Breast Cancer Research and Treatment (2022) 193:37–48
https://doi.org/10.1007/s10549-022-06545-z

PRECLINICAL STUDY

Three-year follow-up of de-escalated axillary treatment after neoadjuvant systemic therapy in clinically node-positive breast cancer: the MARI-protocol

Ariane A. van Loevezijn[1,8] · Marieke E. M. van der Noordaa[1] · Marcel P. M. Stokkel[2] · Erik D. van Werkhoven[3] · Emma J. Groen[4] · Claudette E. Loo[5] · Paula H. M. Elkhuizen[6] · Gabe S. Sonke[7] · Nicola S. Russell[6] · Frederieke H. van Duijnhoven[1] · Marie-Jeanne T. F. D. Vrancken Peeters[1,8]

Received: 8 January 2022 / Accepted: 13 February 2022 / Published online: 3 March 2022

Abstract

Purpose In clinically node-positive (cN+) breast cancer patients, evidence supporting response-guided treatment after neoadjuvant systemic therapy (NST) instead of axillary lymph node dissection (ALND) is increasing, but follow-up results are lacking. We assessed three-year axillary recurrence-free interval (aRFI) in cN+ patients with response-adjusted axillary treatment according to the 'Marking Axillary lymph nodes with Radioactive Iodine seeds' (MARI)-protocol.

Methods We retrospectively assessed all stage II–III cytologically proven cN+ breast cancer patients who underwent the MARI-protocol between July 2014 and November 2018. Pre-NST axillary staging with FDG-PET/CT (less- or more than four suspicious axillary nodes; cALN < 4 or cALN ≥ 4) and post-NST pathological axillary response measured in the pre-NST largest tumor-positive axillary lymph node marked with an iodine seed (MARI-node; ypMARI-neg or ypMARI-pos) determined axillary treatment: no further treatment (cALN < 4, ypMARI-neg), axillary radiotherapy (ART) (cALN < 4, ypMARI-pos and cALN ≥ 4, ypMARI-neg) or ALND plus ART (cALN ≥ 4, ypMARI-pos).

Results Of 272 women included, the MARI-node was tumor-negative in 56 (32%) of 174 cALN < 4 patients and 43 (44%) of 98 cALN ≥ 4 patients. According to protocol, 56 (21%) patients received no further axillary treatment, 161 (59%) received ART and 55 (20%) received ALND plus ART. Median follow-up was 3.0 years (IQR 1.9–4.1). Five patients (one no further treatment, four ART) had axillary metastases. Three-year aRFI was 98% (95% CI 96–100). The overall recurrence risk remained highest for patients with ALND (HR 4.36; 95% CI 0.95–20.04, $p = 0.059$).

Conclusions De-escalation of axillary treatment according to the MARI-protocol prevented ALND in 80% of cN+ patients with an excellent three-year aRFI of 98%.

Keywords Breast cancer · Axillary lymph node dissection · Neoadjuvant therapy · Tailored treatment

✉ Marie-Jeanne T. F. D. Vrancken Peeters
m.vrancken@nki.nl

[1] Department of Surgical Oncology, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[2] Department of Nuclear Medicine, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[3] Department of Biometrics, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[4] Department of Pathology, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[5] Department of Radiology, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[6] Department of Radiation Oncology, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[7] Department of Medical Oncology, Netherlands Cancer Institute - Antoni Van Leeuwenhoek, Amsterdam, The Netherlands

[8] Department of Surgery, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Introduction

In clinically node-positive (cN+) breast cancer patients, axillary lymph node dissection (ALND) is still widely considered the standard of care [1–3]. The ongoing shift from adjuvant to neoadjuvant systemic therapy (NST) however, allows consideration of less extensive axillary surgery for cN+ patients [4, 5]. Currently, a pathologic complete response (pCR) of the axilla (ypN0) is seen in one-third of cN+ patients with NST, with pCR rates of more than 50% in triple-negative and HER2-positive patients [6]. Patients with axillary pCR are unlikely to benefit from ALND, while facing surgical complications and long-term morbidity such as lymphedema and limitation of shoulder motion. Therefore, strategies to de-escalate axillary treatment in cN+ patients are being investigated [7–9].

At the Netherlands Cancer Institute, the Marking Axillary Lymph Nodes with Radioactive Iodine seeds (MARI)-procedure [10] was developed to re-stage the axilla after NST. The largest tumor-positive axillary lymph node (ALN) was marked with an iodine seed pre-NST (MARI-node) and selectively removed and assessed post-NST [11]. This procedure was found to be a reliable measurement of axillary response with a false-negative rate of only 7% [10–12]. Hereafter, an axillary treatment algorithm was developed (i.e., MARI-protocol) which combined the outcome of the MARI-procedure (ypMARI-neg or ypMARI-pos) with a pre-NST acquired fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) scan to determine the presence of less or more than four (cALN < 4 or cALN ≥ 4) tumor-positive ALNs prior to NST [11, 12]. Patients staged cALN < 4, ypMARI-neg received no further axillary treatment, patients staged cALN < 4, ypMARI-pos and cALN ≥ 4, ypMARI-neg received axillary radiotherapy (ART) and patients staged cALN ≥ 4, ypMARI-pos received ALND plus ART [12].

Long-term outcomes of patients treated according to the MARI-protocol have not yet been reported. In this study, we assessed three-year follow-up results and in particular axillary recurrence-free interval (aRFI) of clinically node-positive breast cancer patients who underwent tailored and de-escalated axillary treatment after NST according to the MARI-protocol.

Methods

Patient selection

This is a single-center cohort study including prospectively registered patients. We included all women, 18 years or older, with stage II–III pathologically proven axillary cN+ breast cancer of any subtype, who underwent the MARI-protocol between July 2014 and November 2018 at the Netherlands Cancer Institute. Exclusion criteria were history of breast cancer and non-FDG-avid breast cancer. This study was approved by the institutional review board of the Netherlands Cancer Institute.

Diagnostic procedures

Core needle biopsies of the breast tumor were obtained to determine histological subtype, hormone receptor and HER2- status. Hormone receptor status was defined as positive if estrogen expression was ≥ 10%, and HER2-status was regarded positive if 3 + or 2 + with positive in-situ hybridization, according to ASCO-CAP guidelines [13]. Tumor grade was determined according to the modified Bloom-Richardson method [14]. The size and extent of the primary tumor were assessed by mammography, ultrasound and dynamic contrast-enhanced (DCE) MRI. All patients underwent axillary and peri-clavicular ultrasound. Ultrasound-guided fine needle aspiration (FNA) was performed in case of suspect lymph nodes.

