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Review Article

Efficacy and safety of omitting axillary lymph node dissection in early breast cancer patients with sentinel-node metastases: a systematic review and meta-analysis

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Abstract: *Objective*: This systemic meta-analysis aimed to evaluate the efficacy and safety of omitting axillary lymph node dissection in early stage of breast cancer (T1-2) with positive sentinel lymph node (SLN) and without palpable lymphadenopathy. *Methods*: All available literature of randomized controlled trials (RCT) and cohort studies was pooled from Cochrane library, PubMed, Medline, OVID, Springer Linker, Science Direct, EBSCO. Relevant references were also manually retrieved. The primary outcome was efficacy, including overall survival, disease-free survival, local recurrence. The secondary outcome was safety, including the lymphedema, neuropathy, and dysfunction of arm movement. The meta-analysis was performed by Stata 12.0. *Results*: Five RCTs and three cohort studies that met the inclusion criteria were included in this meta-analysis. It was found that when compared with no axillary lymph node dissection (ALND) group, ALND did not significantly improve the OS (hazard ratio (HR)=1.01, 95% CI: 0.96~1.07, *P*=0.662), DFS (HR=0.96, 95% CI: 0.80~1.15, *P*=0.644) and local recurrence (OR=2.32, 95% CI: 0.91~5.89, *P*=0.78). However, subgroup analysis based on the status of SLN showed that patients with macrometastasis of SLN (defined as tumor deposits>2 mm) had a higher recurrence rate (OR=5.96, 95% CI: 1.33~26.70, *P*=0.02). The incidence of postoperative complications including lymphedema, sensory neuropathy, motor neuropathy and infection in the no-ALND group was significantly lower than that in the ALND group (P<0.05 or 0.01). *Conclusion*: ALND could be omitted in patients with T1-2 primary breast cancer and without palpable lymphadenopathy.

Keywords: Breast cancer, sentinel lymph node biopsy, axillary lymph node dissection, meta-analysis

Introduction

Breast cancer remains the most common malignancy among women worldwide, causing an estimated 1.38 million new cases per year [1]. Despite the increasing incidence rate of breast cancer, its mortality rate has been substantially decreased, which is mostly attributed to the improvement of breast cancer screening programmes and public awareness [1]. Currently, a large number of patients are diagnosed with T1-2 primary breast cancer and without palpable lymphadenopathy. This type of breast cancer has a low incident of metastases [2]. The surgical management for these patients has ranged from standard radical surgical resection to breast-sparing approach [2]. However, the optimal management of the axillary lymph nodes (ALN) remains controversial. In early breast cancer patients, the presence of ALN metastasis remains the most important prognostic factor for survival and recurrence, and thus strongly influences the therapeutic option [3].

Axillary lymph node dissection (ALND) may cause many complications, such as lymphedema, seroma, pain, infection and reduced arm movement [4]. To avoid unnecessary complication caused by ALND, sentinel lymph node biopsy (SLNB) has been employed as an substitution for ALND [5]. The SLN is defined as the first-draining lymph node (LN) on the direct lymphatic pathway from the primary tumor site.

