Towards de-escalation of axillary management after neoadjuvant chemotherapy in breast cancer

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Towards de-escalation of axillary management
after neoadjuvant chemotherapy in breast cancer

Colofon

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Towards de-escalation of axillary management after neoadjuvant chemotherapy in breast cancer

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Contents

Chapter 1	Introduction and thesis outline <i>Partly published in NTvO 2017;14:53-4.</i>	9
Part I	De-escalation of axillary management after neoadjuvant systemic therapy	19
Chapter 2	De-escalation of axillary surgery in breast cancer patients treated in the neoadjuvant setting: a Dutch population-based study <i>Submitted.</i>	21
Chapter 3	Patterns of axillary staging and management in clinically node positive breast cancer patients treated with neoadjuvant systemic therapy: results of a survey amongst breast cancer specialists <i>Eur J Surg Oncol. 2019 Aug. Doi: 10.1016/j.ejso.2019.08.012.</i>	37
Part II	In search of an accurate less invasive axillary staging method for node positive breast cancer	53
Chapter 4	Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis <i>Ann Surg. 2019 Mar;269(3):432-442.</i>	55
Chapter 5	A novel less-invasive approach for axillary staging after neoadjuvant chemotherapy in patients with axillary node-positive breast cancer by combining radioactive iodine seed localization in the axilla with the sentinel node procedure (RISAS): a Dutch prospective multicenter validation study <i>Clin Breast Cancer. 2017 Aug;17(5):399-402.</i>	79
Chapter 6	Excision of both the pretreatment marked positive node and sentinel nodes improves axillary staging after neoadjuvant systemic therapy <i>Br J Surg. 2019 Oct. Doi: 10.1002/bjs.11320.</i>	89

Part III	Prediction of axillary residual disease and prognostic implications	107
Chapter 7	Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy <i>Ann Surg. 2018 Dec. Doi: 10.1097/SLA.0000000000003126.</i>	109
Chapter 8	Prognosis of residual axillary disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastases carry a better prognosis than macrometastases <i>Breast Cancer Res Treat. 2017;163(1):159-166.</i>	125
Chapter 9	Discussion and future perspectives	139
Chapter 10	Dutch summary Nederlandse samenvatting	155
Appendices	Valorisation	163
	Editorial: “Okseelbehandeling van primair klierpositief mammacarcinoom na neoadjuvante systemische therapie: is minder wel veilig?” (NTvO 2017;14:53-4)	169
	List of publications	173
	Acknowledgements Dankwoord	177
	Curriculum Vitae	183

CHAPTER

1

Introduction and thesis outline

Partly published in NTvO 2017;14:53-54

INTRODUCTION

This thesis describes practices regarding axillary management in patients with breast cancer treated with neoadjuvant chemotherapy. It focuses on identifying the most optimal surgical axillary staging procedure, i.e. one that improves quality of life by being less invasive while at the same time guarantees oncologic safety by being highly accurate. The ultimate aim is to help shape response-based axillary management. This introduction provides background information regarding this topic, followed by a brief outline of this thesis.

Trend of de-escalation of surgery in breast cancer

Breast cancer is the most frequently diagnosed malignancy amongst women worldwide.¹ Over the past decades, survival rates of patients with breast cancer have increased considerably following improvements in screening, diagnostics and treatment. In addition, quality of life has improved as a result of a decrease in surgical morbidity with the development of less invasive surgical options. With the increasing number of breast cancer survivors, quality of life post-treatment becomes more and more important.

Radical mastectomy used to be standard of care in breast cancer treatment. This procedure, introduced in 1894 by Halsted, includes removal of the whole breast, the pectoral muscles and all axillary lymph nodes. Over time, the procedure was modified to the current standard of mastectomy in which the pectoral muscles are spared. In the '70s, a major step in de-escalating breast cancer surgery was achieved with the introduction of breast conserving surgery. This technique proved to be non-inferior to mastectomy (even after long-term follow up of over 25 years), provided that breast conserving surgery is followed by radiotherapy.^{2,3} More recent research even suggests that breast conserving surgery may be associated with improved breast cancer specific and overall survival.⁴ In the early 90s, the sentinel lymph node dissection (SLND) was introduced as a less invasive procedure to stage the axilla in clinically node negative (cN0) patients.⁵ Patients without axillary metastases in the SLNs, could thus be spared axillary lymph node dissection (ALND) which causes significant upper extremity morbidity.⁶⁻⁸ Following results from ACOSOG Z011, IBCSG 23-01 and AMAROS, indications for omitting ALND expanded, as SLND only was reported to be non-inferior to completion ALND in case of ≤ 2 positive SLNs.⁹⁻¹¹ Importantly, all patients received adjuvant chemotherapy and mastectomy patients were not included or comprised only small numbers of the study population. For cN0 patients with 3 or more positive SLNs or primary clinically node positive (cN+) patients, ALND remained standard of care.

Timing of chemotherapy

In breast cancer, chemotherapy was traditionally administered following surgery. In the 70s, chemotherapy given prior to surgery, i.e. neoadjuvant chemotherapy, was introduced. Advantages, while achieving similar survival rates, are in vivo tumor response and the possibility to downsize tumor volume disease.¹²⁻¹⁴ Nowadays, neoadjuvant chemotherapy is not only used to convert irresectable breast cancer to operable breast cancer, but also to downsize locally advanced operable breast cancer as well as early stage breast cancer.¹⁵ Neoadjuvant chemotherapy can even result in a pathologic complete response (pCR), which means that there are no vital tumor cells left. This creates potential to further de-escalate surgical treatment.

De-escalation of surgery after neoadjuvant chemotherapy

Neoadjuvant chemotherapy has enabled increased use of breast conserving surgery.¹² Additionally, when performed after chemotherapy compared to the primary setting, breast conserving surgery may involve smaller amounts of tissue. This contributes to improved cosmetic outcome. Currently, trials are even investigating the accuracy of non-operative breast management, i.e. identifying breast pCR with biopsy, to make optimal use of treatment response.¹⁶⁻¹⁹

Regarding the treatment of the axilla, de-escalation of surgery guided by treatment response is still an area of controversy. In cN0 patients treated with neoadjuvant chemotherapy, SLND is increasingly performed after chemotherapy. Since the vast majority of cN0 patients are SLND-*negative* after chemotherapy, it is questioned whether axillary surgery can be completely omitted in subgroups among these patients.^{20,21} Regarding cN0 patients who are SLND-*positive* after chemotherapy, it is yet unknown whether SLND only is non-inferior to completion ALND. This is due to the fact that trials like Z0011 did not include patients treated with neoadjuvant chemotherapy. A positive SLND *after* chemotherapy probably indicates resistance to the administered therapy and may even indicate the need for further (systemic) adjuvant treatment.

In cN+ patients treated with neoadjuvant chemotherapy, de-escalation of axillary surgery is also topic of debate. Approximately 36% of cN+ patients treated with neoadjuvant chemotherapy achieve an axillary pCR.²² These patients will likely not benefit from ALND. Noninvasive techniques, including ultrasound, MRI or PET-CT, are currently not able to accurately identify axillary pCR. In case of an axillary complete response on imaging, residual disease may actually still be present in the axilla. Hence, several less-invasive staging procedures have been proposed as alternatives to ALND. SLND has been thoroughly studied for its diagnostic accuracy in identifying axillary pCR in cN+ patients and is associated with high false negative rates (FNR). This indicates that residual disease can be missed when the SLN is negative.²²⁻²⁵ The high

FNR may be caused by ‘false’ SLNs, caused by metastases blocking normal lymph drainage. In 2010, the MARI procedure (Marking Axillary lymph nodes with a Radioactive Iodine seed) was introduced²⁶, in which the pathologically proven positive lymph node is marked with a radioactive iodine seed prior to chemotherapy and selectively removed after chemotherapy. In a single-center validation trial of 100 cN+ patients, an FNR of 7% and a negative predictive value (NPV) of 83% was reported. The MARI procedure is not hampered by ‘false’ SLNs, however, residual axillary (therapy-resistant) disease can still be missed with the MARI procedure.²⁷ Based on the NPV of 83%, 1 out of 6 patients with a negative MARI node will in fact have residual axillary disease in the remaining nodes. A protocol has been published which suggests combining the outcome of MARI with the number of positive lymph nodes on PET-CT (performed prior to chemotherapy) to guide the extent of further axillary management after neoadjuvant chemotherapy.²⁸ Such a protocol results in a decrease in ALND²⁹, but it is yet unknown whether omission of ALND after chemotherapy in cN+ patients will impact long-term prognosis. In 2016, results of the Targeted Axillary Dissection (TAD) were published³⁰, in which both the pathologically proven positive lymph node (marked prior to chemotherapy) and the SLNs are removed. The marked node was not an SLN in 23% of patients and an excellent FNR (2%) and NPV (97%) were reported for TAD. However, this single-center study consisted of a small cohort and patients were retrospectively identified from a prospective registry.³⁰ The Dutch multicenter RISAS trial was set up in 2015 (funded by KWF Kankerbestrijding) to validate the combination of MARI and SLND in 225 cN+ patients. The RISAS study protocol is presented in this thesis. Whilst awaiting results of ongoing trials, several guidelines have already accepted different less invasive staging procedures as an alternative to ALND.

In conclusion, the optimal axillary management after neoadjuvant chemotherapy is yet unknown for both cN0 and cN+ patients. There is a need for response-based management of the axilla. This thesis aims to provide further insight in current practices regarding axillary management, different less invasive axillary staging procedures, prediction of axillary pCR based on treatment-response in the breast, and the relation between the extent of residual axillary disease and long-term prognosis. Thereby, adding to further delineating response-based axillary management.

Thesis outline

In the first part of this thesis, an overview is provided of trends in and opinions on omission of ALND after neoadjuvant chemotherapy. In chapter 2, a population-based study is presented in which trends in de-escalation of axillary surgery after neoadjuvant chemotherapy are assessed. This study focuses on changes over time in rates of ALND. In chapter 3, current practices regarding axillary staging and

management in cN+ patients treated with neoadjuvant chemotherapy were assessed by an online survey amongst breast cancer specialists.

The second part of this thesis focuses on cN+ patients. In chapter 4, an overview of the diagnostic accuracy of currently available less invasive axillary staging procedures is provided in a systematic review and meta-analysis. In chapter 5, the study protocol of RISAS is presented, a Dutch multicenter prospective validation trial in which the accuracy of MARI in combination with SLND is assessed. In chapter 6, a retrospective multicenter evaluation of axillary staging based on MARI in combination with SLND is reported.

The third part of this thesis focuses on prediction of axillary pCR and on prognostic implications of residual axillary disease. Chapter 7 reports on the association between breast pCR and axillary pCR in cN0 and cN+ patients treated with neoadjuvant chemotherapy. In chapter 8, prognosis of cN+ patients treated with neoadjuvant chemotherapy is studied in relation to the extent of residual axillary disease.

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PART I

De-escalation of axillary management after
neoadjuvant systemic therapy

CHAPTER

2

De-escalation of axillary surgery in
breast cancer patients treated in the
neoadjuvant setting: a Dutch
population-based study

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ABSTRACT

Background

An overall trend is observed towards de-escalation of axillary surgery in patients with breast cancer. The objective of this study was to evaluate this trend in patients treated with neoadjuvant systemic therapy (NST).

Methods

patients with cT1-4N0-3 breast cancer treated with NST (2006-2016), were selected from the Netherlands Cancer Registry. Patients were classified by clinical node status (cN) and type of axillary surgery. Uni- and multivariable logistic regression analysis were performed to determine clinicopathological factors associated with performing ALND in cN+ patients.

Results

A total of 12461 patients treated with NST were identified (5830 cN0 patients (46.8%), 6631 cN+ patients (53.2%)). In cN0 patients, an overall increase in sentinel lymph node biopsy (SLNB) only (not followed by ALND) was seen from 11% in 2006 to 94% in 2016. SLNB performed post-NST increased from 33% to 62%. In cN+ patients, an overall decrease in ALND was seen from 99% in 2006 to 53% in 2016. Age (OR 1.01, CI 1.00-1.02), year of diagnosis (OR 0.47, CI 0.44-0.50), HER2 positive disease (OR 0.62, CI 0.52-0.75), clinical tumor stage (T2 vs. T1 OR 1.32, CI 1.06-1.65, T3 vs. T1 OR 2.04, CI 1.58-2.63, T4 vs. T1 OR 6.37, CI 4.26-9.50) and clinical nodal stage (N3 vs. N1 OR 1.65, CI 1.28-2.12), were correlated with performing ALND in cN+ patients.

Conclusions

ALND decreased substantially over the past decade in patients treated with NST. Assessment of long-term prognosis of patients in whom ALND is omitted after NST is urgently needed.

INTRODUCTION

In breast cancer, systemic therapy is increasingly administered in the neoadjuvant setting (i.e. neoadjuvant systemic therapy (NST)).^{1,2} One of the advantages of NST is the possibility of downsizing or even downstaging disease, which can occur in breast and/or axilla. In the best-case scenario, patients achieve a pathologic complete response (pCR), meaning that there is no histologic evidence of residual tumor. Downstaging is not only associated with a favorable prognosis, it also enables surgeons to opt for less extensive surgery after NST.

In clinically node negative (cN0) patients, sentinel lymph node biopsy (SLNB) is widely accepted as primary regional staging procedure. In the case of a positive SLNB with limited tumor burden it is safe to omit completion axillary lymph node dissection (ALND) in patients treated with lumpectomy in terms of disease-free and overall survival.³⁻⁷ In the AMAROS trial, cT1-2N0 patients with a positive SLNB and treated with lumpectomy or mastectomy, were randomly assigned to completion ALND or axillary radiotherapy.⁸ The 5-year axillary recurrence rate was comparable in both groups, but measurable lymphedema occurred significantly less frequently in the axillary radiotherapy-arm. The results of these trials resulted in decreasing use of ALND, as was proven by several cohort studies over the past years.⁹⁻¹² In these studies, patients treated with NST were not included and it is yet unknown if this decrease in axillary surgery also affects cN0 patients who were treated with NST.

In clinically node positive (cN+) patients, axillary staging is an area of controversy. Traditionally, ALND was performed in all patients. However, at least 1 out of 3 cN+ patients treated with NST, converts to a pathological node negative axilla.¹³ Since cN+ patients with an axillary pCR are not expected to benefit from ALND, different less invasive methods have been proposed to replace ALND. Such as SLNB, MARI (marking the axillary positive lymph node with an iodine seed) and Targeted Axillary Dissection (i.e. a combination of the SLNB and a MARI-like procedure). However, since sufficient data are lacking on the outcome of cN+ patients in whom ALND is omitted after NST, broad implementation of less invasive staging procedures in clinical practice may be hampered.

With the increased use of NST in both cN0 and cN+ patients, and the de-escalation of axillary surgery in patients treated in the adjuvant setting, it is hypothesized that a trend of de-escalation will also be noticed in patients treated with NST. Therefore, the aim of this study was to evaluate trends in de-escalation of axillary surgery in cT1-4N0-3 breast cancer patients treated with NST in the Netherlands.

MATERIALS AND METHODS

Data were collected from the Netherlands Cancer Registry (NCR). The NCR is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). Specially trained registration clerks gather data directly from the patient files in all hospitals in the Netherlands. Patients with cT1-4N0-3 breast cancer treated with NST, between 2006 and 2016, were included. Patients with occult breast cancer were also included. For each patient, the following variables were documented: hospital type (academic, teaching, community), age, morphological subtype, receptor status, TNM status prior to and after NST, NST regimens, type of breast and axillary surgery, axillary pCR, and adjuvant treatment plans. Axillary pCR was defined as the absence of residual axillary disease in all examined lymph nodes independent of the type of axillary surgery. Isolated tumor cells were included in the definition of axillary pCR. Patients were excluded if no lymph nodes were identified during surgery or if the number of positive lymph nodes was unknown. Patients with unknown cN status, distant metastasis or patients in whom surgery of the breast was not performed were also excluded.

Patients

In the Netherlands, the axilla is generally assessed by means of ultrasound at the time of diagnosis. In the case of suspicious lymph nodes, either fine needle aspiration (FNAC) or core needle biopsy (CNB) is performed to assess the presence of metastasis. A cN0 status was defined as the absence of, suspicious lymph nodes on axillary ultrasound or the absence of a positive result on FNAC/CNB when performed. A cN+ status was defined as the presence of suspicious lymph nodes on axillary ultrasound and/or in combination with pathologically confirmed metastasis by FNAC/CNB. For cN0 patients, the following subgroups regarding type of axillary surgery were documented: SLNB only (i.e. not followed by completion ALND), SLNB followed by completion ALND, and ALND (not preceded by SLNB). Patients in whom the timing of SLNB was unknown were excluded from analysis. For cN0 patients in whom SLNB was performed prior to NST, data on ypN status were only available when an ALND was performed. For cN+ patients, the following subgroups were documented: SLNB and/or MARI only (i.e. not followed by completion ALND), SLNB and/or MARI followed by completion ALND and ALND (not preceded by SLNB and/or MARI). MARI includes any procedure in which the pathologically confirmed positive lymph node was marked prior to NST and selectively removed after NST.

When referred to ypN status, this is always based on pathologic examination of lymph nodes and not on post-NST clinical examination of the axilla.

Statistical analysis

Descriptive statistics were performed to evaluate trends over time for omission of ALND in the overall population, in cN0 and cN+ patients. In addition, potential differences were explored in the axillary management associated with the type of hospital where patients were treated. Univariable and multivariable logistic regression analysis was performed to determine clinicopathological factors associated with performing ALND in cN+ patients. Odds ratios (ORs) were presented with 95% confidence intervals (CIs). Two-sided p-values of <0.05 were considered statistically significant. Data analysis was performed using Stata/SE Statistical Software for Windows, version 14.2 (College Station, TX: StataCorp LP).

RESULTS

A total of 15725 breast tumors treated with NST (10% of all breast tumors) were identified between January 2006 and December 2016 and registered in the NCR. Cases were excluded for the following reasons: distant metastasis (n=683), treated with neoadjuvant radiotherapy (n=21), unknown cN status (n=165), unknown cT status (n=136), unknown hospital type (n=1), no breast surgery (n=838), unknown type of axillary surgery (n=674), unknown outcome of axillary surgery (n=193) and unknown timing of SLNB (n=553). Altogether, 12,461 breast tumors were included for the final analysis. See Table 2.1 for clinicopathologic characteristics. In 7106 of 12461 (57%) cases, ALND was performed. From 2006 to 2016, an overall decrease in the rate of ALND was observed from 96% to 29%.

cN0 patients

Nodal status was negative at the time of diagnosis (cN0) in 5830 cases (46.8%). The proportion of cN0 patients treated with NST increased from 35% in 2006 to 50% in 2016. In total, 4301 (73.8%) underwent SLNB only and 1529 (26.2%) underwent ALND (+/- preceded by SLNB). From 2006 to 2016, the rate of SLNB only (not followed by ALND) increased from 11% to 94% (see Figure 2.1). The rate of ALND decreased in both patient groups with ypN0 and ypN+ status (see Table 2.2). In the patients in whom SLNB was not followed by ALND, the proportion of patients with positive SLNs increased from 7% to 19%.

SLNB was performed *prior to* compared with *after* NST in 3401 (65%) and 1815 (35%) cases, respectively. Over time, SLNB was increasingly performed after NST (33% in 2006 vs. 62% in 2016). The overall rate of completion ALND was 23.4% when SLNB was performed prior to NST and 6.7% when SLNB was performed after NST ($p<0.001$). For SLNB performed prior to NST, the rate of completion ALND decreased from 58% to

12%, for SLNB performed after NST the rate of completion ALND decreased from 46% to 2% (see Figure 2.1).

Table 2.1 Clinicopathologic characteristics of all cT1-4N0-3 breast cancer patients treated with NST between 2006 and 2016 (n=12,461).

Characteristics	N (%)
Year of diagnosis	
2006 - 2009	2286 (18.4)
2010 - 2013	4712 (37.8)
2014 - 2016	5463 (43.8)
Age in years, median (range)	50 (range 18-87)
Histologic subtype	
Ductal	9832 (79)
Lobular	1256 (10)
Adenocarcinoma NOS	550 (4.4)
Mixed ductal and lobular	307 (2.5)
Other	516 (4.1)
Receptor Status	
HR-/HER2-	1751 (16.3)
HR-/HER2+	987 (9.2)
HR+/HER2+	1756 (16.4)
HR+/HER2-	6243 (58.2)
HR and/or HER2 status unknown	1724 (13.8)
TNM status	
T0 - 1 - 2 - 3 - 4	14 (0.1) - 1647 (13.2) - 6595 (53) - 2696 (21.6) - 1509 (12.1)
N0 - 1 - 2 - 3	5830 (47) - 5610 (45) - 258 (2) - 760 (8)
M0 - X	12351 (99) - 110 (1)
Lumpectomy	5087 (41)
Mastectomy	7374 (59)
Neoadjuvant systemic regimen	
Chemotherapy only	9382 (75)
Chemotherapy with HER2 therapy	2732 (22)
Chemotherapy with endocrine therapy	286 (2)
Chemotherapy with HER2 and endocrine therapy	61 (1)

NOS, not otherwise specified; HR, hormone receptor; NST, neoadjuvant systemic therapy.

Overall, 4288 of 5830 cN0 patients (74%) were treated with adjuvant radiotherapy (80% in 2006 and 68% in 2016). Data on radiotherapy fields were unknown for the majority of cN0 patients until 2010. From 2011 until 2016, data on radiotherapy fields were known for 91.7% (3244/3539) of cN0 patients treated with adjuvant radiotherapy, ranging from 84% to 95.8% dependent on the year of diagnosis. Adjuvant radiotherapy included regional radiotherapy in 36% (122/339) of cN0 patients treated with radiotherapy in 2011 and in 26% (100/381) of cN0 patients treated with radiotherapy in 2016.

Figure 2.1 Course over time for axillary staging in cN0 patients treated with NST.

cN+ patients

Nodal status was positive at the time of diagnosis (cN+) in 6631 patients (53.2%). In total, 1054 (16%) underwent SLNB and/or MARI only and 5577 cN+ patients (84%) underwent ALND (+/- preceded by SLNB and/or MARI). From 2006 to 2016, the rate of SLNB and/or MARI only increased from 1% to 46% and the rate of (completion) ALND decreased from 99% to 54% (see Figure 2.2). Over this period, the rate of ALND decreased from 98% (55/56) to 42% (48/115) in cN+ypN0 patients and from 100% to 56% (296/526) in cN+ypN+ patients (see Table 2.2). In 2016, 372 cN+ patients (58%) underwent staging by SLNB and/or MARI: in 294 patients (79%) this was not followed by ALND.

In multivariable logistic regression analysis, the following variables were associated with significantly decreased odds ratios for ALND: year of diagnosis (OR 0.47, CI 0.44-0.50) and HER2 positive disease (OR 0.62, CI 0.52-0.75). The following variables were associated with significantly increased odds ratios for ALND: age (OR 1.01, CI 1.00-1.02), clinical tumor stage (T2 vs. T1 OR 1.32, CI 1.06-1.65, T3 vs. T1 OR 2.04, CI 1.58-2.63, T4 vs. T1 OR 6.37, CI 4.26-9.50) and clinical nodal stage (N3 vs. N1 OR 1.65, CI 1.28-2.12) (see Table 2.3).

Table 2.2 Overview of patients that underwent ALND, divided by subgroups based on ypN status for both cN0 and cN+ patients.

Year of diagnosis	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
cN0 patients, N	164	138	191	185	303	523	610	831	943	1280	662
ypN0, % (absolute numbers)	78.3 (65/83)	69.7 (62/89)	63.2 (67/106)	44.2 (42/95)	31.9 (59/185)	13.1 (37/282)	6.1 (22/359)	3.8 (20/520)	3 (19/626)	2.4 (22/927)	1.2 (6/512)
ypN+, % (absolute numbers)	100 (81/81)	95.9 (47/49)	91.8 (78/85)	92.2 (83/90)	88.1 (104/118)	75.9 (183/241)	61.8 (155/251)	50.5 (157/311)	31.2 (99/317)	24.6 (87/353)	22.7 (34/150)

Year of diagnosis	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
cN+ patients, N	302	363	456	487	487	606	608	744	806	1120	652
ypN0, % (absolute numbers)	98.2 (55/56)	98.8 (85/86)	100 (103/103)	100 (82/82)	93.6 (102/109)	92.1 (116/126)	94 (125/133)	80 (133/166)	65.9 (116/176)	45.2 (109/241)	41.9 (49/117)
ypN+, % (absolute numbers)	99.6 (245/246)	99.6 (276/277)	100 (353/353)	99.8 (404/405)	100 (378/378)	97.9 (470/480)	97.3 (462/475)	93.6 (541/578)	84.9 (535/630)	61.7 (542/879)	55.5 (297/535)

Figure 2.2 Course over time for axillary staging in cN+ patients treated with NST.

Table 2.3 Univariable and multivariable analysis for performing ALND in cT1-4N+ patients treated with NST.

