Review Article

Assessment of sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer in two subgroups: Initially node negative and node positive converted to node negative – A systemic review and meta-analysis

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Background: Neoadjuvant chemotherapy (NAC) is increasingly used to treat patients with breast cancer, but the reliability of sentinel lymph node biopsy (SLNB) following chemotherapy is in doubt. In this meta-analysis, we aimed to evaluate studies that examine the results of SLNB after NAC to assess identification rate (IR) and false-negative rate (FNR). **Materials and Methods:** Systemic searches were performed in the PubMed, ISI Web of Sciences, Scopus, and Cochrane databases from January 1, 2000, to November 30, 2016, for studies of SLNB after NAC for breast cancer and followed by axillary lymph node (LN) dissection in two subgroups: initially node negative and node positive converted to node negative. Two reviewers independently review quality of included studies. A random-effects model was used to pool IR and FNR with 95% confidence intervals (CI), and heterogeneity among studies was assessed by I^2 and Q-test. **Results:** A total of 23 studies with 1521 patients in the initially node-negative subgroup and 13 studies with 1088 patients in the node-positive converted to node-negative subgroup, were included in this meta-analysis with IR and FNR of 94% (95% CI: 92–96) and 7% (95% CI: 5–9) in the initially node-negative subgroup and 89% (95% CI: 85–94) and 13% (95% CI: 7–18) in the node-positive converted to node-negative subgroup, respectively. **Conclusion:** Our meta-analysis showed acceptable IR and FNR in initially node-negative group and it seems feasible in these patients, but these parameters did not reach to predefined value in node-positive converted to node-negative group, and thus, it is not recommended in these patients.

Keywords: Breast cancer, meta-analysis, neoadjuvant systemic therapy, sentinel lymph node biopsy

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INTRODUCTION

Axillary lymph node (LN) evaluation plays the most important role in staging, treatment, and prognosis of breast cancer. Therefore, axillary LN dissection (ALND) is traditionally an important part of the breast cancer therapy.[1] However, this procedure has several complications, such as numbness, pain, restriction of shoulder range of motion, and upper limb lymphedema that leads to low quality of life. Hence, for decreasing complication risk, sentinel LN (SLN) – The first LN or group of LNs encountered in the lymphatic drainage – biopsy is recommended.[2-4] SLN biopsy (SLNB) is a minimally invasive technique with high accuracy in determining the status of axilla and led to less morbidity compared with ALND. This procedure is appropriate in early-stage clinically node-negative breast cancer. Approximately, half of the patients with a positive SLN are known to have additional axillary nodal involvement, and even in case

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of omitting an ALND, the risk of developing an axillary recurrence in the presence of a positive SLN is <1%. With the emergence of new medicines that have remarkable effect on breast cancer treatment, adjuvant chemotherapy has gained an integral part of the therapy. In recent years, a positive effect of neoadjuvant chemotherapy (NAC) on tumor and LN downstaging as well as overall prognosis has been identified. Studies have shown axillary pathological complete response (pCR) in 20%–40% of initially node-positive patients. Thus, NAC is widely used in breast cancer therapy. SLNB could be performed before NAC and that women with involved nodes could have ALND after the completion of chemotherapy. Avoiding the possible negative effects of lymphatic scarring or uneven nodal tumor response is the advantage of this strategy. The disadvantage of this approach is that these women would need to undergo two surgeries. Nevertheless, SLNB following NAC is a contraindication as NAC can distort lymphatic drainage and reduce SLN detection rate. However, this issue is recently in doubt, and many clinical researches have been conducted in this field.[3,5-7] The patient selection criteria, technique of mapping, type of tracer, pathologic staining, detection of involved SLN, and definition of positive SLN vary across individual literature. Thus, it is difficult to determine individual patient approach in clinical practice. There are three conditions in this subject: (1) node-negative breast cancer before and after NAC, (2) node positive before NAC that converted to node negative after NAC, and (3) node positive that does not respond to NAC and remains positive. At the present time, SLNB is a contraindication in the latest setting. It is important that the feasibility and reliability of SLNB is determined in two early items.

The aim of this study was to identify all of the clinical studies that have separately examined the results of SLNB after NAC in two subgroups, initially node negative and node positive converted to node negative, to evaluate identification rate (IR) and false-negative rate (FNR) and timing of SLNB in the context of NAC in these two subgroups.

