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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 Nijnatten, 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

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

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

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

METHODS

Criteria for Considering Studies for This Review

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for diagnostic test accuracy.[10] A systematic literature search was performed by the first author (JM) for randomized controlled trials, cohort studies, and case-control studies testing less invasive axillary staging procedures after NST in cN+ breast cancer patients treated with NST. Studies were only included if nodal positivity was pathologically confirmed before starting with NST. Any study in which a less invasive axillary staging procedure was compared with the gold standard, that is, ALND, was included. In case completion ALND (cALND) was not performed routinely, studies were not considered for quantitative analysis. If relevant studies included both cN0 and cN+ patients, only the cN+ patients were

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

Search Methods for Identification of Studies

The following electronic databases were searched until April 20, 2018, with no restriction on language or date of publication: Medline (via PubMed) and EMBASE (via EMBASE.com).

A health sciences librarian was consulted to help develop a detailed search strategy. Details of the full search strategies in both databases are provided in Appendix 1. The reference lists of included studies and existing reviews were manually checked for additional relevant studies.

Selection of Studies and Quality Assessment

Duplicate references were identified and removed with Endnote. Titles and abstracts of all remaining references were scanned independently by 2 authors (JS and TvN). Subsequently, these 2 authors independently assessed the full text papers of all potentially eligible studies. Disagreement was resolved by mutual consensus.

Eligible studies were assessed for quality using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS- 2) questionnaire.[11] The QUADAS-2 was tailored to our analysis, as described in the guideline. Finally, all included studies were evaluated for quality by the 2 independent authors.

Data Extraction and Analysis

For each included study, the following parameters were extracted: first author, year of publication, type of hospital, study design, sample size, characteristics of trial participants (including primary tumor type, TNM-stage, type of evaluation of axillary involvement, and NST regimens), type of less invasive axillary staging procedure after NST and characteristics of the procedure, type of pathological assessment of lymph nodes (including use of immunohistochemistry (IHC), definition of ax-pCR, ax-pCR rate, accuracy, and IFR of the less invasive axillary staging procedure.

For each less invasive axillary staging procedure, the ax-pCR rate, IFR, false-negative rate (FNR), and negative predictive value (NPV) were calculated. Rate of ax-pCR was based on data of the contingency tables. The IFR was defined as the number of successful procedures divided by the total number of patients in whom the procedure was attempted. The FNR was defined as the number of FN divided by the total number of patients with presence of residual axillary disease [FN / (FN + TP)]. The NPV was defined as the number of TN divided by the total number of patients with a negative test result [TN / (TN + FN)]. As FP cannot occur, numbers of TP, TN, and FN were documented for each procedure and FP was always documented

to be 0 (in case FP was reported to be > 0 in the record, this number was added up to the TP number). Statistical analysis was performed with Stata/SE Statistical Software for Windows, version 14.2 (StataCorp LP, College Station, TX). To calculate pooled proportions for ax-pCR rate, IFR and FNR random-effects models for meta-analysis were used with 95% exact confidence intervals (CIs) with help of the metaprop command.[12] All considered outcomes are presented in forest plots including pooled estimates. Chi-squared test was performed to test for statistical heterogeneity and was quantified by I^2-index.[13] As recommended in the Cochrane Handbook for Diagnostic Test Accuracy Reviews,[14] reporting bias (eg, publication bias) was not assessed.

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

RESULTS

Study Selection

In total, 1920 records were identified through database searching and reference checking. After deduplication, 1132 records were screened, which resulted in the selection of 116 records for retrieval of full texts. Assessment of full text for eligibility yielded 27 records for qualitative synthesis; a total of 20 records were included in quantitative synthesis. See 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,[8] and 2 trials investigated a combination procedure.[6,32]