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Year of diagnosis	0.48 (0.45-0.50)	P<.001	0.47 (0.44-0.50)	P<.001
Age (per year)	1.01 (0.99-1.01)	P=.051	1.01 (1.00-1.02)	P=.042
Clinical tumor status				
T1	Reference		Reference	
T2	1.36 (1.14-1.63)	P=.001	1.32 (1.06-1.65)	P=.013
T3	2.09 (1.69-2.58)	P<.001	2.04 (1.58-2.63)	P<.001
T4	9.56 (6.70-13.63)	P<.001	6.37 (4.26-9.50)	P<.001
Clinical node status				
N1	Reference		Reference	
N2	1.12 (0.79-1.60)	P=.531	1.33 (0.88-2.01)	P=.176
N3	1.23 (0.98-1.53)	P=.070	1.65 (1.28-2.12)	P<.001
ER positive	0.97 (0.84-1.12)	P=.703	1.08 (0.91-1.29)	P=.358
HER2 positive	0.83 (0.72-0.96)	P=.013	0.62 (0.52-0.75)	P<.001

Overall, 5,824 out of 6631 cN+ patients (88%) were treated with adjuvant radiotherapy. Data on radiotherapy fields were unknown for the majority of cN+ patients until 2010. From 2011 until 2016, data on radiotherapy fields were known for 91.9% (3671/3996) of cN+ patients treated with adjuvant radiotherapy, ranging from 83.6% to 97% dependent on the year of diagnosis. Adjuvant radiotherapy included *regional* radiotherapy in 67.8% (318/469) of cN+ patients treated with radiotherapy in 2011 and in 80% (368/458) of cN+ patients treated with radiotherapy in 2016.

Trends by hospital type

Overall, 823 (6.6%), 6457 (51.8%), and 5181 (41.6%) patients were treated in academic hospitals, teaching hospitals, and community hospitals, respectively. From 2006 to 2016, an overall decrease in ALND was observed from 97% to 38% in academic hospitals, from 94% to 27% in teaching hospitals and from 97% to 32% in community hospitals. In 2016, staging was performed by means of SLNB and/or MARI in 53% (16/30) of cN+ patients in academic hospitals, 61% (216/354) in teaching hospitals, and 52% (140/268) in community hospitals ($p=.083$). In these patients, SLNB and/or MARI was not followed by ALND in 75% (12/16), 75% (161/216) and 86% (121/140), respectively ($p=.025$).

DISCUSSION

This large Dutch population-based cohort study showed that axillary surgery has changed considerably in daily practice over the past decade in cT1-4N0-3 breast cancer patients treated with NST. In cN0 patients a substantial decrease in ALND and increase in SLNB only was observed, with SLNB being increasingly performed after NST. Additionally, this study revealed that ALND has increasingly been omitted after NST in cN+ patients.

In patients who undergo adjuvant systemic therapy, indications for omitting ALND in cN0 patients have extended over the years from patients with negative SLN(s) to patients with positive SLN(s).¹⁴ Even ten-year survival outcomes from the ACOSOG Z0011 and IBCSG 23-01 trials corroborated non-inferiority of SLNB alone compared to ALND for patients with limited positive SLN(s).^{4,15} Abandoning completion ALND in cN0 patients with positive SLN(s) treated with adjuvant systemic therapy is already ongoing for years, even prior to the publication of the abovementioned trials.¹⁶⁻¹⁹ Ever since the publication of these trial results, implementation of SLNB-only in this population is expanding.^{11,20} The current study shows that abandoning completion ALND in cN0 patients with positive SLN(s) is also taking place in patients treated with NST, even though results of the previous trials only apply to patients treated with *adjuvant* systemic therapy. Over the past decade, SLNB was increasingly performed after NST rather than prior to NST. Several previous studies demonstrated that performing SLNB after NST is associated with lower rates of a positive SLNB.²¹⁻²³ Thus, ALND can be omitted more often when SLNB is performed after NST. Hence, the change in timing of SLNB found in this study contributed to the decreasing use of ALND.

The results presented here prove that clinicians are willing to adopt a SLNB-only strategy in the neoadjuvant setting as well, even though such a strategy is not

evidence-based. Whether SLNB alone instead of the routine use of ALND in patients with limited positive SLN(s) treated in the *neoadjuvant* rather than adjuvant setting provides similar results in terms of overall survival is yet unknown. One should bear in mind that in contrast to the adjuvant setting, positive SLN(s) in the neoadjuvant setting indicates therapy-resistant disease and may represent a different tumor biology. Since long-term follow up of cN0 patients with positive SLNs that did not undergo completion ALND in the neoadjuvant setting is lacking, it is too early to tell whether it is safe to consider and treat these groups similarly. Furthermore, it is unknown to what extent ALND has been replaced by regional radiotherapy in these patients.

Regarding cN+ patients treated with NST, several less invasive procedures have been proposed over the past years in an attempt to prevent unnecessary ALND in patients who achieve axillary pCR: SLNB, excision of a pre-treatment marked positive lymph node (like MARI) or a combination of these two procedures (like Targeted Axillary Dissection and RISAS).^{13,24-26} Despite limited evidence for the safety of replacing ALND by these procedures, implementation of such strategies is occurring worldwide.²⁷ The results of the current study confirm this trend: from 2013 (prior to publications of MARI and TAD), rates of SLNB and/or MARI for axillary staging after NST started increasing up to 58% in 2016. The increase in rates of SLNB and/or MARI in cN+ patients was present in all three types of hospitals. Although SLNB and/or MARI is offered more and more to cN+ patients in order to omit ALND in case of axillary pCR, 42% of patients with an axillary pCR still underwent (completion) ALND in 2016. This indicates that selecting the right patient for the appropriate procedure is challenging. At the same time, completion ALND may have been performed as part of validating studies. In some institutions, ALND is performed in all cN+ patients, irrespective of response to NST, which may also in part explain this finding. Again, it is unknown to what extent ALND has been replaced by regional radiotherapy.

Notably, the decrease in ALND rates in cN+ patients treated with NST is also present in patients who do not achieve an axillary pCR. In 2016, 44% of the cN+ patients with post-NST residual axillary disease, did not undergo completion ALND. Multiple studies reported improved survival for patients with a complete response (ypT0/ypN0) to NST compared to patients without a complete response.^{28,29} These results indicate the necessity of treatment escalation rather than de-escalation in patients without axillary pCR to improve prognosis, especially in certain subtypes (such as triple negative breast cancer).³⁰ Whether current practices of omitting ALND in cN+ patients without axillary pCR will negatively impact prognosis is yet unknown. In the Alliance 11202 trial, prognosis of cN+ patients with positive SLN(s) after NST is compared between those treated with completion ALND and those treated with axillary radiotherapy.³¹

Although the current study describes a large cohort of patients, several limitations have to be taken into account. Regarding adjuvant treatment plans, sufficient data on radiotherapy fields were not available for the whole cohort. It is expected that simultaneously with the decreasing rates of ALND, rates of regional radiotherapy increase. This study did suggest such a trend in cN+ patients, but further research is needed for a thorough assessment of (regional) radiotherapy administration in patients treated with NST. Furthermore, the impact of omitting ALND on prognosis in terms of overall and disease-free survival could not be assessed since data on recurrences are not (yet) available for this cohort.

To conclude, axillary surgical staging changed significantly with a major decrease in ALND rates in breast cancer patients treated with NST over the past decade. However, selecting the right patients for whom omitting ALND is oncologic safe appears challenging, especially in pre-treatment cN+ patients and patients with residual axillary disease. Studies assessing long-term prognosis of such patients in whom ALND is omitted are urgently needed.

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CHAPTER

3

Patterns of axillary staging and
management in clinically node positive
breast cancer patients treated with
neoadjuvant systemic therapy: results
of a survey amongst breast cancer
specialists

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ABSTRACT

Introduction

Various options for axillary staging after neoadjuvant systemic therapy (NST) are available for breast cancer patients with a clinically positive axillary node (cN+). This survey assessed current practices amongst breast cancer specialists.

Materials and methods

A survey was performed amongst members of the European Society of Surgical Oncology and two UK-based Associations: the Association of Breast Surgery and the British Association of Surgical Oncology. The survey included 3 parts: 1. general information, 2. diagnostic work-up and 3. axillary staging after NST.

Results

A total of 310 responses were collected: parts 1, 2 and 3 were fully completed by 282 (91%), 270 (87.1%) and 225 (72.6%) respondents respectively. After NST, 153/267 (57.3%) respondents currently perform ALND routinely and 114 (42.7%) respondents perform less invasive restaging of the axilla with possible omission of ALND. In the latter group, 85% does and 15% does not use nodal response seen on imaging to guide the axillary restaging procedure. Regarding respondents that do use imaging: 95% would perform a less invasive staging procedure in case of complete nodal response on imaging (63% sentinel lymph node biopsy (SLNB), excision of a previously marked positive node with SLNB (21%) and without SLNB (11%)). In case of no nodal response on imaging 77% would perform ALND.

Conclusion

Current axillary staging and management practices in cN+ patients after NST vary widely. To determine optimal axillary staging and management in terms of quality of life and oncologic safety, breast specialists are encouraged to include patients in clinical trials/prospective registries.

INTRODUCTION

The management of the axilla in clinically node-negative breast cancer patients has evolved towards a less or even non-invasive approach. For clinically node-positive breast cancer patients (cN+) however, the axillary lymph node dissection (ALND) has been the standard of care until recently. cN+ patients are increasingly receiving systemic therapy before surgery (i.e. neoadjuvant systemic therapy (NST)). As a result of NST, in at least 1/3 of pre-treatment cN+ patients the axilla converts to node-negative.¹ In case of a pathologic complete response (pCR) in the axilla, ALND may be unnecessary and its purpose is therefore being questioned.^{2,3}

In order to identify cN+ypN0 patients, several less invasive procedures have been proposed. These procedures can be largely divided into 3 groups: sentinel lymph node biopsy (SLNB), excision of a pre-treatment marked positive lymph node (e.g. MARI: Marking Axillary lymph node with Radioactive Iodine seed)⁴ or procedures involving the combination of both (e.g. TAD: Targeted Axillary Dissection⁵, RISAS: Radioactive Iodine Seed localization in the Axilla combined with a SLNB; the iodine seed is placed in the positive axillary lymph node prior to start of NST⁶). Currently, no consensus exists on which procedure is most accurate for axillary staging after NST. Moreover, long-term data on whether these less invasive procedures can safely replace ALND, even in case of axillary pCR, are lacking.

The lack of evidence-based consensus guidelines for cN+ patients treated with NST results into broadly differing patterns of care in the management of the axilla. The present survey focused on breast cancer specialists (mainly European) to assess current practices regarding diagnostic work up and axillary staging in cN+ patients treated with NST.

MATERIALS AND METHODS

Participants and survey

An anonymous survey was made accessible to members of the European Society of Surgical Oncology, the Association of Breast Surgery (ABS) and the British Association of Surgical Oncology (BASO). A link to the survey was uploaded on the websites of these 3 Associations and included in several newsletters. The survey was developed using SurveyMonkey Inc. and consisted of 3 parts: 1. general information, 2. diagnostic work-up/indications for NST and 3. axillary staging after NST. The expected time spent to complete the survey was approximately 5 to 10 minutes. The maximum number of questions was 38.

Collection and analysis of responses

Responses were collected from March to October 2018. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM. Corp, Armonk, New York, USA). For each question, the number of respondents was determined. The selected answers to each question were reported as percentages of the total number of responses to each question. Subgroups were created for respondents that routinely performed ALND and respondents that selectively omitted ALND in cN+ patients. To compare unpaired categorical variables the Chi-squared test was used. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

General information

Characteristics regarding general information of the respondents are summarized in Table 3.1. A total of 310 respondents submitted the survey, of whom 282 (91%) fully completed the first section on general information. All 310 respondents felt this topic to be clinically relevant. Institutional lack of consensus was reported by 113/310 (36.5%) respondents. Dissatisfaction with local protocols for axillary staging and management was reported by 94/310 (30.3%) respondents as a consequence of the lack of consensus or protocols, performing ALND irrespective of response to NST, concerns regarding insufficient data on long-term oncologic safety, management differing per individual case and disagreement between specialties. Respondents experiencing lack of consensus in their institution were less often satisfied with current practices compared to respondents experiencing consensus: 46.9% vs. 82.7% respectively ($p < .001$).

Diagnostic work-up and indications for NST

A total of 270/282 (95.7%) respondents fully completed the second section on diagnostic work-up and indications for NST. Axillary ultrasound was routinely performed to assess the axilla prior to start of NST by 87% of respondents. The main reasons not to perform axillary ultrasound were: a normal physical examination of the axilla or other imaging modalities were performed (i.e. PET-CT or MRI). The majority of respondents (70.9%) did not perform other imaging examinations in addition to axillary ultrasound to determine the axillary tumour load prior to NST. The majority of 210 respondents (74.5%) stated either FNAC or CNB was mandatory to confirm cN+ disease, the remainder relied on physical examination and/or imaging. The main reasons not to perform FNAC or CNB were radiological signs of distant metastasis,

patient age or very high clinical suspicion of axillary lymph node status (i.e. FNAC or CNB outcome would not change treatment plan).

Table 3.1 General information characteristics.

Variable	Total responses n=310 (%)
Confirm Clinical relevance of topic	310 (100.0)
Institutional lack of consensus	113 (36.7)
Dissatisfaction with local protocols	94 (30.5)
<i>Variable</i>	<i>Total responses n= 282 (%)</i>
Qualification	
Surgical oncologist	230 (81.5)
Surgeon, participating in surgical oncology fellowship	25 (8.9)
Surgical resident	12 (4.3)
Other*	15 (5.3)
Practicing in Continent	
Europe	208 (73.8)
Asia	44 (15.6)
North America	5 (1.7)
South America	11 (3.9)
Africa	14 (5.0)
Institution	
University hospital	125 (44.3)
Breast cancer specific hospital	21 (7.4)
Large non-university teaching hospital	79 (28)
Community hospital	29 (10.3)
Other [#]	28 (10)
Years of experience as a specialist	
≤5	67 (23.7)
6-10	58 (20.6)
11-15	46 (16.3)
≥16	111 (39.4)
Number of new breast cancer patients at institutional level (yearly)	
≤500	213 (76.1)
500-1000	45 (16.1)
≥1000	22 (7.8)
Unknown/not sure	2 (not included in percentage calculation)
Percentage of patients treated with NST	
0-15%	112 (41.7)
16-30%	90 (33.2)
31-45%	27 (10.0)
46-60%	26 (9.6)
>61%	16 (5.9)
Unknown/not sure	11 (not included in percentage calculation)
On-site radiotherapy facility present	
Yes	184 (65.2)
No	98 (34.8)

*Other: 1x medical oncologist, 1x radiotherapist, 1x final year trainee in breast surgery, 5x general surgeon, 1x plastic surgeon, 1x pediatric surgeon, 1x pharmacist, 2x gynaecologist, 2x associate specialist; [#]Other: 12x comprehensive cancer center, 10x private hospital, 5x district general hospital, 1x maternity and gynaecology hospital.

For 27.4% of respondents, cN+ status was always an indication for NST in physically fit breast cancer patients aged <70 years and for 11% of respondents this was (almost) never the case. For the remaining respondents, the following factors influence whether NST was indicated in cN+ patients: histological subtype, molecular biology, cN status, size of primary tumour, tumour grade and patient preferences. The vast majority of respondents (79%), indicated that gene expression profiling was (almost) never performed to advice for NST.

The majority of respondents (168/270; 62.2%) never marked the pathologically positive lymph node prior to NST. One quarter breast specialists (69/270; 25.6%) marked the positive lymph node as standard of care and 33/270 (12.2%) only performed this as part of clinical trials. The majority of respondents who mark the positive lymph node prior to NST use a radiopaque clip (76/100; 76%). Other methods to mark the lymph node prior to NST were iodine seed or injection of charcoal. Respondents who omitted ALND in cN+ patients, marked lymph nodes more often than respondents who routinely performed ALND (50.8% vs. 26.8%, $p<.001$).

Axillary staging and treatment after NST

A total of 225/270 (83.3%) respondents fully completed the third and last section of the survey on axillary staging and treatment after NST. After NST, ALND was routinely performed by 153/267 respondents (57.3%). This rate was comparable between European respondents (56.3%) and non-European respondents (59.7%). The remaining 114/267 respondents performed less invasive restaging of the axilla with possible omission of ALND based on several clinicopathologic characteristics including; cN status prior to NST, number of positive lymph nodes prior to NST, age and presence of comorbidities (see Figure 3.1). Besides these characteristics, 85% rely on nodal response seen on imaging to choose the axillary staging procedure (see Figure 3.2). The nodal response was assessed (during and/or after NST) by means of ultrasound (88%) and/or MRI (46.3%) and/or PET/CT (22.2%). In case of complete nodal response on imaging, 95% (77/81) performed a less invasive axillary staging procedure, mainly SLNB (63%). The remainder prefer SLNB combined with excision of a previously marked positive lymph node (21%) or excision of a previously marked positive lymph node without SLNB (11%). Five percent (N=4) of respondents did not perform any surgical staging procedure in patients with complete nodal response on imaging: 1 respondent opted for adjuvant radiotherapy, 2 respondents opted for a “wait and see” approach and 1 respondent stated this would depend on breast response and axillary tumour burden pre-NST. In case of partial or no nodal response on imaging, ALND was performed by the majority of respondents (59% and 76% respectively).

Figure 3.1 Less invasive axillary restaging with possible omission of ALND is performed in cN+ patients dependent on (a combination of) the below characteristics.*

*114 respondents reported to perform less invasive restaging of the axilla with possible omission of ALND in cN+ patients of whom 102 respondents reported on the above characteristics. Respondents could select multiple answers, therefore percentages do not add up to 100%. Sixty-four percent of respondents selected 3 or more characteristics.

Several respondents (28/225) reported that the prescription of adjuvant radiotherapy and extension of fields also depended on factors other than pathologic response, like the number of suspicious or positive lymph nodes prior to NST. In case final pathologic assessment of lymph nodes showed axillary pCR, 70% of remaining respondents (138/197) recommended no further axillary treatment (this rate was similar for respondents that did and did not routinely perform ALND (86/121 (71%) and 52/76 (68%) respectively, $p=.692$). In case final pathologic assessment of lymph nodes showed macrometastasis, 48% of respondents (93/194) recommended adjuvant regional radiotherapy (this rate was similar for respondents that did and did not routinely perform ALND (38/78 (48.7%) and 55/116 (47.4%) respectively, $p=.859$).

Figure 3.2 Type of axillary staging procedure based on the degree of nodal response seen on imaging (A: complete nodal response, B: Partial nodal response, C: no nodal response).

*Other: 2x wait and see, 1x adjuvant radiotherapy, 1x dependent on breast response and axillary tumour burden pre-NST.

*Other: 1x ALND with axillary reverse mapping, 1x level 1 axillary dissection, 5x dependent on breast response and/or axillary tumour burden pre-NST and/or axillary tumour burden post-NST.

*Other: 3x dependent on axillary tumour burden pre-NST and/or breast surgical treatment plan.

NB: 84 of 92 respondents who used nodal response on imaging to guide axillary restaging in cN+ patients submitted an answer. Three respondents were excluded from this analysis because of contradicting answers

Amongst respondents that omitted ALND in cN+ patients compared to respondents that routinely performed ALND, satisfaction rates with local protocols were 74.6% and 66% respectively ($p=.133$) and institutional consensus rates were 60.5% and 66% respectively ($p=.356$). Patient preferences influence axillary staging and management always in 14%, most of the time in 32%, sometimes in 47% and never in 7% of respondents. These rates were similar for respondents that performed ALND routinely and respondents that omitted ALND in cN+ patients.

DISCUSSION

Patients with cN+ breast cancer treated with NST achieve an axillary pCR in up to 74%, depending on tumour characteristics.^{1,6,7} In pursue of omitting ALND in these patients, several less invasive staging procedures have been proposed to identify axillary pCR. This survey displays the great variety of axillary staging procedures and treatment protocols, thereby indicating a worldwide need for consensus regarding the optimal method for axillary staging after NST in cN+ patients.

Our survey shows that axillary staging and management vary from a minimum ‘wait and see’ approach (in case of complete nodal response on imaging) to a ‘most extensive’ ALND combined with adjuvant radiotherapy. A survey amongst members of the American society of breast surgeons indicated that only 15% still performed ALND in all cN+ patients after NST.⁸ In our current survey, as much as 57.3% still performed ALND routinely in all cN+ patients after NST. Interestingly, the survey by Caudle et al. documented that respondents that had not incorporated less invasive staging procedures were more aware of their downsides (like the false negative rates of the Z1071, Sentina and SN-FNAC trials).⁸ We did not explicitly ask respondents to provide reasons for still performing ALND, but several respondents voluntarily reported “concerns on long-term oncologic safety” of less invasive procedures. This indicates that there is still need for convincing evidence to support replacing ALND with less invasive procedures.

Over recent years, two methods have been proposed for axillary staging that involve excision of the pre-treatment marked positive lymph node, i.e. MARI (in which only the marked lymph node is excised after NST)⁴ and TAD/RISAS (in which both the marked lymph node and the sentinel lymph nodes are excised after NST).^{5,9,10} The marking of positive lymph nodes prior to NST, was performed by 1/3 of respondents. Even respondents who routinely performed ALND, reported marking positive lymph nodes prior to NST (27%). This was comparable to the results of the previously mentioned survey, which indicates that specialists do not always aim to retrieve the marked lymph node during surgery. Trial participation might be a reason for this. Widespread implementation of marking the positive lymph node prior to NST may be hampered by lack of resources or experience to perform this procedure.

Besides excision of the marked lymph node, the SLNB has been proposed to replace ALND.^{1,11-13} Although accuracy of SLNB has been questioned, our survey shows that a substantial number of respondents does opt for solitary post-NST SLNB to enable subsequent omission of ALND in cN+ patients. Several currently accruing trials focus on different less invasive axillary management options for cN+ patients treated with NST (amongst others RISAS¹⁰, TAXIS¹⁴, Alliance 11202¹⁵, NSABP-51/RTOG 1304¹⁶). While awaiting results of these ongoing trials to reach consensus and to ensure consistent axillary treatment plans, it is important to inform patients adequately on the benefits and shortcomings of the different available options. Less invasive staging procedures may avoid the morbidity associated with ALND, but may also leave therapy resistant disease behind (of which implications on prognosis are yet unknown).

The vast majority (85%) of respondents who perform less invasive restaging of the axilla with possible omission of ALND relies on the degree of nodal response on

imaging to guide axillary staging. Several imaging modalities have previously been studied for their accuracy regarding nodal response assessment.¹⁷⁻¹⁹ In general, imaging is associated with low accuracy for discriminating between axillary pCR and axillary residual disease. Therefore, its use is impeded in clinical practice. Nonetheless, some studies reported on the accuracy of SLNB when performed only in patients who have a complete nodal response on imaging and concluded that incorporating imaging may decrease the risk of missing residual disease.²⁰⁻²²

This survey has a few limitations. The survey was directed at all breast cancer specialists, yet over 90% of respondents comprised surgeons and surgical oncologists. Approximately 25% of respondents were practicing outside of Europe, which could further add to the wide variety of reported practices. Comments provided by respondents indicated that our survey did not cover all current axillary staging and management practices. Amongst voluntarily reported practices not covered in our survey were: considering breast response as a factor for omission of ALND, sampling lymph nodes with FNAC or CNB after NST to guide axillary surgery, performing SLNB with removing at least 4 sentinel lymph nodes and determining the need for radiotherapy prior to NST. Regarding breast response, previous studies have shown a correlation between a complete response in the breast and ypN0 status.^{23,24} However, this link is especially strong in cN0 patients. When it comes to cN+ patients, this correlation is weak and breast pCR should therefore not be used to guide axillary surgery.

Some respondents questioned whether the development of recurrences following omission of ALND in cN+ patients treated with NST may have legal repercussions. Although the answer options in our survey did not cover all beliefs and practices, our survey did manage to provide a thorough overview of the wide variety of current practices and the associated significant rates for lack of consensus and dissatisfaction with local protocols.

Conclusion

In conclusion, axillary staging and management practices for cN+ patients treated with NST appear to vary widely. This indicates the need for a consensus. Breast cancer specialists should continue to join efforts to encourage cN+ patients to participate in clinical trials or registries regarding axillary staging and management after NST. Consequently, we can gather evidence and crystallize accurate and safe axillary staging and management of cN+ patients treated with NST.

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PART II

In search of an accurate less invasive axillary staging
method for node positive breast cancer

CHAPTER

4

Diagnostic accuracy of different
surgical procedures for axillary staging
after neoadjuvant systemic therapy in
node-positive breast cancer: a
systematic review and meta-analysis

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ABSTRACT

Objective

The aim of this study was to perform a systematic review and meta-analysis to assess the accuracy of different surgical axillary staging procedures compared with ALND.

Summary of background data

Optimal axillary staging after neoadjuvant systemic therapy (NST) in node-positive breast cancer is an area of controversy. Several less invasive procedures, such as sentinel lymph node biopsy (SLNB), marking axillary lymph node with radioactive iodine seed (MARI), and targeted axillary dissection (a combination of SLNB and a MARI-like procedure), have been proposed to replace the conventional axillary lymph node dissection (ALND) with its concomitant morbidity.