METHODS

Literature search strategy

In this study, PubMed, ISI Web of Sciences, Scopus, and Cochrane databases were searched from January 1, 2000, to November 30, 2016. The following free text terms and Medical Subject Headings (Mesh) terms were used: "breast cancer" OR "breast carcinoma" OR "breast neoplasm" AND "sentinel lymph node biopsy" OR "sentinel lymph node dissection" OR "sentinel lymph node mapping" OR "SLNB" AND "preoperative chemotherapy" OR "neoadjuvant chemotherapy." Only articles written in English were selected. The search strategy is depicted in Figure 1.

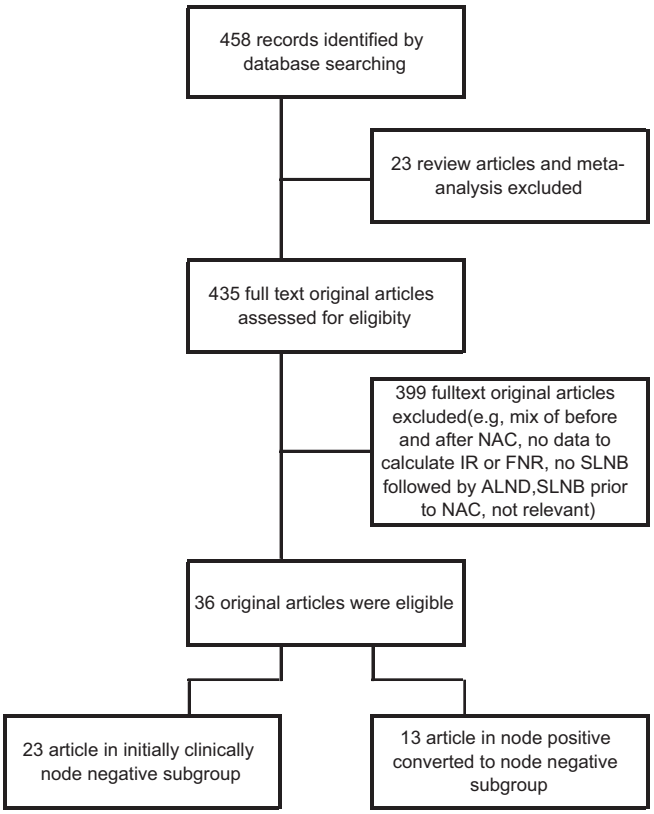

Figure 1: Flow diagram of literature search

Study inclusion and exclusion criteria

The inclusions criteria were as follows: (1) patients with breast cancer who received NAC, (2) patients who underwent SLNB after NAC, (3) patients who underwent ALND regardless of SLNB pathology, and (4) literatures that have clearly stated the status of LNs, either positive or negative, before and after NAC, or those from which we could accurately extract these information. Axillary LN-positive status was verified by clinically (physical examination or ultrasonic image), with or without histologic examination. The patients with inflammatory breast cancer, prior axillary surgery, and radiotherapy were excluded from the study.

Study quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[8] tool was used to perform quality assessment of articles. This tool consists of four domains: patients' selection, index test, references standard, and flow and timing. The risk of bias categorized as "low," "high," and "unclear." If the answer to all the questions for domain is yes, the risk is low; if the answer to all the questions is no, the risk is high; and if there are insufficient data, the risk is unclear [Table 1].

Data extraction and definitions

All studies were independently evaluated by two reviewers and checked by other reviewers for accuracy. Discrepancies were resolved by consensus after

Table 1a: Results of quality assessment according to the Quality Assessment of Diagnostic Accuracy Studies-2 for the initially clinically node negative

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference Standard
Nason *et al*.	2	1	1	1	1	1	1
Tafra *et al*.	2	1	1	1	1	1	1
Miller *et al*.	1	1	1	1	1	1	1
Vigario *et al*.	1	1	1	1	1	1	1
Piato *et al*.	1	1	1	1	1	1	1
Shimazu *et al*.	2	1	1	1	2	1	1
Lang *et al*.	2	1	1	1	2	1	1
Tanaka *et al*.	2	1	1	1	1	2	1
Jones *et al*.	2	1	1	1	2	1	1
Mamounas *et al*.	1	1	1	1	1	1	1
Yu *et al*.	2	1	1	1	2	1	1
Kinoshita *et al*.	2	1	1	1	1	2	1
Gimbergues *et al*.	2	1	1	1	1	2	1
Papa *et al*.	2	1	1	1	1	2	1
Classe *et al*.	2	1	1	1	1	1	1
Hunt *et al*.	2	1	1	1	1	2	1
Cheuny *et al*.	1	1	1	1	1	1	1
Pecha *et al*.	2	1	1	1	1	2	1
Takashia *et al*.	2	1	1	1	1	1	1
Robollo-Aguirre *et al*.	2	1	1	1	1	2	1
Shigekawa *et al*.	1	1	1	1	1	1	1
Piñero-Madrona *et al*.	2	1	1	1	1	2	1
Kida *et al*.	2	1	1	1	1	2	1

