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ORIGINAL ARTICLE – BREAST ONCOLOGY

Axillary Management in Women with Early Breast Cancer and Limited Sentinel Node Metastasis: A Systematic Review and Metaanalysis of Real-World Evidence in the Post-ACOSOG Z0011 Era

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ABSTRACT

Background. After the publication of the Z0011 trial, the American Society of Clinical Oncology published an updated clinical practice guideline stating that clinicians should not recommend axillary lymph node dissection (ALND) for early-stage breast cancer patients with the involvement of one or two sentinel lymph nodes (SLNs). However, these recommendations have been challenged because they were mainly based on data from limited studies. The aim of the current study is to systematically compare the real-world outcomes of SLN biopsy (SLNB) alone and SLNB + ALND in patients with early-stage breast cancers and limited positive SLN metastasis in the post-Z0011 era

Patients and Methods. We searched articles in the PubMed, EMBASE, and Cochrane library databases. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were recurrence rate and the incidence of lymphedema.

Results. One randomized controlled trial and six retrospective studies with 8864 patients were retrieved. For patients with early-stage breast cancer with one or two SLN metastases, receiving SLNB alone showed no significant difference in OS, DFS, and recurrence rate compared with receiving SLNB + ALND. The incidence of lymphedema in patients who received SLNB alone was significantly lower than those who received SLNB + ALND (odds ratio 1.95, 95% confidence interval 1.02–3.71).

Conclusions. Current real-world evidence proved that the Z0011 strategy is safe with respect to survival outcomes and effective in reducing the incidence of lymphedema. ALND should be avoided in patients with early-stage breast cancer with one or two SLN metastases in the post-Z0011 era.

For decades, early-stage breast cancer has been treated with primary surgery with the evaluation of axillary lymph nodes. Because axillary lymph node dissection (ALND) is associated with some complications such as lymphedema, pain, seromas, and paresthesia,[1] sentinel lymph node biopsy (SLNB) has replaced ALND for treatment of patients with clinically node-negative breast cancer since it was introduced. Historically, patients diagnosed with any nodal metastasis through SLNB would undergo completion ALND. However, only approximately 30% of patients with a positive SLNB had residual disease in an axilla.[2] In 2011, the American College of Surgeons Oncology Group (ACOSOG) published a randomized controlled trial (RCT) "Z0011," which divided patients with early-stage breast cancer who had positive SLNB results into groups of SLNB alone and SLNB + ALND to determine their effects on both survival rates and locoregional recurrences.

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The first results with a median follow-up of 6.3 years showed that no significant differences existed between the two groups in 5-year overall survival (OS), disease-free survival (DFS), or locoregional recurrence risk.[3] A detailed follow-up report was published in 2016, concluding that, even after 10 years, no significant differences existed between the two groups in terms of OS, DFS, or locoregional relapse-free survival rates.[4,5] In addition, the AMAROS trial, which was published in 2014, showed comparable regional control with fewer side effects for patients with stage T1–2 primary breast cancer and no palpable lymphadenopathy who had underwent axillary radiotherapy compared with ALND.[2] The excellent regional control corresponded to the results of the Z0011 trial, showing that patients with limited sentinel node metastasis who were treated with breast-conserving treatment, including whole-breast irradiation and adjuvant systemic treatment, could be spared an ALND without compromising locoregional control or survival outcome.

Undoubtedly, the publication of the Z0011 results caused a paradigm shift in the standard axillary management of early-stage breast cancer.[6] The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) had earlier incorporated the Z0011 criteria into their clinical practice guidelines.[7,8] However, arguments have been raised regarding the ASCO 2014 guideline due to several shortcomings identified in the Z0011 trial, including enrollment not meeting the accrual goal, slight differences in several prognostic characteristics between groups,[3,9,10] high rates of loss to follow-up, the absence of standard testing for human epidermal growth factor receptor 2 (HER2) at the time of the study,[7] and doubts concerning its external validity and applicability to other patient populations than Westerners.[11–13] Therefore, British clinicians began their own study, the Positive Sentinel Node: Adjuvant Therapy Alone versus Adjuvant Therapy Plus Clearance or Axillary Radiotherapy (POSNOC) trial, to provide solid evidence from clinical practice by repeating the Z0011 study. The POSNOC trial is ongoing; meanwhile, real-world evidence, which is observational data generated during routine clinical practice following RCTs or derived from retrospective or prospective observational studies, continues to be generated, and clinicians generally follow the suggestion of the Z0011 study globally. We therefore systematically reviewed and metaanalyzed the real-world cases to evaluate the effects of SLNB alone and SLNB + ALND in patients with early-stage breast cancers and limited positive SLN metastases in the post-Z0011 era.