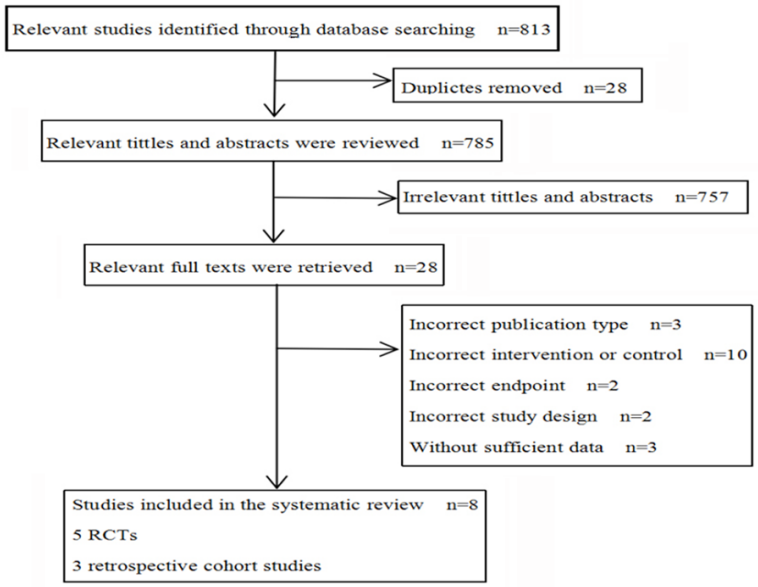

Figure 1. Flow diagram of the literature search and trail selection process.

When the SLN is free from tumor metastasis, it is highly likely that subsequent LNs are also tumor-free [6]. ALND is obviously not necessary for patients without SLN metastasis. NCCN guideline [7] explicitly recommends ALND as the standard management for patients with positive SLN. However, ALND result have shown that 25-50% of SLN-positive patients especially those with only micrometastasis, have no additional lymph node involved [8]. Therefore, it is often hard for oncologists to decide whether ALND is an excessive treatment conferring little benefit to low-risk breast cancer patients with SLN positive and without palpable lymphadenopathy.

Recently, the Z0011 trail [9] recruited breast cancer patients with one or two SLN metastasis to prove that omitting ALND is a no-inferior management compared to completing ALND. Even though this trail was terminated due to unsuccessful patient enrolment, the study has challenged the use of ALND in early breast cancer patients with positive SLN and without palpable lymphadenopathy. In addition, 5 RCTs and 3 retrospective cohort studies [9-16] have also been conducted on this subject. In this systematic review, we identified relevant literature and conducted a meta-analysis to compare the clinical efficiency and safety between omitting ALND and ALND completion in breast cancer patients (T1-2) with positive SLN and without palpable lymphadenopathy.

Methods

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Search strategy

A computer-aided search of the Pubmed/Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL: issue 3, 2011) was performed to identify relevant literature comparing SLNB with ALND for staging early breast cancer. The upper limit of search date was not limited, and the lower limit was March 2011. The following search phrases were used: breast neoplasm/neoplasms, breast cancer, breast carcinoma, breast tumor/tumor, sentinel lymph node, sentinel node, axillary. Both free text and MeSH search for keywords were employed. The language was not limited. To search more potentially relevant trials, reference lists from the selected studies by electronic searching were also screened.

Search criteria

The reference was searched based on the following criteria: 1) Randomized controlled clinical studies or cohort studies. If dual (or multiple) studies were reported by the same institution and/or authors, the one of higher quality or the most recent publication was selected. The language is not restricted; 2) The research objects: TcT1~2N0M0 and SLN positive breast cancer patients; 3) Intervention: experimental group without ALND and the control group with ALND; 4) The curative effect is definite. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded. The following studies were also excluded: 1) Lack relevant outcomes; 2) The maximum tumor diameter more than 5 cm or palpable lymphadenopathy; 3) Prior history of