Studies validating the combination procedure were scarce, yet several studies did report on cohorts of patients in whom a combination procedure was performed without routine cALND. Therefore, we decided to include these studies, 7 in total, in the qualitative analysis.[7,33-38] See Table 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
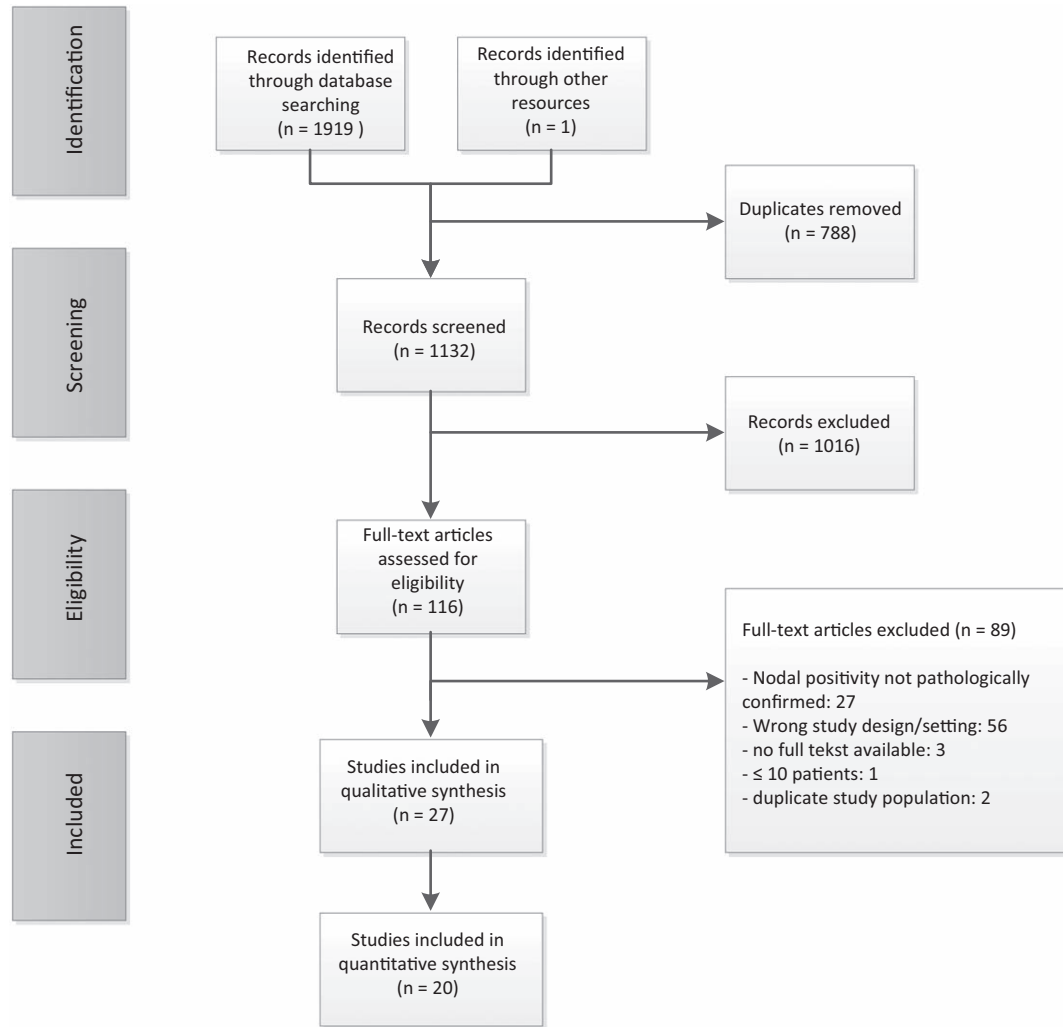
FIGURE 1. Flow diagram depicting the study selection process.

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 ypN0 and 17% when ax-PCR was defined as ypN0/itc+ ($P = 0.61$, 1 study defined ax-pCR as ypN0/itc+/mi+). FNR was reported for single versus dual-tracer sampling separately in 5 studies and another 6 studies used either single-tracer or dual-tracer sampling in 100% of patients. Pooled FNR was 13% for dual-tracer sampling and 16% for single-tracer sampling ($P = 0.53$). 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.