METHODS

Selection Criteria

We reviewed RCTs and retrospective and prospective cohort studies that evaluated the outcomes of SLNB alone versus SLNB + ALND in women with early-stage breast cancer and one or two SLN metastases. The inclusion criteria of our study were as follows: (1) participants included adult women with histologically confirmed invasive breast carcinoma clinically $\leq$ 5 cm; (2) less than three SLNs containing metastatic breast cancer were documented; (3) treatment included breast conserving therapy (BCT) or mastectomy; and (4) the final evaluation of prognostic outcomes was included. We excluded studies that met at least one of the following criteria: (1) the inclusion criteria of the study did not meet the SLNB strategy of Z0011 trial; (2) patients with breast cancer and SLN metastasis were not included, including studies that only enrolled SLN (+) patients with no ALND; (3) only groups receiving radiotherapy or chemotherapy with ALND were compared; or (4) duplicate reporting of patient cohorts was involved.

Search Strategy and Study Selection

Studies were identified by searching for keywords in the PubMed, EMBASE, and Cochrane Library databases. The following terms and Boolean operators were used in MeSH and free-text searches: *breast cancer*, *Z0011*, *sentinel lymph node*, *sentinel lymph node biopsy, axillary lymph node dissection* OR *non-axillary lymph node dissection*. The "related articles" facility in PubMed was used to broaden the search. The searches were restricted to those in English language. A comprehensive search was performed on February 7, 2020. Moreover, we searched the reference sections of relevant papers and contacted known experts in the field. Finally, unpublished studies were searched using the ClinicalTrials.gov registry (http://clinicaltrials.gov/). The systematic review described in this study was registered on the online PROSPERO International prospective register of systematic reviews of the National Institute for Health Research (CRD42020157621).

Data Extraction

Two reviewers independently extracted the details of studies regarding population characteristics, inclusion and exclusion criteria, the pathological definition of SLN metastasis, prognostic outcomes, and surgical complications. The independent recorded decisions of the two reviewers were compared, and any disagreements were resolved based on the evaluation of a third reviewer.

Methodological Quality Appraisal

Two reviewers independently appraised the methodological quality of each study by using the Risk of Bias tool (version 2.0, Bristol, UK)[14] for the RCTs and bias risk in Nonrandomized Studies of Interventions (Bristol, UK, and Boston, MA)[15] for cohort studies. Several RCT domains were assessed, including random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For cohort studies, pre-, at, and postintervention biases as well as overall biases were assessed.

Outcomes Assessment

The primary endpoints were OS and DFS. Secondary endpoints were the disease recurrence rate (DRR), locoregional recurrence rate (LRR), and surgical complications of ALND, such as pain, lymphedema, and wound infections.

Statistical Analyses

Statistical analysis was conducted using Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK). The metaanalysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] The recurrence outcomes and side effects were reported as odds ratios (ORs), and time-related endpoints were reported as hazard ratios (HRs). The precision of an effect size was reported as a 95% confidence interval (CI). A pooled estimate of the OR and HR was calculated using the DerSimonian and Laird random-effects model.[17] This generated relatively wide CIs and an appropriate estimate of the average treatment effect for statistically heterogeneous trials, resulting in a conservative statistical claim. The data were pooled only for studies exhibiting adequate clinical and methodological similarity. Statistical heterogeneity was assessed using the I^2 test, with I^2 quantifying the proportion of the total outcome variability that was attributable to variability among the studies.

RESULTS

Study Characteristics

The flowchart shows the screening and selection process of the studies (Fig. 1). Our initial search yielded 2980 results, 1240 of which were duplicates. After screening the titles and abstracts, 1703 studies were deemed ineligible and excluded. Next, we retrieved the full text of the 37 remaining studies for further review; 29 articles were excluded from our final analysis for the following reasons: 5 consisted of an inappropriate population, 8 made different comparisons, 5 had inappropriate outcomes, 4 were ongoing clinical protocols, and 8 were review articles. The remaining seven eligible studies were included in our analysis, and their characteristics are presented in Table 1.[9,18–23]