Table 1. Main characteristics of the included studies and their patients

Study	Author	Year	Type of study	Follow-up	Criterion	Outcome	Intervention	Population characteristics												
								Age (years)	Clinical tumor stage (%)			size (cm)	Histological tumor grade (%)			Hormone receptor (%)		Nodal metastases		Surgery (%)	
									T1		T2		I	II	III	ER+/PR+	ER+/PR-	Micro	Macro	BCT	ME
Z0011	Ginliano	2011	RCT	6.3 years	T1-T2 1-2 SLNs+	OS, mobidities	SLNB	54	70.6		29.4	1.6	25.6	46.8	27.5	68.9	13.8	44.8	55.2	100	0
						DFS, recurrence	SLNB+ALND	56	67.9		32.1	1.7	22.0	48.9	29.1	66.8	15.9	37.5	62.5	100	0
														II-III		ER+	PR+	Micro	Macro	BCT	ME
AATRM	Sola	2012	RCT	5 years	T <3.5 cm cN0M0	DFS, recurrence	SLNB	53.2		n.r.		1.78		79.8		83	78.8	100	0	93.4	6.6
							SLNB+ALND	55.3		n.r.		1.68		68.2		85.1	73.3	100	0	91.1	8.9
									<2 cm	2-2.9 cm	≥3 cm		I	II	III	ER+	PR+	Micro	Macro	BCT	ME
IBCSG 23-01	Galimberti	2013	RCT	5 years	≤ 5 cm ≥1 SLN+ micro	DFS, OS recurrence	SLNB	54	69	24	6	n.r.	19	52	29	91	75	100	0	91	9
							SLNB+ALND	53	68	23	8	n.r.	25	46	28	88	76	100	0	91	9
									0-2 cm	2-5 cm	5 cm		I	II	III			Micro	Macro	BCT	ME
AMAROS	Donker	2014	RCT	6.1 years	T1-2 cN0M0	5-year axillary recurrence, DFS, OS, axillary recurrence-free survival, mobility	SLNB+AR	55	78	21	<1	1.8	23	46	29	n.r.	n.r.	39	62	82	18
							SLNB+ALND	56	82	18	0	1.7	24	48	26	n.r.	n.r.	41	59	82	17
									T1		T2		I	II	III	ER+	PR+	Micro	Macro	BCT	ME
OTOASOR	Savolt	2016	RCT	97 months	cT≤3 cmcN0	axillary recurrence, DFS, OS	SLNB+AR	54.7	68		32	n.r.	22	48	30	84	73	33.5	60.4	84	16
							SLNB+ALND	55.2	62		38	n.r.	16	51	33	83	73	n.r.		82	17
									T1	T2	T3		low/intermediate		high			Micro	Macro	BCT	ME
NCDB data	Bilimoria	2009	retrospective cohort study	63 months	SLNB nodal+	axillary recurrence survival	SLNB	58	62.9	34.4	2.6	1.8	58.8		32.5	n.r.	n.r.	18.2	81.8	81.4	18.6
							SLNB+ALND	56	49.1	43.7	7.2	2.1	53.1		39.2	n.r.	n.r.	8.5	91.5	49.6	50.4
									T1	T2	T3		low/intermediate		high	ER+	PR+	Micro	Macro	BCT	ME
SEER data	Yi	2010	retrospective cohort study	50 months	cN0M0 Nodal+	OS, disease-specific survival	SLNB	60.7	68.6	28.2	3.2	2.43	23		77	87.5	75.0	54.5	45.5	78.7	21.3
							SLNB+ALND	56.3	50.4	43	6.7	3.11	13.1		86.9	80.8	69.4	17.2	82.8	53.9	46.1
									T1		T2		I	II	III	ER+/PR+	ER+/PR-	Micro	Macro	BCT	ME
SEER data	Bonneau	2015	prospective study	31.6 months	T1-2M0 ≥3LN+	OS, SS	SLNB	57.4	43.3		56.7	2.43	16.2	42.3	41.5	69.8	11.9	0	100	48.4	50.9
							SLNB+ALND	56.4	40.2		59.8	2.47	10.4	45.5	44.1	67.7	12.8	0	100	46.5	53.4

RCT: randomised controlled trail, OS: overall survival, DFS: disease-free survival, SS: specific survival, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection, Micro: micro-metasteses, Macro: macro-metastases, BCT: breast conserving therapy, ME: mastectomy, n.r.: not reported, ER: oestrogen receptor, PR: progesterone receptor.