Methods

PubMed and Embase were searched for studies comparing less invasive surgical axillary staging procedures to ALND to identify axillary burden after NST in patients with pathologically confirmed node-positive breast cancer (cN+). A meta-analysis was performed to compare identification rate (IFR), false-negative rate (FNR), and negative predictive value (NPV).

Results

Of 1132 records, 20 unique studies with 2217 patients were included in quantitative analysis: 17 studies on SLNB, 1 study on MARI, and 2 studies on a combination procedure. Overall axillary pathologic complete response rate was 37%. For SLNB, pooled rates of IFR and FNR were 89% and 17%. NPV ranged from 57% to 86%. For MARI, IFR was 97%, FNR 7%, and NPV 83%. For the combination procedure, IFR was 100%, FNR ranged from 2% to 4%, and NPV from 92% to 97%.

Conclusion

Axillary staging by a combination procedure consisting of SLNB with excision of a pre-NST marked positive lymph node appears to be most accurate for axillary staging after NST. More evidence from prospective multicenter trials is needed to confirm this.

INTRODUCTION

De-escalation of axillary surgery in clinically node positive (cN+) breast cancer patients is a topic of debate. The significant number of patients with axillary pathologic complete response (ax-pCR) resulting from increased use of neoadjuvant systemic therapy (NST) urges the need for a less invasive procedure to replace the conventional axillary lymph node dissection (ALND) in order to diminish unnecessary morbidity in patients with ax-pCR.¹⁻³ Seeking for a less invasive procedure, both prevention of unnecessary morbidity and preservation of oncologic safety are of utmost importance.

Until recently, ALND was routinely performed after NST in cN+ patients, irrespective of axillary response to NST. Recent surveys among members of the American Society of Breast Surgeons as well as Dutch surgeons reported changes in axillary surgery in cN+ patients treated with NST.^{4,5} The majority of specialists were willing to replace ALND by a less invasive staging procedure in patients with a favorable treatment response. A wide variety of less invasive staging procedures such as sentinel lymph node biopsy (SLNB), removal of a marked pathologically-proven positive lymph node (MARI and MARI-like procedures), or a combination of these two procedures (eg, targeted axillary dissection) are incorporated in clinical practice according to local preferences.⁶⁻⁹ These results denote the lack of consensus on the preferred procedure for axillary staging after NST in pretreatment cN+ patients. Up to now, it is not clear which procedure is optimal.

The aim of this review is to provide an overview of different less invasive procedures for axillary staging after NST in pretreatment cN+ patients, which are currently in use. By evaluating the accuracy of different less invasive axillary staging procedures, we aim to determine the optimal procedure for axillary staging after NST in cN+ breast cancer to safely replace ALND.

METHODS

Criteria for considering studies for this review

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for diagnostic test accuracy.¹⁰ A systematic literature search was performed by the first author (JM) for randomized controlled trials, cohort studies, and case-control studies testing less invasive axillary staging procedures after NST in cN+ breast cancer patients treated with NST. Studies were only included if nodal positivity was pathologically confirmed

before starting with NST. Any study in which a less invasive axillary staging procedure was compared with the gold standard, that is, ALND, was included. In case completion ALND (cALND) was not performed routinely, studies were not considered for quantitative analysis. If relevant studies included both cN0 and cN+ patients, only the cN+ patients were considered for analysis. In case only part of the study population consisted of patients with pathologic confirmed nodal positivity, only the pathologically confirmed cN+ patients were considered for analysis. When it was not possible to discriminate between cN0 and cN+ patients or between pathologically confirmed and non-pathologically confirmed cN+ patients, studies were excluded. Reviews, case reports, conference abstracts, and editorials were excluded. In case of inclusion of the same study population in 2 or more papers, the most extensive paper was included. Studies reporting small study populations (10 patients or less) and studies in which nodal positivity was confirmed by SLNB before NST were excluded. The primary outcome was the overall ax-pCR rate and the accuracy of the studied less invasive axillary staging procedure. Studies were therefore excluded if reported data did not allow construction of a 2 x 2 contingency table with absolute numbers of true positive (TP), true negative (TN), false-positive (FP), and false-negative (FN) test results. FP is always 0, as the index test and reference test are considered the same in case of a positive index test result (ie, presence of residual axillary disease). The secondary outcome was the identification rate (IFR) of the studied less invasive axillary staging procedure.

Search methods for identification of studies

The following electronic databases were searched until April 20, 2018, with no restriction on language or date of publication: Medline (via PubMed) and EMBASE (via EMBASE.com). A health sciences librarian was consulted to help develop a detailed search strategy. Details of the full search strategies in both databases are provided in Appendix 4.1. The reference lists of included studies and existing reviews were manually checked for additional relevant studies.

Selection of studies and quality assessment

Duplicate references were identified and removed with Endnote. Titles and abstracts of all remaining references were scanned independently by 2 authors (JS and TvN). Subsequently, these 2 authors independently assessed the full text papers of all potentially eligible studies. Disagreement was resolved by mutual consensus. Eligible studies were assessed for quality using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS- 2) questionnaire.¹¹ The QUADAS-2 was tailored to our analysis, as described in the guideline. Finally, all included studies were evaluated for quality by the 2 independent authors.

Data extraction and analysis

For each included study, the following parameters were extracted: first author, year of publication, type of hospital, study design, sample size, characteristics of trial participants (including primary tumor type, TNM-stage, type of evaluation of axillary involvement, and NST regimens), type of less invasive axillary staging procedure after NST and characteristics of the procedure, type of pathological assessment of lymph nodes (including use of immunohistochemistry (IHC), definition of ax-pCR, ax-pCR rate, accuracy, and IFR of the less invasive axillary staging procedure. For each less invasive axillary staging procedure, the ax-pCR rate, IFR, false-negative rate (FNR), and negative predictive value (NPV) were calculated. Rate of ax-pCR was based on data of the contingency tables. The IFR was defined as the number of successful procedures divided by the total number of patients in whom the procedure was attempted. The FNR was defined as the number of FN divided by the total number of patients with presence of residual axillary disease $[FN / (FN + TP)]$. The NPV was defined as the number of TN divided by the total number of patients with a negative test result $[TN / (TN + FN)]$. As FP cannot occur, numbers of TP, TN, and FN were documented for each procedure and FP was always documented to be 0 (in case FP was reported to be >0 in the record, this number was added up to the TP number). Statistical analysis was performed with Stata/SE Statistical Software for Windows, version 14.2 (StataCorp LP, College Station, TX). To calculate pooled proportions for ax-pCR rate, IFR and FNR random-effects models for meta-analysis were used with 95% exact confidence intervals (CIs) with help of the metaprop command.¹² All considered outcomes are presented in forest plots including pooled estimates. Chi-squared test was performed to test for statistical heterogeneity and was quantified by I^2 -index.¹³ As recommended in the Cochrane Handbook for Diagnostic Test Accuracy Reviews,¹⁴ reporting bias (eg, publication bias) was not assessed.

Subgroup analyses were performed to evaluate the impact of several factors on FNR. Factors that were considered relevant were number of examined lymph nodes, sampling method for SLNB, ycN status, definition of ax-pCR, and use of IHC in addition to standard H&E evaluation. Statistical significance was considered as p-values (2-sided) ≤ 0.05 .

RESULTS

Study selection

In total, 1920 records were identified through database searching and reference checking. After deduplication, 1132 records were screened, which resulted in the selection of 116 records for retrieval of full texts. Assessment of full text for eligibility yielded 27 records for

qualitative synthesis; a total of 20 records were included in quantitative synthesis. See Figure 4.1 for a flow chart depicting the study selection process.

Figure 4.1 Flow diagram depicting the study selection process.

Study characteristics

Index tests

Three different axillary staging procedures were identified: SLNB, excision of a pretreatment marked biopsy-proven positive lymph node (hereinafter all such procedures are referred to as ML), and a combination procedure involving both SLNB and ML. A total of 2217 patients were included (2002 for SLNB, 95 for ML, 120 for the combination procedure) in whom the axillary staging procedure was successful and followed by cALND. See Table 4.1 for general characteristics of all studies included for qualitative analysis.

Table 4.1 General characteristics of all studies included in qualitative analysis sorted by type of procedure.

First Author	Year of publication	Study type	Index test	Reference test	Sample size *	cN-stage	ycN-stage	Definition ax-pCR	IHC
Alvarado	2012	R, S	SLNB	ALND	121	N1-N3	Any	NR	NR
Boileau	2015	P, M	SLNB	ALND	127	N1-2	Any	ypNO/itc+	yes, if H&E negative
Boughey	2013	P, M	SLNB	ALND	637	N1-2	Any	ypNO/itc+	no
Brown	2010	R, S	SLNB	ALND	86	N1-3	Any	ypNO/itc+	no
Carrera	2016	P, M	SLNB	ALND	48	N1-2	ycNO (MRI +/- US)	NR	yes, always
Enokido	2016	P, M	SLNB	ALND	130	N1	ycNO (imaging)	ypNO	NR
Ge	2014	P, S	SLNB	ALND	43	N1-3	Any	NR	yes, but not routinely
Kang	2011	R, S	SLNB	ALND	58	N1-3	Any	NR	yes, always
Kuehn	2013	P, M	SLNB	ALND	123	N1-2	ycNO (PE +/- US)	ypNO/itc+	no
Ozmen	2010	R, S	SLNB	ALND	71	N1-2	ycNO (PE and imaging)	ypNO	yes, if H&E negative
Park	2013	R, S	SLNB	ALND	169	N1-3	Any	ypNO/itc+	yes, but not routinely
Pinero-Madronea	2015	P, M	SLNB	ALND	38	N1-3	Any	NR	NR
Shen	2007	P, S	SLNB	ALND	56	N1-3	Any	NR	no
Thomas	2011	P, S	SLNB	ALND	26	N+	ycNO (PE)	NR	yes, always
Yagata	2013	P, S	SLNB	ALND	81	N1-3	ycNO (MRI; including rPR)	ypNO	yes, if H&E negative
Yu	2016	R, S	SLNB	ALND	46	N+	ycNO (PE)	ypNO/itc+/mi+	yes, always
Zetterlund	2017	P, M	SLNB	ALND	152	N1	Any	ypNO	yes, but not routinely
Donker	2015	P, S	ML	ALND	95	N1-3	Any	ypNO	yes, but not routinely
Caudle	2016	R, S	Combi	ALND	85	N1-3	Any	ypNO	yes, but not routinely
Dashevsky	2017	R, S	Combi	NA	21	N1-2	NR	ypNO/itc+	no
Diego	2016	R, S	Combi	NA	29	N1	ycNO (PE)	ypNO	yes, but not routinely
Kim	2017	P, S	Combi	NA	11	N1-2	Any	ypNO/itc+	no
Nguyen	2017	R, S	Combi	NA	20	N1-3	NR	NR	NR
Park	2017	P, S	Combi	NA	20	N1-3	NR	ypNO/itc+	yes, but not routinely
Plecha	2015	R, S	Combi	NA	19	N1-3	NR	NR	NR
Siso	2017	P, S	Combi	ALND	35	N1-3	Any	ypNO	yes, always
Taback	2018	P, S	Combi	NA	19	N1-2	NR	ypNO	NR

*Number of patients in whom the less invasive axillary staging procedure was successful and in whom this procedure was followed by cALND (if applicable). R=retrospective; P=prospective; M=multicenter; S=single-center; Combi=combination procedure; NR=not reported; NA=not applicable; PE=psychical examination; rPR=radiologic partial response; IHC=immunohistochemistry; H&E=hematoxylin and eosin stain.

Reference tests

In 20 studies, the axillary staging procedure was always followed by ALND as part of trial protocol. A total of 17 trials investigated accuracy of SLNB,^{15–31} 1 trial investigated ML,⁸ and 2 trials investigated a combination procedure.^{6,32} Studies validating the combination procedure were scarce, yet several studies did report on cohorts of patients in whom a combination procedure was performed without routine cALND. Therefore, we decided to include these studies, 7 in total, in the qualitative analysis.^{7,33–38} See Table 4.2 for detailed characteristics of these studies. In this table, we have included results of a study by our own research group (manuscript submitted). As cALND was not routinely performed in these studies, they were excluded from quantitative analysis.

Risk of bias and applicability

Figure 4.2 shows the methodological quality of all included studies. In general, studies included in the quantitative analysis showed a lower risk of bias than studies included only in the qualitative analysis.

Results of individual studies included in quantitative analysis

Pooled prevalence of ax-pCR

The overall prevalence of ax-pCR in all 20 included studies was 37% (see Appendix 4.2). The I^2 -statistic was 57.08% ($p < 0.01$). Test for heterogeneity between subgroups based on staging procedure was not significant, supporting the pooling of all studies in 1 overall rate.

SLNB

The IFR of SLNB was available for 16 of 17 studies. The overall IFR was 89% in a pooled sample of 2154 patients (see Appendix 4.3). For all studies, data to calculate FNR and NPV were available for a total of 2002 patients. An overall FNR of 17% was found (see Figure 4.3) and NPV ranged from 57% to 86% (see Table 4.3 SLNB). The I^2 statistic revealed values of variation due to heterogeneity of 68.3% for IFR and 38.7% for FNR ($p < 0.01$ and $p = 0.05$, respectively). Ten studies documented the definition of ax-pCR: overall FNR was 16% when ax-pCR was defined as ypN0 and 17% when ax-pCR was defined as ypN0/itc+ ($p = 0.61$, 1 study defined ax-pCR as ypN0/itc+/mi+). FNR was reported for single versus dual-tracer sampling separately in 5 studies and another 6 studies used either single-tracer or dual-tracer sampling in 100% of patients. Pooled FNR was 13% for dual-tracer sampling and 16% for single-tracer sampling ($p = 0.53$).

Table 4.2 Characteristics of studies involving the combination procedure without routine ALND.

Author	Sample size*	Pre-NST marking at time of FNA/CNB	Pre-NST marking after FNA/CNB	Post-NST marking	Sampling SLNB	IFR [§] %	ML is SLN %	Confirmation removal ML	Lymph nodes [#] median (range)	ALND%	Ax-pCR %
Dashevsky	21	Clip	NA	Wire	Tc + blue	100.0	NR	XR	NR	0.0	33.3
Diego	29	Clip	NA	Iodine seed	Tc + blue	100.0	91.0	XR	4 (1-11)	23.3	63.0
Kim	11	Clip	NA	Wire	Tc + blue	100.0	NR	XR/palpation	NR	45.5	36.4
Nguyen	20	NA	Clip	Iodine seed	Tc and/or blue	100.0	NR	XR	NR	NR	NR
Park	20	NA	Charcoal	NA	Tc and/or blue	100.0	75.0	NA	3 (1-12)	60.0	50.0
Plecha	19	Clip	NA	Wire	Tc +/- blue	100.0	100.0	XR/PA	5.7 (mean)	NR	NR
Simons	139	NA	Clip/Iodine Seed	Iodine seed/wire	Tc and/or blue	99.3	64.6	XR/PA	2 (1-9)	22.3	36.0
Taback	19	Clip (78.9%)	Electromagnetic Reflector	NA	Tc + blue	100.0	63.2	XR	4 (2-10)	31.6	31.6

* patients who underwent successful ML in combination with SLNB; [§] IFR refers to proportion of patients in whom at least 1 lymph node could be identified with the combination procedure; [#] refers to number of lymph nodes of the combination procedure and not the number of lymph nodes of either ML or either SLNB. NA=not applicable; XR=specimen radiography; NR=not reported; PA=pathologic assessment; Tc=technetium.

A total of 14 studies reported on the use of IHC: overall FNR was 15% when IHC was used (either always or in selected patients) versus 17% when IHC was not used ($p=0.47$). In 6 studies, FNR was reported separately in relation to the number of SLN(s): all 6 studies reported FNR for excision of 3 or more SLNs (NB: in 1 study, this was 2 or more SLNs) and 5 of 6 studies also reported FNR for excision of <3 SLNs. Overall FNR was 8% with removal of at least 3 SLNs and 22% with removal of <3 SLN(s) ($p<0.0001$). In 7 studies, only cN+ patients with ycN0 status were included. In addition to these studies, another 4 studies reported on FNR separately for patients with any ycN status versus ycN0 status. Overall FNR was 14% when only patients with ycN0 status were taken into account versus 18% when patients irrespective of ycN status were taken into account ($p=0.14$).

Figure 4.2(A-B) Assessment of risk of bias.

4.2A. Studies included in quantitative analysis.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Alvarado	?	?	😊	?	😊	😊	😊
Boileau	😊	😊	😊	😊	😊	😊	😊
Boughey	😊	😊	😊	😊	😊	😊	😊
Brown	?	😊	😊	😊	?	😊	😊
Carrera	😊	😊	😊	😊	😊	😊	😊
Enokido	😊	😊	😊	😊	😊	😊	😊
Ge	?	?	😊	😊	?	😊	😊
Kang	⊗	?	😊	?	?	?	😊
Kuehn	😊	😊	😊	😊	😊	😊	😊
Ozmen	?	😊	😊	?	😊	😊	😊
Park	?	😊	😊	?	?	😊	😊
Pinero-Madrone	😊	?	😊	😊	😊	😊	😊
Shen	😊	?	😊	😊	😊	😊	😊
Thomas	😊	?	😊	😊	😊	😊	😊
Yagata	😊	😊	😊	😊	😊	😊	😊
Yu	?	😊	😊	😊	?	😊	😊
Zetterlund	😊	😊	😊	😊	😊	😊	😊
Donker	😊	😊	😊	😊	😊	😊	😊
Caudle	⊗	😊	😊	?	?	😊	😊
Siso	?	😊	😊	?	?	😊	😊

Low Risk
 High Risk
 Unclear Risk

4.2B. Studies included in qualitative analysis only.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Dashevsky	?	😊	😞	😞	?	😊	😞
Diego	😊	😊	😞	😞	😊	😊	😞
Kim	😊	😊	😞	😞	😊	😊	😞
Nguyen	😊	?	😞	😞	😊	😊	😞
Park	?	😊	😞	😞	😊	😊	😞
Plecha	?	?	😞	😞	?	😊	😞
Taback	😊	😊	😞	😞	😊	😊	😞

😊 Low Risk 😞 High Risk ? Unclear Risk

Figure 4.3 Forest plot for the FNR of SLNB.

ES: effect size. The pooled FNR of SLNB is 17% (14-20%).

Table 4.3(A-C) Overview and diagnostic accuracy sorted by type of procedure.

4.3A. SLNB

Author	IFR %	Sampling	SLNs, median (range)	Ax-pCR %*	TP	FP	FN	TN	FNR % (CI)	NPV % (CI)
Alvarado	92.7	Tc and/or blue	2 (1-7)	35	57	0	15	39	21 (12-32)	72 (58-84)
Boileau	87.6	Tc and/or blue	2.7 (mean)	35	76	0	7	44	8 (3-17)	86 (74-94)
Boughey	92.7	Tc and/or blue	NR	40.0	326	0	56	255	15 (11-19)	82 (77-86)
Brown	NR	Tc and/or blue	2 (1-10)	30.2	47	0	13	26	22 (12-34)	67 (50-81)
Carrera	90.5	Single radioactive	2.2 (mean) (1-6)	35.4	28	0	3	17	10 (2-26)	85 (62-97)
Enokido	90.9	Tc and/or blue	1.6 (mean)	52	49	0	13	68	21 (12-33)	84 (74-91)
Ge	84.3	Tc and/or blue	2.4 (1-7)	27.9	25	0	6	12	19 (7-37)	67 (41-87)
Kang	87.9	Tc and/or blue	2.8 (mean) (1-8)	28.8	34	0	7	17	17 (7-32)	71 (49-87)
Kuehn	82.6	Tc +/- blue	NR	48.8	51	0	12	60	19 (10-31)	83 (73-91)
Ozmen	92.2	Tc + blue	2.1 (1-5)	28	44	0	7	20	14 (6-26)	74 (54-89)
Park	94.9	Single, radioactive	2.1 (mean) (1-12)	40.8	78	0	22	69	22 (14-31)	76 (66-84)
Pinero-Madrona	84.0	Tc +/- blue	NR	34.2	15	0	10	13	40 (21-61)	57 (34-77)
Shen	92.8	Tc and/or blue	2 (1-10)	28.6	30	0	10	16	25 (13-41)	62 (41-80)
Thomas	86.7	Single blue	1.57 (mean) (1-4)	31	15	0	3	8	17 (4-41)	73 (39-94)
Yagata	85.3	Tc + blue	2 (1-7)	37	43	0	8	30	16 (7-29)	79 (63-90)
Yu	95.8	Single: Blue	1.48 (mean) (1-4)	52.2	14	0	8	24	36 (17-59)	75 (57-89)
Zetterlund	77.9	Tc and/or Blue	2 (1-5)	39.5	79	0	13	60	14 (8-23)	82 (71-90)

4.3B. ML

Author	IFR %	PreNST marker	PostNST marker	N lymph nodes	Ax-pCR %*	TP	FP	FN	TN	FNR % (CI)	NPV % (CI)
Donker	97	Iodine seed	NA	1	26	65	0	5	25	7 (2-16)	83 (65-94)

4.3C. Combination

Author	IFR %	Sampling SLNB	PreNST marker	PostNST marker	N lymph nodes	Ax-pCR %*	ML is SLN %	TP	FP	FN	TN	FNR% (CI)	NPV% (CI)
Caudle	100%	Tc and/or blue	Clip	Iodine seed	NR	41	77 [#]	49	0	1	35	2 (0-11)	97 (85-1)
Siso	NR	Tc and/or blue	Clip	NA*	3 median	31.7	77	23	0	1	11	4 (0-21)	92 (62-1)

*Ax-pCR rate based on data of 2x2 contingency tables; [#]Rate is based on 134 patients with a clipped node that underwent SLNB (it was documented if the clipped node was identified as an SLN). 85 patients actually underwent TAD followed by cALND. NR=not reported; NA=not applicable; Tc=technetium.

ML

One study reported on a ML procedure: this study involved the validation of the MARI procedure (marking axillary lymph nodes with radioactive iodine seeds) in 95 patients. In this study, the pathologically proven positive lymph node was marked with an I-125 seed pre-NST. After completion of NST, at the time of surgery, the lymph node with the Iodine seed was removed. The IFR was 97%, the FNR 7%, and the NPV 83.3%. See Table 4.3 (ML) for characteristics of this procedure.

Combination procedure

Two studies investigated a combination procedure: one involved clipping of the positive lymph node pre-NST later followed by I-125 seed localization of the clipped node post-NST in combination with SLNB and one involved clipping of the positive lymph node pre-NST followed by US-guided excision of the clipped-node in combination with SLNB. Table 4.3 (Combination) shows values for FNR and NPV for the 2 combination procedures. As only 2 studies were available for analysis, pooling of proportions was not performed. The studies appeared clinically similar, as they targeted the same population in terms of inclusion criteria, definition of ax-pCR, and use of IHC.

DISCUSSION

In this systematic review, the accuracy of 3 different procedures for axillary staging after NST in cN+ patients was evaluated. This is the first review up to now that compared all these different less invasive staging procedures with the gold standard ALND. The goal was to provide an overview of currently available procedures in order to guide decision making regarding replacing ALND in selected cN+ patients.

The SLNB for axillary staging after NST in cN+ patients has been extensively studied over the past years. The SLNB procedure is widely accepted as axillary staging procedure in cN0 patients. Even when performed after NST, the accuracy of SLNB for cN0 patients is accepted.³⁹ SLNB for axillary staging after NST in pre-treatment cN+ patients, however, is associated with unacceptably high rates of FNR. In 2015, the accuracy of SLNB in cN+ patients after NST was evaluated in a systematic review that included 8 studies with pathologically proven cN+ patients.⁴⁰ That review reported an overall FNR of 15% and the NPV of SLNB did not exceed 86%.⁴⁰ In the current meta-analysis, a total of 17 studies with 2002 patients (the 8 studies of the previous review were also included) were analyzed. The overall FNR is 17% and the NPV still does not exceed 86%: in case SLNB predicts ax-pCR, residual axillary disease is actually missed in at least 1 in 6 patients. The overall IFR is 89%. Previous studies reported multiple

factors that may improve IFR and accuracy of SLNB, for example, using dual-tracer sampling technique, evaluating the SLNs with IHC in addition to standard H&E evaluation and removing 3 or more SLNs. As IHC and single- versus dual-tracer sampling was not used consistently within and between studies, it is not possible to draw definite conclusions from this review on whether/or not specific sampling and pathologic evaluation methods should be promoted. Our results did show that FNR was favorable (yet not statistically significant) for both dual-tracer sampling and pathologic evaluation with IHC. FNR was also favorable for patients with ycN0 status based on physical examination and/or imaging compared with any ycN status (FNR of 14% vs. 18%, $p=0.14$). Regarding the number of SLNs, removing ≥ 3 lymph nodes was associated with a significantly better FNR in our meta-analysis (8% vs. 22%, $p<0.0001$). However, removing ≥ 3 SLNs is not achievable in a significant number of patients¹⁷ and whether this will be achieved is unpredictable preoperatively. This renders SLNB impractical, as random node-picking should be discouraged. Currently recruiting studies as Alliance 11202 and NSABP-51/RTOG 1304 will determine whether the SLNB, despite its rather poor overall accuracy and shortcomings, can have a place in axillary staging after NST in cN+ patients.^{41,42}

The MARI procedure was the first ML procedure to be proposed as an alternative to SLNB for axillary staging after NST in cN+ patients.⁸ By marking the pathologically proven positive lymph node before start of NST, it was expected to enable accurate assessment of treatment response after completion of NST. The MARI procedure was validated in 1 single-center trial with 95 patients. This study reported an improved FNR (7%), but the NPV of 83.3% was less favorable, that is, in 1 of 6 patients with a negative MARI, axillary residual disease is left behind. Therefore, equally to SLNB, MARI as a stand-alone procedure is insufficiently accurate to safely replace ALND. Despite the shortcomings of MARI (potential of missing residual axillary disease and limited evidence by 1 single—dedicated breast cancer—center trial to support this procedure), it is already implemented in clinical practice. A recent publication suggests combining information on axillary burden on pre-NST PET-CT (ie, number of suspicious lymph nodes: <4 vs. ≥ 4) with MARI outcome⁹ to determine adjuvant axillary treatment: no further axillary treatment, axillary radiotherapy, or cALND with axillary radiotherapy. Results of 1 prospective implementation study showed that this treatment strategy indeed results in a major reduction of ALND.⁴³ Data of longer follow-up have to determine whether implementation of this protocol is untimely and whether it does not only reduce morbidity but also preserves oncologic safety in terms of disease-free and overall survival. Prospective trials with sufficient follow-up are therefore urgently needed.