1=Low risk; 2=High risk; ?=Unclear risk

Table 1b: Results of quality assessment according to the Quality Assessment of Diagnostic Accuracy Studies-2 for the node positive converted to node negative

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference Standard
Kinoshita *et al*.	2	1	1	1	1	2	1
Ozmen *et al*.	2	1	1	1	1	2	1
Thomas *et al*.	2	1	1	2	1	2	1
Chintamani *et al*.	2	1	1	1	2	1	1
Robollo-Aguirre *et al*.	2	1	1	1	1	2	1
Shigekawa *et al*.	1	1	1	1	1	1	1
Takashia *et al*.	2	1	1	1	1	1	1
Robollo-Aguirre *et al*.	2	1	1	1	1	2	1
Kuehn *et al*.	2	1	1	2	2	1	1
Lee *et al*.	1	2	1	1	1	1	1
Yu *et al*.	2	1	1	1	2	1	1
Carrera *et al*.	1	1	1	1	1	1	1
Cao *et al*.	2	1	1	1	2	1	1

1=Low risk; 2=High risk; ?=Unclear risk

discussion. The first and second authors were separately extracted the following predefine items: first author, year of publication, study design, sample size, country of study, clinical tumor and nodal stage, the use immunohistochemistry (IHC) on axillary nodes, mapping method of SLN, definition of pathologic complete axillary response, IR, and FNR.

The results from each successfully identification SLN was categorized as true positive, true negative or false positive,

taking the outcome of the complete ALND as reference standard. A true-negative SLN was define as a negative SLN and a negative ALND, a false negative as negative SLN with a positive LN in the ALND, and true positive as a positive SLN with or without a positive ALND. Based on these definitions, it was assumed that there was no false-positive case. The IR was defined as the number of patients with successful identification of SLNs was divided by the total number of patients. FNR was defined as the false negatives divided by the sum of false negatives and true positives. Axillary pCR was defined as the absence of cancer according to histological diagnosis after ALND.

Statistical analysis

Statistical analyses were performed using STATA Corp. 2011 (Stata Statistical Software, Release 11, Stata Corp LP, Package, College Station, TX, USA). The analysis heterogeneity was evaluated by a Chi-square test and was quantified by I^2 statistic. The I^2 statistic values of ≤30%, 30%–70%, and ≥70% were considered as mild, moderate, and severe heterogeneity, respectively.[9] P values of the Chi-square test of heterogeneity were considered as statistically significant at 0.1. Due to heterogeneity between studies, random-effects models (using the DerSimonian and Laird methods) for meta-analysis were used to calculate pooled estimates of IR and FNR with 95% confidence intervals (CIs). Potential publication bias was assessed using Egger's weighted regression tests, and the results of Egger's tests were statistically significant at $P < 0.1$. If there was publication bias, "trim-and-fill" method was used to adjust and correct the publication bias.[10] Subgroup analysis was performed according to the type of tracers (single/dual). Sensitivity analysis was used to assess the effect of excluding any study on the overall effect.

RESULTS

Study selection process

The articles search founded 458 studies. After removing 23 review articles and meta-analyses, 435 literature remained, and then, 399 full-text original papers were excluded (e.g., mix of before and after NAC, no data to calculate IR or FNR, no SLNB followed by ALND, SLNB before NAC, and not relevant) that resulted in 36 eligible papers. Twenty-three studies included initially node-negative cases, and 13 studies included cases of node-positive breast cancers converted to node negative after NAC. Overall, 2609 patients were enrolled: 1521 patients in the initially node-negative subgroup with a mean of 66.1 patients per studies (range: 9–320) and 1088 patients in the node positive converted to node negative after NAC subgroup with a mean of 83.6 patients per studies (range: 15–529). The studies are summarized in Table 2.

