

Iodine Seed–Marking Protocol for Response-Guided Axillary Treatment After Systemic Therapy for Node-Positive Breast Cancer

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 Editorial

 Supplemental content

IMPORTANCE Most patients with clinically node-positive (cN⁺) breast cancer receive primary systemic treatment (PST) followed by axillary lymph node dissection (ALND) and/or locoregional radiation (RT). The necessity of axillary treatment in patients achieving nodal pathologic complete response (pCR) after PST remains uncertain.

OBJECTIVE To assess oncologic outcomes of response-guided axillary treatment determined by marking the axillary lymph node with a radioactive iodine seed (MARI) in patients with cN⁺ breast cancer who experience pCR after PST.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted at a single center including patients with breast cancer with 3 or fewer axillary lymph nodes on fluorodeoxyglucose positron emission tomography–computed tomography who were treated according to the MARI protocol from July 2014 to December 2021. Patients with intramammary or periclavicular lymph node involvement were excluded. Median (IQR) follow-up was 49 (32-70) months. Data were analyzed from March to June 2025.

EXPOSURE After PST, the MARI-marked lymph node was excised. Patients with pCR of the MARI node (ypNO) received no further axillary treatment, whereas patients with residual disease (ypN⁺) received locoregional radiation therapy.

MAIN OUTCOMES AND MEASURES The primary outcome measure was axillary recurrence rate. The secondary outcome measures were 5-year invasive disease-free survival (iDFS) and overall survival (OS).

RESULTS In total, 350 patients (median [IQR] age, 49 [41-56] years) were included and analyzed; of these, 135 (39%) had ypNO and received no further axillary treatment. The remaining 215 patients with ypN⁺ (61%) received RT. After a median (IQR) follow-up of 49 (32-70) months, axillary recurrence rate was 0.7% (n = 1; 95% CI, 0.04%-4.1%) in patients with ypNO and 2.3% (n = 7; 95% CI, 1.0%-5.3%) in patients with ypN⁺. In patients with ypNO, the 5-year iDFS was 93% (95% CI, 88%-98%) and the OS was 98% (95% CI, 95%-100%); in patients with ypN⁺, iDFS was 87% (95% CI, 82%-93%) and OS, 93% (95% CI, 89%-97%).

CONCLUSIONS AND RELEVANCE This cohort study found that response-guided axillary treatment, using the MARI protocol, in patients with limited nodal disease who received PST was associated with a very low risk of axillary recurrence and should be considered to protect patients from axillary overtreatment.

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Currently, patients with node-positive (cN⁺) breast cancer, especially patients with triple-negative (TN) or *ERBB2*-positive (*ERBB2*⁺) breast cancer, are often treated with primary systemic therapy (PST). The proportion of patients achieving a nodal pathologic complete response (pCR) after PST has increased. In patients with estrogen receptor-positive (ER⁺) and *ERBB2*-negative (*ERBB2*⁻) breast cancer, nodal pCR rates range from 13% to 35%. Higher rates between 45% to 80% have been reported in patients with TN and *ERBB2*⁺ breast cancer.¹⁻⁶ Nodal pCR is associated with improved survival, especially when breast pCR is achieved as well.⁷⁻¹⁰ Given that it is questionable whether patients with a nodal pCR actually benefit from axillary lymph node dissection (ALND), several less invasive techniques have been investigated to restage the axilla after PST.¹¹ One such technique is the sentinel lymph node procedure; another is the MARI (marking the axillary lymph node with a radioactive iodine seed) protocol in which 1 node is marked with an iodine seed before PST and then selectively removed after PST¹²; and yet another is the targeted axillary dissection (TAD), which combines the sentinel lymph node procedure with removal of a marked node.¹³ All techniques show a low false negative rate (FNR) (3%-14%) for missing residual nodal disease.¹¹ Although there is currently no consensus on the optimal staging technique for patients with cN1 after PST, evidence supporting the omission of ALND in patients achieving nodal pCR is growing. Some retrospective cohort studies report low axillary recurrence rates between 0% and 2.8% when ALND was omitted in patients with a pCR of the sentinel lymph node biopsy.¹⁴⁻²⁰ Although more than 50 studies have been published describing different techniques of TAD,²¹ data on long-term oncologic outcome of these techniques are scarce. Only 4 small studies reported between 0% and 2.8% axillary recurrence rates after 3-year follow-up.²²⁻²⁵

In patients with low axillary burden treated with primary surgery, adjuvant radiation therapy (RT) after sentinel lymph node biopsy provides comparable local control and no difference in 10-year overall and disease-free survival (DFS) compared to ALND, despite many patients having macrometastases of the sentinel node.^{26,27} While waiting for the results of randomized clinical trials comparing ALND with adjuvant radiation treatment in patients with residual disease after PST,^{28,29} ALND remains the standard of care.