A whole body FDG-PET/CT (Philips Gemini, Cleveland, OH, USA) was performed for regional staging and detection of distant metastasis. PET acquisition was followed by a low-dose CT scan (40 mAs, 2 mm slices). Additional PET/CT images in prone position were acquired if patients were scanned at the Netherlands Cancer Institute. The uptake of FDG-positive ALNs was assessed by experienced nuclear medicine physicians and was discussed during multidisciplinary consultations. A lymph node was regarded as highly suspicious for metastasis when the uptake was higher than the blood pool activity. For axillary staging according to the MARI-protocol, the number of FDG-positive ALNs was used rather than the clinical TNM classification. Patients with less than four FDG-positive axillary nodes on PET/CT were defined as cALN < 4 and patients with more than three FDG-positive axillary nodes were defined as cALN ≥ 4, regardless of presence of peri-clavicular or internal mammary chain nodes.

Radioactive seed localization

In all patients, an Iodine seed (STM1251, Bard Brachytherapy Inc., Carol Stream, IL) with an apparent activity varying from 0.2 to 1.0 MBq at time of implementation was placed under ultrasound guidance in the largest pathology proven tumor-positive axillary lymph node (i.e., MARI-node) prior to the start of the first NST cycle. The activity of Iodine seeds used for MARI-node localization is lower than for breast tumor localization (apparent activity 1.0–7.6 Mbq) [15, 16] to minimize irradiation of the node. Marking of

the breast tumor was performed during the same procedure. Adequate position of the markers in the breast and axilla was confirmed by ultrasound and/or mammography. A comprehensive description of the MARI-procedure and radiation safety protocols has been described previously [17].

Treatment and response evaluation

Neoadjuvant systemic therapy was administered according to institutional guidelines as previously described [11]. After completion of NST, surgery of the breast and selective removal of the MARI-node was performed. A gamma probe was used to guide the localization of the Iodine seeds and surgical resection. Additional axillary nodes were removed when a lymph node was located directly adjacent to the MARI-node.

In cALN < 4 patients, the MARI-node was formalin-fixed overnight followed by hematoxylin and eosin (H&E) and cytokeratin staining at a single level. An intraoperative frozen section of the MARI-node was obtained in all cALN ≥ 4 patients. For intraoperative frozen sections, 2 mm tissue slices ware made from which 5 µm H&E sections were prepared and assessed. Hereafter, the tissue was also fixed in formalin overnight followed by a new H&E and a cytokeratin stain at a single level.

Pathological complete response of the axilla was defined as the absence of vital tumor cells in the removed axillary lymph node(s) (ypN0). A pCR of the breast was defined as absence of invasive and in-situ carcinoma in the breast (ypT0).

Tailored and de-escalated axillary treatment

All cALN < 4 patients with pCR of the MARI-node (ypMARI-neg) received no further axillary treatment. Axillary levels I to IV were irradiated in patients staged cALN < 4, ypMARI-pos and cALN ≥ 4, ypMARI-neg. ALND and ART was performed in all patients staged cALN ≥ 4, ypMARI-pos. The ALND was performed in a second operation in patients with a false-negative intraoperative frozen section of the MARI-node.

Patients with ART underwent irradiation to the axillary and infra/supraclavicular nodes, and in case of FDG-positive nodes in the internal mammary chain (IMC), the IMC was included. Delineation of lymph node levels was performed according to the Danish national delineation guidelines, and from January 2015, according to the European Society for Radiotherapy and Oncology consensus guidelines. A dose of 42.56 Gy in 16 fractions of 2.66 Gy was prescribed, or 46.2 Gy in 21 fractions of 2.2 Gy if a simultaneous boost dose was given to the tumor bed in the breast. The radiotherapy technique used was either static field Intensity Modulated RadioTherapy (IMRT) or Volumetic Modulated Arc Therapy (VMAT) planning. Deep Inspiration Breath Hold Technique was applied for all left sided breast tumors.

Patients received adjuvant systemic treatment according to institutional guidelines. Patients with hormone-receptor positive tumors received adjuvant hormonal therapy and all patients with HER2-positive tumors received adjuvant HER2-directed therapy. Following the publication of the CREATE-X trial in 2017 [18], adjuvant Capecitabine was administered in all patients with triple-negative breast cancer with residual disease and a selection of estrogen receptor-positive tumors with residual disease.

Outcomes

The primary endpoint was three-year axillary recurrence-free interval (aRFI), defined as tumor recurrence in lymph nodes in the ipsilateral axilla. Secondary outcomes were local-, regional-,distant and overall- RFI rates and overall survival. Axillary recurrence-free interval was defined as time from the MARI-procedure to axillary recurrence or death from any cause. Patients who died without axillary recurrence or were lost to follow-up were censored in the analysis. Patients who developed (and received treatment) for another event (e.g. local recurrence, distant metastases, or new primary) before axillary recurrence were censored in the analysis, except if it was a synchronous event (i.e., diagnosed at subsequent disease staging). In addition, three-year RFI was assessed in the pre-specified treatment groups (i.e., no further treatment [cALN < 4, ypMARI-neg] ART [cALN < 4, ypMARI-pos and cALN ≥ 4, ypMARI-neg] and ALND plus ART [cALN ≥ 4, ypMARI-pos], as well as factors influencing disease recurrence (i.e., age, clinical stage, subtype and pathological response) were evaluated.

Statistical analysis

Recurrence-free interval and overall survival of the four treatment groups were estimated by the Kaplan–Meier method and compared with log-rank tests. All survival estimates were reported with their 95% confidence intervals. To evaluate associations between patient characteristics, axillary treatment and recurrence-free interval, Cox proportional-hazards models were used. The two-sided 95% confidence intervals for proportions were calculated using the exact Clopper-Pearson method. Baseline characteristics were compared between patients staged cALN < 4 and cALN ≥ 4 with an independent sample t test for sample means and with Pearson Chi-square or Fisher's exact test for categorical variables. Statistical significance for comparisons between groups was defined as $p < 0.05$. All statistical analyses were performed in IBM SPSS Statistics, version 25.0.

Results

Patient characteristics

Between July 2014 and November 2018, 272 (80%) of 341 prospectively registered patients who underwent the MARI-procedure fulfilled eligibility criteria (Fig. 1). Reasons for exclusion were practical issues ($N=34$) (e.g. non-FDG avid or clustered, indistinguishable ALNs) or protocol deviations ($N=35$) (e.g. false-negative intraoperative frozen section not followed by ALND).

Baseline characteristics are shown in Table 1. Median age was 48 years (range 22–79) and the majority of patients had invasive carcinoma of no special type (89%). Staging with FDG-PET/CT prior to NST categorized 174 (64%) patients as cALN < 4 and 98 (36%) patients as cALN ≥ 4. Baseline characteristics differed between the groups: more HER2-positive tumors (38% vs. 23%) and less HR-positive/HER2-negative tumors (43% vs. 57%) were found in cALN ≥ 4 patients compared to cALN < 4 patients ($p=0.012$, Table 1).