The included studies were published between 2011 and 2019, with a total of 8864 patients. The majority of them were multicenter studies,[9,22,23] but some were single-center studies.[18,20,21] The ACOSOG Z0011 trial included four published articles: a comparison of complications associated with ALND and non-ALND treatment,[10] a report of local and regional recurrence information,[3] a determination of the effects of complete ALND on survival,[9] and a long-term follow-up of 10-year survival outcomes and recurrence between two groups.[5] Jung et al.[23] conducted a retrospective study that enrolled Asian patients who fulfilled the Z0011 criteria from five Korean teaching hospitals. Lee et al. conducted a retrospective study that used the Korean Breast Cancer Society data from 41 university hospitals and 61 training hospitals in Korea. They also enrolled patients who fulfilled the Z0011 criteria and determined the survival outcomes between the SLNB-alone and SLNB + ALND groups.[22] Weiss et al.[21] conducted a retrospective study to evaluate the hospital's experience of the practice after the publication of the Z0011 trial results. Fu et al.[20] conducted a retrospective study that included patients with nonmetastatic invasive breast cancer who had undergone mastectomy and lymph node staging surgery (either SLNB or ALND) at the Revlon/UCLA Breast Center. Patients who underwent mastectomy and SLNB with pathological N1 (pN1) disease were further divided into three subgroups: observation, radiation, and additional ALND with or without radiation. Wang et al.[19] conducted a retrospective study and identified patients with invasive lobular carcinoma (ILC) who fulfilled the Z0011 criteria in the Surveillance Epidemiology and End Results database. The objective of the study was to determine whether the Z0011 strategy could be safely applied to patients with ILC. Yi et al.[18] retrospectively identified patients who had undergone BCT or mastectomy with breast tumor sizes $\leq$ 5 cm and fewer than three SLN metastases from the Surgical Breast Oncology Research database at The University of Texas MD Anderson Cancer Center. Regarding SLN metastasis status, most patients in the included studies had one SLN metastasis (Table 1). Patients underwent BCT and SLNB alone or SLNB + ALND in all the included trials; mastectomy was only performed in the study by Fu et al.[20]

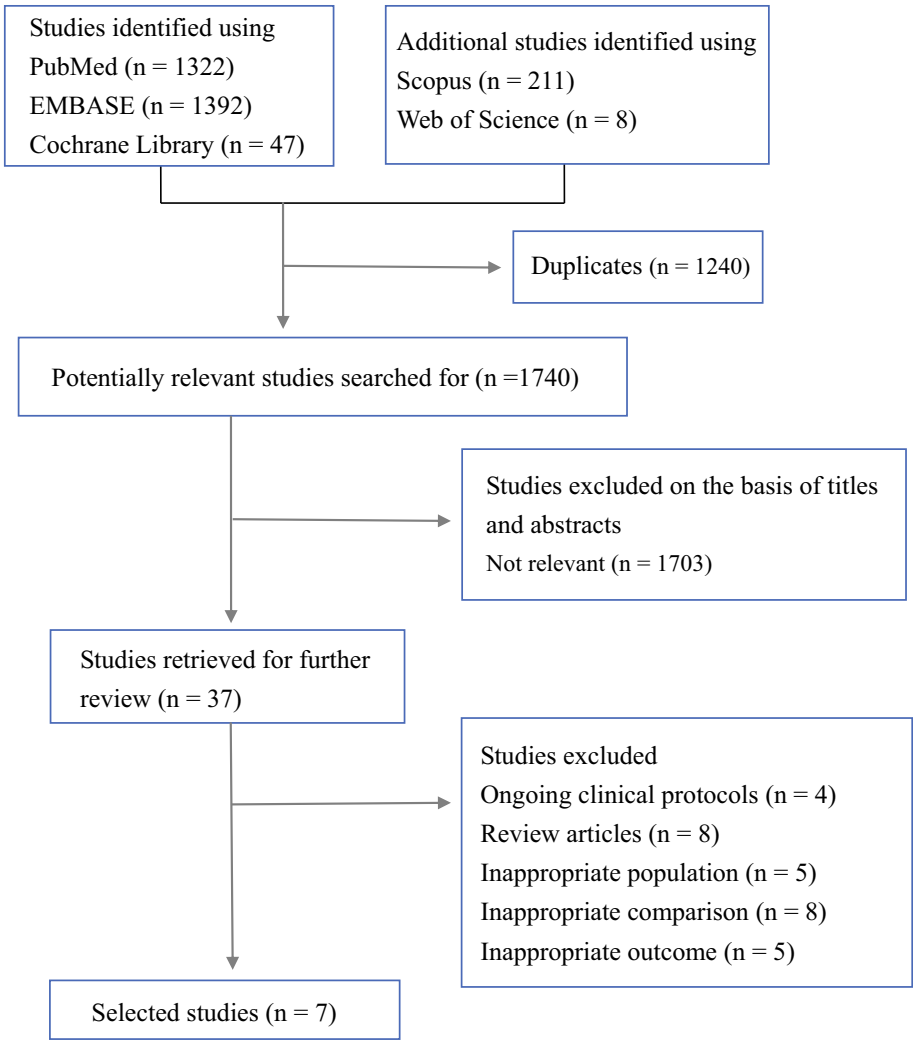

FIG. 1 Flowchart of study selection

Table 2 presents a methodological quality summary of the included studies. The ACOSOG Z0011 trial has moderate risk of allocation bias due to the intended interventions without double blind. Moderate risk of bias also presents due to the high rate of loss to follow-up (166 of 891 patients; 18.6%). Among six retrospective studies, many of them are at moderate risk during the processes of preintervention due to several differences in baseline parameters and significant prognostic characteristics between groups. Most of them also have moderate risk of deviations from intended interventions during post intervention periods because of the significant imbalance in the number of patients between groups. Overall, the ACOSOG Z0011 trial has a moderate risk of bias, while other six retrospective studies have moderate risk of biases.