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
Boughey	2013	P, M	SLNB	ALND	637	N1-2	Any	ypN0/itc+	No
Brown	2010	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
Pinero-Madrona	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	NR	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	NR	NR	NR
Park	2017	P, S	Combi	NA	20	N1-3	NR	ypN0/itc+	Yes, but not routinely
Plecha	2015	R, S	Combi	NA	19	N1-3	NR	NR	NR
Siso	2017	P, S	Combi	ALND	35	N1-3	Any	ypN0	Yes, always
Taback	2018	P, S	Combi	NA	19	N1-2	NR	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).

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 2. Characteristics of Studies Involving the Combination Procedure Without Routine ALND

Author	Sample Size[*]	Pre-NST Marking at Time of FNA/CNB	Pre-NST Marking After FNA/CNB	Post-NST Marking	Sampling SLNB	IFR[†], %	ML is SLN, %	Confirmation Removal ML	Lymph Nodes[‡], Median (Range)	ALND, %	Ax-pCR, %
Dashevsky	21	Clip	NA	Wire	Tc + blue	100.0	NR	XR	NR	0.0	33.3
Diego	29	Clip	NA	Iodine seed	Tc + blue	100.0	91.0	XR	4 (1–11)	23.3	63.0
Kim	11	Clip	NA	Wire	Tc + blue	100.0	NR	XR/palpation	NR	45.5	36.4
Nguyen	20	NA	Clip	Iodine seed	Tc and/or blue	100.0	NR	XR	NR	NR	NR
Park	20	NA	Charcoal	NA	Tc and/or blue	100.0	75.0	NA	3 (1–12)	60.0	50.0
Plecha	19	Clip	NA	Wire	Tc ± blue	100.0	100.0	XR/PA	5.7 (mean)	NR	NR
Simons (data submitted)	139	NA	Clip/Iodine Seed	Iodine seed/wire	Tc and/or blue	99.3	64.6	XR/PA	2 (1–9)	22.3	36.0
Taback	19	Clip (78.9%)	Electromagnetic Reflector	NA	Tc + blue	100.0	63.2	XR	4 (2–10)	31.6	31.6

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	☺	☺	☺	☺	☺	☺	☺
Boughey	☺	☺	☺	☺	☺	☺	☺
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

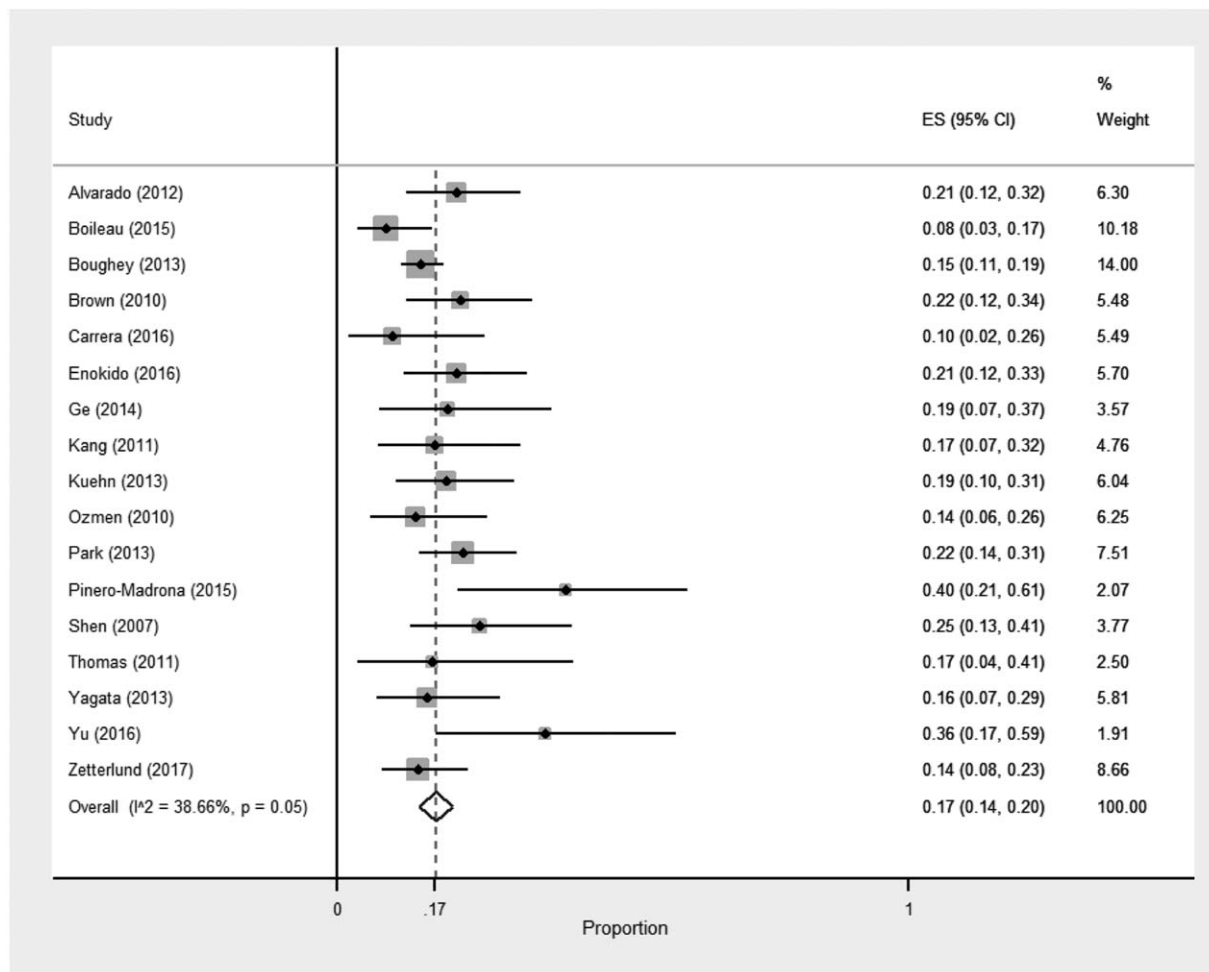**FIGURE 2.** Assessment of risk of bias.