In the MARI protocol, axillary staging before PST is performed with fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) and 1 of the positive axillary nodes is marked with an iodine seed. The intent of the MARI protocol is to tailor axillary treatment according to the patient's response and to omit axillary treatment for those who experience axillary pCR after primary systemic treatment. We hypothesized that tailoring axillary treatment would not be associated with impaired oncologic outcome. Axillary staging after PST is based on the pathologic findings of the marked node (hereafter, the MARI node).³⁰ Previously, we reported on the identification rate (97%), FNR (7%), and feasibility of the MARI protocol.¹² The objective of this study was to report the axillary recurrence rate, invasive DFS (iDFS), and overall survival (OS) of

Key Points

Question Is it safe to omit axillary treatment in patients with breast cancer and limited axillary nodal disease who experienced nodal pathologic complete response (pCR) after primary systemic treatment (PST)?

Findings This cohort study of 350 patients with node-positive breast cancer undergoing PST using the MARI (marking the axillary lymph node with a radioactive iodine seed) protocol found that after 49 months of follow-up, the 135 patients (39%) who experienced pCR and no further axillary treatment had an axillary recurrence rate of 0.7% (95% CI, 0.04%-4.1%) with excellent 5-year survival data.

Meaning These findings suggest that response-guided axillary treatment based on the MARI protocol for patients with limited nodal disease was associated with a very low risk of axillary recurrence and should be considered in patients with node-positive breast cancer who experienced nodal pCR after PST.

response-guided axillary treatment using MARI protocol, which omits ALND for patients with a pCR of the MARI node.

Methods

The institutional review board of the Netherlands Cancer Institute-Antoni van Leeuwenhoek reviewed and approved the study; institutional informed consent was obtained.

Study Design and Participants

This was a prospective single-arm cohort study including patients with cN⁺ (1-3 positive nodes) treated according to the MARI protocol at the Netherlands Cancer Institute-Antoni van Leeuwenhoek from July 2014 to December 2021. We assessed the axillary recurrence rate, iDFS, and OS of response-guided axillary treatment according to the MARI protocol, which omits ALND for patients treated with PST who experienced a pCR of the MARI node (ypNO). Patients with residual disease (ypN⁺) of the MARI node underwent RT. Exclusion criteria were stage cT4d primary tumor, intramammary or periclavicular lymph node involvement, or metastatic disease; no FDG-PET/CT results before PST; axillary lymph nodes that were not FDG-avid; nonidentification of the MARI node at surgery; neoadjuvant hormonal therapy only; and undergoing combined sentinel node and MARI procedures.

Clinical (Axillary) Staging

Size and extent of the primary tumor was assessed by mammography, ultrasonography, and dynamic contrast enhanced magnetic resonance imaging (MRI). FDG-PET/CT was used for regional lymph node staging and detection of distant metastases. Axillary nodal stage was based on the number of FDG-positive axillary lymph nodes. To confirm presence of axillary nodal disease, a fine-needle aspiration or core-needle biopsy procedure was performed.

Table 1. Baseline Characteristics of Study Population With Node-Positive Breast Cancer

Characteristic	Patients by response group, No. (%)		
	Total	ypNO	ypN ⁺
Patients	350 (100)	135 (39)	215 (61)
Age, median (IQR), y	49 (41-56)	48 (39-56)	49 (43-55)
Tumor size index lesion, median (IQR), mm	30 (21-49)	30 (23-50)	31 (21-48)
Clinical tumor stage			
0	3 (1)	3 (2)	0
1	62 (18)	21 (16)	41 (19)
2	193 (55)	77 (57)	116 (54)
3	85 (24)	32 (24)	53 (25)
4	4 (1)	0 (0)	4 (2)
In situ	3 (1)	2 (2)	1 (1)
Axillary lymph nodes by FDG-PET/CT category			
1	187 (53)	70 (52)	117 (54)
2	101 (29)	40 (30)	61 (28)
3	62 (18)	25 (19)	37 (17)
Histologic findings			
NST	308 (88)	128 (95)	180 (84)
ILC	40 (11)	6 (4)	34 (16)
Other ^a	2 (1)	1 (1)	1 (1)
Subtype			
HR ⁺ /ERBB2 ⁻	188 (54)	21 (16)	176 (78)
HR ⁺ /ERBB2 ⁺	57 (16)	36 (27)	21 (10)
HR ⁻ /ERBB2 ⁺	39 (11)	37 (27)	2 (1)
Triple negative	66 (19)	41 (30)	25 (12)