Table 2a: Characteristics of the individual studies in initially node-negative subgroup

Author	Year	Country	Center	Design	Sample size	Tracer	Pathology	Mean SLN	Percentage IR	Percentage FNR
Nason *et al.*[11]	2000	USA	Single	Prospective	9	D, I, LS	H & E, IHC		88.8	22.2
Tafra *et al.*[12]	2001	USA	Multiple	Prospective	29	D, I	H & E, IHC	2.5	93	0
Miller *et al.*[13]	2002	USA	Single	Retrospective	35	D, I	H & E, IHC	2.1	85.7	11.4
Vigario *et al.*[14]	2003	Brazil	Single	Prospective	37	I, LS	H & E, IHC	1.7	97	19.4
Piato *et al.*[15]	2003	Brazil	Single	Retrospective	42	I, LS	H & E		97.5	16.7
Shimazu *et al.*[3]	2004	Japan	Single	Retrospective	25	D, I, LS	H & E, IHC	2.1	96	7.1
Lang *et al.*[16]	2004	USA	Single	Retrospective	30	D, I, LS	H & E	-	96.7	0
Tanaka *et al.*[17]	2005	Japan	Single	Retrospective	17	D	H & E	1.9	100	0
Jones *et al.*[18]	2005	USA	Single	Retrospective	17	-	H & E, IHC	-	94.1	10
Mamounas *et al.*[19]	2005	USA	Multiple	Prospective	326	D, I	H & E, IHC	-	84.4	12.4
Yu *et al.*[20]	2007	Taiwan	Single	Retrospective	127	D	H & E, IHC	-	91.3	9.6
Kinoshita[21]	2007	Japan	Single	Prospective	54	D, I, LS	H & E	-	96.9	14.3
Gimbergues *et al.*[22]	2008	France	Single	Prospective	82	I, LS	H & E, IHC	1.7	93.9	0
Papa *et al.*[23]	2008	Israel	Single	Prospective	31	D, I	H & E	-	87	15.8
Classe *et al.*[24]	2009	France	Multiple	Prospective	130	D, I	H & E, IHC	1.9	94.6	9.4
Hunt *et al.*[25]	2009	USA	Single	Retrospective	84	D, I	H & E, IHC	2.7	97.4	5.9
Cheung *et al.*[26]	2009	China	Single	Prospective	78	D, I	H & E, IHC	-	88.3	10.3
Pecha *et al.*[27]	2011	Czech	Multiple	Retrospective	172	D, I, LS	H & E, IHC	1.3	89.5	16.3
Takahashi *et al.*[28]	2012	Japan	Single	Prospective	41	D, I, LS	H & E, IHC	3	87.8	5.6
Rebollo-Aguirre *et al.*[29]	2012	Spain	Single	Prospective	51	I, LS	H & E, IHC, OSNA	1.7	98	9.5
Shigekawa *et al.*[30]	2012	Japan	Single	Retrospective	21	D, I, LS	H & E, IHC	-	81	0
Piñero-Madrona *et al.*[31]	2015	Spain	Multiple	Prospective	49	D, I	-	-	90	18
Kida *et al.*[32]	2015	Japan	Single	Prospective	34	D	H & E	2.5	97.1	0

D=Dye; I=Radioisotope; LS=Lymphoscintigraphy; H & E=Hematoxylin-eosin; IHC=Immunohistochemistry; OSNA=One-step nucleic acid amplification; IR=Identification rate; FNR=False-negative rate; SLN=Sentinel lymph node

Measures of test performance of initially node negative

Characteristics of included studies

In the initially node-negative subgroup, 3 studies used blue dye alone,[17,20,32] 4 studies used radioisotope alone,[14,15,22,29] 15 studies used both blue dye and radioisotope,[3,11-13,16,19,21,23-28,30,31] and 1 study did not state the type of the tracer used.[18] One study considered abnormal palpable LNs as SLNs.[32] Concerning pathologic assessment, 6 articles used hematoxylin and eosin (H & E) only,[15-17,21,23,32] 10 articles used IHC for negative H & E samples,[11-14,18,20,22,24-26] 5 articles used both H & E and IHC,[3,19,27,28,30] 1 study used H & E, IHC, and one-step nucleic acid amplification (OSNA),[29] and 1 study did not state the type of the tracer used.[31] Importantly, 1 study considered micrometastasis (yp mi) as involved SLN[20] and 3 studies considered micrometastasis (yp mi) and isolated tumor cell (ITC) (yp i+) as positive SLN.[27-30]

Meta-analysis

The reported IR between studies ranged from 81% to 100%. Between-study heterogeneity was high and statistically significant ($I^2 = 73.4\%$, Q-test: 82.68, $P < 0.001$). Due to severe heterogeneity, using random-effects meta-analysis model, the pooled IR estimated 94% (95% CI: 92%–96%).