In the Z1071 trial, a clip was placed in the positive lymph node before NST in a subset of patients.⁴⁴ The trial protocol did not require surgeons to selectively target and

remove the clipped node at time of surgery, but did encourage surgeons and pathologists to document whether the clipped node was located in the SLNB or ALND specimen. In 141 of 170 patients with a clipped node, the location of the clipped node was documented: 75.9% in the SLNB specimen and 24.1% in the ALND specimen. This suggested that removing the clipped node together with SLN(s) at time of surgery may improve accuracy of SLNB and may possibly overcome shortcomings associated with SLNB or MARI if used as stand-alone procedures. Up to now, only 2 trials evaluated accuracy of such a combination procedure and were included in our meta-analysis.^{6,32} This procedure is associated with excellent IFRs. Caudle et al⁶ confirmed that the clipped node does not necessarily have to be a SLN, as this was the case in only 77%. Furthermore, FNR is low (2% to 4%) and NPV is high (92% to 97%). These results are promising: when ax-pCR is predicted, residual axillary disease is missed in 1 in 12 to 33 patients. The evidence for this procedure is yet limited with only 2 trials available (1 retrospective and 1 prospective study), involving small sample sizes and single-center study designs. The ongoing Dutch RISAS trial (NCT02800317 at <https://clinicaltrials.gov>) will prove whether the promising results of a combination procedure can be confirmed in a large, prospective, multicenter trial.⁴⁵

Although evidence to support replacing ALND by less invasive procedures is limited, several reports have been recently published on implementation of such procedures, especially procedures involving excision of the ML and SLNs. A variety of methods are used to target the pathologically proven positive lymph node: marking with a clip pre-NST followed by placing an iodine seed or wire in the clipped node post-NST^{7,33–35,37} and primary marking with an iodine seed, clip, charcoal, or electromagnetic reflector.^{36,38} Also, the time of marking the lymph node pre-NST differs: either immediately at time of FNAC/CNB,^{7,33,34,37} at a second appointment once metastatic burden of the punctured lymph node is confirmed by the pathologist^{35,36} or even at both occasions.³⁸ Currently, further research has to define which combination procedure is most accurate, patient-friendly, and cost-effective. Identification of the ML at time of surgery is highly feasible, provided that clipping (with/without secondary localization of the clip) of the node was successful. Success rates of this part of the procedure are often not sufficiently reported and may be improved to further optimize combination procedures.

The abovementioned 3 different staging procedures intend to offer a less invasive strategy compared with the conventional ALND, yet ≥ 10 lymph nodes are removed in some patients with SLNB and combination procedures. It is important to realize that these procedures serve as a staging procedure to identify ax-pCR and not as a managing procedure to remove all residual diseases. Hence, it should be the primary goal to remove as few lymph nodes as possible. In this way, patients with ax-pCR can truly benefit from less invasive staging procedures. At the same time, when these

procedures identify axillary residual disease, adjuvant axillary treatment plans should consist of cALND. Results of the Alliance 11202 and NSABP-51/RTOG 1304 trials have to be awaited to determine whether cALND may be replaced by axillary radiotherapy.^{41,42}

As this review is limited by the heterogeneity of included studies, results of the review should be interpreted with caution. The random effects model that was used for statistical analysis takes in account that, although similar interventions were studied, different populations were included. Factors such as definition of ax-PCR, sampling method for SLNB, and use of IHC for pathologic assessment of lymph nodes may all impact accuracy of the studied intervention. These factors differed widely among included studies and further research is necessary to determine, among others, what should be the preferred definition of ax-PCR. The prognostic impact of residual ITCs and micrometastasis may be different for patients treated in the neoadjuvant compared with adjuvant setting, as they might be therapy-resistant. A retrospective study of cN+ patients treated with NAC and always followed by ALND suggested that patients with residual ITCs and micrometastases carry a similar prognosis as patients with ypN0.⁴⁶ These results have yet to be confirmed in trials where patients with ypN0 and ITCs or micrometastasis did not undergo ALND. In addition, the value of IHC has not yet been thoroughly studied, as most studies that used IHC in addition to standard H&E evaluation, did so randomly, and not in a routine matter. Contrary to improving accuracy of detecting residual axillary disease, a potential undesired result of IHC may be detection of residual disease that would have otherwise been left undetected (of which implications on prognosis and need for adjuvant treatment are unknown). The question whether IHC may not only result in improved accuracy but may also result in overtreatment is yet left unanswered.

In this review, we only included patients in whom cN+ status was pathologically proven before NST. This is particularly important to determine true accuracy of the different staging procedures. When patients who are expected to be cN+ based on physical examination or imaging only, the number of true negatives rises and the chance to have false negatives decreases. This may result in a false impression of improved rates of FNR and NPV.

In conclusion, the SLNB as well as ML procedures seem insufficiently accurate as stand-alone procedures for axillary staging after NST in cN+ patients. Accuracy of these procedures may improve by taken in account axillary burden on pre-NST and/or post-NST imaging. A combination procedure involving excision of the ML and SLNs appears most accurate for axillary staging and has the lowest risk of missing axillary residual disease when ax-PCR is predicted. More evidence from prospective multicenter trials is needed to confirm this.

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APPENDIX 4.1

PubMed search strategy

("Breast Neoplasms"[Mesh] OR ((carcinoma OR carcinomas OR tumor OR tumours OR tumour OR tumours OR neoplasm OR neoplasms OR malignancy OR adenocarcinoma OR cancer) AND (breast OR mamma))) AND ("Sentinel Lymph Node Biopsy"[Mesh] OR sentinel lymph node biopsy OR slnb OR (MARI[tiab]) OR (Axilla* AND staging[tiab]) OR targeted axillary dissection) AND (sensitivity OR specificity OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR negative predictive value OR positive predictive value OR likelihood ratio OR diagnosis OR "false-negative" OR "false-positive") AND ("Lymph Nodes"[Mesh] OR "Lymphatic Vessels"[Mesh] OR "Lymphatic Metastasis"[Mesh] OR "Lymphatic System"[Mesh] OR "Axilla"[Mesh] OR axilla*) AND (("Neoadjuvant Therapy"[Mesh] OR neoadjuvant OR preoperative* OR primary) AND ("Antineoplastic Agents"[Mesh] OR chemotherapy OR immunotherapy OR systemic therapy))

EMBASE search strategy*

((breast OR mamma) AND (cancer OR carcinoma OR neoplasm OR malignancy OR adenocarcinoma OR 'breast cancer'/exp OR tumor OR carcinomas OR tumors OR tumour OR tumours)) AND (('sentinel lymph node biops*' OR slnb OR 'sentinel node*' OR 'sentinel lymph node biopsy'/exp OR 'mari':ab,ti OR (axilla* AND staging) OR 'targeted axillary dissection')) AND (sensitivity OR specificity OR 'predictive value' OR 'likelihood ratio' OR ppv OR npv OR diagnosis OR 'false negative' OR 'false positive') AND ((axilla* OR lymph*) AND (node* OR metastasis)) AND ((neoadjuvant OR primary OR preoperative*) AND (therapy OR immunotherapy OR chemotherapy OR systemic))

*Search results were restricted to articles, reviews, articles in press, conference paper, conference review

APPENDIX 4.2

Forest plot of the ax-pCR rate.

ES: effect size. The pooled ax-pCR is 37% (33-40%).

APPENDIX 3

Forest plot for the identification rate of SLNB.

ES: effect size. The pooled identification rate of SLNB is 89% (87-92%).

CHAPTER

5

A novel less-invasive approach for axillary staging after neoadjuvant chemotherapy in patients with axillary node-positive breast cancer by combining radioactive iodine seed localization in the axilla with the sentinel node procedure (RISAS): a Dutch prospective multicenter validation study

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ABSTRACT

Background

In 1 of 3 patients with initial lymph node-positive (cN+) breast cancer, neoadjuvant chemotherapy (NAC) results in an axillary pathologic complete response (ax-pCR). This urges the need for a less-invasive axillary staging method. Recently introduced less-invasive procedures have been insufficient in accurately identifying ax-pCR. Therefore, we propose a novel less-invasive axillary staging procedure: the Radioactive Iodine Seed localization in the Axilla with the Sentinel node procedure (RISAS), a combination of the procedure of marking axillary lymph nodes with radioactive iodine seeds (MARI) and sentinel lymph node biopsy (SLNB).

Patients and methods

In the present open single-arm multicenter validation study, 225 cN+ (biopsy-proven) patients will undergo the RISAS procedure, in which a positive lymph node is marked by an iodine-125 seed before NAC. After NAC completion, this iodine-125 seed-marked lymph node is removed, together with any additional sentinel lymph nodes. The RISAS procedure is subsequently followed by completion axillary lymph node dissection (ALND). The RISAS lymph nodes will be compared with the lymph nodes from the completion ALND specimen. The primary endpoint is accuracy of the RISAS procedure. The identification rate, false-negative rate, negative predictive value, and possible concordance between the MARI and SLNB will be reported.

Conclusion

The present prospective multicenter RISAS trial will enable us to validate the combination of MARI and SLNB for assessing the axillary response to NAC in cN+ patients. If RISAS proves to be an accurate axillary staging procedure, ALND could safely be abandoned in the case of ax-pCR confirmed using the RISAS procedure.

INTRODUCTION

Surgical management of the axilla in breast cancer evolved greatly in the past decades. In clinically node negative patients axillary staging has shifted from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB). In clinically node positive patients (cN+), ALND is still recommended for axillary staging.^{1,2} However, the shift from adjuvant to neoadjuvant chemotherapy (NAC) has resulted in an increasing need for a less-invasive axillary staging approach, because NAC enables downstaging of axillary disease.^{3,4} In $\leq 36\%$ of all patients, conversion of cN+ to an axillary pathologic complete response (ax-pCR) as a result of NAC has been reported.⁵ In the case of HER2neu positive patients, ax-pCR can be achieved in $\leq 74\%$ of patients when NAC is combined with HER2-targeted therapy.^{6,7} Patients in whom ax-pCR is achieved are not expected to benefit from ALND; however, a significant proportion will experience side effects. Consequently, routine ALND is increasingly being regarded as overtreatment in these patients.

To date, imaging techniques have not been able to accurately identify the presence of an ax-pCR. As for surgical techniques, various less-invasive axillary staging procedures have been proposed for cN+ patients after NAC completion. The SLNB seems to be insufficient, with reported false negative rates (FNRs) ranging from 7% ⁸ to 25% .⁹ Because the SLNB aims to identify patients with an ax-pCR without missing residual disease, a negative predictive value (NPV) of $\geq 95\%$ would be desirable. A high NPV is especially important since residual tumour is considered resistant to administered chemotherapy and might require additional treatment. However, the NPVs for SLNB have not exceeded 86% ⁵; thus residual axillary disease will be missed in 1 of every 6 patients for whom an ax-pCR is suggested by the SLN(s). Factors contributing to the improvement of the FNR/NPV of SLNB include using the dual tracer technique and removal of ≥ 3 SLNs.^{8,10-12} In daily practice, the latter is not always achievable, as was demonstrated by the SENTINA (sentinel neoadjuvant) trial, in which most patients had only 1 to 2 SLNs removed.¹² Donker et al.¹³ introduced an alternative, less-invasive axillary staging procedure: the MARI procedure (marking axillary lymph nodes with radioactive iodine seeds). In the MARI procedure, an I-125 seed is placed in the biopsy-proven positive axillary lymph node before NAC. After NAC completion, the I-125 seed-containing node is removed at breast surgery. In 98 pretreatment cN+ patients, an identification rate of 97% and an FNR of 7% was reported. The MARI procedure has a reported NPV of 83% , indicating that residual axillary disease is still overlooked to the same extent as with the SLNB.^{13,14} In summary, both MARI and SLNB remain insufficiently accurate to use as solitary staging procedures.

Caudle et al.¹⁵ proposed Targeted Axillary Dissection (TAD), involving clip placement in a biopsy-proven positive axillary lymph node before NAC, followed by localization of

this clipped node with an I-125 seed after NAC completion. Excision of the I-125 seed-marked node was combined with excision of SLNs. All cN+ patients treated with NAC and in whom the biopsied node was marked with a clip were included in a prospective registry. Retrospectively, 85 patients who had undergone TAD, followed by a completion ALND, were identified. An FNR of 2% and an NPV of 97% were reported.¹⁵ These results are promising; however, the study was hampered by the single-center study design and small sample size, with only 35 patients in whom an ax-PCR was achieved. Consequently, widespread implementation of TAD cannot be recommended before a large, preferably multicenter, validation study has been performed.

Therefore, we propose a multicenter, open, single-arm validation study in which the RISAS (Radioactive Iodine Seed localisation in the Axilla combined with the SLNB) procedure is investigated. To validate RISAS, completion ALND will be performed in all patients. The I-125 seed will be placed before the start of NAC. If the results prove that RISAS accurately predicts axillary nodal status after NAC completion, completion ALND and its concomitant morbidity can safely be omitted and prevented in patients with an ax-PCR predicted by RISAS.

PATIENTS AND METHODS

The RISAS study is an open, single-arm, noninferiority multicenter validation study to assess the accuracy of RISAS for axillary staging after NAC in pretreatment cN+ breast cancer patients. Nodal positivity will always be confirmed by pathologic assessment before the start of NAC in the case of suspicious lymph nodes found on axillary ultrasonography. Patients will be recruited from approximately eight participating hospitals in the Netherlands during a 2-year period. Each hospital has $\geq$ one year of experience with I-125 seed-guided localization. Given a noninferiority margin of 6.25% and assuming a prevalence of positive ALND findings of 64%, a total of 225 patients will be needed to test the noninferiority of RISAS compared with ALND.

Patients fulfilling all eligibility criteria will – after completion of NAC – undergo the RISAS procedure and, subsequently, completion ALND (Table 5.1). Patients in whom I-125 seed placement is not possible and in whom the RISAS procedure is not followed by completion ALND will be excluded from final analysis.

The chemotherapy regimens will be determined according to current Dutch breast cancer guidelines¹ and multidisciplinary team decision making. In HER2neu positive patients, NAC will be combined with HER2-targeted therapy.

Table 5.1 Eligibility criteria.

Inclusion criteria	Exclusion criteria
Female, age ≥ 18 years	Pregnancy or nursing
Invasive breast cancer with biopsy proven positive axillary lymph node(s)	Contraindications to RISAS (e.g. allergic reaction to blue dye)
NAC	Recurrent breast cancer
	History of axillary surgery or radiotherapy
	Positive infra- and / or supraclavicular lymph nodes
	Distant metastasis

NAC, neoadjuvant chemotherapy; RISAS, Radioactive Iodine Seed localisation in the Axilla combined with the Sentinel node procedure.

The RISAS procedure consists of the MARI procedure combined with SLNB. First, the most suspicious node is sampled using core needle biopsy or fine needle aspiration to confirm nodal positivity. Subsequently, the MARI procedure is performed. This consists of marking the pathologically proven positive lymph node with an I-125 seed before the start of NAC using ultrasound guidance. Retrieval of the sampled node is facilitated by reporting multiple characteristics of the node (eg, diameter of the node and diameter of the cortex). Furthermore, the radiologist will capture an image of the biopsied lymph node. Iodine seeds with a maximum activity of 7.4 MBq (0.2 mCi) will be used.¹⁶ SLNB will be performed using the standard dual tracer technique. After excision of the RISAS nodes, the surgeon will proceed with completion ALND. The RISAS nodes and the remaining nodes of the axillary basin will be secured separately.

The pathologist will assess the RISAS nodes and remaining nodes removed in the completion ALND specimen separately. The presence of isolated tumor cells, micrometastases, and / or macrometastases will be registered. Routine hematoxylin and eosin staining will be performed on all lymph nodes. Immunohistochemistry will only be performed on each RISAS node that is negative on hematoxylin and eosin staining, irrespective of the ALND specimen findings.

The institutional review board of the Erasmus Medical Centre approved the present study (approval no. MEC-2016-412), which was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT02800317).

Basic statistical analysis will be used. The test outcome of both RISAS and completion ALND can be either negative or positive. If the test outcome of RISAS is positive, the test outcome of the completion ALND will also be considered positive. The outcomes will be formulated in a 2x2 contingency table. The primary endpoint of our study is accuracy of the RISAS procedure and will be defined by calculating sensitivity, NPV, and FNR.

DISCUSSION

With the increasing need for less-invasive axillary staging after NAC, various procedures have been proposed. MARI and SLNB remain insufficient for this purpose, because they miss potentially therapy-resistant disease to a rather high extent.^{5,11,13} TAD has shown promising results; however, owing to the retrospective analysis of patients and small sample size of the single-center study, it seems premature to implement this procedure as standard practice in replacement of ALND.¹⁵ Our present RISAS study will provide answers to questions regarding TAD, the role of immunohistochemistry, and the appropriate procedure if fewer than 2 nodes will be removed.¹⁷ An overview of the studies proposing different less-invasive axillary staging procedures is provided in Table 5.2.

Table 5.2 Overview of studies comparing less invasive surgical procedures with axillary lymph node dissection for axillary staging after NAC in pre-treatment cN+ patients.

	ACOSOG Z107111	MARI-procedure13	TAD15	RISAS
Type of procedure	SLNB	MARI	SLNB + I-125 seed placement in the clipped node after completion of NAC	SLNB + I-125 seed placement prior to NAC
Sample size*	687	98	85	225
Prevalence axillary ax-pCR	40.0	26.0	41.0	#
Identification rate (%)	92.7	97.0	100	#
FNR (%)	14.7	7.0	2.0	#
NPV (%)	82.0	83.0	97.2	#

* This includes all patients in whom concomitant ALND is performed, # pending on results. *SLNB* sentinel lymph node biopsy, *MARI* Marking the Axillary lymph node with Radioactive Iodine seeds, *TAD* Targeted Axillary Dissection, *RISAS* Radioactive Iodine seed localisation in the Axilla combined with Sentinel node procedure, *I-125 seed* iodine-125 seed, *NAC* neoadjuvant chemotherapy, *ax-pCR* pathologic complete response, *FNR* false-negative rate, *NPV* negative predictive value.

Because RISAS combines MARI and SLNB, the accuracy of RISAS is thought to not be hindered by the shortcomings of the solitary techniques. Metastatic lymph nodes can block and deviate normal lymphatic drainage, resulting in “false SLNs”. Given that the RISAS procedure not only retrieves (false) SLNs but also pretreatment pathologically proven metastatic lymph nodes, it has the potential to be equal to ALND in staging of the axilla. Caudle et al.¹⁵ have already demonstrated that the clipped node was not retrieved as an SLN in 23% of patients.

An advantage of RISAS compared with TAD is that the biopsy-proven positive node is primarily marked by an I-125 seed and not preceded by clip placement. The exact placement of the I-125 seed directly adjacent to the clip might be challenging and,

thus, could possibly hamper accuracy. Furthermore, direct marking of the lymph node by an I-125 seed obviates an extra hospital visit after NAC completion, which minimizes patient burden and obviates an additional procedure, reducing logistical issues.

Conclusion

The RISAS study is a multicenter prospective noninferiority study to validate the combination of MARI and SLNB for predicting the axillary response to NAC in pretreatment cN+ patients. The ultimate goal is to identify ax-pCR patients using a minimally invasive procedure to prevent unnecessary ALND, with its associated side effects, without comprising oncologic safety. ALND could then become a management procedure reserved for patients with residual axillary disease.

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CHAPTER

6

Excision of both the pretreatment marked positive node and sentinel nodes improves axillary staging after neoadjuvant systemic therapy study

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ABSTRACT

Background

Marking the axilla with radioactive iodine seed and sentinel lymph node (SLN) biopsy have been proposed for axillary staging after neoadjuvant systemic therapy in clinically node-positive breast cancer. This study evaluated the identification rate and detection of residual disease with combined excision of pretreatment-positive marked lymph nodes (MLNs) together with SLNs.

Methods

This was a multicentre retrospective analysis of patients with clinically node-positive breast cancer undergoing neoadjuvant systemic therapy and the combination procedure (with or without axillary lymph node dissection). The identification rate and detection of axillary residual disease were calculated for the combination procedure, and for MLNs and SLNs separately.

Results

At least one MLN and/or SLN(s) were identified by the combination procedure in 138 of 139 patients (identification rate 99.3%). The identification rate was 92.8% for MLNs alone and 87.8% for SLNs alone. In 88 of 139 patients (63.3%) residual axillary disease was detected by the combination procedure. Residual disease was shown only in the MLN in 20 of 88 patients (23%) and only in the SLN in ten of 88 (11%), whereas both the MLN and SLN contained residual disease in the remainder (58 of 88, 66%).

Conclusion

Excision of the pretreatment-positive MLN together with SLNs after neoadjuvant systemic therapy in patients with clinically node-positive disease resulted in a higher identification rate and improved detection of residual axillary disease.

INTRODUCTION

Over the past few decades, there has been a trend towards de-escalation of surgical management of the axilla. In patients with clinically node-positive (cN+) disease, axillary lymph node dissection (ALND) is still performed frequently, providing both regional control and information for adjuvant therapy recommendations. Neoadjuvant systemic therapy (NST) is often given to patients with cN+ disease, leading to a pathological complete response (pCR) in the axilla in approximately one-third of patients.¹ Patients with an axillary pCR do not benefit from ALND, yet do suffer from both short- and long-term side-effects of the operation. There is a need for less invasive axillary staging methods for these patients.

Various less invasive procedures have been proposed for axillary staging after NST in patients with cN+ tumours before treatment. However, neither the sentinel lymph node (SLN) nor the marking the axilla with a radioactive iodine seed (MARI) procedure have low enough false-negative rates (FNRs) for these techniques to comfortably replace ALND.¹⁻⁴ Based on the negative predictive values (NPVs) of these procedures, residual axillary disease may be missed in at least one in six patients with cN+ disease in whom an axillary pCR is suggested.⁵⁻⁷ To improve accuracy, Caudle and colleagues⁸ introduced targeted axillary dissection, which is a combination of SLN biopsy (SLNB) and a MARI-like procedure; this was shown to have a FNR of 2% and a NPV of 97% in a cohort of 85 patients. Based on this, residual axillary disease would be missed in only one of 33 patients in whom an axillary pCR is suggested. The ongoing Dutch RISAS trial (NCT02800317)⁹ will assess whether these promising results of a combination procedure can be validated in a prospective multicentre study.

In the absence of high-level evidence, various protocols involving less invasive axillary staging are being implemented in clinical practice. Those in favour of SLNB alone believe that pretreatment marking of the positive lymph node is an unnecessary extra procedure, and instead support the removal of at least three sentinel nodes to improve accuracy. Advocates of the MARI procedure believe that SLNB is not of additional benefit if removal of the marked lymph node (MLN) is guaranteed, whereas others stress the need to combine these procedures to secure accurate staging. At the same time, omission of ALND is controversial as long-term follow-up of patients with cN+ disease in whom ALND is omitted is not yet available.

This large multicentre retrospective study analysed a cohort of patients with cN+ breast cancer who underwent a combination procedure after NST. The combination procedure comprised excision of both a pretreatment-positive MLN and SLN(s) instead of performing standard ALND for axillary staging after NST. The identification

rate and detection of residual disease of the combination procedure, and its advantages over either the MARI procedure or SLNB alone, are reported.

METHODS

This retrospective cohort study included patients with pathologically proven node-positive breast cancer who underwent a combination procedure with excision of the MLN and SLN(s) after NST. Patients with distant metastasis and those who underwent SLNB before NST were not eligible. Patients were treated between September 2014 and November 2017 in four hospitals in the Netherlands: University Medical Centre Utrecht in Utrecht, Amphia Hospital in Breda, Haaglanden Medical Centre in The Hague and Alrijne Hospital in Leiderdorp. Multidisciplinary tumour boards at these centres reviewed local protocols for axillary staging, which led to replacing or preceding ALND with excision of the MLN and SLN(s) after NST in patients with cN+ disease. Type of adjuvant axillary surgery and/or radiation therapy was also decided by the multidisciplinary tumour boards. Medical records were obtained to collect data on age, breast cancer subtype, receptor status, TNM classification (AJCC cancer staging manual, 7th Edition, 2010) before and after NST, NST regimens, imaging findings, radiological and surgical procedures, and adjuvant treatment.