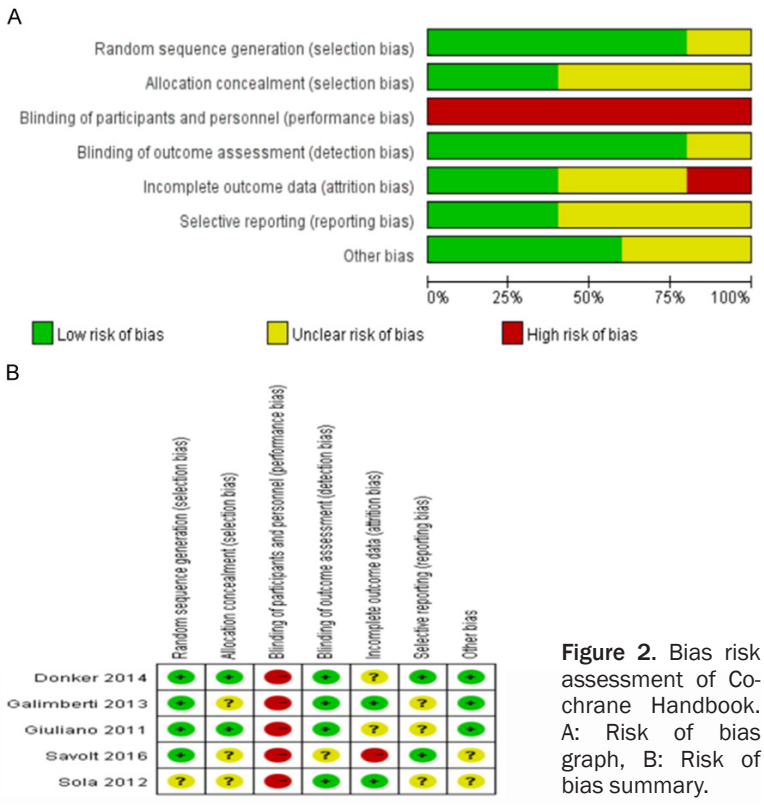

Figure 2. Bias risk assessment of Cochrane Handbook. A: Risk of bias graph, B: Risk of bias summary.

malignant tumor, neoadjuvant chemotherapy, axillary lymph node surgery or radiotherapy before enrollment.

Data extraction

Two reviewers independently extracted the following parameters from each study: (1) first author and year of publication; (2) number of patients, patients' characteristics, study design; and lastly (3) treatment outcome. All relevant text, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by discussion and consensus.

Study objectives

The primary outcome was efficacy, including overall survival, disease-free survival, local recurrence. The secondary outcome was safety, including the lymphedema, sensory neuropathy, motor neuropathy and infection.

Statistical analysis

The hazard ratios (HRs) for overall survival (OS) and disease free survival (DFS) and odds ratio (OR) for local recurrence were extracted and calculated based on a fixed-effect model first using STATA 12.0. In case that the data were not directly reported in primary literature, we derived HRs and their 95% CIs from the survival curves using published methodology [18, 19]. Subgroup analysis compared non-ALND with axillary recurrence (AR) and whether the SLN status affects patients' prognosis. Heterogeneity chi-square test was performed. $P>0.05$ and $I^2<50\%$ can be considered as fixed effects model. When $P<0.05$ and $I^2>50\%$, the random effects model is used. The bias potential was detected by a funnel plot.

Quality assessment

The Cochrane Handbook for Systematic Reviews of Interventions and Jadad scale were used to assess the quality of randomized studies [20]. And the Newcastle-Ottawa Scale (NOS) was used to assess the quality of nonrandomized studies [21].

Results

Study characteristics

A total of 813 English articles were initially extracted according to the retrieval strategy. Unqualified 785 articles were excluded by reading the abstract. The remaining 28 studies were carefully read, and 5 randomized studies [9-13] and 3 retrospective cohort studies [14-16] were eventually selected. The trail selection process was summarized in **Figure 1**. As shown in **Table 1**, there is no significant difference in baseline characteristics of patients (including age, clinical tumor stage, tumor size, histological tumor grade, hormone receptor, nodal metastases and type of surgery) between no-ALND and ALND groups. The results of assessment through Cochrane tool show low risk of bias (**Figure 2**). The quality is higher with all the 5 randomized studies (Jadad score≥3). And the quality of 3 non-randomized studies was also higher (NOS score≥6).