Survival Outcome

Five studies investigated the OS between SLNB alone and SLNB + ALND groups.[9,18–20,22] Two of these five studies recorded the OS rates in multiple months of 24,[19–22] and another study presented the OS rates in years.[9] Therefore, we statistically analyzed the intersection of these three studies with the 6-year OS rates.[9,19,22] Our result indicated no significant difference in the 6-year OS time between the SLNB alone and SLNB + ALND groups, with a pooled OR of 1.59 (95% CI: 0.77–3.26; Fig. 2A). The other two studies presented the 5-year OS as HR.[9,22] Similarly, the result showed no significant difference in the 5-year OS between the two groups, with a pooled HR of 0.85 (95% CI: 0.64–1.12; Fig. 2B).

Two of the included studies had assessed 5-year DFS between the SLNB alone and SLNB + ALND groups.[9,18] The pooled HR of 0.57 (95% CI: 0.22–1.47) of our meta-analysis showed no significant difference in the 5-year DFS between the two groups (Fig. 2C).

TABLE 1 Characteristics of studies that fulfilled the metaanalysis inclusion criteria

Study [year]	Study design [country]	Inclusion criteria	Number of patients	Age, years	Tumor size, cm	SLN metastatic status	Intervention
ACOSOG Z0011 Giuliano [2011]; Giuliano [2017]	RCT [USA]	Tumor ≤ 5 cm; SLN metastasis < 3	D: 420 N: 436	D: 56 (24–92)* N: 54 (25–90)*	D: 1.7 (0.4–7.0)* N: 1.6 (0.0–5.0)*	D: 0: 4 (1.2%) 1: 199 (58.0%) 2: 68 (19.8%) 3: 25 (7.3%) ≥ 4: 47 (13.7%) N: 0: 29 (7.0%) 1: 295 (71.1%) 2: 76 (18.3%) 3: 11 (2.7%) ≥ 4: 4 (1.0%)	D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)
Jung [2019]	Retrospective cohort [Korea]	Tumor ≤ 5 cm; SLN metastasis < 3	D: 990 N: 707	D: 50 (25–88)* N: 50 (25–88)*	D: 2.2† N: 2.0†	D: 1: 763 (77.1%) 2: 227 (22.9%) N: 1: 646 (91.4%) 2: 61 (8.6%)	D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)
Lee [2018] D: N: 1.14 ± 0.34	Retrospective cohort [Korea] 1.30 ± 0.46	Tumor ≤ 5 cm; SLN metastasis < 3 D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)	D: 3174 N: 1268	D:		49.26 ± 9.54‡ N: 49.55 ± 9.29‡	D: 1.88 ± 0.84‡ N: 1.81 ± 0.84‡
Weiss [2018]	Retrospective cohort [USA]	Tumor ≤ 5 cm; SLN metastasis < 3	D: 4 N: 44	D: 48 (38–76)* N: 59.5 (29–82)*	D: 1.6 (1.5–1.8)* N: 1.6 (0.6–5.0)*	D: 1: 2 (50.0%) 2: 2 (50.0%) N: 1: 43 (97.7%) 2: 1 (2.3%)	D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)
Fu [2014]	Retrospective cohort [USA]	SLN metastasis < 4	D: 64 R: 16 O: 23	D: 49 (21–77)* R: 54 (40–81)* O: 51 (31–70)*	No data	No data	D: mastectomy + SLNB (+) + ALND R: mastectomy + SLNB (+) + RT O: mastectomy + SLNB (+) + observation
Wang [2014]	Retrospective cohort [USA]	ILC; tumor ≤ 5 cm; SLN metastasis < 3	D: 876 N: 393	D: 60 (28–87)* N: 64 (35–91)*	D: 1.8 (0.1–5.0)* N: 1.7 (0.1–5.0)*	D: 1: 607 (69.3%) 2: 269 (30.7%) N: 1: 347 (88.3%) 2: 46 (11.7%)	D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)
Yi [2013]	Retrospective cohort [USA]	Tumor ≤ 5 cm; SLN metastasis < 3	D: 328 N: 121	D: 55 (22–82)* N: 57 (37–88)*	D: 1.5 (0.1–5.0)* N: 1.3 (0.5–3.5)*	Micrometastasis: D: 69 (21.0%) N: 87 (71.9%) Macrometastasis:	D: BCT + SLNB (+) + ALND N: BCT + SLNB (+)