This study protocol was reviewed by the Medical Research Ethics Committee of University Medical Centre Utrecht (number 18/111); the requirement for written informed consent was waived.

Neoadjuvant systemic therapy

Systemic therapy regimens were determined according to the Dutch breast cancer guidelines (2012) and local multidisciplinary tumour board preferences. In human epidermal growth factor receptor 2 (HER2)-positive disease, NST was combined with HER2-targeted therapy.

Pretreatment marking of positive lymph node

Suspicious lymph nodes identified on imaging were examined pathologically by sampling the (most) suspicious lymph node using fine-needle aspiration or core needle biopsy. Subsequently, the same lymph node, if proven N+, was marked by a radiologist under ultrasound guidance before the start of NST by means of either an iodine seed or a radio-opaque clip, depending on local practice. If a clip was used, a wire or iodine seed was placed within the clipped lymph node after completion of NST, to facilitate removal of the clipped node during surgery. If there were multiple suspicious lymph nodes, only one node was biopsied, and marked if positive.

Sentinel lymph node biopsy

SLNB was performed by a single-tracer method (^{99m}Tc) in Haaglanden Medical Centre, and by a dual-tracer method (Tc and blue dye) in the other three centres. In the event of negative lymphoscintigraphy, Tc was reinjected before surgery depending on local protocols. In some patients, sampling with blue dye alone was performed. Suspicious and/or enlarged non-SLN(s) were removed at the discretion of the surgeon.

Surgery

The combination procedure was performed simultaneously with removal of the breast by a dedicated breast surgeon. The MLN containing the iodine seed was excised under guidance of a hand-held γ probe set to detect ^{125}I . If the MLN contained a wire, the wire was used to guide excision of the MLN. The probe was then set to detect Tc and used to identify SLN(s). Surgeons were trained to note whether the MLN also showed Tc radioactivity or blue dye uptake, that is whether the MLN was the sentinel node. In all patients with an iodine seed, excision of this seed was confirmed by means of a specimen radiograph and/or the absence of ^{125}I radioactive counts in the axilla. Specimen radiography was not undertaken routinely in patients who had wire localization.

Pathology

All lymph nodes were sectioned and stained with haematoxylin and eosin, and the pathologist could opt to use immunohistochemical analysis of the MLN and/or SLN(s). The following items were reported: number of lymph nodes, presence of an iodine seed or clip, number of positive lymph nodes and extent of residual disease. The number of examined lymph nodes reported by the pathologist was documented for the MLN and SLN separately. Their sum was the number of examined lymph nodes for the combination procedure, unless the MLN was the sentinel node. The pathological outcome of the combination procedure was based on the combined outcome of the MLN and SLNB (Table S6.1, supporting information).

Adjuvant treatment

Adjuvant treatment was based on national guidelines and local multidisciplinary tumour board preferences. As residual disease may have been missed by the combination procedure in a limited number of patients, adjuvant axillary radiotherapy was frequently recommended, and also in the event of an axillary pCR. The need for completion ALND was determined on an individual basis.

Statistical analysis

The aim was to report on experiences with the combination procedure and not the accuracy of the combination procedure, as completion ALND was not undertaken in all patients. The focus was therefore on identification rate and detection of axillary residual disease for the MLN, SLNB and the combination procedure. In terms of identification rate, the combination procedure was considered successful if at least one lymph node (MLN and/or SLN) was identified. Regarding the detection of axillary residual disease, it was determined if the ML and the SLN were one and the same node based on data from the surgery and/or pathology report.

Either the X^2 test or Fisher's exact test was used to compare unpaired data. The McNemar exact test was used for analysis of paired assessments of the proportion of patients with cN+ disease in whom residual axillary disease was detected by the MLN, SLN(s) or by the combination of MLN with SLN(s). Statistical analysis was performed using SPSS® for Windows® version 24 (IBM, Armonk, New York, USA).

RESULTS

A total of 139 patients from four institutions were included in this study (Figure 6.1). Patient, tumour and treatment characteristics are shown in Tables 6.1 and 6.2. An overall axillary pCR was identified in 50 of 139 patients (36.0%) (74% for patients with HER2-positive, 44% for those with triple-negative, and 7.4% for patients with hormone receptor-positive, HER2-negative tumours respectively), based on final pathological assessment of MLN, SLNs and, if applicable, completion ALND. A breast pCR was identified in 48 of 139 patients (34.5%), and a pCR in both the breast and axilla in 40 of 139 (28.8%).

Preoperative details of nodal assessment

Data on the number of suspicious lymph nodes before NST was available for 130 of 139 patients (93.5%). The median number of suspicious lymph nodes identified on ultrasound examination was 1 (range 0-5). The median number identified by MRI and/or PET-CT was 2 (range 0-9), with data available for 126 of 139 patients (90.6%). The MLN was marked primarily with an iodine seed in 68 of 139 patients (48.9%) and with a clip in 71 (51.1%). When a clip was used, a wire (58 of 71, 82%) or iodine seed (12 of 71, 17%) was placed within the lymph node after completion of NST. In one patient (1%), placement of a wire was not attempted owing to the location of the lymph node and the risk of pneumothorax.

Lymphoscintigraphy was undertaken in 131 of 139 patients (94.2%) as part of the SLNB procedure, and one or more hotspots were identified in 104 of 131 (79.4%).

SLNB was performed using a dual-tracer technique in 76 of 139 patients (54.7%) and a single-tracer technique in 63 (45.3%); 55 of the latter patients (87%) patients had lymphoscintigraphy with Tc only and eight (13%) with blue dye only.

Figure 6.1 Flow chart for the study.

* If completion ALND was performed. cALND; completion ALND. cALND, completion axillary lymph node dissection; ITC, isolated tumor cells; mi, micrometastases.

Table 6.1 Patient and tumour characteristics among patients with clinically node-positive disease.

Characteristic	No. of patients* (n=139)
Treating centre	
University Medical Centre Utrecht	23 (16.5)
Amphia Hospital	22 (15.8)
Medical Centre Haaglanden	59 (42.4)
Alrijne Hospital	35 (25.2)
Age (years)†	56 (26–82)
Clinical tumour category‡	
cT1	19 (14)
cT2	78 (57.4)
cT3	27 (19.9)
cT4	12 (8.8)
Clinical node category	
cN1	102 (73.4)
cN2	26 (18.7)
cN3	11 (7.9)
Histology	
Ductal	117 (84.2)
Lobular	10 (7.2)
Ductulolobular	7 (5.0)
Other§	5 (3.6)
Molecular subtype	
HR+/HER2+	24 (17.3)
HR–/HER2+	22 (15.8)
HR+/HER2–	68 (48.9)
Triple-negative	25 (18.0)
Method of confirmation of nodal positivity	
FNAC	126 (90.6)
CNB	13 (9.4)

* With percentages in parentheses are unless indicated otherwise; † values are median (range). ‡ Data available for 136 patients; one patient had relapse in mastectomy scar (patient A), one had ductal carcinoma in situ after neoadjuvant systemic therapy (NST) but no histopathological diagnosis before NST (patient B), and one had axillary relapse without signs of local relapse (patient C). § Tubulolobular carcinoma in one patient, tubular carcinoma in one patient, data missing for three patients (including patients B and C). HR, hormone receptor; HER2, human epidermal growth factor receptor 2; FNAC, fine-needle aspiration cytology; CNB, core needle biopsy.

Identification rates

The MLN procedure had an overall identification rate of 92.8% (129 of 139). The identification rate was 93% both for primary marking with an iodine seed and with a clip ($p=0.994$). In patients with a clip, the identification rate was 93% (55 of 58) for patients with a clip–wire combination and 95% (11 of 12) for those with a clip–seed combination ($p=0.668$). The iodine seed was retrieved in all patients, but a lymph node was not identified in six, meaning that the iodine seed was not located within a lymph node but in the adjacent adipose tissue. SLN(s) were identified in nine of ten patients in whom the MLN was not identified.

Table 6.2 Treatment characteristics.

Characteristic	No. of patients (n = 139)
Neoadjuvant regimen	
Chemotherapy only	82 (59.0)
Chemotherapy + HER2-directed therapy	44 (31.7)
Endocrine therapy only	13 (9.4)
Type of pretreatment lymph node marker	
Iodine seed	68 (48.9)
Clip	71 (51.1)
Breast surgery*	
Breast-conserving surgery	87 (63.5)
Mastectomy	50 (36.5)
Axillary surgery	
Combination procedure only	108 (77.7)
Combination procedure + completion ALND	31 (22.3)

Values in parentheses are percentages. *Excluding patients A and C in Table 6.1. HER2, human epidermal growth factor receptor 2; ALND, axillary lymph node dissection.

The SLNB procedure had an overall identification rate of 87.8% (122 of 139). The identification rate was 86% for the dual-tracer and 90.4% for the single-tracer technique ($p=0.375$). Three or more SLNs were removed from 46 of 122 patients (37.7%). An MLN was identified in 16 of 17 patients in whom no SLN(s) were identified.

The combination procedure had an overall identification rate of 99.3% (138 of 139). At least one MLN and/or SLN was identified in 138 patients. No nodes were retrieved from one patient because no SLN was identified during surgery and the iodine seed was not located within or adjacent to a lymph node. Completion ALND in this patient showed an axillary pCR. The median number of lymph nodes resected with the combination procedure was 2 (mean 2.6; range 1–9, i.q.r. 1–3). Both the MLN and SLN(s) were identified in 113 of 139 patients (81.3%); either the MLN alone (16 of 139, 11.5%) or only the SLN(s) (9 of 139, 6.5%) were identified in the remaining 25 patients (Figure 6.2). Whether the MLN and the sentinel node were the same was reported for 96 of 113 patients (85.0%), and this was the case in 62 of 96 (65%).

Detection of residual axillary disease with the combination procedure

Residual axillary disease was detected in 88 of 139 patients (63.3%) with the combination procedure. The median number of lymph nodes resected with the combination procedure was 2 (range 1–9) among patients with and 2 (1–7) in those without residual disease. Both the MLN and SLN(s) contained residual disease in 58 of 88 patients (66%). Residual disease was detected only in the MLN in 20 of 88 (23%); no SLN(s) were identified in 11 of these patients, and in nine patients the SLN did not

contain residual disease whereas the MLN did. Residual disease was detected only in the SLN(s) in ten of 88 patients (11%); no MLN was identified in one patient, and in nine patients the MLN did not contain residual disease but the SLN(s) did (Figure 6.3). The proportion of all patients in whom residual axillary disease was identified by the combination procedure (MLN and SLN(s)) was 63.3% and this was significantly higher than the proportion identified using either MLN (56.1%; $p=0.002$) or SLN (48.9%; $p<0.001$) procedures alone. The proportion of patients in whom residual axillary disease was identified did not differ significantly between the MLN and the SLN procedures (56.1 *versus* 48.9%; $p=0.100$).

Palpable or suspicious lymph nodes were removed in addition to the MLN and/or SLN(s) in 29 of 139 patients (20.9%) at the discretion of the surgeon. Additional nodes were removed in 21 of 122 patients (17.2%) with SLNs identified, and in eight of 17 (47%) with no SLNs identified. The additionally removed nodes showed macrometastasis, whereas the MLN and/or SLN(s) were negative, in three of 29 patients. In the remaining 26 patients, the additional nodes did not change the outcome based on the MLN and/or SLN(s); the disease was classified as ypN+ in 15 patients and as ypN0 in 11.

Figure 6.2 Success rate in identifying both the marked lymph node and sentinel lymph nodes in a patient.

The figure represents 138 of 139 patients, as no marked lymph node (MLN) or sentinel lymph node (SLN) was identified in one patient. Patients in whom the MLN and SLN were one and the same were included in the group with both MLN and SLN(s) identified. In 25 of 138 patients, it was not possible to identify both the MLN and SLNs, but either the MLN or SLN(s) was identified.

Figure 6.3 Types of node in which disease was found among patients with residual axillary disease identified by the combination procedure.

The population comprises all 88 patients in whom residual axillary disease was detected by the combination procedure. Residual disease was found only in the marked lymph node (MLN) and not in the sentinel lymph node (SLN) (either because no SLN was identified or because the SLN was free from disease), only in the SLN(s) and not in the MLN (either because no MLN was identified or because the MLN was free from disease) or in the MLN as well as the SLN(s). *Including palpable non-SLN(s) if applicable.

Adjuvant axillary radiotherapy

Adjuvant radiotherapy treatment plans were available for 138 of 139 patients (99.3%). Adjuvant radiotherapy of the axilla was planned in 114 of 138 patients (82.6%), including the periclavicular nodes in 74.6% and including internal mammary nodes in 2.6%.

DISCUSSION

This retrospective analysis of a large multicentre cohort of patients who presented with biopsy-confirmed cN+ disease evaluated the identification rate and detection of residual disease of the MLN in combination with SLNB after NST. This less invasive combination procedure had an excellent identification rate of 99.3%, and enabled improved detection of residual axillary disease compared with either the MLN alone or the SLNB procedure alone.

The optimal staging and management of the axilla in patients with cN+ disease who receive NST is controversial. The need for consensus on the most appropriate method for axillary staging in this situation is reflected by the varying practices worldwide. Although SLNB has proven accurate in patients with clinically node-negative disease, both before and after NST¹⁰, it is associated with less favourable accuracy in those with cN+ tumours treated with NST. The St Gallen International Expert Consensus Conference¹¹ on axillary surgery after NST considered SLNB to be adequate for axillary staging before NST in patients with cN+ disease. The recommendation for patients with a clinically positive axilla after NST, and with a limited number of SLN(s) resected (fewer than 3) or with macrometastatic disease identified in the SLNs, remains ALND. It has been reported that the accuracy of SLNB in patients with cN+ tumours treated with NST depends on the number of excised SLN(s) and whether the dual-tracer technique is used. Although the dual-tracer technique was used in only 54.7% of patients in the present cohort, the identification rate for SLNB was high at 87.8%. However, only 37.7% had three or more SLNs removed. To act in accordance with the St Gallen recommendations would have required completion ALND in a significant number of patients, including those with an axillary pCR. As most patients will not have at least three SLNs identified at surgery, ensuring removal of the MLN in addition to the SLN(s) may be a better strategy. Targeted axillary dissection, developed at MD Anderson Cancer Center, appears promising, with a FNR of 2% and NPV of 97%.⁸ Recently, the prospective ILINA trial¹² was reported, which included ultrasound-guided excision of the MLN in combination with SLNB. Of 46 patients with cN+ disease treated with NST, 35 completed the protocol followed by ALND, resulting in a FNR of 4.1% and NPV of 91.7%. Although both studies reported promising results, evidence is hampered by single-centre study designs and small sample sizes. The Dutch multicentre RISAS trial⁶ is currently accruing with the aim of enrolling a prospective cohort of 225 patients with cN+ disease.

A survey¹³ among members of the American Society of Breast Surgeons revealed that only 15% of 638 respondents still perform ALND in all patients with cN+ tumours treated with NST, and that 54% offer SLNB with possible omission of ALND in over half of their patients. The survey also showed that different methods are used for localization of the clipped and marked lymph node (73% wire, 13% iodine seed, 14% other) after completion of NST. In the present cohort, identification rates were similar for patients in whom the positive lymph node was marked primarily with an iodine seed *versus* a clip. For patients in whom a clip was placed, identification rates were also similar between placing a wire or an iodine seed after NST. Other marking techniques reported previously, such as charcoal tattooing^{14,15}, were not used here. Besides using a combination of the MLN and SLN(s), recent reports^{16,17} have suggested combining the outcome of MARI with the number of fluorodeoxyglucose-avid lymph

nodes on PET–CT carried out before NST to determine the need for further axillary treatment. Among 159 patients with cN+ disease included in the analysis, the proposed treatment algorithm resulted in no further axillary treatment in 24.5%, axillary radiotherapy in 57.3%, and ALND in combination with axillary radiotherapy in 18.2%. As in the present cohort, longer follow-up is needed to prove the long-term oncological safety of omitting ALND with the risk of leaving residual disease behind. Sufficient data have not yet been reported on the long-term outcome of patients with cN+ disease in whom ALND was replaced by less invasive staging procedures.

In previous cohorts that received combination procedures^{15,18,19}, sometimes ten or more lymph nodes were retrieved, even though these procedures aim to offer a less invasive alternative to ALND. In the present cohort, only one to three lymph nodes were excised in half of the patients. Furthermore, the median number of excised lymph nodes was the same for patients with and without residual axillary disease. This suggests that the improved detection of residual disease achieved with the combination procedure did not result from removing more lymph nodes.

As ALND was not performed routinely in the present cohort, it was not possible to calculate the FNR and NPV for the combination procedure. Although not all patients underwent ALND, the combination procedure improved the detection rate of residual axillary disease compared with that had the MLN procedure or SLNB been performed as a stand-alone staging procedure. This might be because one method covered the failure of the other. An axillary pCR may be predicted based on the MLN, whereas residual axillary disease is predicted based on the SLN(s) and vice versa. A possible explanation for false-negative SLN(s) could be residual disease obstructing normal lymphatic drainage or NST altering normal lymphatic drainage. The phenomenon of false-negative SLN(s) has been reported previously by Caudle and colleagues¹³, who noted that the clipped node was not retrieved as a SLN in 23% of patients in their cohort. A possible explanation for a false-negative MLN could be unsuccessful marking of the most suspicious lymph node, with the marker located in adipose tissue or in non-metastatic lymph nodes, or the existence of differential responses to chemotherapy in the axilla.

The present study is limited by its retrospective design. The combination procedure differed between institutions, although these differences reflect real-world clinical practice. Optimal axillary management after NST in patients with cN+ disease before treatment is currently being investigated in the Alliance A011202²⁰ and National Surgical Adjuvant Breast and Bowel Project 51/Radiation Therapy Oncology Group 1304²¹ trials. These trials will determine optimal management of the axilla based on response to chemotherapy. Until then, the combination procedure for axillary staging

in patients with cN+ tumours treated with neoadjuvant chemotherapy can be recommended when omission of ALND is considered.

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SUPPLEMENTAL TABLE

Table S6.1 Pathologic outcome of the combination procedure.

	Outcome ML*	Outcome SLNB*	Outcome combination procedure
Scenario A	ypN+	ypN0	<i>ypN+</i>
Scenario B	ypN0	ypN+	<i>ypN+</i>
Scenario C	ypN+	ypN+	<i>ypN+</i>
Scenario D	ypN0	ypN0	<i>ypN0</i>

*If the ML and SLN were one and the same node (concordant ML), the same pathologic outcome was documented for ML and SLNB. In case additional SLNs were removed, the highest extent of disease was documented as outcome for SLNB (e.g. concordant ML shows ypN0, but additional SLN shows macrometastasis, hence ML outcome is ypN0 but SLNB outcome is ypN+).

PART III

Prediction of axillary residual disease and
prognostic implications

CHAPTER

7

Correlation between pathologic
complete response in the breast and
absence of axillary lymph node
metastases after neoadjuvant systemic
therapy

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ABSTRACT

Objective

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

Background

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

Methods

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

Results

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

Conclusions

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

INTRODUCTION

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

Over the past decade, improvements in the efficacy of chemotherapy and targeted therapies have increased pCR rates. A meta-analysis, performed by Cortazar et al, found that breast pCR was achieved in 22.0% of patients after NST with higher pCR rates in HER2+ and triple negative breast cancer subtypes.⁸ Concerning axillary lymph nodes, NST can eradicate metastases⁹ in clinically node positive patients with a reported axillary pCR rate of 37.0%. The axillary pCR rate for HER2+ patients increases with the use of HER2-targeted therapy to between 43% and 74%.^{6,7,10,11} Patients who achieved axillary pCR were more likely to have breast pCR.^{6,11,12}

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

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

METHODS

In this study, 4084 consecutive patients were included who had all been diagnosed with primary invasive breast cancer in the Netherlands and treated with NST (chemotherapy with or without trastuzumab) between January 2010 and September 2016. To be considered for final analyses, patients needed to be staged as cT1- 3N0-1 breast cancer prior to NST administration. After the completion of NST, all patients underwent standard breast and axillary surgery. Patients were excluded if the sentinel lymph node biopsy (SLNB) had been performed before NST administration. Other exclusion criteria were unknown pathological tumor stage, distant metastases at primary breast cancer diagnosis or within 91 days after surgery, unknown breast cancer subtype, neoadjuvant endocrine therapy, or unknown number of lymph node metastases at final pathology (Figure 7.1).

Figure 7.1 Flow diagram of patient inclusion.

NST, neoadjuvant systemic therapy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; cN1, clinically node positive; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR, and HER2

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

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

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

Data were obtained from the Netherlands Cancer Registry (NCR) after this study had been approved by the Privacy Review Board of NCR, managed by the Netherlands Comprehensive Cancer Organisation (IKNL). On site trained registrars from the NCR extract data from patients' medical records after notification. Data were collected on age, tumor histology, receptor status, surgical procedures, systemic therapy, radiation therapy, clinical TNM stage, and pathology results, including stage after NST (ypTNM), tumor grade and number of axillary lymph nodes with and without metastases. Breast pCR was defined as the absence of both invasive and in situ breast cancer, with ypN0 being defined as the absence of both macro- and micrometastases in the axillary lymph nodes.¹⁸ Isolated tumor cells were considered as ypN0.¹⁸

Statistical analyses were performed by using Statistical Package for the Social Sciences software (SPSS, version 24, IBM, Armonk, NY). Patients were subdivided into breast pCR or without breast pCR for the following breast cancer subtypes: ER

positive(+)HER2+, ER negative-HER2+, ER+HER2-, and triple negative. For each subtype, the number of axillary lymph nodes with and without metastases at final pathology was reported. The χ^2 test and Fisher exact test were used to compare patients with breast pCR and without breast pCR. Univariable logistic regression analysis was conducted to determine the association between relevant clinicopathological variables and ypN0. Multivariable analysis was performed to identify the independent clinicopathological variables correlated with ypN0. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Two-sided p values of <0.05 were considered statistically significant.

RESULTS

Of the 4084 patients (median age, 49 yrs; range, 18-83 yrs) included for analyses, 585 patients had ER+HER2+, 361 ER- HER2+, 2336 ER+HER2- and 802 had triple negative breast cancer subtype. A total of 1674 (41.0%) patients were cN0 and 2410 (59.0%) were cN1. Breast conserving surgery was performed in 1835 (44.9%) patients and 2249 (55.1%) underwent mastectomy. SLNB was performed in 1483 (36.3%) patients and 2601 (63.7%) underwent ALND (Table 7.1).

Overall, 986 out of 4084 patients (24.1%) achieved breast pCR. Of the patients with breast pCR, 68.7% (677 of 986) had ypN0 compared with 34.2% (1058 of 3098) without breast pCR ($p<0.001$). In the case of cN0, 97.7% (432/442) with breast pCR had ypN0 compared with 71.6% (882/1232) without breast pCR ($p<0.001$). In the case of cN1, 45.0% (245/544) with breast pCR had ypN0 compared to 9.4% (176/1866) without breast pCR ($p<0.001$) (Table 7.2).

In univariable analysis, clinicopathological variables associated with lower odds of ypN0 were age 35 to 50 years (OR 0.70, 95% CI 0.54-0.90, $p<0.006$), age 50 to 75 years (OR 0.60, 95% CI 0.47-0.79, $p<0.001$), clinical T3 stage (OR 0.51, 95% CI 0.41-0.62, $p<0.001$), cN1 stage (OR 0.06, 95% CI 0.05-0.07, $p<0.001$), ER+HER2- subtype (OR 0.32, 95% CI 0.27-0.39, $p<0.001$), and triple negative subtype (OR 0.31, 95% CI 0.26-0.37, $p<0.001$). Tumor grade 3 (OR 1.67, 95% CI 1.28-2.19, $p=0.045$) and breast pCR (OR 4.22, 95% CI 3.62-4.93, $p<0.001$) were associated with higher odds of ypN0. In multivariable analysis after correcting for confounders, the odds of ypN0 was decreased in the case of clinical T3 stage (OR 0.59, 95% CI 0.40-0.87, $p<0.007$), cN1 (OR 0.03, 95% CI 0.02-0.04, $p<0.001$) and ER+HER2- subtype (OR 0.30, 95% CI 0.20-0.44, $p<0.001$), and increased in the case of breast pCR (OR 4.53, 95% CI 3.27-6.28, $p<0.001$) (Table 7.3).

Table 7.1 Overview of patient, tumor and treatment characteristics.

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

^a Includes adenocarcinoma not further defined, mucinous adenocarcinoma, medullary carcinoma, metaplastic carcinoma among other things. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR and HER2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; pCR, pathologic complete response

Table 7.2 Overview of number of lymph node metastases for each breast cancer subtype differentiated between breast pCR and without breast pCR after NST.