The FNR ranged from 0% to 22%. Due to high and significant heterogeneity between studies ($I^2 = 86.4\%$, Q-test: 161.84, $P < 0.001$), random-effects meta-analysis estimated the pooled FNR 7% (95% CI: 5%–9%) [Figure 2].

Publication bias

Results of the Egger's test showed that there was no publication bias for IR. Results of the Egger's test showed that publication bias was existed between studies for FNR. Therefore, the

Table 2b: Characteristics of the individual studies in node-positive converted to node-negative subgroup

Author	Year	Country	Center	Design	Sample size	Tracer	pathology	Mean SLN	Percentage IR	Percentage FNR
Kinoshita[21]	2007	Japan	Single	Prospective	50	D, I, LS	H & E	-	90	7
Ozmen *et al*.[33]	2010	Turkey	Single	Retrospective	77	D, I	H & E, IHC	2.1	92	13.7
Thomas *et al*.[34]	2011	India	Single	Prospective	30	D	H & E, IHC	1.5	86.6	20
Chintamani *et al*.[35]	2011	India	Single	Retrospective	15	D	-	-	100	0
Rebollo-Aguirre *et al*.[29]	2012	Spain	Single	Prospective	37	I, LS	H & E, IHC, OSNA	1.7	88.7	6.7
Shigekawa *et al*.[30]	2012	Japan	Single	Retrospective	47	D, I, LS	H & E	-	83	29.2
Takahashi *et al*.[28]	2012	Japan	Single	Prospective	46	D, I, LS	H & E, IHC	3	87	27.3
Rebollo-Aguirre *et al*.[36]	2013	Spain	Single	Prospective	53	I, LS	H & E, IHC, OSNA	1.9	84.9	8.3
Kuehn *et al*.[37]	2013	Germany	Multiple	Prospective	592	D, I, LS	H & E	2.7	80.1	13.5
Lee *et al*.[38]	2015	Korea	Single	Prospective	55	I	H & E, IHC	2	87.3	6.7
Yu *et al*.[39]	2016	China	Single	Retrospective	48	D	H & E, IHC	1.4	95	36
Carrera *et al*.[40]	2016	Spain	Multiple	Prospective	53	I, LS	H & E, IHC	2.2	90.5	9.7
Cao *et al*.[6]	2016	China	Single	Prospective	48	D, I, LS	H & E	2	100	17.2

D=Dye; I=Radioisotope; LS=Lymphoscintigraphy; H & E=Hematoxylin-Eosin; IHC=Immunohistochemistry; OSNA=One-step nucleic acid amplification; IR=Identification rate; FNR=False-negative rate; SLN=Sentinel lymph node

