis, zowel over onderzoek als over mezelf. Ik had het echt voor geen goud willen missen. Er zijn dan ook veel mensen die ik wil bedanken voor de afgelopen 4 jaar.

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List of publications

This thesis

SR de Wild, JM Simons, MTFD Vrancken Peeters, ML Smidt, LB Koppert
De-escalating axillary surgery in node-positive breast cancer treated with neoadjuvant systemic therapy.
Breast Care 2021;16(6):584-489.

SR de Wild, LM van Roozendaal, JHW de Wilt, T van Dalen, JA van der Hage, FH van Duijnhoven, JM Simons, RJ Schipper, L de Munck, SMJ van Kuijk, LJ Boersma, SC Linn, MBI Lobbes, PMP Poortmans, VCG Tjan-Heijnen, KKBT van de Vijver, J de Vries, AH Westenberg, LJA Strobbe, ML Smidt
De-escalation of axillary treatment in case of a positive sentinel lymph node biopsy in cT1-2N0 breast cancer treated with mastectomy: a nationwide registry study to provide insight into oncologic safety (BOOG 2013-07).
Accepted for publication in the British Journal of Surgery

SR de Wild, LB Koppert, TJA van Nijnatten, LFS Kooreman, MTFD Vrancken Peeters, ML Smidt, JM Simons
A systematic review on targeted axillary dissection in node-positive breast cancer treated with neoadjuvant systemic therapy: variation in type of marker, and timing of placement.
Accepted for publication in the British Journal of Surgery

SR de Wild, L de Munck, JM Simons, J Verloop, T van Dalen, PHM Elkhuizen, RMA Houben, AE van Leeuwen, SC Linn, RM Rijnappel, PMP Poortmans, LJA Strobbe, J Wesseling, AC Voogd, LJ Boersma
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SR de Wild*, JM Simons*, MTFD Vrancken Peeters, ML Smidt**, LB Koppert**, MINIMAX group
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Clinical Breast Cancer 2022;22(1):e59-e64.
*/** Both authors contributed equally to this work.

SR de Wild, LB Koppert, MTFD Vrancken Peeters, ML Smidt, JM Simons
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A descriptive systematic review of the relationship between personality traits and quality of life of women with non-metastatic breast cancer.
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Pediatric Dermatology 2019;36(6):958-960.

HAW Meijer, M Graafland, MC Obdeijn, S van Dieren, JC Goslings, MP Schijven, ReValidate! Collaborative Study Group
Serious game versus standard care for rehabilitation after distal radius fractures: a protocol for a multicentre randomised controlled trial.
BMJ Open 2021;11(3):e042629.

HAW Meijer, M Graafland, MC Obdeijn, S van Dieren, JC Goslings, MP Schijven, ReValidate! Collaborative Study Group
Gaming as an effective medical treatment: a multicentre randomised controlled trial on the use of a serious game versus standard care for rehabilitation after wrist fractures.
Under review

About the author

Sabine de Wild was born on the 6th of August 1992 in Rheden, the Netherlands, and grew up in Arnhem. In 2011, she graduated from high school (Lorentz Lyceum) and started medical school at Radboud university medical centre in Nijmegen. After obtaining her medical degree in 2018, she began working as a surgical resident, not in training, at Gelre ziekenhuizen in Apeldoorn. In 2019, she moved to Maastricht for a full-time clinical research position on axillary strategies in breast cancer, under the supervision of Marjolein Smidt, Marie-Jeanne Vrancken Peeters, Linetta Koppert, and Janine Simons. As part of this position, she coordinated the implementation of a multicentre study that she initiated in 35 Dutch hospitals. Furthermore, among other projects, she had the opportunity to write a paper together with Liesbeth Boersma, as well as other colleagues, which was published in The Lancet Oncology. In May 2024 she will pursue her clinical career as a medical doctor at the department of internal medicine at Maastricht University Medical Centre+.

In her spare time, she loves to spend time with friends and family and perform sports. In July 2023, she took part in the four days marches in Nijmegen (‘Walk of the World’) for the 5th time.

Cover

The front cover depicts Onze Lieve Vrouweplein in Maastricht during wintertime, with the beautiful lights up in the trees. This has been my favourite place in Maastricht ever since I arrived during the winter of 2019. To stick to the theme of this thesis, the lights and branches of the trees represent lymph nodes and lymph vessels.

The surrounding darkness reflects the end of a four-year era of research. The illuminating lights stand for everything I have learned and for all the amazing people that I was fortunate enough to meet in these four years.

The back cover illustrates the Waalbrug in Nijmegen, which is where my adventure began in 2011. It is the bridge I crossed to study medicine in Nijmegen. It is also the bridge I crossed every day while working at the surgery department in Gelre ziekenhuizen in Apeldoorn. The orange and purple colouring represents Gelre ziekenhuizen and has been incorporated in the colours of the sky. Most importantly, the Waalbrug always makes me feel happy when I see it. Nijmegen will always feel like home.

Lieve mama, heel erg bedankt voor het maken van deze prachtige kaft. Het is nog zoveel meer waard omdat jij het gemaakt hebt. Ik hou van je, dikke kus.

With love and special thanks to my mother, Brigitte Korving, for the front and back cover illustrations.