FIGURE 3. Forest plot for the FNR of SLNB.

2 studies were available for analysis, pooling of proportions was not performed. The studies appeared clinically similar, as they targeted the same population in terms of inclusion criteria, definition of ax-pCR, and use of IHC.

DISCUSSION

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

The SLNB for axillary staging after NST in cN+ patients has been extensively studied over the past years. The SLNB procedure is widely accepted as axillary staging procedure in cN0 patients. Even when performed after NST, the accuracy of SLNB for cN0 patients is accepted.[39] SLNB for axillary staging after NST in pre-treatment cN+ patients, however, is associated with unacceptably high rates of FNR. In 2015, the accuracy of SLNB in cN+ patients after NST was evaluated in a systematic review that included 8 studies with pathologically proven cN+ patients.[40] That review reported an

overall FNR of 15% and the NPV of SLNB did not exceed 86%.[40] In the current meta-analysis, a total of 17 studies with 2002 patients (the 8 studies of the previous review were also included) were analyzed. The overall FNR is 17% and the NPV still does not exceed 86%: in case SLNB predicts ax-PCR, residual axillary disease is actually missed in at least 1 in 6 patients. The overall IFR is 89%. Previous studies reported multiple factors that may improve IFR and accuracy of SLNB, for example, using dual-tracer sampling technique, evaluating the SLNs with IHC in addition to standard H&E evaluation and removing 3 or more SLNs. As IHC and single- versus dual-tracer sampling was not used consistently within and between studies, it is not possible to draw definite conclusions from this review on whether/or not specific sampling and pathologic evaluation methods should be promoted. Our results did show that FNR was favorable (yet not statistically significant) for both dual-tracer sampling and pathologic evaluation with IHC. FNR was also favorable for patients with ycN0 status based on physical examination and/or imaging compared with any ycN status (FNR of 14% vs 18%, $P = 0.14$). Regarding the number of SLNs, removing $\geq$ 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 patients[17] and whether this will be achieved is unpredictable preoperatively. This