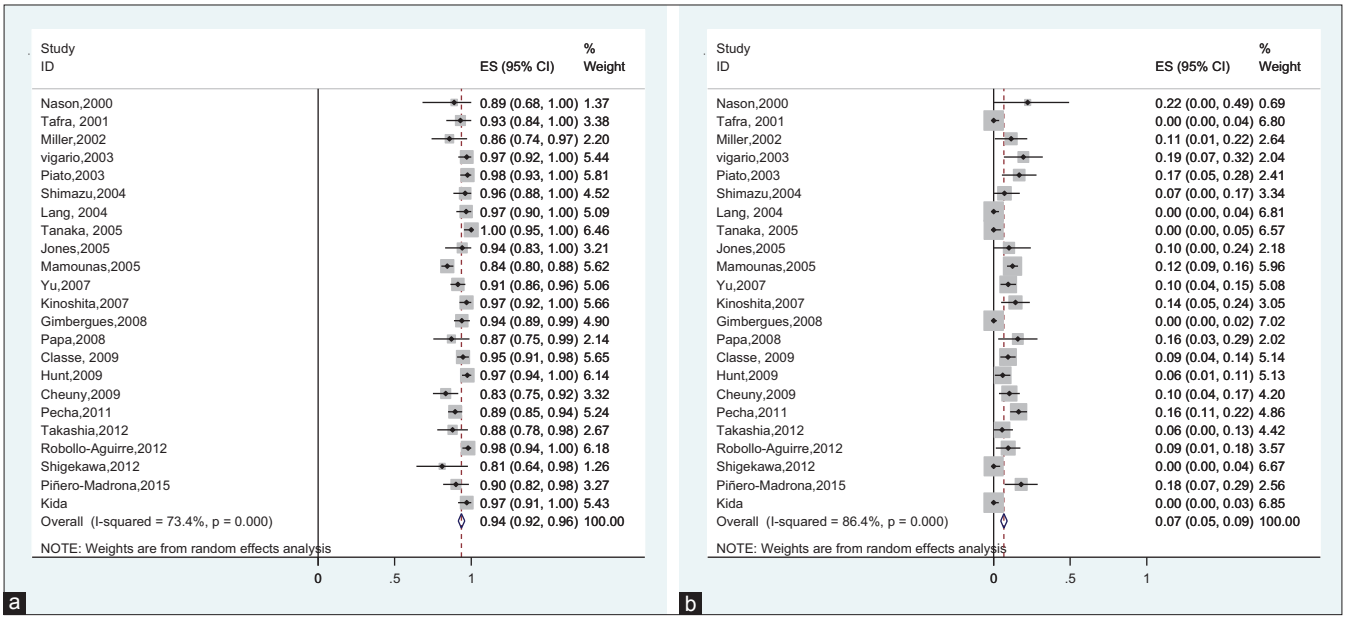

Figure 2: (a) Forest plot of the identification rate in initially node-negative patients, (b) forest plot of the false-negative rate in initially node-negative patients

missing data were imputed using "trim-and-fill" method to reduce the publication bias in pooled estimates of FNR. The results of this method showed that there were six missing studies, which after imputing these studies, the corrected overall FNR was estimated 5.5% (95% CI: 2.9%–8.1%).

Subgroup analysis

Subgroup analysis according to the type of tracer showed that the pooled IR for single and dual tracers was 97% (95% CI: 95%–99%) and 91% (95% CI: 86%–94%), respectively. Moreover, the pooled FNR for single and dual tracers was 4% (95% CI: 1%–7%) and 8% (95% CI: 5%–11%), respectively.

Sensitivity analysis

Results of sensitivity analysis showed that excluding none of the studies could not change the overall FNR and IR significantly.

Measures of test performance of node-positive converted to node-negative subgroup

Characteristics of included studies

In the node-positive converted to node-negative subgroup, 3 studies used blue dye alone,[34,35,39] 4 studies used radioisotope alone,[29,36,38,40] 6 studies used both blue dye and radioisotope,[6,14,33,30,28,37] and 1 study also included abnormal palpable LNs as SLN.[39] Regarding pathologic assessment, 4 studies used only H & E,[6,14,30,37] 2 studies performed IHC when H & E was negative,[33,38] 4 studies used both IHE and H & E,[34,28,39,40] 2 studies used OSNA,[29,36] and 1 study did not state the type of the pathologic staining.[35] One article considered (yp mi) as involved SLN[36] and 3 articles included (yp mi) and (yp i+) as positive SLN.[6,29,30]

Meta-analysis

The reported IR between studies ranged from 80.1% to 100%. Between-study heterogeneity was high and statistically significant (I^2 = 80.5%, Q-test: 71.18, P < 0.001). Due to sever heterogeneity, using random-effects meta-analysis model, the pooled IR estimated 89% (95% CI: 85%–94%).

The FNR ranged from 6.7% to 36%. Due to high and significant heterogeneity between studies (I^2 = 91.3%, Q-test: 138.54, P < 0.001), random-effects meta-analysis estimated the pooled FNR 13% (95% CI: 7%–18%) [Figure 3].

Publication bias

Results of the Egger's test showed that there was no publication bias for IR. Results of the Egger's test showed that publication bias was existed between studies for FNR. Therefore, the missing data were imputed using "trim-and-fill" method to reduce the publication bias in pooled estimates of FNR. The results of this method showed that there were two missing studies, which after imputing these studies, the corrected overall FNR was estimated 10.5% (95% CI: 5.1%–15.9%).

Subgroup analysis

Subgroup analysis according to the type of tracer showed that the pooled IR for single and dual tracers was 92% (95% CI: 87%–96%) and 89% (95% CI: 80%–98%), respectively. Moreover, the pooled FNR for single and dual tracers was 9% (95% CI: 3%–15%) and 14% (95% CI: 10%–19%), respectively.

Sensitivity analysis

Sensitivity analysis showed that removing studies by Chintamani *et al.*,[35] Kuehn *et al.*,[37] and Cao *et al.*[6] can considerably change the effect of IR to 89% (95% CI: 83%–95%), 99% (95% CI: 97%–100%), and 89% (95% CI: 83%–95%), respectively. Moreover, excluding none of the studies could not change the overall FNR significantly.