Abbreviations: FDG-PET/CT, fluorodeoxyglucose positron emission tomography–computed tomography; HR, hormone receptor; ILC, invasive lobular carcinoma; MARI, marking the axillary lymph node with a radioactive iodine seed protocol; NST, no special type; ypNO, pathologic complete response of the MARI node; ypN⁺, residual disease of the MARI-node.

^a One patient with ductal carcinoma in situ of the breast (ypN⁺) and 1 patient with mucinous carcinoma (ypNO).

Primary Systemic Treatment

All study patients received PST. Patients with HR⁺/ERBB2⁻ breast cancer received 4 cycles of biweekly dose-dense doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) followed by 12 weeks of once weekly paclitaxel (80 mg/m²). Patients with ERBB2⁺ disease were treated with up to 9 cycles of paclitaxel (80 mg/m²), carboplatin (area under the curve, 6), and trastuzumab (6 mg/kg) plus pertuzumab (420 mg). Patients with TN breast cancer received 4 cycles of biweekly dose-dense doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) followed by 12 weeks of once weekly paclitaxel (80 mg/m²) and concurrent carboplatin (area under the curve, 5) every 3 weeks.

MARI Procedure and Response-Guided Axillary Treatment

The MARI protocol and safety procedures have been described in detail elsewhere.^{12,30} Briefly, ultrasonography is used to mark the largest pathologically proven axillary lymph node with a radioactive iodine seed before beginning PST. This marked node is further referred to as the *MARI node*. After PST and during breast surgery, a γ probe is used

to locate the iodine seed for resection of the MARI node. The MARI node is formalin-fixed overnight and followed by hematoxylin and eosin and cytokeratin staining evaluations at a single level. Axillary pCR is defined as the absence of vital tumor cells in the removed axillary node(s) (ypNO). Breast pCR is defined as ypT0.

All study patients treated with breast conserving surgery received RT of the breast. In case of ypNO of the MARI node, patients receive no further axillary treatment. Patients with ypN⁺ were treated with RT, which included the breast (after breast conserving surgery) or chest wall (after mastectomy) and the axillary levels I, II, III, and IV (supraclavicular fossa) and the interpectoral nodes.³¹ We followed the 2015 European Society for Radiotherapy and Oncology consensus guidelines.³¹ Prescribed doses were either 42.56 Gy (16 fractions of 2.66 Gy) to the breast or chest wall and the axillary nodes. If a simultaneous boost was given to the tumor bed in the breast, the rest of the breast and the axilla were treated to 46.20 Gy (21 fractions of 2.20 Gy). If the axilla was irradiated, the target volume included all axillary levels, the interpectoral nodes, and the supraclavicular fossa. Static field intensity modulated radiotherapy or volumetric modulated arc therapy planning was used to irradiate, and the deep inspiration breath hold technique was used for all left-sided breast tumors to minimize cardiac exposure.

Adjuvant Systemic Treatment

According to institutional guidelines, hormonal therapy was administered to all patients with HR⁺ breast cancer. Patients with ERBB2⁺ disease received a total of 12 months of trastuzumab. Following the results of the KATHERINE trial³² and the CREATE X trial³³, beginning in 2019, patients with residual ERBB2⁺ disease were treated with adjuvant trastuzumab emtansine, and beginning in 2017, adjuvant capecitabine was given to patients with TN residual disease.

Primary and Secondary Outcomes

The primary outcome measure was axillary recurrence rate, defined as the percentage of patients with an ipsilateral axillary lymph node recurrence. Secondary outcome measures were local, regional, and distant recurrence rate. iDFS (ie, axillary, local and/or regional recurrence; ipsilateral, contralateral, or distant metastases) and OS (ie, death from any cause) were calculated from date of surgery to date of death.³⁴ Patients were followed up from date of surgery until the data cut-off (October 2023) or their last documented visit before this date. Patients with shorter follow-up due to later inclusion were subject to noninformative censoring, which was accounted for in the survival analysis.

