Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer

A Systematic Review and Meta-analysis

Janine M. Simons, MD,*† Thiemo J. A. van Nijmatten, MD, PhD,‡ Carmen C. van der Pol, MD,§ Ernest J. T. Luiten, MD, PhD,¶ Linetta B. Koppert, MD, PhD,* and Marjolein L. Smidt, MD, PhD¶¶

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.

Keywords: axillary staging, breast cancer, iodine seed, neoadjuvant systemic therapy, node-positive, sentinel lymph node biopsy

From the *Erasmus Medical Center Rotterdam, Surgical Oncology, Rotterdam, the Netherlands; †University Medical Center Utrecht, Surgical Oncology, Utrecht, the Netherlands; ‡Maastricht University Medical Center+, Radiology and Nuclear Medicine, Maastricht, the Netherlands; §Altnie Hospital, Surgical Oncology, Leiden, the Netherlands; ¶Amphia Hospital, Surgical Oncology, Breda, the Netherlands; ¶¶Maastricht University Medical Center+, Surgical Oncology, Maastricht, the Netherlands; and *Erasmus Medical Center Rotterdam, Surgical Oncology, Rotterdam, the Netherlands.

Reprints: Janine M. Simons, MD, Department of Surgical Oncology, Erasmus Medical Center, Postbus 5201, 3008 AE Rotterdam, the Netherlands.

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

DOI: 10.1097/SLA.0000000000003075

Meta-Analysis

DIAGNOSTIC ACCURACY OF DIFFERENT SURGICAL PROCEDURES FOR AXILLARY STAGING AFTER NEOADJUVANT SYSTEMIC THERAPY IN NODE-POSITIVE BREAST CANCER

The aim of this review is to provide an overview of different less invasive procedures for axillary staging after NST in 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 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 inclusion.
considered for analysis. In case only part of the study population consisted of patients with pathologic confirmed nodal positivity, only the pathologically confirmed cN0 patients were considered for analysis. When it was not possible to discriminate between cN0 and cN1 patients or patients both 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 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 I²-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 Fig. 1 for a flow chart 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 1 for general characteristics of all studies included for qualitative analysis.

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,4 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 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 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

© 2018 The Author(s). Published by Wolters Kluwer Health, Inc.
The overall prevalence of ax-pCR in all 20 included studies was 37% (see Appendix 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 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 Fig. 3) and NPV ranged from 57% to 86% (see Table 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 ypNO and 17% when ax-pCR was defined as ypNO/itc+ ($P = 0.61$, 1 study defined ax-pCR as ypNO/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 ($P = 0.53$). 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 ($P = 0.14$).

**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 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 3 (Combination) shows values for FNR and NPV for the 2 combination procedures. As only

TABLE 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       | ypn0/itc+        | Yes, if H&E negative |
| Boughay      | 2013                | P, M       | SLNB       | ALND           | 637         | N1-2     | Any       | ypn0/itc+        | No  |
| Brown        | 2014                | R, S       | SLNB       | ALND           | 86          | N1-3     | Any       | ypn0/itc+        | No  |
| Carrera      | 2016                | P, M       | SLNB       | ALND           | 48          | N1-2     | ycN0 (MRI +/- US) | NR  | Yes, always   |
| Enokido      | 2016                | P, M       | SLNB       | ALND           | 130         | N1       | ycN0 (imaging) | ypn0 | 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     | ycN0 (PE +/-US) | ypn0/itc+ | No            |
| Ozmen        | 2010                | R, S       | SLNB       | ALND           | 71          | N1-2     | ycN0 (PE and imaging) | ypn0 | Yes, if H&E negative |
| Park         | 2013                | R, S       | SLNB       | ALND           | 169         | N1-3     | Any       | ypn0/itc+        | Yes, but not routinely |
| Pineroso     | 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+       | ycN0 (PE) | NR               | Yes, always   |
| Yagata       | 2013                | P, S       | SLNB       | ALND           | 81          | N1-3     | ycN0 (MRI; including rPR) | ypn0 | Yes, if H&E negative |
| Yu           | 2016                | R, S       | SLNB       | ALND           | 46          | N+       | ycN0 (PE) | ypn0/itc+//mi+   | Yes, always |
| Zetterlund   | 2017                | P, M       | SLNB       | ALND           | 152         | N1       | Any       | ypn0             | Yes, but not routinely |
| Donker       | 2015                | P, S       | ML         | ALND           | 95          | N1-3     | Any       | ypn0             | Yes, but not routinely |
| Caudle       | 2016                | R, S       | Combi      | ALND           | 85          | N1-3     | Any       | ypn0             | Yes, but not routinely |
| Dashevsky    | 2017                | R, S       | Combi      | NA             | 21          | N1-2     | Any       | ypn0/itc+        | No  |
| Diego        | 2016                | R, S       | Combi      | NA             | 29          | N1       | ycN0 (PE) | ypn0             | Yes, but not routinely |
| Kim          | 2017                | P, S       | Combi      | NA             | 11          | N1-2     | Any       | ypn0/itc+        | No  |
| Nguyen       | 2017                | R, S       | Combi      | NA             | 20          | N1-3     | Any       | NR               | NR  |
| Park         | 2017                | P, S       | Combi      | NA             | 20          | N1-3     | Any       | ypn0/itc+        | No  |
| Plecha       | 2017                | R, S       | Combi      | NA             | 19          | N1-3     | Any       | NR               | NR  |
| Siso         | 2017                | P, S       | Combi      | ALND           | 35          | N1-3     | Any       | ypn0             | Yes, always   |
| Taback       | 2018                | P, S       | Combi      | NA             | 19          | N1-2     | Any       | ypn0             | NR  |