Breast pCR (n=986)		Number of Lymph Node Metastases on Final Pathology (%)				
		0	1	2	3	≥4
ER+HER2+ (n=236)	cT1N0	29 (100)	0	0	0	0
	cT2N0	73 (99)	1 (1)	0	0	0
	cT3N0	20 (95)	1 (5)	0	0	0
	cT1N1	9 (60)	6 (40)	0	0	0
	cT2N1	33 (53)	26 (42)	0	2 (3)	1 (2)
	cT3N1	16 (46)	17 (48)	0	1 (3)	1 (3)
ER-HER2+ (n=247)	cT1N0	13 (100)	0	0	0	0
	cT2N0	72 (100)	0	0	0	0
	cT3N0	12 (100)	0	0	0	0
	cT1N1	12 (48)	13 (52)	0	0	0
	cT2N1	33 (43)	42 (55)	1 (1)	1 (1)	0
	cT3N1	25 (52)	23 (48)	0	0	0
ER+HER2- (n=208)	cT1N0	27 (94)	1 (3)	1 (3)	0	0
	cT2N0	44 (94)	3 (6)	0	0	0
	cT3N0	12 (92)	1 (8)	0	0	0
	cT1N1	4 (17)	12 (49)	4 (17)	0	4 (17)
	cT2N1	25 (35)	33 (46)	6 (8)	2 (3)	6 (8)
	cT3N1	9 (39)	10 (43)	0	2 (9)	2 (9)
Triple negative (n=295)	cT1N0	29 (97)	0	1 (3)	0	0
	cT2N0	99 (100)	0	0	0	0
	cT3N0	2 (67)	1 (33)	0	0	0
	cT1N1	16 (49)	15 (45)	1 (3)	0	1 (3)
	cT2N1	47 (47)	45 (44)	6 (6)	1 (1)	2 (2)
	cT3N1	16 (55)	10 (35)	2 (7)	0	1 (3)

No Breast pCR (n=3098)		Number of Lymph Node Metastases on Final Pathology (%)				
		0	1	2	3	≥4
ER+HER2+ (n=349)	cT1N0	25 (83)	5 (17)	0	0	0
	cT2N0	87 (89)	8 (8)	2 (2)	0	1 (1)
	cT3N0	18 (72)	5 (20)	1 (4)	0	1 (4)
	cT1N1	9 (33)	10 (37)	2 (7)	1 (4)	5 (19)
	cT2N1	15 (13)	63 (53)	10 (8)	7 (6)	24 (20)
	cT3N1	15 (30)	13 (26)	4 (8)	3 (6)	15 (30)
ER-HER2+ (n=114)	cT1N0	2 (100)	0	0	0	0
	cT2N0	14 (88)	2 (12)	0	0	0
	cT3N0	12 (92)	0	1 (8)	0	0
	cT1N1	2 (50)	0	0	2 (50)	0
	cT2N1	14 (33)	13 (30)	6 (14)	4 (9)	6 (14)
	cT3N1	9 (25)	14 (39)	6 (17)	4 (11)	3 (8)

Table 7.2 (continued)

No Breast pCR (n=3098)		Number of Lymph Node Metastases on Final Pathology (%)				
		0	1	2	3	≥4
ER+HER2- (n=2128)	cT1N0	97 (75)	24 (18)	5 (4)	0	4 (3)
	cT2N0	341 (67)	124 (24)	23 (4)	10 (2)	12 (3)
	cT3N0	107 (53)	58 (29)	11 (5)	4 (2)	23 (11)
	cT1N1	7 (4)	63 (34)	34 (18)	19 (10)	63 (34)
	cT2N1	36 (5)	217 (31)	111 (16)	88 (13)	249 (35)
	cT3N1	22 (6)	72 (18)	45 (11)	46 (12)	213 (53)
Triple negative (n=507)	cT1N0	27 (87)	4 (13)	0	0	0
	cT2N0	126 (89)	12 (8)	2 (2)	1 (1)	0
	cT3N0	26 (79)	4 (12)	2 (6)	0	1 (3)
	cT1N1	5 (12)	15 (37)	4 (10)	5 (12)	12 (29)
	cT2N1	35 (20)	64 (36)	20 (11)	15 (8)	45 (25)
	cT3N1	7 (9)	18 (22)	10 (12)	7 (9)	40 (52)

pCR, pathological complete response; NST, neoadjuvant systemic therapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR, and HER2.

ER+HER2+ subtype

Trastuzumab in neoadjuvant setting was administered in 531 out of 585 (90.8%) ER+HER2+ patients. In this subtype, 236 out of 585 (40.3%) patients achieved breast pCR. In all ER+HER2+ patients with breast pCR, 76.3% (180 of 236) had ypN0 compared to 48.4% (169 of 349) without breast pCR ($p<0.001$). In the case of cN0 with breast pCR, only 2 out of 124 patients (1.6%) had 1 axillary lymph node metastasis at final pathology, compared to 15.0% (23 of 153) without breast pCR ($p<0.001$). In the case of cN1 with breast pCR, 51.8% (58 of 112) of the patients had ypN0 compared to 19.9% (39 of 196) without breast pCR ($p<0.001$) (Table 7.4).

ER-HER2+ subtype

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

Table 7.3 Univariable and multivariable analyses for clinicopathological variables and the outcome ypN0 after NST.

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

pCR, pathologic complete response; NST, neoadjuvant systemic therapy; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR, and HER2.

ER+HER2- subtype

In the ER+HER2- subtype, 208 out of 2336 (8.9%) patients achieved breast pCR of whom 58.2% (121 of 208) had ypN0 compared to 28.7% (610 of 2128) without breast pCR (p<0.001). In cN0 patients with breast pCR, 6 out of 89 patients (6.7%) had 1 or 2 axillary lymph node metastases at final pathology, compared to 35.3% (298 of 843) without breast pCR (p<0.001). In cN1 patients with breast pCR, 31.9% (38 of 119) of the patients had ypN0 compared to 5.1% (65 of 1285) without breast pCR (p<0.001).

Table 7.4 Overview of ypN0 in the case of breast pCR and without breast pCR after NST for the different breast cancer subtypes.

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

pCR, pathologic complete response; NST, neoadjuvant systemic therapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Triple negative, negative for ER, PR, and HER2. ^a χ^2 test and Fisher's exact test between patients with breast pCR and ypN0 versus patients without breast pCR and ypN0. Data are presented as percentages with the numbers in parentheses.

Triple negative subtype

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

DISCUSSION

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

Recently, Tadros et al¹⁴ have demonstrated that breast pCR is strongly correlated with axillary nodal status after NST. They showed a total breast pCR rate of 36.6% (193 of 527) with a slightly higher rate of breast pCR in the triple negative group (37.5%) compared to the HER2+ group (35.7%). In contrast to the Tadros et al study, patients with clinical T3 stage and ER+HER2- subtype were also included in the present study which can explain the lower total breast pCR rate here. We found that in the case of

ER+HER2- breast cancer, pCR rates of the breast and axilla were lower compared to the other breast cancer subtypes. For this subtype, the most important systemic therapy (ie, hormonal therapy) generally follows in the adjuvant setting. Previous studies had reported breast and axillary pCR rates for the ER+HER2- subtype ranging from 7.5% to 16.5%.^{4,7,8} We have shown similar breast pCR rates, but higher ypN0 rates due to the included number of cN0 patients. In the Tadros et al study, all 527 cT1-2N0 patients with HER2+ and triple negative breast cancer who achieved breast pCR after NST were found to have ypN0.¹⁴ We have confirmed this strong correlation here between breast pCR and ypN0 in cN0 patients for ER+HER2+, ER-HER2+, and triple negative breast cancer subtypes.

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

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

In our study, only 45.0% of all cN1 patients who achieved breast pCR also had ypN0. Consequently, these cN1 patients remain at risk of having axillary lymph node

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

Limitations

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

Conclusions

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

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CHAPTER

8

Prognosis of residual axillary disease
after neoadjuvant chemotherapy in
clinically node-positive breast cancer
patients: isolated tumor cells and
micrometastases carry a better
prognosis than macrometastases

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ABSTRACT

Purpose

The aim of this study was to compare disease-free survival (DFS) and overall survival (OS) between clinically node-positive breast cancer patients, treated with neoadjuvant chemotherapy (NAC), with axillary pathologic complete response (ypN0), residual axillary isolated tumour cells or micrometastases (ypN1c/mi), and residual axillary macrometastases (ypN1-3).

Methods

All patients diagnosed with clinically node-positive primary invasive breast cancer treated with NAC and subsequent axillary lymph node dissection between 2005 and 2008 were retrospectively analyzed. Data were obtained from the Netherlands Cancer Registry. Patients were stratified by final pathological axillary status: ypN0, ypN1c/mi, or ypN1-3. The main outcome measures DFS and OS were analyzed using Kaplan–Meier survival analysis. Uni- and multivariable cox regression analyses were used to determine independent predictors for DFS and OS.

Results

A total of 1347 patients were included. Pathologic nodal status was ypN0 in 22.2%, ypN1c/mi in 3.8%, and ypN1-3 in 74.0% of patients. Overall, 5-year DFS was 57.8% and mean OS was 7.4 years. DFS and OS were comparable between ypN0 and ypN1c/mi (HR 1.38 (0.40-4.79, $p=0.613$) and HR 0.92 (0.27-3.09, $p=0.889$), respectively), but significantly different between ypN0 and ypN1-3 (HR 1.78 (1.06-3.00, $p=0.031$) and HR 1.70 (1.07-2.71, $p=0.026$), respectively).

Conclusions

Clinically node-positive patients, treated with NAC, with axillary nodal status ypN0 or ypN1c/mi carry similar prognosis regarding DFS and OS. Axillary nodal status ypN1-3 is associated with a less favorable prognosis. Future studies should consider ypN0 and ypN1c/mi as one entity.

INTRODUCTION

Over the past 20 years, a trend toward a less invasive approach regarding the surgical management of the axilla in breast cancer patients has been observed. Nowadays, a sentinel lymph node biopsy (SLNB) has been widely adopted for staging of early-stage clinically node-negative breast cancer.¹ In case of a sentinel lymph node (SLN) containing isolated tumour cells (ITCs) or micrometastases, a completion of axillary lymph node dissection (ALND) does not improve survival, nor does it reduce regional recurrence. Consequently, ALND following SLNB has been abandoned in these patients.²⁻⁴ The ACOSOG Z0011 trial demonstrated no significant effect on prognosis when ALND is omitted in case of a SLN containing a limited number of metastases, even macrometastases, in patients treated with breast conserving therapy.³

In clinically node-positive (cN+) patients, ALND is regarded as standard surgical therapy. However, increased utilization of neoadjuvant chemotherapy (NAC) results in axillary pathologic complete response (pCR) in 30-40% of patients.⁵ Consequently, the value of ALND is topic of debate. Various studies demonstrated that axillary pCR after NAC is associated with improved prognosis.⁶⁻⁸ Residual axillary disease has a less favorable prognosis, but it is unknown whether different degrees of residual axillary disease (i.e., ITCs, micrometastases, macrometastases) all have similar prognosis. Hence, the purpose of this study was to compare prognosis of axillary pCR, residual ITCs, or micrometastases and residual macrometastases in cN+ patients treated with NAC.

METHODS

Data collection

In this study, all pathologically confirmed cN+ patients diagnosed with primary invasive breast cancer and treated with NAC (with or without immunotherapy) followed by ALND between 2005 and 2008 were included. Exclusion criteria were synchronous breast cancer, primary surgical treatment, neoadjuvant radiation therapy, neoadjuvant endocrine therapy, unknown pathological nodal status, and distant metastases diagnosed within 91 days after primary breast cancer diagnosis. Patients who did not undergo ALND were also excluded.

Data were obtained from the Netherlands Cancer Registry (NCR), which is managed by the Netherlands Comprehensive Cancer Organisation (NCCO). The PALGA foundation (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), a nationwide network and registry of histopathology and cytopathology diagnosis in the Netherlands, regularly submits reports of all diagnosed malignancies to the cancer registry. After

notification, trained data collection registrars from the NCR extracted data from patients' records. Data were collected on age, tumour type, receptor status, surgical procedures, systemic therapy, adjuvant radiation therapy, and pathology results, including pathological TNM stage and tumour grade. During a 5-year period after initial diagnosis, the first of the following breast cancer events was registered: any local, regional, or contralateral recurrence or distant metastasis. Date of death or date of emigration was derived from the Municipal Personal Records Database (Basisregistratie Personen, BRP) and files until December 31, 2014 were analyzed. Patients were stratified into three subgroups according to final pathologic axillary nodal status after completion of NAC and definitive surgery: pCR (ypN0), residual isolated tumour cells or micrometastases (ypN1c/mi), and residual macrometastases (ypN1-3).

Neoadjuvant chemotherapy (NAC) with/without immunotherapy

During the study period, the Dutch national guideline of 2005 was in use.⁹ This guideline recommended chemotherapy regimens consisting of five courses 5 Fluorouracil, Epirubicin, Cyclophosphamide (FEC), or six courses of Taxotere, Adriamycin, and Cyclophosphamide (TAC). In case of Her2Neu receptor (Her2) amplification, targeted therapy (trastuzumab) was recommended in addition to chemotherapy.

Statistics

Statistical analyses were performed using Statistical Package for the Social Sciences software (Version 22, IBM, Armonk, New York, USA). General characteristics between the three subgroups were compared using Chi squared test for categorical data and One-way ANOVA for continuous data, after confirmation of Levene's test for equality of variances. If Levene's test demonstrated significant differences among the population variances, Kruskal-Wallis test was used.

DFS was defined as time from diagnosis to any local (including carcinoma in situ), regional, or contralateral recurrence, distant metastasis or mortality within 5 years after the primary diagnosis. Events occurring 0-91 days after diagnosis were considered synchronous to the original tumour and were not counted as recurrence. OS was defined as the time interval between date of diagnosis and date of death, date of first event, date of last follow-up, or date of emigration.

DFS and OS for the three subgroups were calculated with Kaplan–Meier curves and compared with the log-rank test. P-values (two-sided) <0.05 were considered statistically significant. Relevant clinicopathological variables associated with DFS and

OS were examined using univariable and, where applicable, multivariable Cox proportional hazards regression, with Hazard Ratio (HR) and corresponding 95% confidence intervals.

RESULTS

Between 2005 and 2008, 8176 patients were diagnosed with cN+ breast cancer in the Netherlands. Patients were excluded for several reasons: 6553 patients underwent primary surgery; 204 patients did not undergo ALND; 9 patients were treated with neoadjuvant radiotherapy; 61 patients were treated with neoadjuvant endocrine therapy; and ypN status was unknown for 11 patients (Figure 8.1). A final total of 1347 patients were included for this study: 299 ypN0, 51 ypN1c/mi and 997 ypN1-3.

The incidence of pCR of the primary tumour was higher in patients with ypN0 compared to ypN1c/mi and ypN1-3 patients (41.1% vs. 19.6% and 7.1%, respectively, $p<0.001$). Furthermore, lobular carcinoma was observed more often in patients with ypN1-3 than in ypN0 and ypN1c/mi patients (9.4% vs. 5.4% and 3.9%, respectively, $p=0.039$). Adjuvant radiation therapy was applied more often in ypN1-3 as compared to ypN0 and ypN1c/mi patients (92.1% vs. 80.9% and 80.4%, respectively, $p<0.001$, Table 8.1).

Figure 8.1 Flowchart of included patients.

cN+ clinically node positive status, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, ypN0 axillary pathologic complete response, ypN1c/mi axillary residual isolated tumour cells or micrometastases, ypN1-3 axillary residual macrometastases.

Table 8.1 General characteristics.

	ypN0 (n=299)	ypN1c/mi (n=51)	ypN1-3 (n=997)	p-value
Mean age (years) (range)	48.9 (27 – 77)	48.2 (29 – 81)	50.4 (22 – 85)	0.053
Clinical T-stage (%)				
cT0-is	1 (0.3)	0	5 (0.5)	0.826
cT1-2	138 (47.0)	26 (52.0)	458 (47.0)	0.780
cT3-4	153 (52.0)	24 (48.0)	509 (52.0)	0.853
cTx	7	1	25	
Pathologic T-stage (%)				
ypT0-is	123 (50.8)	10 (26.3)	71 (8.5)	<0.001
ypT1-2	107 (44.2)	25 (65.8)	570 (68.5)	<0.001
ypT3-4	12 (5.0)	3 (7.9)	191 (23.0)	<0.001
Unknown	57	13	165	
Tumor grade (%) [*]				
1-2	28 (31.5)	7 (50.0)	197 (43.9)	<0.001
3	61 (68.5)	7 (50.0)	252 (56.1)	0.051
Unknown	210	37	548	
Tumor type (%)				
Ductal	227 (75.9)	41 (80.4)	746 (74.8)	0.739
Lobular	16 (5.4)	2 (3.9)	94 (9.4)	0.039
Other [#]	56 (18.7)	8 (15.7)	157 (15.8)	0.470
Subtype (%)				
ER+PR+, Her2-	35 (12.8)	11 (22.5)	349 (37.3)	<0.001
ER+PR-, Her2-	21 (7.7)	7 (14.3)	122 (13.0)	0.035
ER+Her2+	47 (17.1)	20 (40.8)	152 (16.3)	<0.001
ER-Her2+	97 (35.4)	5 (10.2)	146 (15.6)	<0.001
Triple negative	74 (27.0)	6 (12.2)	166 (17.8)	0.003
Unknown	25	2	62	
Breast surgery (%)				
Breast conserving therapy	62 (20.7)	12 (23.5)	181 (18.2)	0.421
Mastectomy	237 (79.3)	39 (76.5)	816 (81.8)	0.421
Unknown	0	0	1	
Radiation therapy (%)				
Yes	242 (80.9)	41 (80.4)	918 (92.1)	<0.001
Endocrine therapy to ER+ subtype (%)				
Yes	95 (84.8)	35 (92.1)	600 (91.5)	0.080
Trastuzumab to Her2+ subtype (%)				
Yes	127 (92.0)	19 (76.0)	247 (89.2)	0.057

^{*} In case of ypT0, tumor grade of biopsy prior to surgery was used. [#] Including adenocarcinoma not otherwise specified, mucinous carcinoma, and mixed carcinoma. ypN0 axillary pathologic complete response, ypN1c/mi axillary residual isolated tumor cells or micrometastases, ypN1-3 axillary residual macrometastases, cT-stage clinical tumor stage, pT-stage pathologic tumor stage, ER estrogen, PR progesterone, Her2 human epidermal growth factor receptor 2.

Disease-free survival

Five-year follow-up was available for 944 patients (70.1%; n=206 ypN0, n=34 ypN0i+/ypN1mi, n=704 ypN1-3): Recurrence occurred in 377 patients (39.9%) and 22 patients died within 5 years (2.3%). This resulted in a DFS event in 42.2% of the patients. DFS did not differ significantly between ypN0 and ypN1tc/mi (71.8 vs. 70.6%, $p=0.978$). When DFS was compared between ypN0 and ypN1-3, a significant difference was found (71.8 vs. 53.4%; $p=0.049$) (Figure 8.2A).

Multivariable Cox regression analyses demonstrated no significant difference in DFS between ypN0 and ypN1tc/mi (HR 1.38 (0.40-4.79), $p=0.613$), but a significant difference in DFS between ypN0 and ypN1-3 (HR 1.78 (1.06-3.00), $p=0.031$) (Table 8.2).

Furthermore, higher ypT stage (ypT 1-2: HR 2.73 (1.39-5.39), $P=0.004$ and ypT 3-4: HR 4.71 (2.35-9.43), $p<0.001$) and higher tumour grade (HR 1.69 (1.19-2.40), $p=0.004$) were identified as independent predictors of decreased DFS, whereas endocrine therapy was identified as independent predictor of increased DFS (HR 0.55 (0.36-0.85), $p=0.007$).

Figure 8.2 Kaplan–Meier curves for disease-free (A) and overall survival (B), including number at risk.

ypN status pathologic nodal status after neoadjuvant chemotherapy, ypN0 axillary pathologic complete response, ypN1tc/mi axillary residual isolated tumour cells or micrometastases, ypN1-3 axillary residual macrometastases.

Table 8.2 Uni- and multivariable analyses of predictors of disease-free survival at 5 years.

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value
ypN0	Reference		Reference	
ypN1c/mi	1.02 (0.52 – 1.99)	0.964	1.38 (0.40 – 4.79)	0.613
ypN1-3	1.89 (1.43 – 2.50)	<0.001	1.78 (1.06 – 3.00)	0.031
Age (per year increment)	1.02 (1.01 – 1.02)	0.001	1.01 (0.99 – 1.02)	0.479
ypT-stage				
T0 or Tis	Reference		Reference	
T1-2	1.88 (1.31 – 2.70)	0.001	2.73 (1.39 – 5.39)	0.004
T3-4	3.74 (2.53 – 5.54)	<0.001	4.71 (2.35 – 9.43)	<0.001
Tumor type				
Ductal	Reference		Reference	
Lobular	0.78 (0.53 – 1.14)	0.193	1.11 (0.59 – 2.07)	0.751
Other	0.89 (0.69 – 1.15)	0.386	0.89 (0.58 – 1.37)	0.595
Tumor grade				
3 vs. 1-2	1.64 (1.22 – 2.20)	0.001	1.69 (1.19 – 2.40)	0.004
Subtypes				
ER+PR+Her2+: Yes vs. No [#]	0.63 (0.50 – 0.80)	<0.001		
ER+PR+Her2+: Yes vs. No [#]	1.32 (0.99 – 1.75)	0.057		
ER+Her2+: Yes vs. No ^{#,*}	0.63 (0.47 – 0.85)	0.002		
ER+Her2+: Yes vs. No [*]	1.20 (0.95 – 1.53)	0.129		
Triple negative: Yes vs. No	1.94 (1.46 – 2.32)	<0.001	1.16 (0.69 – 1.93)	0.577
Trastuzumab				
Yes vs. No	0.81 (0.65 – 1.00)	0.052	0.76 (0.47 – 1.23)	0.263
Endocrine therapy				
Yes vs. No	0.57 (0.47 – 0.69)	<0.001	0.55 (0.36 – 0.85)	0.007
Radiation therapy				
Yes vs. No	1.09 (0.78 – 1.52)	0.626	0.74 (0.45 – 1.23)	0.251

[#] Excluded from multivariable analysis due to collinearity with endocrine therapy. ^{*} Excluded from multivariable analysis due to collinearity with trastuzumab. ypN0 axillary pathologic complete response, ypN1c/mi axillary residual isolated tumor cells or micrometastases, ypN1-3 axillary residual macrometastases, ypT-stage pathologic tumor stage after neo-adjuvant chemotherapy, ER estrogen, PR progesterone, Her2 human epidermal growth factor receptor 2, HR Hazard ratio.

Overall survival

Mean OS was 7.4 years (range 0.4-10 years): 8.3 years for ypN0, 8.2 years for ypN1c/mi, and 7.0 years for ypN1-3 (Figure 8.2B). OS was comparable between ypN0 and ypN1c/mi ($p=0.875$). However, OS was significantly lower for ypN1-3 as compared to ypN0 ($p=0.014$).

Multivariable Cox regression analyses demonstrated no significant difference in OS between ypN0 and ypN1c/mi (HR: 0.92 (0.27-3.09), $p=0.889$), but a significant difference in OS between ypN0 and ypN1-3 (HR 1.70 (1.07-2.71), $p=0.026$) (Table 8.3). Other independent predictors of decreased OS were higher ypT stage ((ypT 1-2: HR 2.40 (1.32-4.36), $p=0.004$) and (ypT 3-4: HR 4.38 (2.37-8.12), $p<0.001$)) and higher

tumour grade (HR 1.72 (1.25-2.36), $p=0.001$). Furthermore, endocrine therapy (HR 0.49 (0.34-0.72), $p<0.001$) was identified as an independent predictor of increased OS.

Table 8.3 Uni- and multivariable analyses of predictors for overall survival.