Table 1 (continued)

Study [year]	Study design [country]	Inclusion criteria	Number of patients	Age, years	Tumor size, cm	SLN metastatic status	Intervention
						D: 259 (78.5%) N: 34 (28.1%)	

ALND axillary lymph node dissection, *BCT* breast conserving therapy, *D* axillary lymph node dissection group, *ILC* primary invasive lobular breast carcinoma, *LN* lymph node, *N* nonaxillary lymph node dissection group, *O* observation group, *R* axillary lymph node radiation group, *RCT* randomized controlled trial, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy

*Indicates median (range)

†Indicates mean (range)

‡Indicates mean ± SD

Recurrence Rates

One included study compared disease recurrence between the SLNB alone and SLNB + ALND groups using the DRR.[23] The SLNB alone group had a significant lower DRR than that of the SLNB + ALND group (OR 2.03; 95% CI: 1.26–3.28; Fig. 3A).

Evaluation of LRR between the SLNB alone and SLNB + ALND groups was reported in five studies.[9,18–20,23] Among these five studies, only Wang et al.[19] subdivided categories of locoregional recurrence into ipsilateral breast tumor recurrence (IBTR) and regional disease. Therefore, we combined the incidences of IBTR and regional disease as the locoregional recurrence of the study. Regarding the result of our metaanalysis, we could see a trend toward the SLNB-alone group, which seemed to have a lower LRR than the SLNB + ALND group, even though no significant difference existed between the two groups, with a pooled OR of 1.63 (95% CI: 0.96–2.77; Fig. 3B).

Incidence of Lymphedema

The incidences of lymphedema were reported in two studies.[9,20] Significant differences were observed between the SLNB alone and SLNB + ALND groups in the postoperative follow-up, with a pooled OR of 1.95 (95% CI: 1.02–3.71; Fig. 4).

DISCUSSION

Our metaanalysis revealed that performing SLNB alone in patients with early-stage breast cancer and one or two SLN metastases showed equivalent survival and recurrence outcomes to those receiving SLNB + ALND. Furthermore, omitting ALND could decrease the incidence of lymphedema.

In the post-Z0011 era, the standard axillary management of early-stage breast cancer has changed dramatically. The ASCO 2014 guideline states that clinicians should not recommend ALND for patients with early-stage breast cancer and one or two SLN involvements who will undergo breast-conserving surgery with whole-breast radiotherapy.[7] In addition to reiterating the above recommendation, the ASCO guideline updated in 2016 also stated that clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found in SLNB specimens who will receive mastectomy.[24] Several studies have indicated that many surgeons around the world are showing increasing acceptance of the Z0011 result and have already modified their clinical practice.[25] However, the most debatable point of such recommendation and clinical practice is that the evidence is mainly

TABLE 2 Assessment of methodological quality of included studies

RCT [year]		ACOSOG Z0011 [2011, 2017]
RCT evaluated by RoB 2.0		
Bias arising from the randomization process		Low risk
Bias due to deviations from intended interventions		Moderate risk[a]
Bias due to missing outcome data		Moderate risk[b]
Bias in measurement of the outcome		Low risk
Bias in selection of the reported result		Low risk
Overall risk of bias		Moderate

Author [year]		Jung (2019)	Lee [2018]	Weiss [2018]	Fu [2014]	Wang [2014]	Yi [2013]
Retrospective study evaluated by ROBINS-I							
Preintervention	Bias due to confounding	Low[c]	Moderate[d]	Moderate[d]	Moderate[d]	Moderate[d]	Moderate[d]
	Selection bias	Low	Moderate[e]	Moderate[f]	Moderate[g]	Low	Low
At intervention	Bias in classification of interventions	Low	Low	Low	Low	Moderate[h]	Low
Postintervention	Deviation from intended interventions	Moderate[i]	Moderate[i]	Low	Moderate[j]	Some concern[k]	Moderate[i]
	Bias due to missing data attrition	Low	Low	Low	Low	Low	Low
	Bias in measurement of outcomes	Low	Low	Low	Low	Moderate[l]	Low
	Bias in selection of reported results	Low	Low	Moderate[m]	Low	Low	Low
Overall bias		Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

[a]Without double blind

[b]High rate of loss to follow-up (166 of 891 patients; 18.6%)

[c]Although there was some significant difference in baseline parameters between the two groups, authors had used propensity score for matching