The MARI-procedure

The total number of ALNs removed during the MARI-procedure ranged from one to six, with a median of one (IQR 1–2). A pCR of the MARI-node (ypMARI-neg) was found in 56 (32%) of 174 cALN < 4 patients and in 43 (44%) of 98 cALN ≥ 4 patients ($p=0.054$) and varied per subtype, with rates of 9% (13 of 140) in HR-positive/HER2-negative tumors, 59% (27 of 46) in HR-positive/HER2-positive tumors, 94% (30 of 32) in HR-negative/HER2-positive tumors and 54% (29 of 54) in triple-negative tumors ($p<0.001$). In all patients with a tumor-negative MARI-node, the additionally removed ALNs were negative as well.

Breast pCR occurred in 78 (29%; 95% CI 23–34) patients and 64 (24%; 95% CI 19–29) patients had both pCR of the breast and the MARI-node (ypT0N0).

Tailored axillary treatment

Axillary treatment according to the MARI-protocol is presented in Fig. 2 and resulted in omission of ALND in a total of 217 (80%) patients: no further axillary treatment was administered in 56 (21%) patients (cALN < 4, ypMARI-neg), and 161 (59%) patients (118 cALN < 4, ypMARI-pos and 43 cALN ≥ 4, ypMARI-neg) received ART. Fifty-five (20%) cALN ≥ 4 patients had residual tumor in the MARI-node and underwent ALND plus ART. Adjuvant systemic therapy was administered in 228 (84%) patients and included chemotherapy in 44 (16%) patients, HER2-directed therapy in 80 (29%) patients and hormonal therapy in 183 (67%) patients.

Axillary recurrence

Median follow-up was 3.0 years (IQR 1.9–4.1, range 0.3–5.4). Axillary recurrences occurred in a total of five (1.8%) patients, and three-year aRFI was 98% (95% CI 96–100). All five were cALN < 4 patients with synchronous other metastases. Subtype was triple-negative in four

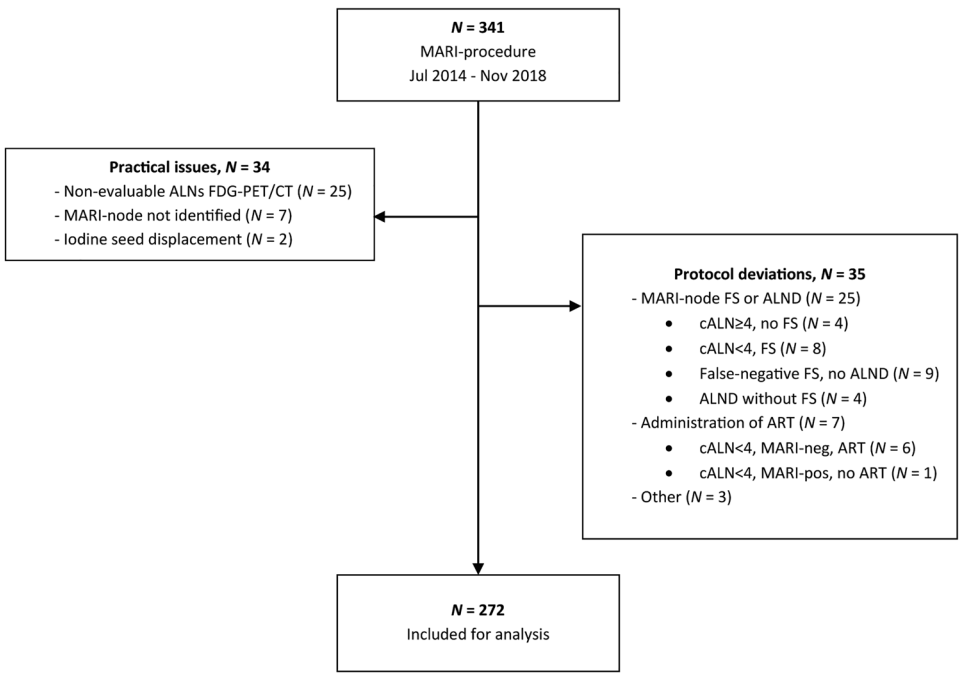


Fig. 1 Patient inclusion. *MARI* Marked axillary lymph node with radioactive iodine seed, *FDG-PET/CT* fluorodeoxyglucose—positron emission tomography/computed tomography; *ALNs* Axillary lymph nodes, *FS* frozen section, *ALND* axillary lymph node dissection, *cALN < 4* less than four FDG-PET/CT-positive axillary lymph nodes, *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *ART* axillary radiotherapy

Table 1 Baseline patient and tumor characteristics

	Total $N=272$		cALN < 4 $N=174$		cALN ≥ 4 $N=98$		*P* value
Age (y)	48	(41–56)	48	(40–55)	49	(42–56)	0.981
Diagnostic imaging							
Tumor size MRI (mm)	32	(22–50)	31	(22–46)	36	(24–55)	0.109
PET/CT-positive ALNs	2	(1–4)	1	(1–2)	5	(4–7)[a]	< 0.001
Histology							0.797
No special type[a]	242	(89%)	153	(88%)	89	(91%)	
Lobular	29	(11%)	20	(11%)	9	(9%)	
Other	1	(1%)	1	(1%)	0	–	
Tumor subtype							0.012
HR + / HER2 −	140	(51%)	99	(57%)	41	(43%)	
HR + / HER2 +	46	(17%)	27	(15%)	19	(19%)	
HR − / HER2 +	32	(12%)	13	(8%)	19	(19%)	
Triple-negative	54	(20%)	35	(20%)	19	(19%)	
Bloom-Richardson grade							0.565
Grade 1	9	(4%)	7	(4%)	2	(2%)	
Grade 2	135	(53%)	90	(55%)	45	(51%)	
Grade 3	110	(43%)	68	(41%)	42	(47%)	
Unknown	18	–	9	–	9	–	

Data are median (IQR) or *N* (%)

cALN < 4 less than four FDG-PET/CT-positive axillary lymph nodes, *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *MARI* marked axillary lymph node with radioactive iodine seed, *ALNs* axillary lymph nodes, *ALND* axillary lymph node dissection

[a]The number of ALNs was reported as 'multiple' in 26 patients. +formerly known as invasive ductal carcinoma. All characteristics were assessed before administration of neoadjuvant systemic therapy