Combi indicates combination procedure; H&E, hematoxylin and eosin stain; IHC, immunohistochemistry; M, multicenter; NA, not applicable; NR, not reported; P, prospective; PE, psychical examination; R, retrospective; rPR, radiologic partial response; S, single-center.

Number of patients in whom the less invasive axillary staging procedure was successful and in whom this procedure was followed by cALND (if applicable).

TABLE 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                             | NA               | Wire         | Tc + blue | 100.0       | XR                     | NR                          | 0.0      | 33.3      |
| Diego         | 29          | Clip                             | NA                             | Iodine seed      | Wire         | Tc + blue | 100.0       | 91.0     | XR                     | 4 (1–11) | 23.3      | 63.0      |
| Kim           | 11          | Clip                             | NA                             | Iodine seed      | Wire         | Tc + blue | 100.0       | NR               | XR/ palpation             | 45.5     | 36.4      |
| Nguyen        | 20          | NA                               | Clip                           | Iodine seed      | Wire         | Tc + or/ blue | 100.0 | NR               | XR                     | NR                          | NR       | NR        |
| Park          | 20          | NA                               | Charcoal                       | NA               | Wire         | Tc + or/ blue | 100.0 | 75.0   | NA                     | 3 (1–12) | 60.0      | 50.0      |
| Plecha        | 19          | Clip                             | NA                             | Clip/Iodine Seed | Wire         | Tc ± blue | 100.0       | 100.0 | XR/PA            | 5.7 (mean) | NR       | NR        |
| Simons (data submitted) | 139 | NA     | Clip/Iodine Seed | Wire | Tc ± blue | 99.3 | 64.6 | XR/PA | 2 (1–9) | 22.3      | 36.0      |
| Taback        | 19 (78.9%)  | Clip                             | Electromagnetic Reflector      | NA               | Tc + blue | 100.0 | 63.2       | XR | 4 (2–10) | 31.6      | 31.6      |

NA indicates not applicable; NR, not reported (a pathologic assessment); TC, technetium; XR, specimen radiography.

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.

Number of lymph nodes of the combination procedure and not the number of lymph nodes of either ML or either SLNB.
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       | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Boughhey      | ?             | ?          | ☺               | ?             | ☺             | ?          | ?               |
| Brown         | ☺            | ☺          | ?               | ?             | ?             | ☺          | ☺               |
| Carrera       | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Enokido       | ☺            | ☺          | ☺               | ?             | ☺             | ?          | ?               |
| Ge            | ?             | ?          | ☺               | ?             | ?             | ☺          | ☺               |
| Kang          | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Kuehn         | ☺            | ☺          | ☺               | ?             | ☺             | ?          | ?               |
| Ozmen         | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Park          | ?             | ?          | ☺               | ?             | ?             | ☺          | ☺               |
| Pinero-Madrona| ☺            | ?          | ☺               | ?             | ?             | ☺          | ☺               |
| Shen          | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Thomas        | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Yagata        | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |
| Yu            | ?             | ?          | ☺               | ?             | ?             | ☺          | ☺               |
| Zetterlund    | ☺            | ☺          | ☺               | ?             | ?             | ☺          | ☺               |

Donker

Caudle

Siso

A ☺Low Risk ☺High Risk ☺Unclear Risk

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        | ☺            | ☺          | ☺               | ☺             | ☺             | ☺          | ☺               |