TABLE 3. Overview and Diagnostic Accuracy Sorted by Type of Procedure

SLNB

Author	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 (1–10)	30.2	47	0	13	26	22 (12–34)	67 (50–81)
Carrera	90.5	Single radioactive	2.2 (mean) (1–6)	35.4	28	0	3	17	10 (2–26)	85 (62–97)
Enokido	90.9	Tc and/or blue	1.6 (mean)	52	49	0	13	68	21 (12–33)	84 (74–91)
Ge	84.3	Tc and/or blue	2.4 (1–7)	27.9	25	0	6	12	19 (7–37)	67 (41–87)
Kang	87.9	Tc and/or blue	2.8 (mean) (1–8)	28.8	34	0	7	17	17 (7–32)	71 (49–87)
Kuehn	82.6	Tc ± blue	NR	48.8	51	0	12	60	19 (10–31)	83 (73–91)
Ozmen	92.2	Tc + blue	2.1 (1–5)	28	44	0	7	20	14 (6–26)	74 (54–89)
Park	94.9	Single, radioactive	2,1 (mean) (1–12)	40.8	78	0	22	69	22 (14–31)	76 (66–84)
Pinero-Madrona	84.0	Tc ± blue	NR	34.2	15	0	10	13	40 (21–61)	57 (34–77)
Shen	92.8	Tc and/or blue	2 (1–10)	28.6	30	0	10	16	25 (13–41)	62 (41–80)
Thomas	86.7	Single blue	1,57 (mean) (1–4)	31	15	0	3	8	17 (4–41)	73 (39–94)
Yagata	85.3	Tc + blue	2 (1–7)	37	43	0	8	30	16 (7–29)	79 (63–90)
Yu	95.8	Single: Blue	1,48 (mean) (1–4)	52.2	14	0	8	24	36 (17–59)	75 (57–89)
Zetterlund	77.9	Tc and/or Blue	2 (1–5)	39.5	79	0	13	60	14 (8–23)	82 (71–90)

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 SLNB	Pre-NST Marker	Post-NST Marker	N Lymph Nodes	Ax-pCR %*	ML is SLN %	TP	FP	FN	TN	FNR% (CI)	NPV% (CI)
Caudle	100%	Tc and/or blue	Clip	Iodine seed	NR	41	77†	49	0	1	35	2 (0–11)	97 (85–1)
Siso	NR	Tc and/or blue	Clip	NA*	3 median	31.7	77	23	0	1	11	4 (0–21)	92 (62–1)

NA indicates not applicable; NR, not reported; Tc, technetium.

*Ax-pCR rate based on data of 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.

renders SLNB impractical, as random node-picking should be discouraged. Currently recruiting studies as Alliance 11202 and NSABP-51/RTOG 1304 will determine whether the SLNB, despite its rather poor overall accuracy and shortcomings, can have a place in axillary staging after NST in cN+ patients.[41,42]

The MARI procedure was the first ML procedure to be proposed as an alternative to SLNB for axillary staging after NST in cN+ patients.[8] By marking the pathologically proven positive lymph node before start of NST, it was expected to enable accurate assessment of treatment response after completion of NST. The MARI procedure was validated in 1 single-center trial with 95 patients. This study reported an improved FNR (7%), but the NPV of 83.3% was less favorable, that is, in 1 of 6 patients with a negative MARI, axillary residual disease is left behind. Therefore, equally to SLNB, MARI as a stand-alone procedure is insufficiently accurate to safely replace ALND. Despite the shortcomings of MARI (potential of missing residual axillary disease and limited evidence by 1 single—dedicated breast cancer—center trial to support this procedure), it is already implemented in clinical practice. A recent publication suggests combining information on axillary burden on pre-NST PET-CT (ie, number of suspicious lymph nodes: <4 vs ≥ 4) with MARI outcome[9] to determine adjuvant axillary treatment: no further axillary treatment, axillary radiotherapy, or cALND with axillary radiotherapy. Results of 1 prospective implementation study showed that this treatment strategy indeed results in a major reduction of ALND.[43] Data of longer follow-up have to determine whether implementation of this protocol is untimely and whether it does not only reduce morbidity but also preserves oncologic safety in terms of disease-free and overall survival. Prospective trials with sufficient follow-up are therefore urgently needed.