Statistical Analysis

Kaplan-Meier analyses were used to estimate survival and are reported with 95% CIs. Logistic regression analysis was performed to assess associated factors. Variables included were selected based on clinical relevance. Results are reported as odds ratio (OR) with 95% CIs. Tests were 2-tailed and a *P* value <.05 was considered statistically significant. No correction for multiple testing was applied. All calculations were performed

Table 2. Surgical Outcome and MARI Protocol Pathology Results, By Response Group

Variable	Patients by response group, No. (%)		
	Total	ypNO	ypN ⁺
Patients	350 (100)	135 (39)	215 (61)
Surgery ^a			
Breast-conserving surgery	226 (65)	94 (70)	132 (61)
Mastectomy	122 (35)	39 (30)	83 (39)
Clinical tumor stage ^a			
0	105 (30)	82 (61)	23 (11)
1	147 (42)	28 (21)	119 (55)
2	56 (16)	3 (2)	53 (25)
3	15 (4)	3 (2)	12 (6)
4	1 (<1)	0	1 (1)
In situ	24 (7)	17 (13)	7 (3)
MARI node pathology result			
pCR	135 (48)	135 (100)	
Macrometastases	167 (39)	0	167 (78)
Micrometastases	30 (9)	0	30 (14)
Isolated tumor cells	18 (5)	0	18 (8)
Removed lymph node, No. (MARI procedure)	1 (1-2)	1 (1-2)	1 (1-2)
Positive lymph node, No.	0 (0-1)	0	1 (1-1)
Adjuvant therapy			
Endocrine	242 (69)	55 (41)	187 (87)
Chemotherapy	42 (12)	6 (4)	36 (17)
Targeted therapy	99 (28)	73 (54)	26 (12)
Follow-up, median (IQR), mo	48 (32-70)	49 (32-70)	48 (32-69)

Abbreviations: MARI, marking the axillary lymph node with a radioactive iodine seed protocol; MARI node, the axillary lymph node marked with a radioactive iodine seed; pCR, pathologic complete response; ypNO, pathologic complete response of the MARI node; ypN⁺, residual disease of the MARI node.

^a No breast surgery was performed in 2 patients with occult breast cancer.

from March to June 2024 using SPSS Statistics, version 25.0 (IBM Corp).

Results

The analysis included 350 patients with breast cancer and 1 to 3 involved axillary lymph nodes on FDG-PET/CT scan and were registered between July 2014 and December 2021. The median (IQR) age was 49 (41-56) years; additional baseline characteristics are presented in Table 1. Of the 350 patients, 135 (39%) had a pCR of the MARI node (ypNO) and 215 (61%) had residual disease in the MARI node (ypN⁺). More specifically, 6 of 40 patients (15%) with lobular carcinoma achieved ypNO vs 128 of 308 patients (42%) with no special type breast cancer; 21 of 188 patients (11%) with HR⁺/ERBB2⁻ subtype; 36 of 57 patients (63%) with HR⁺/ERBB2⁺ subtype; 37 of 39 patients (95%) with HR⁻/ERBB2⁺ subtype; and 41 of 66 patients (62%) with TN breast cancer achieved ypNO.

Locoregional and Adjuvant Systemic Treatment

Most patients were treated with breast-conserving surgery (65%; n = 226). A median (IQR) of 1 (1-2) lymph node was removed during the MARI procedure (Table 2). Patients with

Table 3. Site of Breast Cancer Recurrence, by Response Group per MARI Node Results

Site	Response group, No.		Total
	ypNO (n = 135)	ypN ⁺ (n = 215)	
Axillary and local	0	0	0
Axillary and distant	1	5	6
Local	6	2	8
Local and distant	1	0	0
Regional ^a and distant	0	2	2
Distant	2	16	18
Total	10	25	34

Abbreviations: MARI node, the axillary lymph node marked with a radioactive iodine seed; ypNO, pathologic complete response of the MARI node; ypN⁺, residual disease of the MARI node.

^a Regional recurrence included periclavicular and/or intramammary nodes.

ypNO (n = 135) underwent no further axillary treatment, while those with ypN⁺ (n = 215) received locoregional RT.