B ☺Low Risk ☺High Risk ☺Unclear Risk

FIGURE 2. Assessment of risk of bias.
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.43 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 \( \geq 3 \) lymph nodes was associated with a significantly better FNR in our meta-analysis (8% vs 22%, \( P < 0.0001 \)). However, removing \( \geq 3 \) SLNs is not achievable in a significant number of patients47 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.43 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.44,45 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 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.46

![Image of a page from a document](https://www.annalsofsurgery.com)

### TABLE 3. Overall and Diagnostic Accuracy Sorted by Type of Procedure

| SLNB | **Identification Rate** | **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 (10–1) | 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 | 30 | 0 | 6 | 12 | 19 (7–37) | 67 (41–87) |
| Kang | 88.9 | Tc and/or blue | 2.8 (mean) (1–8) | 28.8 | 34 | 0 | 7 | 17 | 17 (7–32) | 71 (49–87) |
| Kuehn | 92.6 | 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 (58–84) |
| 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) |

**ML**

| Author | IFR % | Pre-NST Marker | Post-NST 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) |

**Combination**

| Author | IFR % | Sampling | ML or SLNB | Pre-NST Marker | Post-NST Marker | N Lymph Nodes | Ax-pCR % | ML or SLNB % | 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) |

**Notes:**
- NA indicates not applicable; NR, not reported; Tc, technetium.
- Ax-pCR rate based on 2 × 2 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). Eighty-five patients actually underwent TAD followed by cALND.

438 | www.annalsofsurgery.com
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 \(^{33,34,37}\) and primary marking with an iodine seed, clip, charcoal, or electromagnetic reflector. \(^{36,38}\) Also, the time of marking the lymph node post-NST differs: either immediately at time of FNAC/CNB, \(^{7,33,34,37}\) or 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 identifying 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 radiation therapy. \(^{39,42}\)

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 micrometastases 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. \(^{36}\) These results have yet to be confirmed in trials where patients with ypN0 and ITCs or micrometastases 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 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.

ACKNOWLEDGMENTS

We thank the following individuals for assistance with search strategies and statistical analysis: P.H. Wiersma and F.P. Weijdema, health science librarians, Utrecht University Library. J.B. Reitsma, clinical epidemiologist, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. R.J.P.M. Scholten, professor of clinical epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.

REFERENCES

1. van Bommel AC, Sprook PE, Francken Peeters MT, et al. Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: the National NABON Breast Cancer Audit. J Surg Oncol. 2017;115:243–249.
2. Vugts G, Maaskant-Braat AJ, Nieuwenhuijzen GA, et al. Patterns of care in the administration of neo-adjuvant chemotherapy for breast cancer. A population-based study. Breast J. 2016;22:316–321.
3. DICA. Annual Report of the NABON Breast Cancer Audit 2016 - Dutch Institute for Clinical Auditing. Available at: https://dica.nl/jaarrapportage-2016/nbca. Accessed May 1, 2018.
4. Caudle AS, Bedrośian I, Milton DR, et al. Use of sentinel lymph node dissection after neoadjuvant chemotherapy in patients with node-positive breast cancer at diagnosis: practice patterns of American Society of Breast Surgeons Members. Ann Surg Oncol. 2017;24:2925–2934.
5. Vugts G, Maaskant-Braat AJ, de Roos WK, et al. Management of the axilla after neoadjuvant chemotherapy for clinically node-positive breast cancer: a nationwide survey study in The Netherlands. Eur J Surg Oncol. 2016;42:956–964.
6. Caudle AS, Yang WT, Krishnamurthy S, et al. 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. 2016;34:1072–1078.
7. Diego EJ, McAuliffe PF, Soran A, et al. Axillary staging after neoadjuvant chemotherapy for breast cancer: a pilot study combining sentinel lymph node biopsy with radioactive seed localization of pre-treatment positive axillary lymph nodes. Ann Surg Oncol. 2016;23:1549–1553.
8. Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Ann Surg. 2015;261:378–382.
9. Koolen BB, Donker M, Straver ME, et al. 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. 2017;104:1188–1196.
10. McNees MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA. 2018;319:388–396.
11. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529–536.
12. Nyaga VN, Arbyn M, Aerts M. MetaProp: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014:72:39.
13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.
14. Macaskill P, Gatsinos C, Deeks JJ, et al. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Version 1.0. Vol. Chapter 10. Analysing and Presenting Results. The Cochrane Collaboration; 2010:46–47.
15. Alvarado R, Yi M, Le-Petross H, et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. Ann Surg Oncol. 2012;19:3177–3184.