[d]Some baseline parameters between the two groups had significant difference

[e]Duration of enrollment of this article ranged from 1995 to 2014, spanning the publish of Z0011 study

[f]Number of patients in the SLNB + ALND group was too small to represent the population

[g]Duration of enrollment of this article ranged from 2002 to 2010, spanning the publish of Z0011 study

[h]Database did not clearly specify whether a patient underwent SLNB alone or SLNB + ALND, therefore surrogates were used to distinguish them

[i]Significant difference was noted in number of patients who had received chemotherapy between the two groups

[j]Significant difference was noted in number of patients who had received endocrine therapy between the two groups

[k]Database did not provide specific data of which radiation therapy and systemic therapy patients had used in both groups

[l]Database did not provide information of locoregional recurrence, therefore authors identified registered entries after primary surgery instead

[m]Nomogram prediction of additional positive non-SLN was used to present final result rather than survival or recurrence outcomes

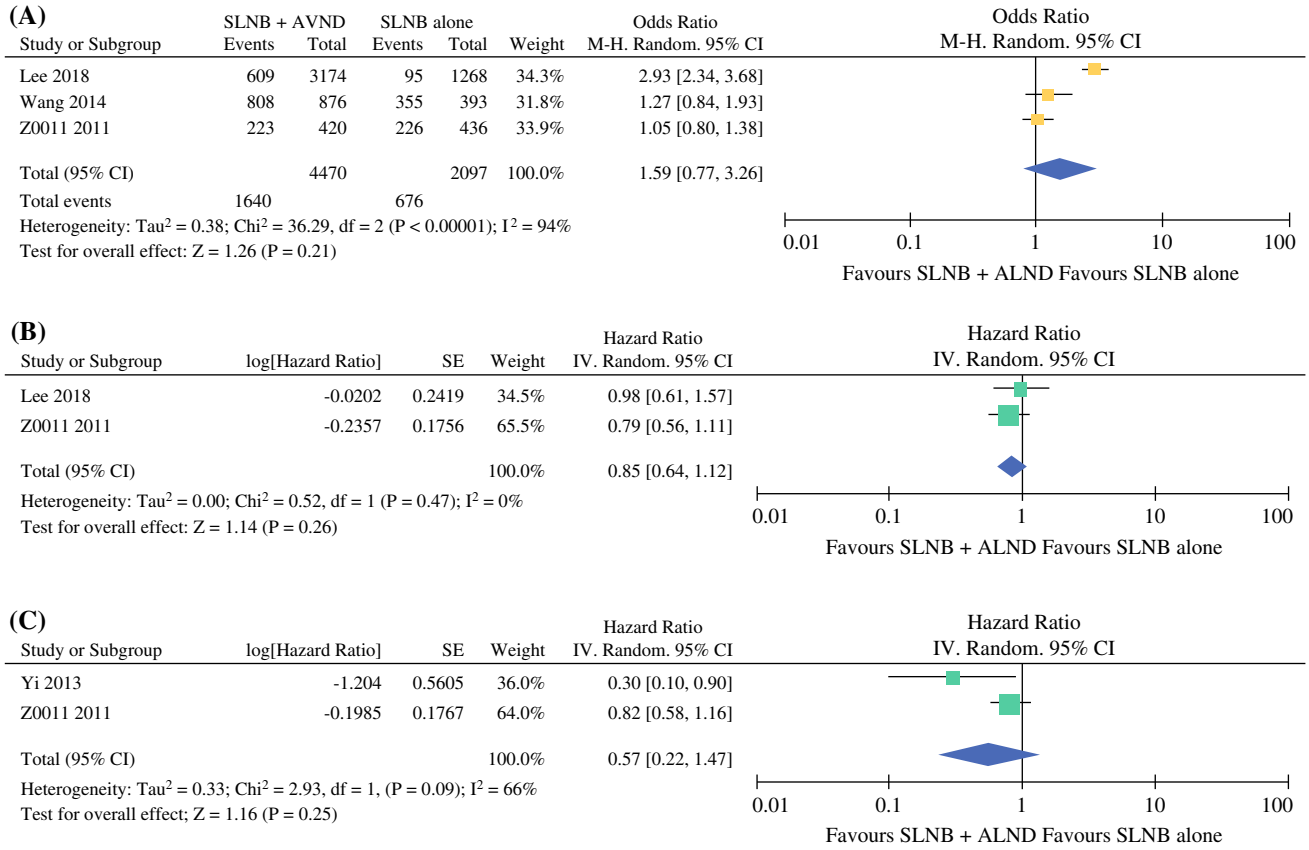

FIG. 2 Forest plot of comparison of outcomes between the SLNB-alone and SLNB + ALND management groups for overall survival presented using odds ratio (**a**) and hazard ratios (**b**). Forest plot of comparison of outcomes between the SLNB alone and SLNB + ALND management groups for disease-free survival presented using hazard ratios (**c**)