Of the 135 patients with ypNO, 82 (61%) also had a pCR of the breast. Of the 215 patients with ypNO, 34 (16%) that had invasive residual breast disease, adjuvant systemic treatment was applied according to subtype. Only 23 patients with ypN⁺ (11%) had a pCR of the breast.

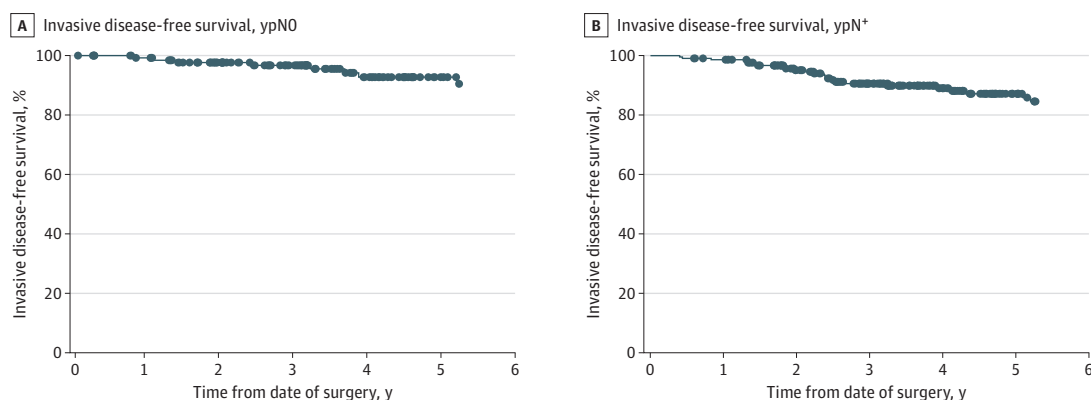
Of patients with ypN⁺, 167 (78%) had a macrometastasis of the MARI node, 30 (14%) had a micrometastasis and 18 (8%) had isolated tumor cells. All patients with ypN⁺ patients received adjuvant systemic treatment according to the subtype unless patients preferred differently (4%; n = 9).

Recurrence Rate

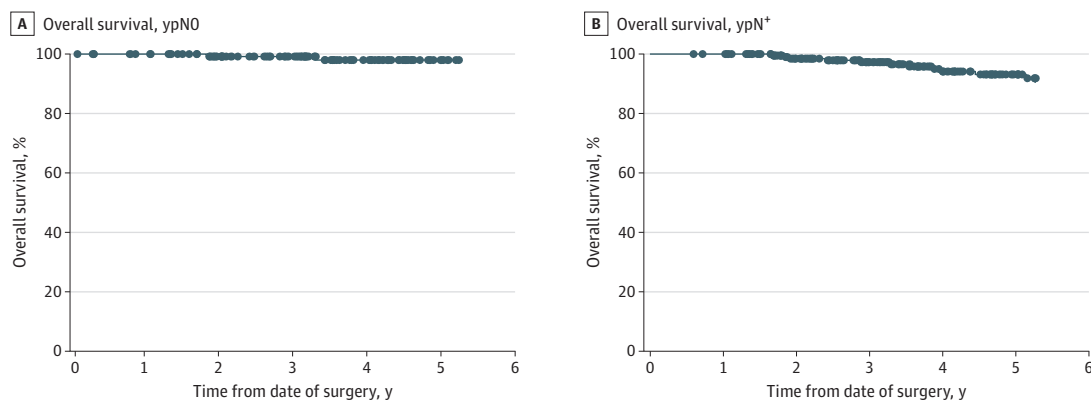
After a median (IQR) follow-up of 49 (32-70) months, axillary recurrence rate in the ypNO group was 0.7% (n = 1; 95% CI, 0.04%-4.1%). This patient had TN breast cancer, was treated with breast conserving surgery followed by whole breast irradiation, and developed an axillary recurrence with concurrent level V cervical lymph node metastases. We administered induction chemotherapy followed by axillary lymph node dissection, extended locoregional radiation, and hyperthermia. After subsequent development of distant metastases, palliative chemotherapy was started. The annual axillary recurrence rate per person in the ypNO group was 0.2%.