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P-value	HR (95%CI)	p-value
ypN0	Reference		Reference	
ypN1c/mi	1.07 (0.59 – 1.94)	0.816	0.92 (0.27 – 3.09)	0.889
ypN1-3	2.07 (1.62 – 2.67)	<0.001	1.70 (1.07 – 2.71)	0.026
Age (per year increment)	1.02 (1.02 – 1.03)	<0.001	1.01 (1.00 – 1.02)	0.082
ypT-stage				
T0 or Tis	Reference		Reference	
T1-2	1.60 (1.19 – 2.15)	0.002	2.40 (1.32 – 4.36)	0.004
T3-4	3.33 (2.41 – 4.59)	<0.001	4.38 (2.37 – 8.12)	<0.001
Tumor type				
Ductal	Reference		Reference	
Lobular	0.98 (0.72 – 1.33)	0.906	1.33 (0.78 – 2.27)	0.288
Other	0.98 (0.78 – 1.24)	0.882	1.03 (0.69 – 1.53)	0.887
Tumor grade 3 vs. 1-2	1.84 (1.41 – 2.40)	<0.001	1.72 (1.25 – 2.36)	0.001
Subtypes				
ER+PR+Her2-: Yes vs No [#]	0.62 (0.51 – 0.76)	<0.001		
ER+PR+Her2-: Yes vs No [#]	1.28 (1.00 – 1.65)	0.050		
ER+Her2+: Yes vs No ^{#,*}	0.58 (0.43 – 0.73)	<0.001		
ER+Her2+: Yes vs No [*]	1.15 (0.93 – 1.42)	0.201		
Triple negative: Yes vs No	2.10 (1.73 – 2.56)	<0.001	1.38 (0.90 – 2.13)	0.145
Trastuzumab Yes vs No	0.72 (0.59 – 0.88)	0.001	0.70 (0.46 – 1.07)	0.101
Endocrine therapy Yes vs No	0.56 (0.47 – 0.66)	<0.001	0.49 (0.34 – 0.72)	<0.001
Radiation therapy Yes vs No	1.31 (0.96 – 1.77)	0.086	1.06 (0.64 – 1.74)	0.829

[#] Excluded from multivariable analysis due to collinearity with endocrine therapy. ^{*} Excluded from multivariable analysis due to collinearity with trastuzumab. ypN0 axillary pathologic complete response, ypN1c/mi axillary residual isolated tumor cells or micrometastases, ypN1-3 axillary residual macrometastases, ypT-stage pathologic tumor stage after neo-adjuvant chemotherapy, ER estrogen, PR progesterone, Her2 human epidermal growth factor receptor 2, HR Hazard ratio.

DISCUSSION

This is the first study comparing prognosis of ypN0 with ypN1c/mi and ypN1-3 in cN+ breast cancer patients treated with NAC. It is well known that axillary pCR is an important prognostic factor.⁶⁻⁸ Residual axillary disease after completion of NAC is associated with a less favourable prognosis. However, to our knowledge, this is the first study that compares the long-term effect of different degrees of residual disease

on prognosis. Our study showed that ypN0 and ypN1c/mi carry similar prognosis and that ypN1-3 carries a significantly different and less favourable prognosis in terms of DFS and OS.

Current guidelines still recommend to perform ALND in cN+ patients following NAC irrespective of axillary response.^{10,11} However, cN+ patients converting to axillary pCR after completion of NAC remain a topic of debate since they are not expected to benefit from ALND. A non-invasive technique to accurately diagnose pCR is currently unavailable. Various minimally invasive procedures have been suggested for this purpose. The SLNB was studied extensively and its reliability seems questionable with a reported overall false negative rate (FNR) of 15.1% and negative predictive values (NPV) of 86% or lower.⁵ Other recently introduced minimally invasive techniques, the MARI procedure (Marking the Axillary lymph node with Radioactive Iodine seeds) and TAD (Targeted Axillary Dissection), are promising with FNRs of 7 and 2%, respectively. However, with only evidence available of single center studies comprising small cohorts that support these techniques it is not (yet) safe to implement them in clinical practice.^{12,13}

In our cohort, all patients underwent an ALND and thus our results do not directly support a change in surgical axillary treatment after the completion of NAC. Considering the comparable prognosis between ypN0 and ypN1c/mi, our results do question whether ypN1c/mi may mimic ypN0 more than residual axillary disease. Thus, when minimally invasive procedures prove to predict the status of the axilla accurately, the indications for omitting ALND may not just be limited to ypN0. Therefore, current research on reducing axillary management in cN+ patients should not focus only on ypN0 patients, but also on patients with ypN1c/mi. In future, ALND may be rendered as a procedure only to manage residual macrometastases.

In clinically node-negative patients in adjuvant setting, the SLNB with a relatively high FNR of about 8% is permitted since axillary recurrences are rare and previous studies have shown that not all axillary residual disease eventually converts to clinically overt disease.^{2,3,14} This is in part effectuated by adjuvant therapy (i.e., radiation and/or systemic therapy) and by biological subtypes influencing recurrence patterns. In cN+ patients, however, no studies have adequately evaluated prognostic impact of omitting ALND in case of residual axillary disease. Despite this, a trend toward replacing ALND by less invasive axillary staging procedures that are known to miss potentially therapy-resistant disease is already ongoing worldwide. Therefore, it is of utmost importance to prospectively collect data of these patients to detect potential influences on prognosis.

Since prognosis seems comparable between post-ALND ypN0 and ypN1c/mi in cN+ patients treated with NAC, imaging might play an important role in axillary staging

after NAC in the future. Since ITCs and micrometastases are not detectable on high-resolution exams, such as MRI or 18F-FDG PET/CT, imaging techniques were considered inaccurate for nodal assessment after completion of NAC. Yet, with our current observations in mind, dedicated axillary imaging is re-entering the arena as a modality to non-invasively identify residual macrometastases rather than ‘any’ extent of residual disease (including ITCs and micrometastases).

The strength of the current study is the large cohort of patients that all underwent ALND after NAC. But our study also has several limitations. Subgroups ypN0 and ypN1-3 comprised 299 and 997 patients, respectively, where subgroup ypN1tc/mi comprised only 51 patients. Our ypN1tc/mi subcohort was too small to explore the influence of single versus multiple tumour-positive lymph nodes on prognosis, and further studies are needed to explore this concept. Yet, this subset of patients can be considered unique since ypN1tc/mi in cN+ breast cancer is rare and a previously reported study included only a few ypN1tc/mi patients.¹⁵

Furthermore, our cohort was treated up to a decade ago. In that time frame, different guidelines were effective, and therefore results should be interpreted carefully regarding current practice. For example, some Her2+ patients did not receive trastuzumab in our cohort (19.6%), since trastuzumab was just introduced by that time.

Finally, our results are based on a retrospective study design. Consequently, details on additional radiation therapy could not be taken into account since radiation therapy fields were not recorded for each patient. Therefore, its influence on prognosis could not be explored in more detail.

In conclusion, our study showed that prognosis of cN+ patients who receive NAC is affected by the degree of axillary residual disease as measured in ALND specimens. Prognosis of isolated tumour cells and micrometastases was comparable to prognosis of ypN0 and more favorable than prognosis of macrometastases in terms of DFS and OS irrespective of tumour type. Ongoing and future studies should therefore consider ypN0 and ypN1tc/mi as one entity. Future research must explore which patients may safely receive a different, less invasive approach than the current standard of performing ALND after completion of NAC in all patients that were cN+ prior to NAC.

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CHAPTER

9

Discussion and future perspectives

SUMMARY AND GENERAL DISCUSSION

Neoadjuvant chemotherapy is commonly used in patients with locally advanced breast cancer and increasingly used in patients with early stage breast cancer. By downsizing disease, it allows for de-escalation of subsequent surgery of the breast and axilla. De-escalation of axillary surgery in breast cancer treatment is an ongoing trend. In search of the optimal less invasive axillary management after neoadjuvant chemotherapy, both improving quality of life by omitting unnecessary ALND and guaranteeing oncologic safety are of utmost importance.

This thesis demonstrated a lack of consensus regarding axillary management after neoadjuvant chemotherapy. The additional insights provided in this thesis aim to contribute to creating consensus and shaping response-based management of the axilla.

Axillary staging in node negative breast cancer

In cN0 patients treated with adjuvant chemotherapy, SLND has been the technique for axillary staging since the 90s. As shown in Chapter 2, SLND has also increasingly replaced ALND over the past decade in cN0 patients treated with neoadjuvant chemotherapy. Furthermore, a change in timing of SLND was detected, with SLND being increasingly performed after chemotherapy. Since neoadjuvant chemotherapy can eradicate axillary nodal disease, a positive SLND occurs less frequent after chemotherapy.¹ This contributes to a further reduction in the need for ALND. This finding was also confirmed in Chapter 2: SLND performed after chemotherapy is less frequently followed by ALND. In a different population-based cohort study (Chapter 7), we assessed the correlation between breast pCR and axillary pCR. It was reported that 97.7% of cN0 patients who achieved a pCR of the breast, also achieved a pCR of the axilla.² This correlation was especially strong in Her2 positive and triple negative subtypes. These findings suggest that breast pCR may guide complete omission of axillary surgery in selected cN0 patients treated with neoadjuvant chemotherapy.

In the adjuvant setting, indications for omitting ALND have extended from cN0/SLN-negative patients to cN0/SLN-positive patients (≤ 2 positive SLNs), following 10 year follow-up results from trials like Z0011.³ Despite the fact that results of these trials only apply to patients treated with *adjuvant* systemic therapy, our study showed that completion ALND is also omitted in cN0/SLN-positive patients treated with neoadjuvant chemotherapy. In the ongoing SENOMAC trial, in which the need for completion ALND in SLN-positive patients is investigated, patients treated with neoadjuvant chemotherapy are also included.⁴ Breast-cancer specific survival and axillary recurrence rate will be compared between cN0/SLN positive patients treated with or without completion ALND. Results are expected by the end of 2029. In the

currently recruiting POSNOC trial, patients are randomized between axillary treatment (ALND or axillary radiotherapy) and no axillary treatment.⁵ Patients treated with neoadjuvant chemotherapy are only eligible if the SLND is performed prior to chemotherapy. The primary endpoint is axillary recurrence at 5 years and results are expected in 2023.

Axillary staging in node positive breast cancer

In cN+ patients treated with neoadjuvant chemotherapy, a less invasive procedure that accurately identifies axillary pCR is needed to enable safe omission of ALND. Non-invasive techniques (i.e. imaging methods) are not able to accurately identify axillary pCR. Several less-invasive surgical techniques have been developed over the past years. In our systematic review and meta-analysis (Chapter 4)⁶, we compared the diagnostic accuracy of three different staging procedures, i.e. SLND, excision of a pre-treatment marked biopsy-proven positive lymph node (like the MARI-procedure) and a combination procedure (like Targeted Axillary Dissection). In all included studies, completion ALND was also performed. A total of 17 studies reported on SLND, compared to only one single center study for MARI and two for the combination procedure. SLND was associated with a rather poor overall accuracy (overall FNR of 17% and NPV <86%). Only when 3 or more SLNs were removed, SLND was statistically significantly associated with an improved FNR of 8%. Unfortunately, only 1 or 2 SLNs can be identified in most of the patients. This renders SLND not feasible for clinical practice. One single-center study including 95 patients reported on the MARI procedure, which was associated with an FNR of 7%. Current NPV's of both SLND and MARI (<86% and 83%, respectively) mean that in 1 out of every 6 patients with a negative test result, axillary residual disease is missed.^{6,7} The Targeted Axillary Dissection procedures, consisting of simultaneous SLND with a MARI/MARI-like procedure, were associated with a markedly improved NPV, ranging from 92% to 97%. This means residual axillary disease is missed in only 1 in 12 to 33 patients. Although the combination procedure was associated with the highest accuracy, the lack of evidence (only 2 single-center studies consisting of 85 and 35 patients) to support this procedure has to be taken in mind. The ongoing multicenter RISAS trial⁸ in the Netherlands (Chapter 5), will prove whether the combination of SLND and MARI can safely replace ALND for axillary staging after neoadjuvant chemotherapy in cN+ patients. The total accrual of 225 cN+ patients is expected to be complete by the end of 2019.

Validation studies for the combination procedure (i.e. SLND combined with MARI or a MARI-like procedure always followed by ALND) are scarce, yet multiple studies have been published describing clinical practice experiences with a combination procedure.⁶ In these studies, the outcome of the combination procedure guided

decision-making on completion ALND and/or adjuvant regional radiotherapy. A wide variety of techniques is used for marking the biopsy proven positive lymph node: radiopaque clips⁹⁻¹², charcoal tattooing¹³, wires^{11,14,15}, iodine seeds^{8,16,17} and electromagnetic reflectors¹⁸. Apart from this, timing of marking differs: either primarily prior to chemotherapy (at the time of cytology/biopsy or during a second procedure once the pathology result is available) or secondary after chemotherapy (provided that a clip has been placed prior to chemotherapy to retrieve the right node). Since ALND was not always performed, these studies cannot report on the accuracy of the combination procedure, nevertheless they can provide useful insights. In Chapter 6 we reported on a retrospective cohort of cN+ patients that underwent the combination procedure (the need for completion ALND was determined by the multidisciplinary tumour board). We found that the combination procedure was associated with significantly improved detection of residual disease over SLND only or MARI only. Further research has to define which combination procedure is most accurate, patient-friendly, and cost-effective.

In addition to the abovementioned less invasive procedures, a different less invasive axillary staging procedure involves preoperative fine needle aspiration of clipped nodes after neoadjuvant chemotherapy. Results of a prospective registry study including 50 cN+ patients were published in 2018: the identification rate was 92%, the FNR 57.6% and the NPV 40.6%.¹⁹ Thus, contrary to the pre-chemotherapy setting in which FNA is highly accurate in identifying the presence of nodal metastasis, FNA is of no use in predicting the axillary treatment- response in cN+ patients. Residual axillary disease is missed in more than half of the patients (of which implications on prognosis are yet unknown). Looking at the results from our survey in Chapter 3, FNA or biopsy of the axilla after chemotherapy in cN+ patients was in fact reported to be part of clinical practice by some respondents.²⁰ This is worrisome and again demonstrates the need for consensus and evidence based guidelines.

Oncologic safety of omitting ALND

In our retrospective analysis of 1347 cN+ patients treated with neoadjuvant chemotherapy (Chapter 8), we reported that isolated tumor cells and/or micrometastases after chemotherapy have a comparable prognosis to axillary pCR.²¹ This finding suggests that indications to omit ALND may be extended to patients with limited residual axillary disease. This could be relevant for the clinical use of the MARI procedure, since 2 of 5 false negative MARI results consisted of isolated tumor cells only.¹⁶ However, all included patients in our study underwent ALND with/without adjuvant regional radiotherapy and whether this contributed to our findings is unclear. Whether omission of ALND in patients with ypN0 or only limited residual axillary disease is indeed safe in terms of long-term prognosis, has yet to be answered.

Three studies reported on the prognosis of cN0/SLN-negative patients treated with neoadjuvant chemotherapy in whom completion ALND was not performed. In the retrospective cohort study by Nogi et al., axillary recurrence free survival was found to be similar between 147 patients treated with neoadjuvant chemotherapy and 849 patients treated with surgery first after a follow up period of 51 months (100% vs. 99.2%).²² Results of the prospective GANEA-2 trial showed a 3-year event free survival of 97.8% in 419 cN0 patients with a negative SLND and no completion ALND.²³ In a retrospective cohort of 249 cN0 patients treated with neoadjuvant chemotherapy, SLN-negative patients (in whom ALND was omitted) had a significantly improved (distant) disease-free and overall survival compared to SLN-positive patients (in whom completion ALND was performed).²⁴ To our knowledge, no studies have yet adequately assessed outcome of cN0/SLN-positive or cN+ patients in whom ALND has been omitted after neoadjuvant chemotherapy. Nevertheless, in our population-based cohort study of changes over time in axillary surgery, we found that ALND is already being omitted in cN0/SLN positive patients, and even in cN+ patients with residual axillary disease. The decrease in ALND rates was not as large as in cN0 and cN+ patients with an ypN0 status, but it was clearly present and gradually expanding. Positive lymph nodes detected after chemotherapy differ from positive lymph nodes detected at initial work-up. In the latter, patients still have to receive systemic treatment which contributes to locoregional control of the disease. Whereas patients treated with neoadjuvant chemotherapy already completed systemic therapy and positive lymph nodes indicate resistant disease. Therefore, leaving positive lymph nodes untreated after neoadjuvant chemotherapy, may in fact negatively impact locoregional control of disease. Studies assessing outcome in such patients in whom ALND is omitted are urgently needed. Additionally, studies comparing adjuvant regional radiotherapy with ALND are urgently needed. In our population-based study, simultaneously with a decrease in ALND, we noticed an increase in adjuvant regional radiotherapy in cN+ patients from 2011 to 2016. Currently, it is unknown whether adjuvant regional radiotherapy can safely replace ALND in such cases.

In patients in whom an ALND is still indicated, axillary reverse mapping (ARM) in combination with ALND may be considered to reduce morbidity²⁵, since this procedure aims to preserve lymphatic drainage to the arm. In cN+ patients treated with neoadjuvant chemotherapy, a significant decrease in metastases in the ARM lymph nodes has been reported.²⁶ Furthermore, the chance of metastases in the ARM lymph nodes is very low in patients with a complete or partial nodal response on imaging after neoadjuvant chemotherapy.²⁷ Future studies have to determine the long-term oncologic safety of ALND with ARM in breast cancer patients treated with neoadjuvant chemotherapy.

Main findings

- In cN0 patients, breast pCR is strongly correlated with ypN0 and may guide complete omission of axillary surgery in selected patients. In cN+ patients this correlation is also present, but weaker and therefore not relevant to clinical practice.
- The rate of ALND has declined significantly over the past decade in both cN0 and cN+ patients. This decline is also observed in patients with ypN+ disease, though implications on prognosis of leaving residual disease behind untreated are yet unknown. Whether adjuvant regional radiotherapy may safely replace ALND in such cases is yet unknown.
- The worldwide lack of consensus regarding axillary management after neoadjuvant chemotherapy in cN+ patients results in a wide variety of practices: from a minimum ‘wait and see’ approach (in case of complete nodal response on imaging) to a ‘most extensive’ approach of ALND combined with adjuvant radiotherapy.
- When the accuracy of the three most commonly used less invasive axillary staging methods for cN+ patients is compared, a combination procedure (like Targeted Axillary Dissection or RISAS) appears most accurate. Results of the RISAS trial have to be awaited to confirm this. When omission of ALND is already being considered in clinical practice, a combination procedure is the recommend staging procedure.
- In node positive breast cancer, patients with axillary pCR and limited residual axillary disease carry a comparable prognosis. Whether indications to omit ALND may be extended beyond axillary pCR remains thus far unknown, as data on long-term outcome are lacking.

FUTURE PERSPECTIVES

Non-surgical approach

The use of neoadjuvant chemotherapy has paved the way to explore a non-surgical approach for breast cancer. Previous attempts of omitting breast surgery after neoadjuvant chemotherapy resulted in unacceptably high rates of recurrent disease.²⁸ With advances in imaging modalities and increased knowledge on subtypes and corresponding pCR rates, several studies are currently investigating the diagnostic accuracy of breast biopsy in identifying a pCR of the breast in “excellent responders”. The ultimate goal is to forego unnecessary invasive surgery of the breast. In the currently accruing Dutch MICRA trial, breast-response is assessed with 8 ultrasound-guided biopsies in patients with a partial or complete breast response on MRI.²⁹

Subsequently, either breast conserving surgery or mastectomy is performed to determine accuracy of the biopsies. A total of 525 patients is needed and all subtypes are included.

Another validation trial is ongoing in Germany; the RESPONDER trial.³⁰ It is planned to enroll 600 patients (all subtypes included) with a partial or complete response on imaging that will undergo at least 12 image-guided vacuum assisted biopsies of the breast, subsequently followed by breast conserving surgery or mastectomy. The primary endpoint of the trial is the false negative rate of the biopsies.

While awaiting the results of these trials, MD Anderson Cancer Center has taken the next de-escalation step by evaluating the omission of surgery in excellent responders. In a prospective, multicenter trial, 50 patients with triple negative or HER2-positive breast cancer with a breast pCR as documented by 12 image-guided vacuum assisted core biopsies of the breast, will not undergo any subsequent surgery of the breast (Clinicaltrials.gov NCT02945579). All patients will undergo whole breast radiotherapy followed by external beam radiation therapy boost. The primary endpoint is the 6 months, 1, 2, 3, and 5-year biopsy confirmed ipsilateral breast tumor recurrence rate. If these trials determine safety of omission of breast surgery in selected patients, the next question is how to handle the axilla in such patients. Considering the strong correlation between breast pCR and ypN0^{2,31}, a pCR of the breast may guide omission of axillary surgery in selected cN0 patients. However, future trials have to determine if and in which patients that are eligible for omission of breast surgery, axillary surgery may also be omitted and in which patients axillary surgery should indeed be performed, even when surgery of the breast is omitted.

Currently, no trials are investigating a non-surgical approach of the axilla for patients treated with neoadjuvant chemotherapy specifically. This is apart from the previously mentioned study investigating FNA of the clipped node in the neoadjuvant setting, which reported a very low accuracy.¹⁹ In the adjuvant setting however, several trials are investigating omission of axillary surgery in cN0 patients (since, following results from trials like Z0011, a positive SLN has no treatment consequences). In the Dutch prospective, multicenter BOOG 2013-08 trial³², cT1-2cN0 patients that undergo breast conserving surgery are randomized between sentinel lymph node biopsy (+/- ALND) or no axillary surgery at all. So far, over 60% of the target sample size (1092/1644) has been accrued. The primary end point is regional recurrence rate at five and ten years. The first results are expected in 2027. Patients treated with neoadjuvant chemotherapy are also eligible for this trial and stratified analysis will be performed. In the SOUND trial (Sentinel node vs. Observation after axillary Ultra-souND; Clinicaltrials.gov NCT02167490), a similar approach is investigated in a prospective, multicenter, randomized, controlled, non-inferiority trial. Patients with small breast

tumours who are candidates for breast conserving surgery and have a negative preoperative axillary assessment (negative ultrasound or negative FNA) are randomized between no axillary surgery or SLND (+/- ALND). Overall, 1560 patients will be enrolled, and the primary endpoint is distant disease-free survival. In a third trial, the INSEMA trial (Clinicaltrials.gov NCT02466737), patients with cT1-2 breast cancer planned for breast conserving surgery are randomized to no SLND or SLND (+/- ALND) in a 1 to 4 ratio. Approximately 6000 patients will be randomized, and the primary endpoint is invasive disease-free survival.

It is well known that the presence of axillary metastasis at diagnosis is an important prognostic factor, yet so is axillary treatment-response. Patients who achieve axillary pCR have improved survival over patients who do not achieve axillary pCR, irrespective of treatment-response in the breast. In patients with pCR, we aim to avoid overtreatment. Simultaneously, we should provide appropriate adjuvant treatment in patients with residual disease. Future research should therefore also focus on this latter group, which has a dismal prognosis, to determine whether escalation rather than de-escalation of treatment may be necessary. Two recent trials, CREATE-X in HER2 negative patients³³ and KATHERINE in HER2 positive patients³⁴, reported an improved disease-free survival in patients with residual disease who were treated with adjuvant systemic therapy (capecitabine in CREATE-X and TDM-1 in KATHERINE). These findings demonstrate the potential to improve long-term prognosis and the importance of accurate staging to guide adjuvant treatment.

Imaging

Currently, imaging has no place yet in identifying axillary pCR. A systematic review on the diagnostic accuracy of different imaging techniques in cN+ patients showed that both MRI and PET-CT are associated with high FNRs (up to 52%) and low NPVs (<86%).³⁵ In the systematic review, axillary ultrasound turned out to be more accurate than MRI or PET-CT, but was still associated with high FNRs. Another disadvantage of imaging compared to surgical staging is the possibility of having a false positive finding, which results in overtreatment. Future studies should determine whether imaging and less invasive staging procedures may complement each other and when combined, may decrease the rate of both false negatives and false positives. New imaging techniques, such as the combination of hybrid PET-CT with MRI, may be more accurate and might be useful in assessing the axilla after neoadjuvant chemotherapy. A feasibility study reported that this technique may improve the diagnostic performance of the standard work-up for axillary staging in cN+ patients.³⁶ Future research has to determine if this may also apply for axillary staging in cN+ patients after neoadjuvant chemotherapy. Our group is currently applying for funding for the

OPTIMA trial. This trial aims to develop a deep learning approach for breast MRI in order to design a non-invasive prediction model for the extent of treatment-response.

Prognostic implications of omitting ALND in node positive breast cancer

As mentioned previously, data regarding long-term outcome of cN+ patients in whom ALND is omitted after neoadjuvant chemotherapy are unavailable. Three currently accruing trials focus on this matter. In the Alliance 011202 trial (Clinicaltrials.gov NCT01901094), a total of 2918 cN1 patients with a clinically negative axilla on physical examination after chemotherapy and who have at least 1 positive SLN will be randomized between ALND with nodal radiotherapy (undissected axilla, supraclavicular and internal mammary nodes) or axillary and nodal radiotherapy (levels 1 to 3 of the axilla in addition to the undissected axilla, supraclavicular and internal mammary nodes). The primary and secondary outcomes are invasive breast cancer recurrence free survival, overall survival and Ipsilateral/Local/regional invasive breast cancer recurrence at 5 years. First results of this trial are expected in 2024.

In the NSABP B51/RTOG 1304 trial (Clinicaltrials.gov NCT01872975), a total of 1636 cN1 patients with an axillary pCR after chemotherapy (documented by SLND or ALND) are randomized between regional nodal radiotherapy (undissected axilla, internal mammary nodes and ipsilateral supraclavicular fossa) or no regional nodal radiotherapy. The primary outcome is ipsilateral breast cancer recurrence free interval and amongst the secondary outcomes are overall survival and locoregional recurrence free interval. Patients will be followed for 10 years and results are expected in 2028. The outcomes of the NSABP B51/RTOG 1304 trial will inform us whether the poor accuracy of SLND in detecting pCR in cN+ patients treated with neoadjuvant chemotherapy is nullified by extensive adjuvant axillary radiotherapy. In this way, undertreatment of potentially missed residual disease is prevented, yet it may result in overtreatment in case of a true pCR. With a highly accurate staging method, the risk of missing residual axillary disease is negligible, and adjuvant regional radiotherapy may no longer be of added value. In this light, results of the RISAS trial are much anticipated. The German TAXIS trial³⁷ assesses long-term prognosis after performing a combination procedure. In this international trial, 1500 cN+ patients (treated with or without neoadjuvant chemotherapy) will undergo SLND with removal of the clipped node and palpably suspicious nodes. Patients with a positive node will then be randomized between radiotherapy levels 1-4 or ALND with radiotherapy of level 3-4 (Henke et al). The primary endpoint is disease-free survival at 20 years and these results are expected in 2043.