In the Z1071 trial, a clip was placed in the positive lymph node before NST in a subset of patients.[44] The trial protocol did not require surgeons to selectively target and remove the clipped node at time of surgery, but did encourage surgeons and pathologists to document whether the clipped node was located in the SLNB or ALND specimen. In 141 of 170 patients with a clipped node, the location of the clipped node was documented: 75.9% in the SLNB specimen and 24.1% in the ALND specimen. This suggested that removing the clipped node together with SLN(s) at time of surgery may improve accuracy of SLNB and may possibly overcome shortcomings associated with SLNB or MARI if used as stand-alone procedures. Up to now, only 2 trials evaluated accuracy of such a combination procedure and were included in our meta-analysis.[6,32] This procedure is associated with excellent IFRs. Caudle et al[6] confirmed that the clipped node does not necessarily have to be a SLN, as this was the case in only 77%. Furthermore, FNR is low (2% to 4%) and NPV is high (92% to 97%). These results are promising: when ax-pCR is predicted, residual axillary disease is missed in 1 in 12 to 33 patients. The evidence for this procedure is yet limited with only 2 trials available (1 retrospective and 1 prospective study), involving small sample sizes and single-center study designs. The ongoing Dutch RISAS trial (NCT02800317 at https://clinicaltrials.gov) will prove whether the promising results of a combination procedure can be confirmed in a large, prospective, multicenter trial.[45]

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

The abovementioned 3 different staging procedures intend to offer a less invasive strategy compared with the conventional ALND, yet ≥ 10 lymph nodes are removed in some patients with SLNB and combination procedures. It is important to realize that these procedures serve as a staging procedure to identify ax-pCR and not as a managing procedure to remove all residual diseases. Hence, it should be the primary goal to remove as few lymph nodes as possible. In this way, patients with ax-pCR can truly benefit from less invasive staging procedures. At the same time, when these procedures identify axillary residual disease, adjuvant axillary treatment plans should consist of cALND. Results of the Alliance 11202 and NSABP-51/RTOG 1304 trials have to be awaited to determine whether cALND may be replaced by axillary radiation therapy.[41,42]

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

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

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

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Appendix 1

PubMed search strategy

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

EMBASE search strategy∗

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

((breast OR mamma) AND (cancer OR carcinoma OR neoplasm OR malignancy OR adenocarcinoma OR 'breast cancer'/exp OR tumor OR carcinomas OR tumors OR tumour OR tumours)) AND (('sentinel lymph node biops∗' OR slnb OR 'sentinel node∗' OR 'sentinel lymph node biopsy'/exp OR 'mari':ab,ti OR (axilla∗