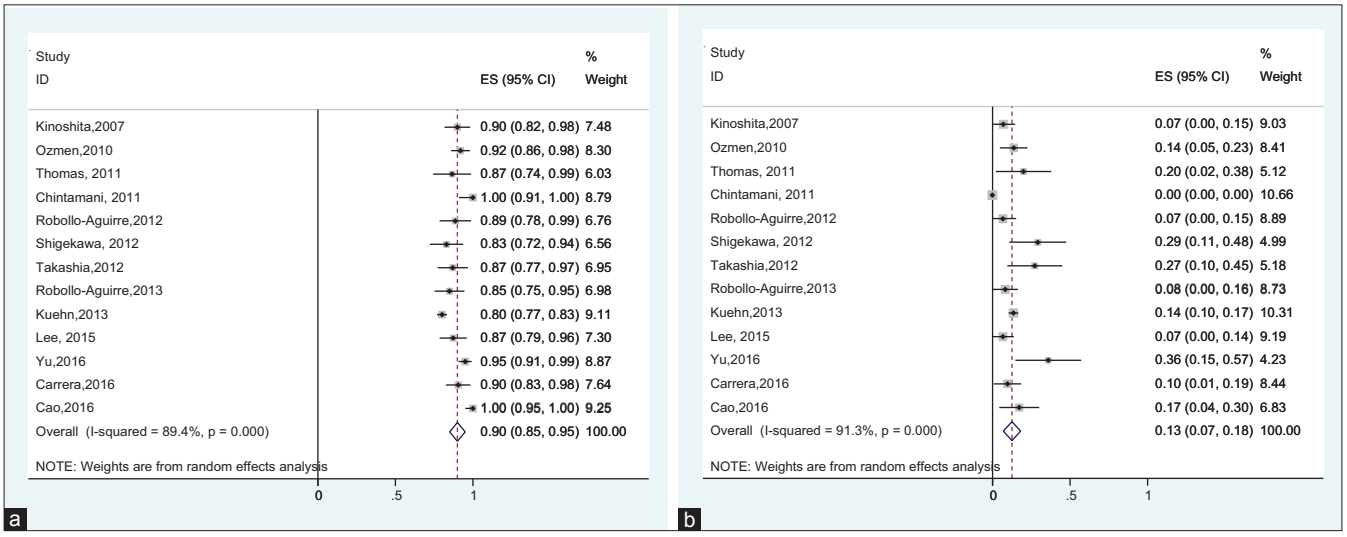

Figure 3: (a) Forest plot of the identification rate in node-positive converted to node-negative patients, (b) forest plot of the false-negative rate in node-positive converted to node-negative patients

DISCUSSION

The present study analyzed literature about the feasibility and accuracy of SLNB after NAC in two subgroups of breast cancer: the initially node negative and node positive converted to node negative after NAC. IRs and FNRs were evaluated because of the most important test clinically. The most important meta-analyses related to this issue were published without regarding the node status before and after NAC, and overall results were stated. We found only one meta-analysis that refers to the node status before and after NAC, specifically initially clinically node-negative cases, which was published by Geng *et al*.[41] The meta-analyses in this subject are summarized in Table 3. We think that the present meta-analysis is one of the most unique and comprehensive studies in this territory.

Based on studies of SLNB in node-negative patients with upfront surgery, IR >90% and FNR <10% have been accepted as oncologically aspect. In the patients who underwent NAC and then SLNB, these cutoff values were also considered; however, keep in mind that, these figures are arbitrary.[49,50] In the meta-analysis established by Geng *et al*.,[41] the pooled IR and FNR were 96% and 6%, respectively. The present study revealed pooled IR of 94% and FNR of 7% in the initially node-negative subgroup, while the pooled IR and FNR were 80.5% and 13%, respectively, in the node-positive converted to node-negative subgroup. Theoretically, chemotherapy leads to fibrosis and shrinkage and induces emboli and debris depositions in lymphatic routes that can alter lymphatic mapping and decrease IR. In addition, uneven disappear tumor burdens in LNs so as SLNs are sterilized, but non-SLNs remain involved, leading to high FNR.[29,41,42,51] However, this concept has not been proved. Van der Heiden-van der Loo *et al*.[52] showed that there was no statistical difference between IR of SLN before or after NAC. However, it seems that IR in upfront SLNB is higher than in IR of SLNB after NAC.[18,23,48,53] In a study established by Hunt *et al*.,[25] there were no differences in FNR between upfront SLN and SLN after NAC. Furthermore, some studies in clinically node negative have revealed identical accuracy in primary SLNB and SLNB after NAC.[53,54]