Axillary recurrence rate in the ypN⁺ group was 2.3% (n = 5; 95% CI, 1.0%-5.3%): 3 patients had ER⁺/ERBB2⁻ breast cancer and 2 patients had TN breast cancer. Three patients had breast conserving surgery followed by locoregional irradiation including boost (2 with ER⁺/ERBB2⁻ and 1 with TN breast cancer) and 2 patients had mastectomy and locoregional irradiation. All 5 patients had concurrent distant metastases and received palliative therapy (Table 2). Axillary recurrence rate per person per year in the ypN⁺ group was 0.5%.

Overall recurrence rate (local, regional, and distant metastases) was 7.4% (n = 10; 95% CI, 3.6%-13.2%) in patients with ypNO, and 11.6% (n = 25; 95% CI, 8.0%-16.6%) in patients with ypN⁺ (Table 3). In the ypN⁺ group (n = 215) invasive lobular carcinoma was associated with higher risk of any recurrence (OR, 2.95; 95% CI, 1.16-7.53; P = 0.02) as shown by univariate analysis in eTable 1 in Supplement 1. No significant association was

Figure 1. Five-Year Invasive Disease-Free Survival in Patients With ypN0 and ypN⁺ Breast Cancer

MARI node indicates the axillary lymph node marked with a radioactive iodine seed; ypN0, pathologic complete response of the MARI node; ypN⁺, residual disease of the MARI node.

Figure 2. Overall Survival in Patients With ypN0 and ypN⁺ Breast Cancer

MARI node indicates the axillary lymph node marked with a radioactive iodine seed; ypN0, pathologic complete response of the MARI node; ypN⁺, residual disease of the MARI node.

found between subtype and disease recurrence. eTable 2 in Supplement 1 shows characteristics of patients with a local or regional recurrence.

Overall Survival

Median (IQR) follow-up was 49 (32-70) months. Estimated 5-year iDFS (Figure 1A and B) was 93% (95% CI, 88%-98%) in ypN0 and 87% (95% CI, 82%-93%) in patients with ypN⁺. Estimated 5-year OS is shown in Figure 2A and B. Three patients in the ypN0 group died of breast cancer, resulting in an OS rate of 98% (95% CI, 95%-100%). In the ypN⁺ group, 15 patients died, 12 of breast cancer, resulting in an OS rate of 93% (95% CI, 89%-97%) (eTable 3 in Supplement 1).

Discussion

To our knowledge, this is the first prospective study on response-guided axillary treatment after PST with omission of any axillary treatment for patients with cN1 breast cancer

achieving axillary pCR and omission of ALND in patients with residual nodal disease. After a median follow-up of 49 months, axillary recurrence rate was 0.7%; 5-year iDFS, 93.0%; and OS, 98.0% in ypN0 patients. Patients with residual axillary disease after PST underwent axillary radiation with axillary recurrence rate of 2.3%, iDFS of 82.0%, and OS of 93.0%.

The extreme low axillary recurrence rate of patients with ypN0 reported in this cohort is comparable with the literature. The FNR of the MARI node is 7.0%,¹² which is higher than the FNR of TAD (2.4%) but lower than the FNR of the sentinel lymph node biopsy (8.0%-14.0%).¹¹ However, lowering the FNR seems less important considering the results of Montagna et al.²⁵ In their recent multicenter retrospective analysis of 1144 patients with cN⁺ treated with PST between 2013 and 2020 and achieving nodal pCR (assessed with sentinel lymph node biopsy or TAD) axillary recurrence rates of 0.7% and 1.0% after respectively 3- and 5-year follow-up were reported.²⁵ Notably, 81% of these patients received nodal RT.²⁵ Other retrospective single center studies including patients with cN⁺ achieving nodal pCR

reported axillary recurrence rates varying from 0% to 1.6% after 5 years.^{14-16,19}

Data on axillary recurrence rates in patients with cN⁺ with ypN⁺ after PST treated with RT only are scarce. Four retrospective studies^{16,19,35,36} with sample sizes varying from 9 to 103 patients reported recurrence rates between 0% and 22.0%. A recent Dutch population-based study³⁷ with more than 18 000 patients, of whom 11 878 patients had cN⁺ disease with or without nodal pCR after PST reported the following OS data: in patients with cN1 and ypN0, 5-year OS was 91.2% (95% CI, 90.2%-92.1%), whereas 5-year OS was 79.8% (95% CI, 78.7%-80.8%) in patients with ypN⁺³⁷—lower than the 5-year OS data reported in our cohort (98% [95% CI, 95%-100%] and 93% [95% CI, 89%-97%]).