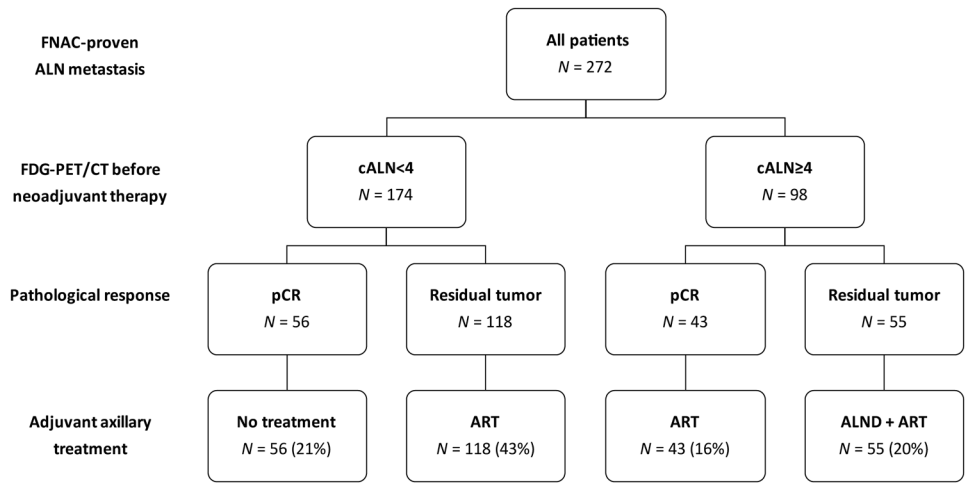


Fig. 2 Tailored adjuvant axillary treatment strategy according to the MARI protocol. *FNAC* fine needle aspiration cytology, *cALN < 4* less than four FDG-PET/CT-positive axillary lymph nodes, *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *MARI* marked axillary lymph node with radioactive iodine seed, *pCR* pathological complete response, *ALN* Axillary lymph node, *ALND* axillary lymph node dissection, *ART* axillary radiotherapy

patients and HR-positive/HER2negative in one. One of the five patients had pCR of the MARI-node and therefore received no further axillary treatment. In this patient, extensive metastases were found in the axilla, lower neck and cervical region. The remaining four patients had residual disease in the MARI-node and underwent radiation treatment. Of these, one patient had axillary and IMC metastases, one patient had axillary metastases with concurrent metastases in the breast/thoracic wall, supraclavicular nodes and in the IMC, and two patients had axillary metastases with synchronous distant metastases.

Secondary outcomes

In total, 27 (9.9%) patients developed one or more recurrences (distant, regional or local). Distant metastases were found in 19 (7.0%) patients, regional nodal recurrences (including the five patients with axillary metastases) occurred in 10 (3.7%) patients and a local recurrence was detected in 6 (2.2%) patients. The corresponding overall three-year RFI and distant, regional, and local RFI rates were 90% (95% CI 86–94), 93% (95% CI 90–96), 96% (95% CI 94–99) and 98% (95% CI 95–100), respectively. Sixteen (5.9%) patients died, al due to breast cancer recurrence, resulting in a three-year overall and breast cancer survival of 95% (95% CI 91–98).

The first documented site(s) of recurrence by axillary treatment group are shown in Table 2. In total, fewest recurrences (5%) occurred in cALN < 4, ypMARI-neg patients with no further axillary treatment. Nine percent recurrences were found in both ART groups (cALN < 4 and cALN ≥ 4) and 18% in the ALND group (Table 2). The corresponding three-year RFI rates were 100% (95% CI n.a.), 91% (95% CI 85–97), 88% (95% CI 76–100) and 79% (95% CI 66–92) (Fig. 3). In an exploratory analysis, the trend in increased risk of disease recurrence for cALN ≥ 4, ypMARI-pos patients remained after adjusting for age, subtype and pathological response of the breast (HR 4.36, 95% CI 0.95–20.04, $p = 0.059$).

Baseline characteristics associated with increased risk of disease recurrence in univariate analysis were clinical stage cALN ≥ 4 (HR 2.25, 95% CI 1.05–4.79, $p = 0.036$) and triple-negative breast cancer (HR 2.89, 95% CI 1.23–6.81, $p = 0.015$) (Table 3). In multivariate analysis, triple-negative breast cancer (HR 4.32, 95% CI 1.74–10.53, $p = 0.002$) and residual tumor in the MARI-node (HR 3.13, 95% CI 1.02–9.68, $p = 0.047$) were significantly associated with disease recurrence.

Discussion

This study demonstrates that tailored de-escalated axillary treatment after NST according to the MARI-protocol in cN+ breast cancer patients is safe with an 80% reduction in ALNDs and excellent three-year aRFI and regional RFI of 98% and 96%, respectively. As axillary recurrences occur at a median of two years following treatment [19–21], the high aRFI of 98% we found at a median follow-up of three years can be considered a significant result.

Previously reported regional RFS rates in cN+ patients who underwent complete ALND after NST included rates of 96% at 3 years follow-up [22], 94–96% at years follow-up [23–27] and 91–95% at ten years follow-up [28]. Notably, the number of cN2-3 patients we included was generally higher (36% cALN ≥ 4 patients), and the high RFS we found is therefore less likely to result from a more favorable patient selection. Several studies have established the significance of clinical stage and especially pathological axillary response as prognostic factors [24, 28–31]. Accordingly, we found fewest recurrences in cALN < 4 patients with MARI-node pCR and most recurrences in patients staged cALN ≥ 4, ypMARI-pos who underwent ALND plus ART. Baseline factors associated with disease recurrence in multivariable analysis were residual tumor in the MARI-node (HR 3.1) and triple-negative subtype (HR 4.3).

Post-NST axillary staging strategies for cN+ patients other than the MARI-procedure include the post-NST sentinel lymph node biopsy (SLNB) and targeted axillary dissection (TAD) [8], which combines removal of a pre-NST clipped node with SLNB [4, 5]. The accuracy of the post-NST SLNB is a much-debated topic. While the MARI-procedure has a false-negative rate (FNR) of 7% with a risk of undertreatment in only 3% of patients [10, 11], FNRs of 8% to 40% have been reported for the post-NST SLNB [5, 7, 32, 33]. A clinically considered acceptable FNR of ≤ 10% was only achieved when three or more sentinel nodes (SNs) were removed and dual-tracer mapping was used [7, 33]. In the ACOSOG Z1071 and SENTINA trial, retrieval of three or more SNs occurred only in 56% and 34% of patients, respectively [7, 33].

The FNR of TAD was reported to be as low as 2–4% [8–10, 34], and could be lower than the FNR of the MARI-procedure due to assessment of more ALNs. In the study by Caudle et al. [8], three or more ALNs were removed in 47% (63 of 134) of patients, while a median of only one (IQR 1–2) ALN is removed with the MARI-procedure. Compared to the MARI-procedure, TAD also requires an additional visit to the outpatient clinic for both the localization of the clipped node and the sentinel-node procedure.