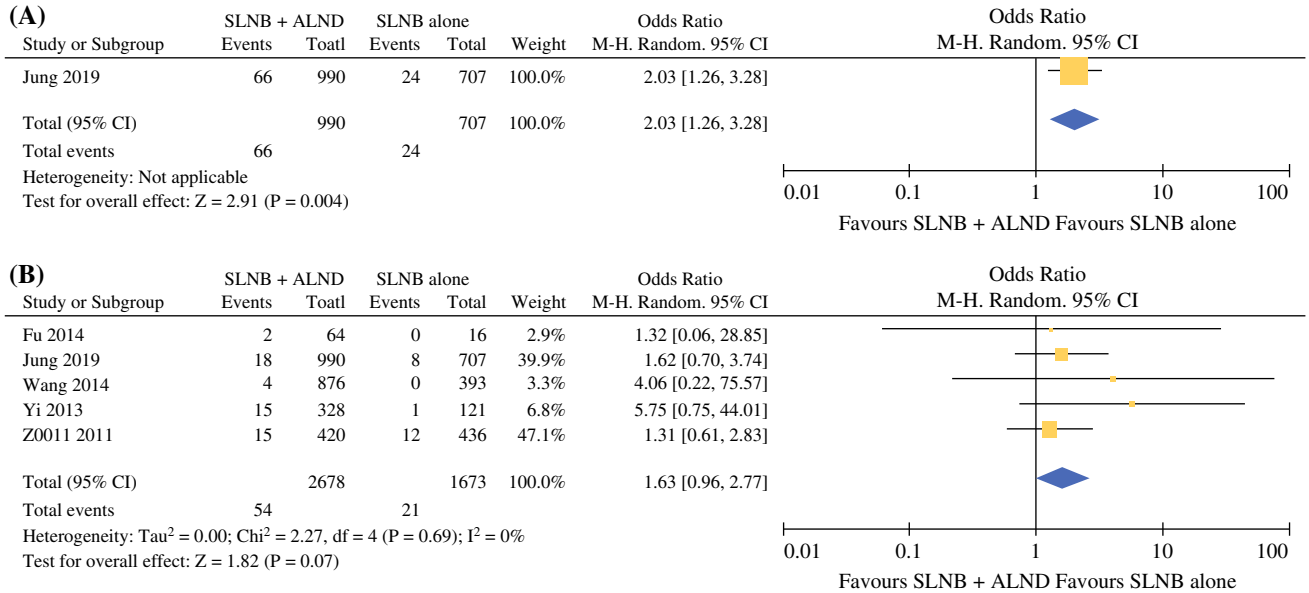

FIG. 3 Forest plot of comparison of outcomes between the SLNB alone and SLNB + ALND management groups for disease recurrence presented using odds ratio (**a**) and, for locoregional recurrence, presented using odds ratio (**b**)

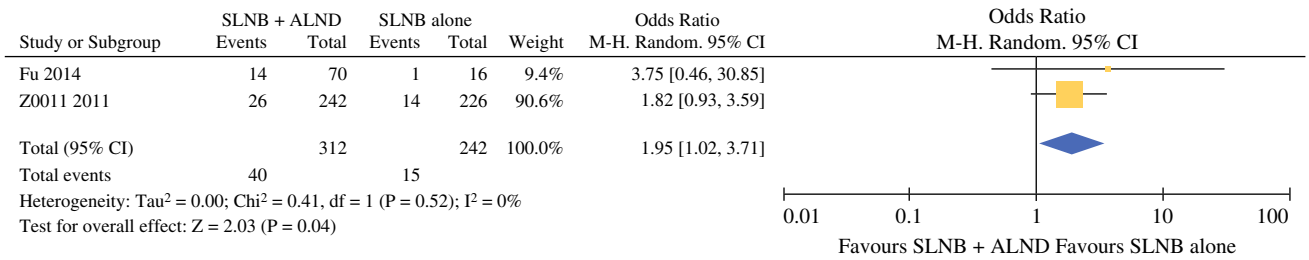

FIG. 4 Forest plot of comparison of outcomes between the SLNB alone and SLNB + ALND management groups for lymphedema incidence presented using odds ratio

based on limited studies, which has been criticized prematurely.[26] Therefore, a metaanalysis of the real-world evidence is critical to enable clinicians to integrate the current results into clinical practice.[27] In our study, we included one RCT [9] and six cohort studies,[18–23] which were conducted in different areas in the world. Our results indicate that omitting ALND is safe for patients with early-stage breast cancer and one or two metastatic SLNs because the results are synonymous with the outcomes of the Z0011 trial. An ongoing trial, the aforementioned POSNOC (ISRCTN54765244), which aims to repeat the Z0011 trial and provide stronger evidence to inform clinical practice, is expected to be completed in March 2023. Instead of waiting for a decade to clarify these recommendations, we generated confirmatory real-world evidence of the safety of the Z0011 strategy through our metaanalysis.