AND staging) OR 'targeted axillary dissection')) AND (sensitivity OR specificity OR 'predictive value' OR 'likelihood ratio' OR ppv OR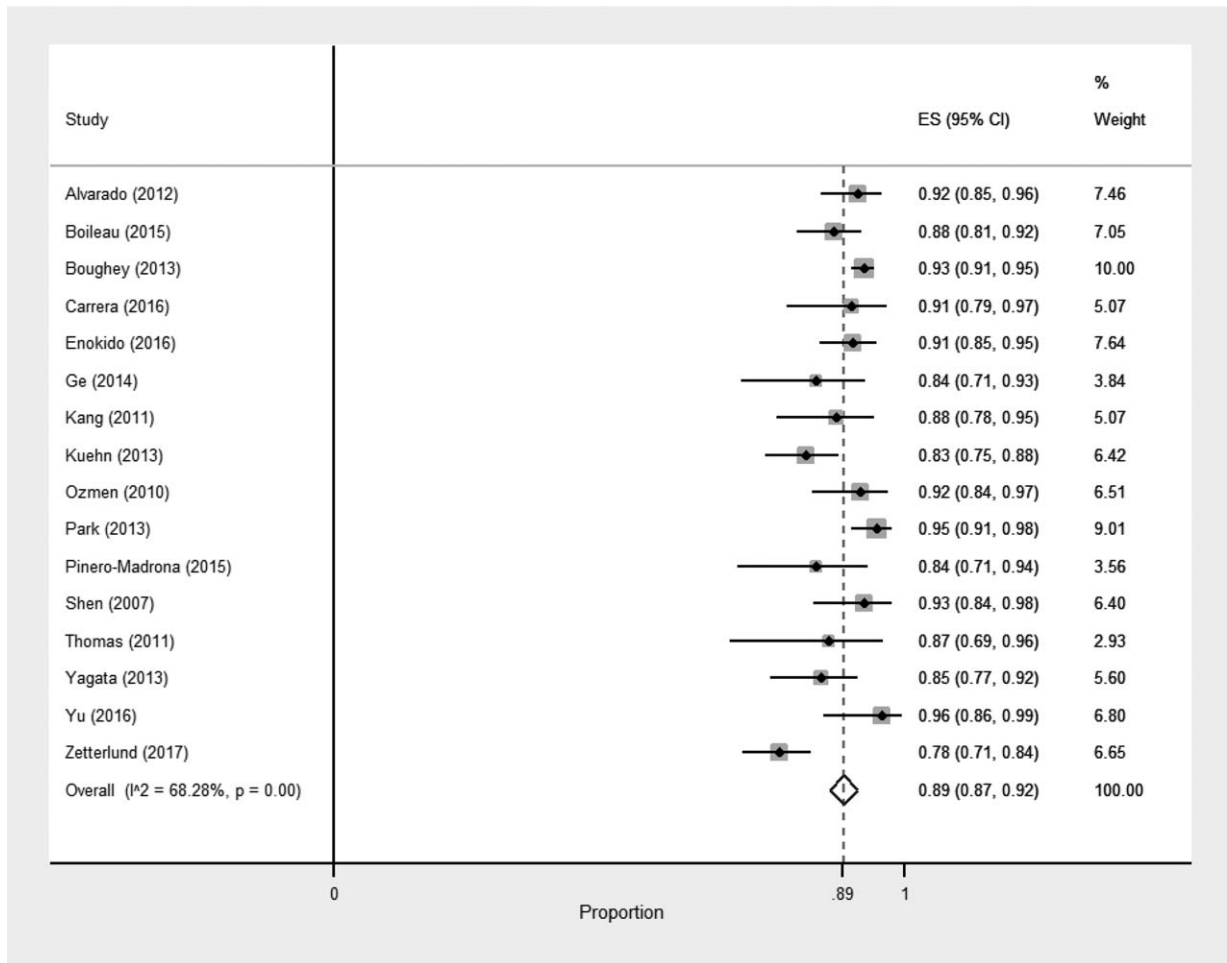 npv OR diagnosis OR 'false negative' OR 'false positive') AND ((axilla* OR lymph*) AND (node* OR metastasis)) AND ((neo-adjuvant OR primary OR preoperative*) AND (therapy OR immunotherapy OR chemotherapy OR systemic))