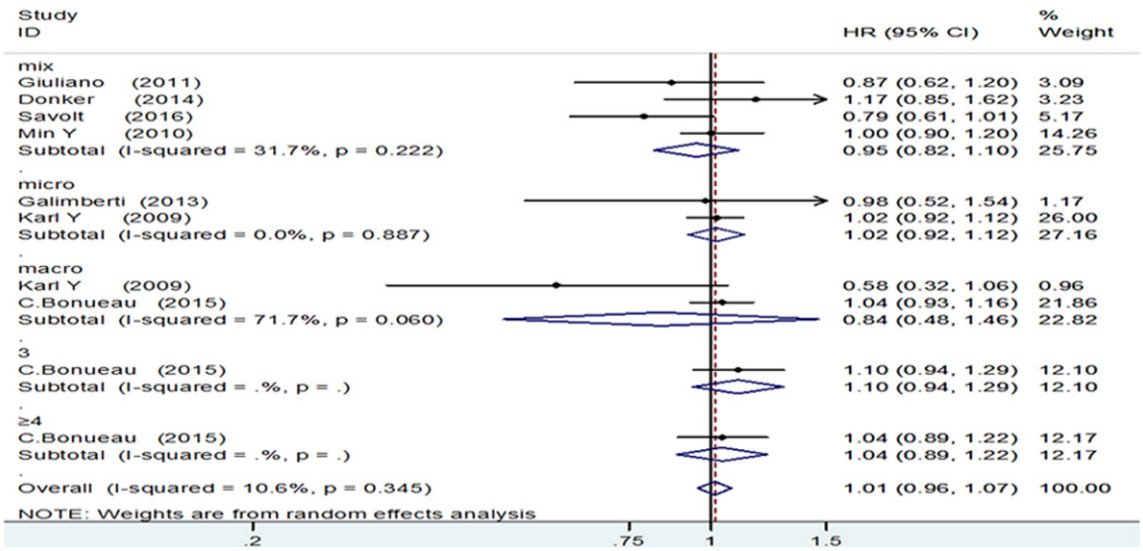

Figure 3. Forest plots of the pooled HRs for overall survival (OS) of axillary lymph node dissection (ALND) and no axillary lymph node dissection (no-ALND) groups. The results indicated that there was no significant difference in OS between no-ALND and ALND groups (HR=1.01, 95% CI: 0.96~1.07, P=0.662).