Although the removal of more ALNs may decrease the FNR, it also increases the risk of lymphedema [35]. Moreover, it is important to note that lowering the FNR of post-NST axillary staging methods further below 10% may not significantly lower the axillary recurrence rate. With the MARI-procedure, we found an excellent three-year aRFI of 98%.

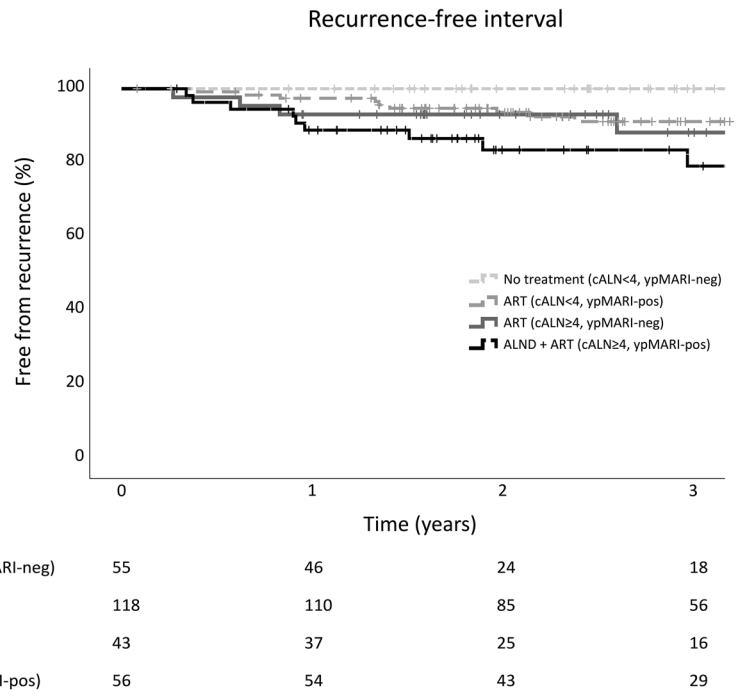
Several other studies indicate that limited axillary residual disease may safely be left in situ without compromising aRFI. In patients treated with SLNB in the primary surgery setting, 5–10 year axillary recurrence rates of 0–2% were found, which is lower than expected based on the reported FNRs of 5–10% [4, 20, 36–40], and the ACOSOG Z0011 and IBCSG 23–01 trials reported excellent locoregional control in patients with limited disease at SLNB without further axillary treatment [20, 36]. In addition, the AMAROS trial found that ART was as effective as ALND for the treatment patient with tumor-positive SLN's (5-year axillary

Table 2 Locations of breast cancer recurrence by response adjusted axillary treatment group

	cALN < 4		cALN ≥ 4		
	MARI pCR	MARI tumor +	MARI pCR	MARI tumor +	
	No treatment	*ART*	*ART*	*ALND + ART*	Total
	N = 56	*N* = 118	*N* = 43	*N* = 55	*N* = 272
Total patients with event per treatment group[a]					
Axillary + local	0	1	0	0	1
Axillary + regional	1	1	0	0	2
Axillary + distant	0	2	0	0	2
Local	1	0	0	2	3
Local + regional	0	0	0	1	1
Local + distant	0	0	1	0	1
Regional	0	0	0	1	1
Regional + distant	0	0	1	2	3
Distant	1	6	2	4	13
Total	3 (5.4%)	10 (8.5%)	4 (9.3%)	10 (18.2%)	27 (9.9%)
Total patients with event by location					
Axillary	1	4	0	0	5 (1.8%)
Local	1	1	1	3	6 (2.2%)
Regional (incl. axilla)	1	4	1	4	10 (3.7%)
Distant	1	8	4	6	19 (7.0%)

cALN < 4 less than four FDG-PET/CT-positive axillary lymph nodes, *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *MARI* marked axillary lymph node with radioactive iodine seed, *pCR* pathological complete response, *tumor +* tumor-positive, *ART* axillary radiotherapy, *ALND* axillary lymph node dissection

[a]Axillary recurrences were reported separately from non-axillary regional nodal metastases; Lower neck/cervical metastases were considered regional metastases



No. at risk				
No treatment (cALN<4, ypMARI-neg)	55	46	24	18
ART (cALN<4, ypMARI-pos)	118	110	85	56
ART (cALN≥4, ypMARI-neg)	43	37	25	16
ALND + ART (cALN≥4, ypMARI-pos)	56	54	43	29

Fig. 3 Overall recurrence-free interval by axillary staging and treatment. *cALN < 4* less than four FDG-PET/CT-positive axillary lymph nodes, *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *MARI* marked axillary lymph node with radioactive iodine seed, *ypMARI-neg/ypMARI-pos* pathology analysis of MARI-node after neoadjuvant systemic therapy tumor-negative/tumor-positive, *ART* axillary radiotherapy, *ALND* axillary lymph node dissection

recurrence of 1.2% vs. 0.4%) [41]. Of note, four or more tumor-positive ALNs (pN2) were found in 8% of the patients in the ALND-arm, which supports the efficacy of ART even in patients with higher axillary tumor load.

Reports on axillary recurrence after de-escalated locoregional axillary treatment in cN+ patients with NST are limited. Four- and five year recurrence rates of 2% and 0% were described in cN1 patients with a tumor-negative post-NST SLNB in whom ALND was omitted [38, 42, 43]. Results of comprehensive trials investigating the impact of de-escalated axillary treatment after NST such as the ongoing NSABP B-51/RTOG 1304 (NCT01872975) [44] and the Alliance A011202 trial (NCT01901094) [45], are currently unknown. In addition, whether ALND can be avoided after NST in patients with cN2-3 disease is not investigated in these trials [46]. Notably, in the present study we showed that the MARI-protocol is not only an effective method for de-escalation of axillary treatment in cN1 patients, but also for patients with more extensive axillary disease prior to NST.

Limitations to implementation of the MARI-protocol could be the use of radioactive iodine seeds. Although iodine seeds are increasingly being used for tumor localization due to improved surgical planning and diminished patient discomfort [16], extensive regulations often apply for handling and disposal of the seeds. According to our protocol, iodine seeds should be allowed to remain in situ for the duration of NST.

Furthermore, FDG-PET/CT it is not yet part of the diagnostic work-up for cN+ breast cancer patients in several countries. The costs (± €1260[47] [$1545[48]]) may therefore not always be fully covered by health insurance [47–49]. Staging breast cancer patients with FDG-PET/CT, however, can replace diagnostic imaging with CT, chest X-ray and ultrasound with higher diagnostic accuracy and cost-effectiveness [50, 51]. In addition, the diagnostic accuracy of FDG-PET/CT for axillary staging is higher compared to other modalities and therefore essential when tailoring axillary treatment [52–54].