Table 3: Systematic reviews and meta-anaiyses

Study	Year of publication	Number of literatures	Number of patients
Geng *et al*[41]	2016	16	1456
Mocellin *et al*[42]	2016	72	7451
Van Nijnatten *et al*[43]	2015	8	1395
Fu *et al*[44]	2014	15	2471
Fontein *et al*[45]	2013	40	3328
Tan *et al*[46]	2011	10	449
Van Deurzen *et al*[47]	2009	27	2148
Xing *et al*[48]	2006	21	1273

The SENTINA study has shown that dual tracer increases IR.[37] The GANEA series has stated an IR of 90% with dual tracer.[24] In the NASBP-B27 study, IR was 78.1%, 88.9%, and 87.6% in blue dye alone, radioisotope alone, and in combination, respectively.[19] In the SN-FNAC trial, the use of dual tracer was associated with lower FNR.[55] The Alliance research has revealed low FNR with dual tracer.[56] Hunt *et al*.[25] reported lower FNR with radioisotope alone or combination of two tracers. It seems that for increasing IR and decreasing FNR, dual-tracer mapping is required. However, Geng *et al*.[41] concluded that there were no differences between the type of tracer mapping agents. In particular, it has been suggested that this difference may be related to the fact that the initial axillary status varied among the patients included in their study. With respect to these studies, dual tracer deems better than one.

The SENTINA and Alliance trials have resulted that for decreasing FNR <10%, at least 3 SLNs should be harvested.[37,56] SN-FNAC study has recommended that at least 2 SLNs should be retrieved for this goal.[55] Furthermore, some studies had demonstrated a higher FNR when 1 SLN was biopsied, instead of 2 or more.[56,57] Wong *et al*.[58] stated higher FNR in initially node-negative patients in whom only 1 SLN was biopsied compared to 2 or more (14.3% vs. 4.3%). The average of SLNs excised in the SENTINA, SN-FNAC, and GANEA trials were 2, 2.7, and 1.9, respectively.[24,37,55] Our analysis showed an average SLN dissection of 2.09 and 2.05 in the initially node-negative and node-positive converted to node-negative subgroups, respectively. In the meta-analysis conducted by Fu *et al*.,[44] it was concluded that for decreasing FNR, both mapping and suspicious palpable LNs should be considered as SLNs. However, in our study, only 2 articles considered suspicious palpable LNs as SLNs.[33,39] It appears that to increase IR and decrease FNR, especially in the node-positive converted to node-negative subgroup, at least 2 SLNs should be harvested and the use of dual tracer is mandatory.

In the primary SLNB without NAC, evaluation of the ITC and micrometastasis were not recommended because there was no effect on survival. However, in SLNB after NAC, ITC and micrometastasis can result from partial response and downstage of macrometastasis before NAC.[41,43,59] The ACOSOG Z0010 trial has concluded that IHC-detected metastases in SLNs have no influence on overall survival.[60] The SN-FNAC study has recommended that ITC and micrometastasis should be considered positive in SLN to decrease FNR in the NAC setting.[55] Meta-analyses established by Tan *et al*.[46] and Geng *et al*.[41] have shown low FNR when IHC adds H and E stain. However, there was no consensus regarding the utility of IHC for evaluating SLN in the NAC setting.

CONCLUSION

There are great discrepancies between studies concerning SLNB after NAC in breast cancer. Therefore, this issue resulted in conflicting guideline recommendations. In initially node-negative patients, with regard to IR (94%) and FNR (7%) in our meta-analysis, it seems that SLNB after NAC in this group is feasible with acceptable accuracy.

In node-positive converted to node-negative patients, we did not found any meta-analysis to address this subject. Our results in this group were IR (89%) and FNR (13%) that did not reach to predefined value. Thus, SLNB after NAC in node-positive converted to node-negative patients is not recommended at this time, and novel techniques for increasing IR and decreasing FNR are required.

ASH contributed in the conception of the work, conducting the study, revising the draft, interpretation of data for the work, approval of the final version of the manuscript, and agreed for all aspects of the work.

HM contributed in the drafting and revising the draft, conducting the study, approval of the final version of the manuscript, and agreed for all aspects of the work.

MQ contributed in statistical calculations, interpretation of data for the work, approval of the final version of the manuscript, and agreed for all aspects of the work.

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Conflicts of interest

There are no conflicts of interest.

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