In the present study, the MARI protocol was used for response-guided axillary treatment. This protocol is based on axillary staging before PST with FDG-PET/CT scan combined with the axillary response to PST defined by the pathologic response in the MARI node.³⁰ One retrospective study³⁸ reported on the oncologic outcome of patients with cN⁺ treated with PST followed by axillary staging with TAD with a similar approach to axillary treatment. Patients with ypN0 received no further axillary treatment (n = 40) and locoregional radiation was given to patients with residual nodal disease (n = 153). After a median follow-up of 2.8 years, none of the patients achieving pCR developed an axillary recurrence. In patients treated with axillary RT, 5 axillary recurrences were reported, resulting in an axillary recurrence rate of 3.3%.³⁸

A phase 2 randomized clinical trial³⁹ evaluated the benefit of additional regional RT in 1556 patients with cN1 converted to ypN0 after PST, randomized between regional RT and no regional RT after sentinel lymph node biopsy and/or ALND (45%). Its results showed similar 5-year invasive breast cancer recurrence-free interval (regional RT, 92.7% vs no regional RT, 91.8%; hazard ratio [HR], 0.88; 95% CI, 0.60-1.29; *P* = .51). This supports the approach of no further axillary treatment in patients who achieve pCR.

Brooks et al⁴⁰ recently reported on recurrence rates and survival in patients with cN⁺ breast cancer and ypN⁺ disease after PST and ALND (n = 401) or sentinel lymph node biopsy (n = 19). All patients received regional nodal RT, and no significant differences were reported for local, distant, or any recurrence, DFS and OS. Although these are small numbers, they support the hypothesis that RT is sufficient to control limited residual nodal disease.

In our study's ypN⁺ group, a relatively high breast cancer recurrence was observed in patients with lobular carcinoma. The association with lobular carcinoma may be explained by possible underestimation of the nodal involvement in patients with lobular carcinoma.⁴¹ In future studies, fluorine-18 fluoroestradiol (¹⁸F-FES) PET/CT could be performed in patients

with lobular carcinoma given that ¹⁸F-FES-PET/CT shows more accurate identification of metastases than FDG-PET/CT.⁴²

It is noteworthy that in HR⁺/ERBB2⁻ breast cancer, ALND is currently being used to determine whether adjuvant cyclin-dependent kinase 4 inhibitor is indicated. A recent post hoc analysis of the SENOMAC trial⁴³ revealed a high risk of ALND associated morbidity, with only a limited survival benefit from adjuvant abemaciclib. Therefore, it is highly debatable whether an invasive surgical procedure such as ALND should be performed solely as a staging method.

Omission of ALND in patients with cN1 treated with PST is also being investigated in the OPBC3-TAXIS trial.⁴⁴ The AXSANA trial⁴⁵ will provide clarity on oncological outcomes of different axillary staging techniques in ypN0 patients after PST. The ALLIANCE A011202 trial⁴⁶ randomizing patients with cN1 between ALND and locoregional RT will further guide clinical practice.

Limitations

Limitations of our study are mainly its single-arm design, and an inclusion bias cannot be completely prevented. Improved systemic therapies may have contributed to our favorable outcomes when compared with previously reported survival and recurrence rates. Given that patients in this cohort were included from 2014 to 2021, comparison with results from the abovementioned Dutch study,³⁷ including patients diagnosed between 2005 to 2019 seems reliable. Another limitation is the use of radioactive iodine seeds. Although these are increasingly used for tumor localization, it requires strict regulation. Alternative localization techniques include the magnetic seed.²¹

Lastly, PET/CT scans are not yet implemented in every center; however, they are currently internationally recognized⁴⁷ for initial staging. Although the prognostic value of cN status is likely to be less than that of ypN status, cN status remains an important prognostic factor for recurrence and survival.⁴⁸⁻⁵¹ When ALND or ALND and RT are omitted after PST, it is crucial to use the most reliable staging technique before PST. With improvements of (PET) MRI imaging techniques,^{52,53} it is to be expected that MRI may replace FDG-PET.

Conclusions

This cohort study showed that omission of ALND in patients with cN1 breast cancer who underwent PST is safe. Omission of ALND and RT altogether in patients with ypN0, as assessed with the MARI procedure, was associated with low axillary recurrence rate and an excellent 5-year OS. Therefore, response-guided axillary treatment should be considered to protect patients from axillary overtreatment.

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Author Contributions: Dr van Hemert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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