Limitations of this study are its single-center character and prospective registration design. Ten percent of the patients undergoing tailored axillary treatment after NST according to the MARI-protocol were excluded from analysis due to deviations from the protocol. The type of protocol violations varied, and included both patients with overtreatment (e.g. cALN ≤ 4 patients with intraoperatively assessed extensive residual axillary disease treated with ALND) as well as patient who were undertreated (no ALND or ART in case of a tumor-positive MARI-node) according to protocol.

In conclusion, in this study we demonstrated that the MARI-protocol is an effective axillary staging and treatment algorithm which resulted in omission of ALND in 80% of cN+ patients undergoing NST while maintaining excellent three-year axillary- and regional RFI rates of 98% and 96%. Therefore, the MARI-protocol may be considered a suitable method to de-escalate axillary treatment in selected patients. Longer follow-up is needed to evaluate these results at five- and ten years follow-up.

Table 3 Cox regression analysis for overall recurrence-free interval

	Events		Univariate			Multivariate		
	N	*(%)*	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years	27	(10%)	1.01	0.98–1.05	0.517	1.01	0.97–1.05	0.582
Subtype								
HR + / HER2 −	10	(7%)	Ref					
HR + / HER2 +	3	(7%)	0.99	0.27–3.58	0.981	1.57	0.40–6.10	0.519
HR − / HER2 +	3	(9%)	1.33	0.37–4.84	0.666	3.39	0.63–18.12	0.154
Triple-negative	11	(20%)	2.89	1.23–6.81	0.015	4.28	1.74–10.53	0.002
Clinical tumor stage								
≤ cT1	2	(4%)	Ref					
cT2	16	(10%)	2.72	0.63–11.85	0.182	2.91	0.66–12.81	0.157
≥ cT3	9	(14%)	4.06	0.88–18.82	0.073	3.68	0.78–17.49	0.101
Clinical ALN group								
cALN < 4	13	(8%)	Ref					
cALN ≥ 4	14	(14%)	2.25	1.05–4.79	0.036	1.96	0.88–4.35	0.100
Pathology MARI node(s)								
Tumor-negative	7	(7%)	Ref					
Tumor-positive	20	(12%)	1.67	0.71–3.95	0.244	3.13	1.02–9.68	0.047
Pathology breast								
Residual disease	23	(12%)	Ref					
Complete response	4	(5%)	0.45	0.15–1.29	0.137			
Adjuvant axillary treatment[a]								
No further treatment	3	(5%)	Ref					
ART (cALN < 4)	10	(9%)	1.64	0.45–5.97	0.451			
ART (cALN ≥ 4)	4	(9%)	2.04	0.46–9.13	0.351			
ALND plus ART	10	(18%)	4.18	1.15–15.22	0.030			

HR hazard ratio; *cALN < 4* less than four FDG-PET/CT-positive axillary lymph nodes; *cALN ≥ 4* more than four FDG-PET/CT positive axillary lymph nodes, *MARI* marked axillary lymph node with radioactive iodine seed, *ART* axillary radiotherapy, *ALND* axillary lymph node dissection

[a]Adjuvant axillary treatment was not included in multivariate analysis due to collinearity with clinical axillary lymph node group and pathology MARI node(s) ($R^2 \geq 0.6$)

Author contributions MVP was the principal investigator and conceived and designed the study together with FvD, CL, PE, NR and MS. Material preparation, data collection and analysis were performed by AvL, MvdN, MS, EG and EvW. The first draft of the manuscript was written by AvL, MvdN, EvW, GS, FvD and MVP and all authors commented on previous versions of the manuscript and wrote, revised, and approved the final version of the manuscript.

Funding This work was not supported by research Grants.

Declarations

Conflict of interest GS received institutional research support from AstraZeneca, Merck, Novartis, and Roche outside the scope of this manuscript. All other authors declare no competing interests.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board of the Netherlands Cancer Institute approved this study.

Informed consent This study was conducted retrospectively from data obtained for clinical purposes. An official waiver of ethical approval was granted from the institutional review board.

Availability of data and material The datasets generated for the current study are available from the corresponding author on reasonable request.