Appendix 2. Forest plot of the ax-pCR rate.
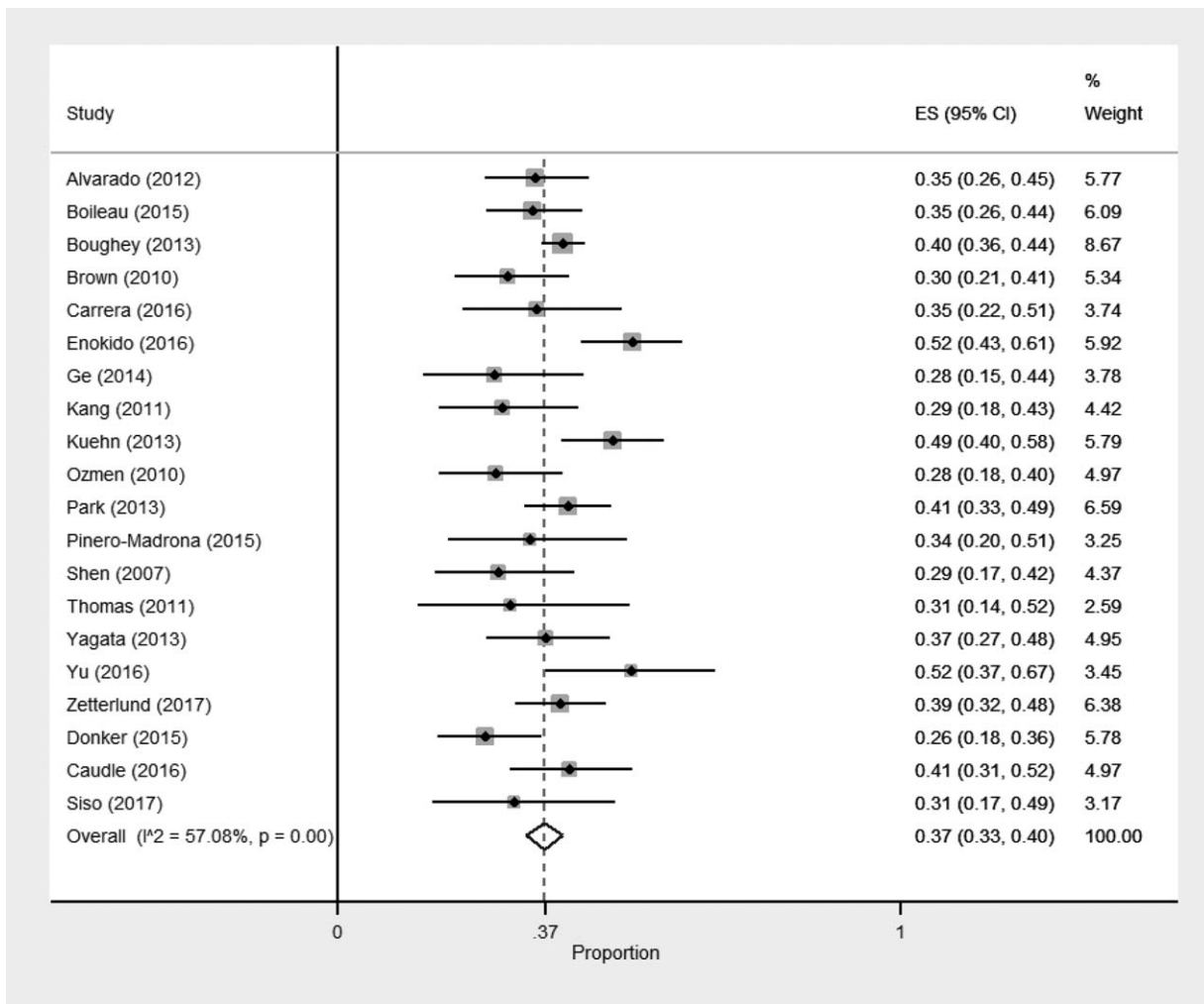
ES effect size. The pooled ax-pCR is 37% (33% to 40%).

Appendix 3. Forest plot for the identification rate of SLNB.

Study	ES (95% CI)	% Weight
Alvarado (2012)	0.92 (0.85, 0.96)	7.46
Boileau (2015)	0.88 (0.81, 0.92)	7.05
Boughey (2013)	0.93 (0.91, 0.95)	10.00
Carrera (2016)	0.91 (0.79, 0.97)	5.07
Enokido (2016)	0.91 (0.85, 0.95)	7.64
Ge (2014)	0.84 (0.71, 0.93)	3.84
Kang (2011)	0.88 (0.78, 0.95)	5.07
Kuehn (2013)	0.83 (0.75, 0.88)	6.42
Ozmen (2010)	0.92 (0.84, 0.97)	6.51
Park (2013)	0.95 (0.91, 0.98)	9.01
Pinero-Madrona (2015)	0.84 (0.71, 0.94)	3.56
Shen (2007)	0.93 (0.84, 0.98)	6.40
Thomas (2011)	0.87 (0.69, 0.96)	2.93
Yagata (2013)	0.85 (0.77, 0.92)	5.60
Yu (2016)	0.96 (0.86, 0.99)	6.80
Zetterlund (2017)	0.78 (0.71, 0.84)	6.65
Overall ($I^2 = 68.28\%$, $p = 0.00$)	0.89 (0.87, 0.92)	100.00

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