Omitting ALND in patients with different molecular subtypes of breast cancer has been criticized since HER2 testing was not reported in the publication of the Z0011 study. For patients with HER2-positive disease who might have available efficacious targeted therapies, omitting ALND may produce only small percentages of complete response. Moreover, it is particularly debatable in triple-negative patients for whom currently no proved targeted therapy is available to control residual disease.[26] Although the applicability of Z0011 results to various molecular subtypes of breast cancer remains controversial, four retrospective cohorts in our study provided the HER2 status of patients in the SLNB alone and SLNB + ALND groups;[20–23] the baseline characteristics of molecular subtypes were similar among patients of these two groups, and the final survival and recurrence outcomes were not inferior in the SLNB alone group. [20–23] Jung et al. performed a univariable analysis according to estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 gene expression status, and Ki-67 expression status of patients, showing that ALND omission did not increase the disease-recurrence risk for any of these subgroups.[23] This result might correspond to the fact mentioned by the author of the Z0011 study that the locoregional recurrence of HER2-positive breast cancer has decreased due to its sensitivity to trastuzumab and response to adjuvant systemic therapy.[28]

Slight differences in terms of tumor stage (T stage), grade, and lymphovascular invasion were noted between the SLNB alone and SLNB + ALND groups; therefore, the result of the Z0011 study has been challenged, in particular these differences were all favoring the SLNB-alone group.[26] However, the concerns might be resolved based on some of our included studies. Wang et al. included more patients with T1 stage breast cancer (555 vs. 266) and histologic grade I (173 vs. 97) in the SLNB + ALND group than in the SLNB-alone group.[19] Moreover, Lee et al. noted similar positive and negative percentages of lymphatic invasion between the SLNB-alone and SLNB + ALND groups (positive: 40.7% vs. 40.8%; negative: 59.3% vs. 59.2%). Additionally, comparing with the SLNB-alone group, a low percentage of patients presented with vascular invasion in the SLNB + ALND group (SLNB alone vs. SLNB + ALND: 24.3% vs. 23.4%).[22] On the basis of the above characteristics of our included studies, the final survival and recurrence outcomes were not inferior in the SLNB alone group, and even the inequalities of the baseline characteristics in T stage, grade, and lymphovascular invasion between the two groups were diminished.

Our study has some heterogeneity. First, the median follow-up periods of the studies included in our meta-analysis ranged from 40 months [23] to 9.3 years,[5] which were relatively short, given that our participants had early-stage disease. Some of the patients in our included studies had typically ER-positive tumors, which have long-term disease-recurrence risk.[29,30] Prolonged follow-up might be needed to determine whether a significant difference exists between the SLNB alone and SLNB + ALND groups in terms of late recurrence. Second, preoperative axillary evaluations and surgery performance varied based on clinicians.

Some limitations were noted in our study. First, six retrospective cohorts might have caused high selection bias owing to their retrospective nature. Some databases did not

specify whether a patient underwent SLNB alone or SLNB + ALND, and therefore, surrogates were needed to distinguish them.[19] Some unexpected treatments based on preoperative axillary evaluations were noted; For example, clinically node-negative patients who routinely underwent axillary sonography might have undergone upfront ALND or neoadjuvant systemic therapy, which would have resulted in these cases being excluded from retrospective cohort studies.[23] Furthermore, the factors that prompted clinicians to recommend further surgery were unclear. Last, ALND may had been avoided in patients due to favorable clinical-pathologic characteristics in retrospective cohort studies.

To conclude, our metaanalysis revealed that patients with early-stage breast cancer and one or two metastatic SLNs undergoing SLNB alone did not experience decreased disease control, DFS, or OS with the elimination of ALND. Moreover, ALND morbidities such as lymphedema could be avoided without decreasing cancer control. Therefore, we recommended to avoid ALND in patients with early-stage breast cancer with one or two SLN metastases in the post-Z0011 era. However, these findings must not be applied in clinical practice for the management of patients who are noneligible for Z0011 criteria. ALND is still indicated for patients with extensive axillary disease and those undergoing mastectomy with any SLN metastases present.[31] Surgeons should carefully choose available options which are supported by evidence, and patient preferences should also be considered in clinical decision-making.

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