References

1. Garcia-Etienne CA, Ferrari A, Della Valle A, Lucioni M, Ferraris E, Di Giulio G, Squillace L, Bonzano E, Lasagna A, Rizzo G, Tancredi R, Scotti Foglieni A, Dionigi F, Grasso M, Arbustini E, Cavenaghi G, Pedrazzoli P, Filippi AR, Dionigi P, Sgarella A (2020) Management of the axilla in patients with breast cancer and positive sentinel lymph node biopsy: an evidence-based update in a European breast center. Eur J Surg Oncol 46:15–23. https://doi.org/10.1016/j.ejso.2019.08.013
2. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, Cochran AJ, Cody HS 3rd, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CL, Podoloff DA, Sivasubramaniam VH, Turner RR, Wahl R, Weaver DL, Wolff AC, Winer EP (2005) American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 23:7703–7720. https://doi.org/10.1200/jco.2005.08.001
3. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE (2017) Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:561–564. https://doi.org/10.1200/jco.2016.71.0947
4. Pilewskie M, Morrow M (2017) Axillary nodal management following neoadjuvant chemotherapy: a review. JAMA Oncol 3:549–555. https://doi.org/10.1001/jamaoncol.2016.4163
5. Simons JM, van Nijnatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML (2019) Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis. Ann Surg 269:432–442. https://doi.org/10.1097/sla.0000000000003075
6. Samiei S, van Nijnatten TJA, de Munck L, Keymeulen K, Simons JM, Kooreman LFS, Siesling S, Lobbes MBI, Smidt ML (2020) Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg 271:574–580. https://doi.org/10.1097/sla.0000000000003126
7. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Kuerer HM, Bowling M, Flippo-Morton TS, Byrd DR, Ollila DW, Julian TB, McLaughlin SA, McCall L, Symmans WF, Le-Petross HT, Haffty BG, Buchholz TA, Nelson H, Hunt KK (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 310:1455–1461. https://doi.org/10.1001/jama.2013.278932
8. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, Bedrosian I, Hobbs BP, DeSnyder SM, Hwang RF, Adrada BE, Shaitelman SF, Chavez-MacGregor M, Smith BD, Candelaria RP, Babiera GV, Dogan BE, Santiago L, Hunt KK, Kuerer HM (2016) Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol 34:1072–1078. https://doi.org/10.1200/jco.2015.64.0094
9. van Nijnatten TJA, Simons JM, Smidt ML, van der Pol CC, van Diest PJ, Jager A, van Klaveren D, Kam BLR, Lobbes MBI, de Boer M, Verhoef K, Koppert LB, Luiten EJT (2017) 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. Clin Breast Cancer 17:399–402. https://doi.org/10.1016/j.clbc.2017.04.006
10. Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, van Tinteren H, Sonke GS, Rutgers EJ, Vrancken Peeters MJ (2015) Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Ann Surg 261:378–382. https://doi.org/10.1097/sla.0000000000000558
11. Koolen BB, Donker M, Straver ME, van der Noordaa MEM, Rutgers EJT, Valdes Olmos RA, Vrancken Peeters M (2017) Combined PET-CT and axillary lymph node marking with radioactive iodine seeds (MARI procedure) for tailored axillary treatment in node-positive breast cancer after neoadjuvant therapy. Br J Surg 104:1188–1196. https://doi.org/10.1002/bjs.10555
12. van der Noordaa MEM, van Duijnhoven FH, Straver ME, Groen EJ, Stokkel M, Loo CE, Elkhuizen PHM, Russell NS, Vrancken Peeters M (2018) Major reduction in axillary lymph node dissections after neoadjuvant systemic therapy for node-positive breast cancer by combining PET/CT and the MARI procedure. Ann Surg Oncol 25:1512–1520. https://doi.org/10.1245/s10434-018-6404-y
13. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M (2018) Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 36:2105–2122. https://doi.org/10.1200/jco.2018.77.8738
14. Elston CW, Ellis IO (1991) Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 19:403–410. https://doi.org/10.1111/j.1365-2559.1991.tb00229.x
15. Alderliesten T, Loo CE, Pengel KE, Rutgers EJ, Gilhuijs KG, Vrancken Peeters MJ (2011) Radioactive seed localization of breast lesions: an adequate localization method without seed migration. Breast J 17:594–601. https://doi.org/10.1111/j.1524-4741.2011.01155.x
16. Donker M, Drukker CA, Valdés Olmos RA, Rutgers EJ, Loo CE, Sonke GS, Wesseling J, Alderliesten T, Vrancken Peeters MJ (2013) Guiding breast-conserving surgery in patients after neoadjuvant systemic therapy for breast cancer: a comparison of radioactive seed localization with the ROLL technique. Ann Surg Oncol 20:2569–2575. https://doi.org/10.1245/s10434-013-2921-x
17. Straver ME, Loo CE, Alderliesten T, Rutgers EJ, Vrancken Peeters MT (2010) Marking the axilla with radioactive iodine seeds (MARI procedure) may reduce the need for axillary dissection after neoadjuvant chemotherapy for breast cancer. Br J Surg 97:1226–1231. https://doi.org/10.1002/bjs.7073
18. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, Kuroi K, Im SA, Park BW, Kim SB, Yanagita Y, Ohno S, Takao S, Aogi K, Iwata H, Jeong J, Kim A, Park KH, Sasano H, Ohashi Y, Toi M (2017) Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 376:2147–2159. https://doi.org/10.1056/NEJMoa1612645
19. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 347:567–575. https://doi.org/10.1056/NEJMoa020128
20. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Morrow M, Hunt KK (2016) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. Ann Surg 264:413–420. https://doi.org/10.1097/sla.0000000000001863

21. Morrow M, Van Zee KJ, Patil S, Petruolo O, Mamtani A, Barrio AV, Capko D, El-Tamer M, Gemignani ML, Heerdt AS, Kirstein L, Pilewskie M, Plitas G, Sacchini VS, Sclafani LM, Ho A, Cody HS (2017) Axillary dissection and nodal irradiation can be avoided for most node-positive Z0011-eligible breast cancers: a prospective validation study of 793 patients. Ann Surg 266:457–462. https://doi.org/10.1097/sla.0000000000002354
22. Ling DC, Iarrobino NA, Champ CE, Soran A, Beriwal S (2019) Regional recurrence rates with or without complete axillary dissection for breast cancer patients with node-positive disease on sentinel lymph node biopsy after neoadjuvant chemotherapy. Adv Radiat Oncol. https://doi.org/10.1016/j.adro.2019.09.006
23. Caudle AS, Yu TK, Tucker SL, Bedrosian I, Litton JK, Gonzalez-Angulo AM, Hoffman K, Meric-Bernstam F, Hunt KK, Buchholz TA, Mittendorf EA (2012) Local-regional control according to surrogate markers of breast cancer subtypes and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast conserving therapy. Breast Cancer Res 14:R83. https://doi.org/10.1186/bcr3198
24. Gillon P, Touati N, Breton-Callu C, Slaets L, Cameron D, Bonnefoi H (2017) Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: an analysis of the EORTC 10994/BIG 1–00 study. Eur J Cancer (Oxford, Engand: 1990) 79:226–234. https://doi.org/10.1016/j.ejca.2017.04.012
25. Haffty BG, McCall LM, Ballman KV, Buchholz TA, Hunt KK, Boughey JC (2019) Impact of radiation on locoregional control in women with node-positive breast cancer treated with neoadjuvant chemotherapy and axillary lymph node dissection: results from ACOSOG Z1071 clinical trial. Int J Radiat Oncol Biol Phys 105:174–182. https://doi.org/10.1016/j.ijrobp.2019.04.038
26. Jwa E, Shin KH, Kim JY, Park YH, Jung SY, Lee ES, Park IH, Lee KS, Ro J, Kim YJ, Kim TH (2016) Locoregional recurrence by biology in breast cancer patients after preoperative chemotherapy and breast conservation treatment. Cancer Res Treatment 48:1363–1372. https://doi.org/10.4143/crt.2015.456
27. Swisher SK, Vila J, Tucker SL, Bedrosian I, Shaitelman SF, Litton JK, Smith BD, Caudle AS, Kuerer HM, Mittendorf EA (2016) Locoregional control according to breast cancer subtype and response to neoadjuvant chemotherapy in breast cancer patients undergoing breast-conserving therapy. Ann Surg Oncol 23:749–756. https://doi.org/10.1245/s10434-015-4921-5
28. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, Taghian A, Wickerham DL, Wolmark N (2012) Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 30:3960–3966. https://doi.org/10.1200/JCO.2011.40.8369
29. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE Jr, Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet (London, England) 384:164–172. https://doi.org/10.1016/s0140-6736(13)62422-8
30. Fayanju OM, Ren Y, Thomas SM, Greenup RA, Plichta JK, Rosenberger LH, Tamirisa N, Force J, Boughey JC, Hyslop T, Hwang ES (2018) The clinical significance of breast-only and node-only pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT): a review of 20,000 breast cancer patients in the National Cancer Data Base (NCDB). Ann Surg 268:591–601. https://doi.org/10.1097/sla.0000000000002953
31. van Nijnatten TJ, Simons JM, Moossdorff M, de Munck L, Lobbes MB, van der Pol CC, Koppert LB, Luiten EJ, Smidt ML (2017) Prognosis of residual axillary disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated cells and micrometastases carry a better prognosis than macrometastases. Breast Cancer Res Treat 163:159–166. https://doi.org/10.1007/s10549-017-4157-0
32. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, Meterissian S, Arnaout A, Brackstone M, McCready DR, Karp SE, Trop I, Lisbona A, Wright FC, Younan RJ, Provencher L, Patocskai E, Omeroglu A, Robidoux A (2015) Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 33:258–264. https://doi.org/10.1200/jco.2014.55.7827
33. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, Lebeau A, Liedtke C, von Minckwitz G, Nekljudova V, Schmatloch S, Schrenk P, Staebler A, Untch M (2013) Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14:609–618. https://doi.org/10.1016/s1470-2045(13)70166-9
34. Siso C, de Torres J, Esgueva-Colmenarejo A, Espinosa-Bravo M, Rus N, Cordoba O, Rodriguez R, Peg V, Rubio IT (2018) Intraoperative ultrasound-guided excision of axillary clip in patients with node-positive breast cancer treated with neoadjuvant therapy (ILINA Trial): a new tool to guide the excision of the clipped node after neoadjuvant treatment. Ann Surg Oncol 25:784–791. https://doi.org/10.1245/s10434-017-6270-z
35. DiSipio T, Rye S, Newman B, Hayes S (2013) Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 14:500–515. https://doi.org/10.1016/S1470-2045(13)70076-7
36. Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, Mazzarol G, Massarut S, Zgajnar J, Taffurelli M, Littlejohn D, Knauer M, Tondini C, Di Leo A, Colleoni M, Regan MM, Coates AS, Gelber RD, Goldhirsch A (2018) Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23–01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 19:1385–1393. https://doi.org/10.1016/s1470-2045(18)30380-2
37. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. Lancet Oncol 14:297–305. https://doi.org/10.1016/s1470-2045(13)70035-4
38. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, Steccanella F, Vento AR, Intra M, Naninato P, Caldarella P, Iorfida M, Colleoni M, Viale G, Grana CM, Rotmensz N, Luini A (2016) Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol 42:361–368. https://doi.org/10.1016/j.ejso.2015.11.019
39. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569–575. https://doi.org/10.1001/jama.2011.90
40. Solá M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S (2013) Complete axillary lymph node dissection versus clinical follow-up in breast cancer

patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol 20:120–127. https://doi.org/10.1245/s10434-012-2569-y

41. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ (2014) Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 15:1303–1310. https://doi.org/10.1016/s1470-2045(14)70460-7
42. Choi HJ, Kim I, Alsharif E, Park S, Kim JM, Ryu JM, Nam SJ, Kim SW, Yu J, Lee SK, Lee JE (2018) Use of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with axillary node-positive breast cancer in diagnosis. J Breast Cancer 21:433–441. https://doi.org/10.4048/jbc.2018.21.e54
43. Schwartz GF, Tannebaum JE, Jernigan AM, Palazzo JP (2010) Axillary sentinel lymph node biopsy after neoadjuvant chemotherapy for carcinoma of the breast. Cancer 116:1243–1251. https://doi.org/10.1002/cncr.24887
44. Standard or Comprehensive Radiation Therapy in Treating Patients With Early-Stage Breast Cancer Previously Treated With Chemotherapy and Surgery (NSABP B-51/RTOG 1304 trial). ClinicalTrials.gov Identifier: NCT01872975. https://clinicaltrials.gov/ct2/show/NCT01872975.
45. Alliance for Clinical Trials in Oncology. Comparison of Axillary Lymph Node Dissection With Axillary Radiation for Patients With Node-Positive Breast Cancer Treated With Chemotherapy (ALLIANCE A011202). ClinicalTrials.gov Identifier: NCT01901094. https://clinicaltrials.gov/ct2/show/NCT01901094.
46. Morrow M, Khan AJ (2020) Locoregional management after neoadjuvant chemotherapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38:2281–2289. https://doi.org/10.1200/jco.19.02576
47. Buck AK, Herrmann K, Stargardt T, Dechow T, Krause BJ, Schreyögg J (2010) Economic evaluation of PET and PET/CT in oncology: evidence and methodologic approaches. J Nucl Med Technol 38:6–17. https://doi.org/10.2967/jnmt.108.059584
48. Chuck A, Jacobs P, Logus JW, St Hilaire D, Chmielowiec C, McEwan AJ (2005) Marginal cost of operating a positron emission tomography center in a regulatory environment. Int J Technol Assess Health Care 21:442–451. https://doi.org/10.1017/s0266462305050610
49. Berger M, Gould MK, Barnett PG (2003) The cost of positron emission tomography in six United States Veterans Affairs hospitals and two academic medical centers. AJR Am J Roentgenol 181:359–365. https://doi.org/10.2214/ajr.181.2.1810359
50. Adler LP, Faulhaber PF, Schnur KC, Al-Kasi NL, Shenk RR (1997) Axillary lymph node metastases: screening with [F-18]2-deoxy-2-fluoro-D-glucose (FDG) PET. Radiology 203:323–327. https://doi.org/10.1148/radiology.203.2.9114082
51. Miquel-Cases A, Teixeira S, Retèl V, Steuten L, Valdés Olmos R, Rutgers E, van Harten WH (2015) MD4—cost-effectiveness of 18f-Fdg Pet/Ct for screening distant metastasis in stage Ii/Iii breast cancer patients of the UK, the United States and the Netherlands. Value Health 18:A337. https://doi.org/10.1016/j.jval.2015.09.123
52. Koolen BB, Valdes Olmos RA, Elkhuizen PH, Vogel WV, Vrancken Peeters MJ, Rodenhuis S, Rutgers EJ (2012) Locoregional lymph node involvement on 18F-FDG PET/CT in breast cancer patients scheduled for neoadjuvant chemotherapy. Breast Cancer Res Treat 135:231–240. https://doi.org/10.1007/s10549-012-2179-1
53. Koolen BB, Vrancken Peeters MJ, Aukema TS, Vogel WV, Oldenburg HS, van der Hage JA, Hoefnagel CA, Stokkel MP, Loo CE, Rodenhuis S, Rutgers EJ, Valdes Olmos RA (2012) 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. Breast Cancer Res Treat 131:117–126. https://doi.org/10.1007/s10549-011-1767-9
54. Samiei S, van Nijnatten TJA, van Beek HC, Polak MPJ, Maaskant-Braat AJG, Heuts EM, van Kuijk SMJ, Schipper RJ, Lobbes MBI, Smidt ML (2019) Diagnostic performance of axillary ultrasound and standard breast MRI for differentiation between limited and advanced axillary nodal disease in clinically node-positive breast cancer patients. Sci Rep 9:17476. https://doi.org/10.1038/s41598-019-54017-0