© 2018 The Author(s). Published by Wolters Kluwer Health, Inc. www.annalsofsurgery.com | 439
16. Boileau JP, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol. 2015;33:258–264.

17. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310:1455–1461.

18. Brown AS, Hunt KK, Shen J, et al. Histologic changes associated with false-negative sentinel lymph nodes after preoperative chemotherapy in patients with confirmed lymph-node-positive breast cancer before treatment. Cancer. 2010;116:2878–2883.

19. Carrera D, de la Flor M, Galera J, et al. Validation of sentinel lymph node biopsy in breast cancer women N1-N2 with complete axillary response after neoadjuvant chemotherapy. Multicentre study in Tarragona. Rev Esp Med Nucl Imagen Mol. 2016;35:221–225.

20. Enokido K, Watanabe C, Nakamura S, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with an initial diagnosis of cytology-proven lymph-node-positive breast cancer. Clin Breast Cancer. 2016;16:299–304.

21. Ge WK, Yang B, Zuow S, et al. Sentinel lymph node biopsy does not apply to all axillary lymph node-positive breast cancer patients after neoadjuvant chemotherapy. Thorac Cancer. 2014;5:550–555.

22. Kang E, Chung IY, Han SA, et al. Feasibility of sentinel lymph node biopsy in breast cancer patients with initial axillary lymph node metastasis after primary systemic therapy. J Breast Cancer. 2011;14:147–152.

23. Kuehn T, Baufeld T, Fehm T, et al. Sentinel lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14:609–618.

24. Ozmen V, Unal ES, Muslanoglu ME, et al. Axillary sentinel node biopsy after neoadjuvant chemotherapy. Eur J Surg Oncol. 2010;36:23–29.

25. Park S, Park JM, Cho JH, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with cytologically proven node-positive breast cancer at diagnosis. Ann Surg Oncol. 2013;20:2858–2865.

26. Pinero-Madrona A, Escudero-Barea MJ, Fernandez-Robayna F, et al. Selective sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer: results of the GEICAM 2005-07 study. Cir Esp. 2015;93:23–30.

27. Shen J, Gilcrease MZ, Babiera GV, et al. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. Cancer. 2007;109:1255–1267.

28. Thomas S, Prakash A, Goyal V, et al. Evaluation of sentinel node biopsy in locally advanced breast cancer patients who become clinically node-negative after neoadjuvant chemotherapy: a preliminary study. Int J Breast Cancer. 2011;2011:870263.

29. Yagata H, Yamauchi H, Tsugawa K, et al. Sentinel node biopsy after neoadjuvant chemotherapy in cytologically proven node-negative breast cancer. Clin Breast Cancer. 2013;13:471–477.

30. Yu Y, Cui N, Li HY, et al. Evaluation of sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer: retrospective comparative evaluation of clinically axillary lymph node positive and negative patients, including those with axillary lymph node metastases confirmed by fine needle aspiration. BMC Cancer. 2016;16:808.

31. Zetterlund LH, Frisell J, Zouros A, et al. Swedish prospective multicenter trial evaluating sentinel lymph node biopsy after neoadjuvant systemic therapy in clinically node-negative breast cancer. Breast Cancer Res Treat. 2017;163:103–110.

Appendix 1

**PubMed search strategy**

"Breast Neoplasms"[Mesh] OR ((canceroma OR carcinomas OR tumor OR tumours OR tumour OR tumours OR neoplasm OR disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastases carry a better prognosis than macrometastases. Breast Cancer Res Treat. 2017;163:159–166.

**EMBASE search strategy**

"Breast Neoplasms"[Mesh] OR ((canceroma OR carcinomas OR tumor OR tumours OR tumour OR tumours OR neoplasm OR disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastases carry a better prognosis than macrometastases. Breast Cancer Res Treat. 2017;163:159–166.

**EMBASE search strategy**

"Breast Neoplasms"[Mesh] OR ((canceroma OR carcinomas OR tumor OR tumours OR tumour OR tumours OR neoplasm OR disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastes carry a better prognosis than macrometastases. Breast Cancer Res Treat. 2017;163:159–166.
Appendix 2. Forest plot of the ax-pCR rate.

ES effect size. The pooled ax-pCR is 37% (33% to 40%).
Appendix 3. Forest plot for the identification rate of SLNB.

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