Future studies should not just focus on whether ALND can be safely replaced by regional radiotherapy, but also on identifying patients in whom both ALND and

regional radiotherapy can be safely omitted. This will help further shape response-based and patient-tailored management of the axilla.

A Dutch joined effort between our group and other dedicated breast cancer specialists has recently been granted funding to set up a multicenter, prospective, observational, registry study for cN+ patients treated with neoadjuvant chemotherapy. In the Netherlands, cN+ patients undergo either a less invasive staging procedure or an ALND depending on the institution where the patient is treated. Consequently, a nationwide cohort of cN+ patients can be developed that allows for comparison between less and more invasive staging and treatment procedures. The primary aim is to determine 5- and 10-year disease-free, breast cancer specific and overall survival as well as axillary recurrence rates for the currently practiced less and more invasive staging and treatment procedures. In addition, the effect of the different procedures on quality of life will be assessed. The trial will commence in 2020. Since both retrospectively and prospectively collected data will be used to assess the endpoints, the first results of the trial are already expected in 2023.

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CHAPTER

10

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Borstkanker is de meest voorkomende vorm van kanker onder vrouwen wereldwijd. De overlevingskansen van patiënten met borstkanker zijn over de afgelopen decennia aanzienlijk verbeterd ten gevolge van verbeteringen in screening, diagnose en behandeling. Daarnaast is de kwaliteit van leven van patiënten met borstkanker sterk verbeterd met de ontwikkeling van minder invasieve behandelopties. De kwaliteit van leven krijgt een steeds belangrijkere rol nu meer en meer patiënten borstkanker overleven.

De radicale mastectomie, waarin de gehele borst, borstspieren en alle okselklieren worden verwijderd, was van oudsher de standaardbehandeling voor borstkanker. Deze zeer invasieve ingreep werd na verloop van tijd aangepast tot de huidige standaard voor een mastectomie, waarin de borstspieren gespaard blijven. In de jaren '70 werd de borstsparende operatie geïntroduceerd. Deze operatie is een stuk minder invasief, en biedt wel dezelfde overlevingskansen als een mastectomie, mits de borstsparende operatie gevolgd wordt door aanvullende bestraling. De okselklierdissectie, waarbij alle okselklieren verwijderd worden, bleef de standaardbehandeling voor de oksel. De okselklierdissectie is een invasieve operatie die levenslange klachten van de arm kan geven, zoals lymfoedeem, functiestoornissen en pijnklachten. Deze klachten hebben een negatieve impact op de kwaliteit van leven van patiënten. Begin jaren '90 werd een minder invasieve okseloperatie geïntroduceerd: de schildwachtklierprocedure. Bij deze operatie worden alleen de okselklieren verwijderd die als eerste het lymfevocht uit de borst draineren in plaats van alle okselklieren. Wanneer deze 'poortwachtersklieren' vrij zijn van uitzaaiingen, is het heel waarschijnlijk dat de overige okselklieren ook vrij zijn van uitzaaiingen. Zodoende kunnen patiënten geselecteerd worden bij wie een okselklierdissectie achterwege gelaten kan worden. In sommige gevallen kan er zelfs veilig van een okselklierdissectie worden afgezien wanneer de schildwachtklieren slechts hele kleine (tot 2 mm) uitzaaiingen bevatten. Wanneer in 2 of meer schildwachtklieren uitzaaiingen worden gevonden, is er in principe een indicatie voor een aanvullende okselklierdissectie. Patiënten met op het moment van diagnose al direct uitzaaiingen in de oksel (vastgesteld met behulp van echo en punctie), komen helaas niet in aanmerking voor de schildwachtklierprocedure. Bij hen bestaat er direct een indicatie voor een okselklierdissectie.

Naast de chirurgische behandeling, is chemotherapie een belangrijk onderdeel van de behandeling van borstkanker. Bij borstkanker werd chemotherapie traditioneel toegediend na een operatie. In de jaren '70 werd neoadjuvante chemotherapie geïntroduceerd, dat wil zeggen chemotherapie gegeven voorafgaand aan de operatie. Dit brengt een aantal voordelen met zich mee: men kan evalueren hoe de borstkanker reageert op de chemotherapie en het is mogelijk de tumor kleiner te maken.

Tegenwoordig wordt neoadjuvante chemotherapie veelvuldig gebruikt. Niet alleen om niet-operabele borsttumoren operabel te maken, maar ook om reeds operabele borsttumoren kleiner te maken, zodat uiteindelijk minder borstweefsel verwijderd hoeft te worden. Neoadjuvante chemotherapie kan er zelfs voor zorgen dat alle kankercellen verdwijnen. Dit wordt een pathologisch complete respons genoemd. Patiënten met een pathologisch complete respons hebben waarschijnlijk geen baat bij een operatie. Helaas kunnen we op dit moment juist alleen maar middels een operatie met zekerheid vaststellen of iemand een pathologisch complete respons heeft bereikt. Om deze reden is men op zoek naar minder invasieve procedures om de invasieve operaties te kunnen vervangen in deze patiënten. In dit proefschrift ligt de focus op de operatie van de oksel. Het doel is om de meest optimale okseloperatie te identificeren. Deze operatie moet enerzijds zo minimaal invasief als mogelijk zijn om de kwaliteit van leven te verbeteren, anderzijds mag deze operatie geen kankercellen missen, want de oncologische veiligheid moet wel gegarandeerd blijven.

Deel I De-escalatie van okselbehandeling na neoadjuvante chemotherapie

In het eerste deel van dit proefschrift hebben we onderzoek gedaan naar de huidige trends in en gedachten over de okselbehandeling van borstkanker patiënten die behandeld zijn met neoadjuvante chemotherapie. In hoofdstuk 2 werd geëvalueerd hoe de okselbehandeling is veranderd over het afgelopen decennium. We konden aantonen dat het aantal okselklierdissecties sterk is afgenomen over de tijd. In kliernegatieve patiënten daalde het percentage okselklierdissecties van 89% tot 6% en in klierpositieve patiënten daalde dit van 99% tot 54%. De dalende trend in het aantal okselklierdissecties werd daarnaast geobserveerd in zowel patiënten met een pathologisch complete respons als in patiënten bij wie nog wel positieve klieren gevonden werden na de chemotherapie. Toekomstige studies moeten uitwijzen of en hoe deze trend de lange termijn prognose beïnvloedt. In hoofdstuk 3 werden borstkanker specialisten gevraagd naar hun gedachten en gebruiken ten aanzien van de okselbehandeling in klierpositieve borstkanker die behandeld wordt met neoadjuvante chemotherapie. Er werd een vragenlijst onderzoek uitgevoerd waarop 310 voornamelijk Europese chirurgen hebben gereageerd. Een kleine meerderheid (57.3%) gaf aan nog routinematig een okselklierdissectie te verrichten. Van de respondenten die niet routinematig een okselklierdissectie uitvoerden (42.7%), maakte 85% gebruik van beeldvorming om het beleid ten aanzien van de okselbehandeling vast te stellen. In geval van een complete respons op beeldvorming, koos 95% voor een minder invasieve okseloperatie. In geval van een gedeeltelijke of geen respons op beeldvorming, koos respectievelijk 59% en 77% voor een okselklierdissectie. Middels deze vragenlijst studie hebben we kunnen aantonen dat

er wereldwijd een gebrek aan consensus is en dat men behoefte heeft aan eenduidige, goed onderbouwde, richtlijnen.

Deel II De zoektocht naar een accurate, minder invasieve, okseloperatie voor klierpositieve borstkanker

Zoals reeds genoemd dient de meest optimale okseloperatie én zo minimaal invasief als mogelijk én zo accuraat als mogelijk te zijn. Zodoende kan de kwaliteit van leven verbeterd worden, zonder hierbij de oncologische veiligheid uit het oog te verliezen. In hoofdstuk 4 werd de diagnostische accuratesse van drie verschillende minder invasieve okseloperaties met elkaar vergeleken. De gouden standaard in alle meegenomen studies was de okselklierdissectie. Er werden in totaal 20 studies geïnccludeerd: 17 studies over de schildwachtklierprocedure, 1 studie over de MARI-procedure en 2 studies over een okseloperatie waarin de schildwachtklierprocedure gecombineerd wordt met de MARI-procedure. In de MARI-procedure wordt de positieve klier voorafgaand aan de chemotherapie gemarkeerd met een klein, radioactief jodiumbronnetje. Dit bronnetje blijft tijdens de chemotherapie periode in de klier zitten. Na de chemotherapie wordt tijdens de operatie de klier met het jodiumbronnetje opgespoord en verwijderd. De schildwachtklierprocedure had een gepoolde identificatiewaarde van 89%, een gepoolde fout-negatieve ratio van 17% en een negatief voorspellende waarde van 57% tot 86%. De MARI-procedure had een identificatiewaarde van 97%, een fout-negatieve ratio van 7% en een negatief voorspellende waarde van 83.3%. De combinatie operatie had een identificatiewaarde van 100%, een fout-negatieve ratio van 2% tot 4% en een negatief voorspellende waarde van 92% tot 97%. De combinatie operatie was derhalve het meest accuraat, echter is de bewijskracht met slechts 2 studies beperkt en is er meer onderzoek nodig om dit te bevestigen. In hoofdstuk 5 werd het studieprotocol van de RISAS-studie beschreven. De RISAS-studie is een Nederlandse, prospectieve, multicenter, validatie-studie naar de diagnostische accuratesse van de okseloperatie waarin de schildwachtklierprocedure wordt gecombineerd met de MARI-procedure. Naar verwachting zullen eind 2019 in totaal 225 klierpositieve patiënten geïnccludeerd zijn en volgen de resultaten medio 2020. Deze resultaten zullen bevestigen of een combinatie operatie daadwerkelijk het meest accuraat is. In hoofdstuk 6 werd het gebruik van de combinatie okseloperatie in de klinische praktijk onderzocht. Er werden retrospectief 139 klierpositieve patiënten uit vier ziekenhuizen geïnccludeerd. Het combineren van de schildwachtklierprocedure en de MARI-procedure resulteerde in een hogere identificatie-waarde (99.3%) dan wanneer alleen de schildwachtklier-procedure (87.8%) of alleen de MARI-procedure zou zijn uitgevoerd (92.8%). Met de combinatie operatie was ook de detectie van nog resterende positieve klieren beter.

Deel III Voorspellen van restziekte in de oksel en implicaties voor de prognose

In hoofdstuk 7 werd de correlatie tussen een pathologisch complete respons van de borst en de oksel onderzocht in een cohort van 4084 patiënten. In kliernegatieve borstkanker was deze correlatie sterk: van de patiënten met een pathologisch complete respons van de borst had 97.7% een tumorvrije oksel. In klierpositieve borstkanker was deze correlatie veel minder sterk: van de patiënten met een pathologisch complete respons van de borst had slechts 45% dit ook in de oksel. Toekomstig onderzoek zal moeten uitwijzen of de respons in de borst mogelijkheden biedt om van een okseloperatie af te zien in kliernegatieve patiënten. In hoofdstuk 8 werd de prognose van klierpositieve patiënten die behandeld zijn met neoadjuvante chemotherapie beoordeeld op basis van de klierstatus na chemotherapie. Drie groepen werden met elkaar vergeleken: patiënten met een complete respons, patiënten met slechts geïsoleerde tumorcellen of micrometastasen en patiënten met macrometastasen. In een cohort van 1347 patiënten werd aangetoond dat patiënten met geïsoleerde tumorcellen of micrometastasen een vergelijkbare prognose hadden als patiënten met een complete respons (ziektevrije-overleving: hazard ratio (HR) 1.38 (0.40-4.79), $p=0.613$; totale overleving: HR 0.92 (0.27-3.09), $p=0.889$). Patiënten met macrometastasen hadden een significant minder gunstige prognose dan patiënten met een complete respons (ziektevrije-overleving: HR 1.78 (1.06-3.00), $p=0.031$; totale overleving: HR 1.70 (1.07-2.71), $p=0.026$). In de toekomst kunnen een pathologisch complete respons en geïsoleerde tumorcellen of micrometastasen mogelijk als één entiteit beschouwd worden.

APPENDICES

Valorisation

Editorial (NTvO 2017;14:53-4)

List of publications

Acknowledgements | Dankwoord

Curriculum Vitae

VALORISATION

Breast cancer is the most commonly diagnosed cancer amongst women worldwide. In the Netherlands, approximately 16.000 patients are diagnosed with invasive breast cancer each year. Survival rates of these patients have increased substantially over the past decades and are still improving with the development of new therapies (such as immunotherapy). With increasing numbers of breast cancer survivors, improving quality of life becomes more and more important. About 20% of newly diagnosed patients are treated with neoadjuvant chemotherapy and these rates increased gradually over the past years. Currently, there is much debate on what constitutes the optimal axillary management in patients treated with neoadjuvant chemotherapy. On the one hand, specialists are striving for a least invasive strategy, on the other hand, specialists can't justify improving quality of life at the expense of oncologic safety. The aim of this thesis was to help shape response-based axillary management.

Relevance of scientific results in this thesis

This thesis evaluated current practices and trends regarding axillary management in patients with breast cancer treated with neoadjuvant chemotherapy. Especially in node positive breast cancer, the management of the axilla is an area of controversy. Traditionally, an axillary lymph node dissection was always performed. However, when clinically node positive patients are treated with neoadjuvant chemotherapy, a substantial part achieves a pathologic complete response of the axilla. These patients will probably not benefit from an axillary lymph node dissection. This thesis therefore focused on identifying the most optimal less invasive surgical procedure for axillary staging after neoadjuvant chemotherapy in node positive breast cancer patients. The systematic review and meta-analysis we performed, showed that a combination of sentinel lymph node biopsy with the MARI-procedure is the most optimal procedure in terms of identification rate and accuracy (false negative rate and negative predictive value). Importantly, only 2 studies addressed the accuracy of a combination procedure and only 1 study that of the MARI procedure, compared to 17 studies for the sentinel lymph node biopsy. Despite convincing evidence, axillary lymph node dissection is already being replaced by different less invasive procedures in daily practice at some institutions. This also occurs in the Netherlands, as we confirmed in chapter 2 of this thesis. To take optimal use of this ongoing trend, we evaluated a cohort of patients in whom axillary lymph node dissection is already being replaced by a combination procedure in daily practice. In this study, we found that the sentinel lymph node biopsy and MARI procedure complement each other, resulting in an improved identification rate and improved detection of residual axillary disease. Both the results of the systematic review and this cohort study, provide valuable considerations for specialists who already have implemented or who are about to

start implementing a less invasive staging procedure in daily practice. Based on the findings of these two studies, performing a combination procedure is recommended instead of performing either sentinel lymph node biopsy or the MARI procedure alone when omission of axillary lymph node dissection is considered.

Target population

The results of this thesis provide breast cancer specialists with insights in current practices worldwide regarding axillary management in patients treated with neoadjuvant chemotherapy. It furthermore provides steppingstones for specialists to help shape their local protocols regarding management of the axilla. Apart from this, the results of this thesis are helpful for patients diagnosed with breast cancer. The results can be used to inform patients accordingly and may aid in shared-decision making. While patients should be informed on the side effects of axillary lymph node dissection, they certainly should also be informed on the lack of evidence regarding oncologic safety of less invasive staging procedures. With the results of this thesis, we furthermore demonstrated that patients may receive a different axillary management plan dependent on where or by whom they are treated. Patients should be aware of this and informed accordingly by the treating specialist. These results stress the importance of continuing to join efforts to encourage patients to participate in clinical trials or registry studies. Ultimately, evidence-based guidelines can be determined to provided patients with a personalized - yet consistent amongst institutions – axillary staging and management plan that is optimal in terms of quality of life and oncologic safety.

Innovation and future

Although combining sentinel lymph node biopsy with a MARI-like procedure has been reported before, the RISAS trial is the first trial to validate such a combination procedure following a prospective and multicenter study design. Furthermore, a large cohort of 225 patients will be included. The results of this trial will confirm whether a combination procedure is indeed the most accurate less invasive axillary staging procedure for node positive breast cancer patients treated with neoadjuvant chemotherapy. If this procedure is proven to be accurate, these results will be implemented in guidelines worldwide. Consequently, more patients can benefit from a less invasive procedure and be spared the high risk of comorbidity that is associated with axillary lymph node dissection. Future research has to determine what kind of combination procedure is most optimal in terms of accuracy, cost-effectiveness and patient-friendliness. The MINIMAX trial, which will start accruing in the near future, will take the next step in providing evidence on the appropriate staging and treatment procedures concerning prognosis and quality of life. A less invasive staging procedure

is already standard of care for cN+ patients treated with NST in many institutions. In other institutions the axillary lymph node dissection is still routinely performed. Consequently, a nationwide cohort of cN+ patients can be developed to compare less and more invasive axillary staging and treatment procedures. Therefore, a multicenter, retro- and prospective, observational, registry study will be initiated in cN+ breast cancer patients treated with NST in the Netherlands. The primary aim is to determine five- and ten-year disease-free survival, breast cancer-specific survival, overall survival, and axillary recurrence rates, for the less and more invasive axillary staging and treatment procedures. The secondary aim is to determine their effect on QoL, assessed at baseline, at one year and at five years after diagnosis. The first results of the MINIMAX trial are expected in 2023.

OKSELBEHANDELING VAN PRIMAIR KLIERPOSITIEF MAMMACARCINOOM NA NEOADJUVANTE SYSTEMISCHE THERAPIE: IS MINDER WEL VEILIG?

Editorial bij de bijdrage van M.E.M. van der Noordaa, F.H. van Duijnhoven en M.T.F.D. Vrancken Peeters, getiteld 'Minder okselklierdissecties bij borstkankerpatiënten na neoadjuvante systemische therapie door gebruik van PET/CT en de MARI-procedure'

JM Simons, LB Koppert, TJA van Nijnatten, ML Smidt, CC van der Pol, EJT Luiten
(NTvO 2017;14:53-4)

Inleiding

De-escalatie van okselbehandeling bij patiënten met axillaire lymfekliermetastasen is zeer actueel. Het groeiende aantal patiënten met axillaire pathologisch complete respons (pCR) dankzij neoadjuvante systemische therapie (NST) vereist een minder invasieve stadiëringmethode dan de conventionele okselklierdissectie (OKD) met bijkomende morbiditeit. Van der Noordaa et al. presenteren een protocol waarbij de uitslag van PET/CT voorafgaand aan NST gecombineerd met de MARI-procedure na NST bepalen of en zo ja, welke vorm van aanvullende axillaire therapie een patiënt ontvangt. Dit zou resulteren in 80% correcte behandeling, 16% overbehandeling en 3% onderbehandeling. Het NKI is een van de toonaangevende instituten op het gebied van mammachirurgie en het ontwikkelen van minder invasieve behandelmethoden. De vraag is echter of het voorgestelde protocol niet te voorbarig is? En of dit protocol niet alleen morbiditeit reduceert, maar ook de oncologische veiligheid?

De MARI-procedure

In de unicentrische studie waarin MARI is gevalideerd werden 100 patiënten geïnccludeerd, waarvan er bij 26% pCR werd bereikt.¹ Het percentage fout-negatieven bedroeg 7%. Echter, met name de negatief-voorspellende waarde (NVW) is belangrijk bij validatie van diagnostische procedures en betreft hier 83%: bij 1 op de 6 patiënten met een negatieve MARI-klier is toch restziekte aanwezig.² Daarnaast is het onbekend of de MARI-procedure, vanwege de leercurve, vergelijkbare resultaten zal behalen in andere centra. De combinatie van een soortgelijke procedure als MARI met de schildwachtklierprocedure, de 'targeted axillary dissection', wordt kort benoemd als alternatieve stadiëringmethode.³ In een unicentrische, retrospectieve studie met 85 patiënten werd een NVW van 97% gerapporteerd: de kans op restziekte is daarmee nog slechts 1 op 33 bij een negatieve testuitslag. Bij 23% kwam de gemarkeerde klier niet overeen met (één van) de schildwachtklier(en). Gezien het beperkte bewijs voor deze veelbelovende methode is in Nederland de multicentrische RISAS-studie gestart

(KWF-grant NCT02800317) om bij 225 patiënten de MARI-procedure gecombineerd met de schildwachtklierprocedure te valideren. In deze studie ondergaan alle patiënten aansluitend een completerende okselklierdissectie.

De behandel mogelijkheden in het gepresenteerde protocol

Alleen patiënten met >3 FDG-avide klieren op PET/CT en een positieve MARI-klier ondergaan een OKD. Naast de OKD worden radiotherapie en geen behandeling als aanvullend alternatief genoemd, maar is deze 'sparende okselbehandeling' onderbouwd? Is het terecht om niet alleen bij pCR maar ook bij beperkte restziekte voor een sparende okselbehandeling te kiezen? Kan radiotherapie veilig de aanvullende OKD vervangen bij deze geselecteerde patiënten? En krijgen in dit protocol wellicht juist de lager risico hormoongevoelige patiënten, van wie bekend is dat zij het minst vaak pCR vertonen, de meest uitgebreide okselbehandeling? Al deze vragen blijven tot dusver onbeantwoord. Het gepresenteerde protocol is inspirerend, maar vooralsnog onvoldoende wetenschappelijk onderbouwd. Er wordt vooruitgelopen op resultaten van lopende studies (NSABP B-51/RTOG 1304, Alliance A11002002). Daarnaast worden resultaten van 'adjuvante setting'-studies (AMAROS) geëxtrapoleerd naar de patiëntenpopulatie met primair axillaire lymfekliermetastasen in 'neoadjuvante setting'. De stelling dat 80% van de patiënten volgens het nieuwe protocol correct zou zijn behandeld is wellicht te voorbarig, aangezien de langetermijnresultaten vooralsnog onbekend zijn. Centra die dit protocol toepassen moeten sterk overwegen patiënten in een prospectieve database te includeren om deze resultaten inzichtelijk te maken.

Conclusie

Concluderend is er behoefte aan okselbehandeling gestuurd op NST-respons. Het protocol geopperd door Van der Noordaa et al. maakt hierin een grote stap voorwaarts in het streven naar de-escalatie. Wij benadrukken het belang van verkrijgen van meer wetenschappelijk bewijs en het prospectief registreren van patiënten bij wie een OKD en/of radiotherapie reeds achterwege wordt gelaten op basis van NST-respons. Daarnaast kan deelname aan de RISAS-studie worden overwogen. Zodoende kan straks betrouwbaar worden vastgesteld welke stadiëringsprocedure voldoende accuraat is en wat de aanvullende okselbehandeling moet zijn in geval van restziekte. Vooralsnog blijft dit echter onbeantwoord.

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LIST OF PUBLICATIONS

This thesis

1. **JM Simons**, MLMA v Pelt, AWKS Marinelli, ME Straver, AM Zeillemaker, LM Pereira Arias-Bouda, TJA v Nijnatten, LB Koppert, ML Smidt, EJT Luiten, CC vd Pol
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Appendices

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Appendices

CURRICULUM VITAE

Janine Simons was born on the 18th of August, 1989, in Naarden and grew up in Huizen. In 2007 she finished high school (Erfgooiers College) and started medical school at the Vrije Universiteit in Amsterdam. In the second year, she was selected to participate in a summer research exchange project at the Centro de Onco-Hematologia Pediátrica (University of Pernambuco) in Recife, Brazil. During her master studies she did an extra-curricular internship in Tanzania, at Machame Hospital in the Kilimanjaro region. Her interest in research was stimulated by her research internship at the Burn Center Beverwijk (Rode Kruis Ziekenhuis). After she

obtained her medical degree in 2014, she started working as a surgical resident (not in training) at the Meander Medical Center in Amersfoort. She also worked at the Intensive Care department for three months. Subsequently, she continued working as a surgical resident at the University Medical Center in Utrecht. During this residency, she did research on ductoscopy and wrote several grant proposals. Following her ambitions to pursue a PhD, she applied for a full-time clinical research position on axillary management in breast cancer, supported by the Dutch Cancer Society. She started as a PhD Candidate in May 2016, under the supervision of Marjolein Smidt, Ernest Luiten, Linetta Koppert and Carmen van der Pol. As part of this position, she set up a prospective trial and initiated this trial at 14 Dutch institutions. She furthermore initiated multiple collaborations with other specialists and institutions both national and international. In 2018, she received several travel grants, which made it possible to work as a research assistant for five months at the department of breast surgical oncology at MD Anderson Cancer Center in Houston, under the supervision of dr. Hunt. Janine is looking forward to, after obtaining her PhD, combining a clinical position with postdoctoral research. In her spare time, she loves to go traveling and to spend time with friends and family. Janine is living together with Pablo in Amsterdam.