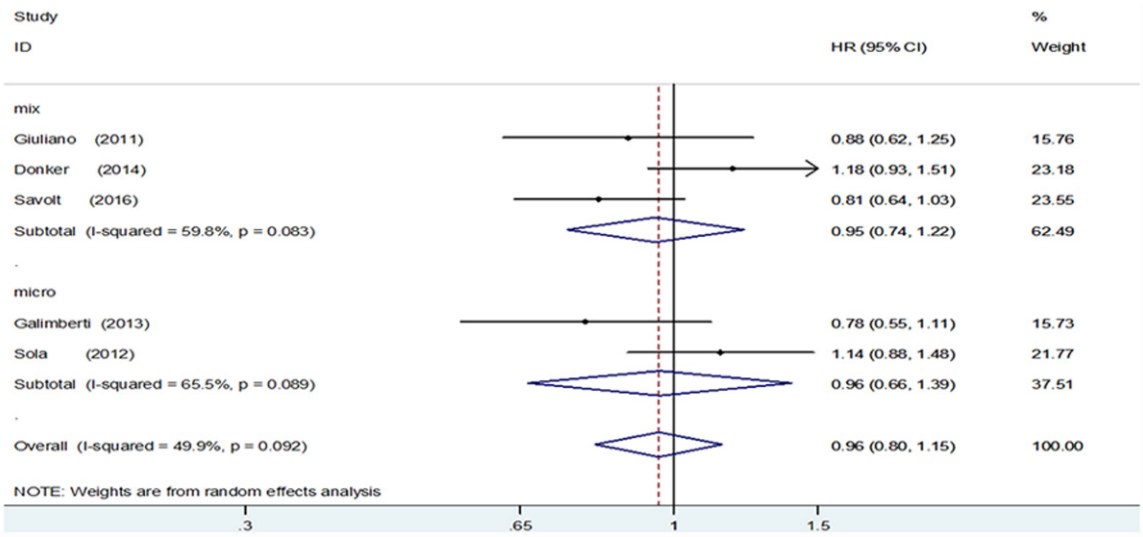

Figure 4. Forest plots of the pooled HRs for disease-free survival (DFS) of axillary lymph node dissection (ALND) and no axillary lymph node dissection (no-ALND) groups. The results indicated that there was no significant difference in DFS between no-ALND and ALND groups (HR=0.96, 95%; CI: 0.80~1.15, P=0.644).

Comparison of OS between no-ALND and ALND groups

HRs for OS data were available for seven studies. Heterogeneity test result indicated that a random-effect model was used. The pooled hazard ratio (HR) for OS showed that there was no significant difference between no-ALND and ALND groups (HR=1.01, 95% CI: 0.96~1.07, P=0.662; **Figure 3**). Considering that OS might be influenced by the status of SLN, we performed subgroup analysis according to the status of SLN. The pooled HR was also no significant difference between subgroup. This suggested that OS was not influenced significantly by SLN status between no-ALND and ALND groups.

Comparison of DFS between no-ALND and ALND groups

HRs for DFS data were available for five studies. Heterogeneity test result indicated that a random-effect model was used. The pooled HR

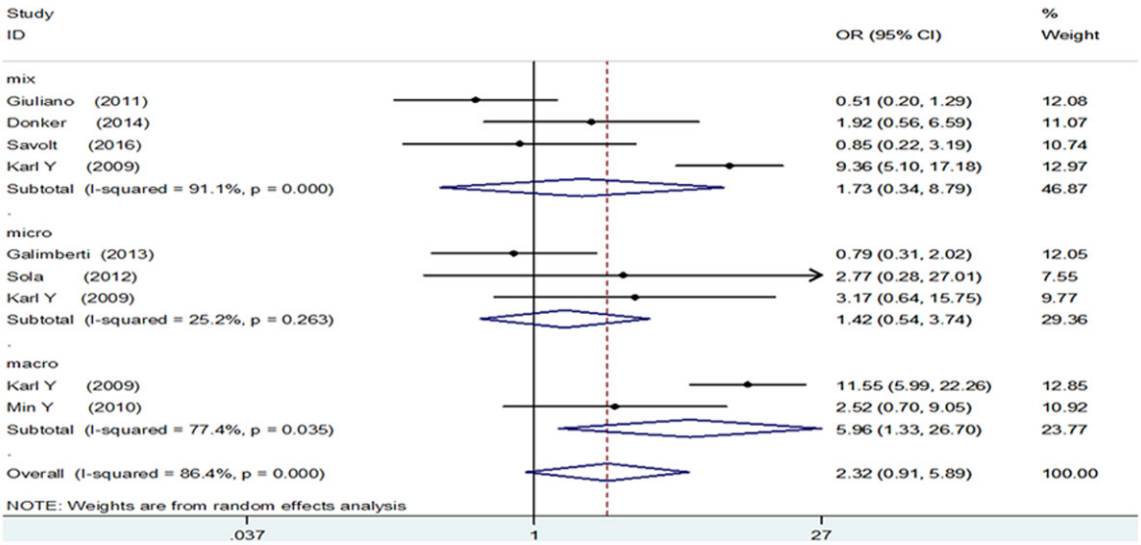

Figure 5. Forest plots of the pooled ORs for local recurrence of axillary lymph node dissection (ALND) and no axillary lymph node dissection (no-ALND) groups. The results indicated that there was no significant difference in the recurrence rate between no-ALND and ALND groups (OR=2.32, 95% CI: 0.91~5.89, P=0.78).

Table 2. Summary of complications occurred in the included trials

Author	Intervention	Sensory neuropathy	Lymphedema	Motor neuropathy	Infection
Galimberti	ALND vs. no ALND	18% vs. 12%	13% vs. 3%	8% vs. 3%	
		p=0.012	*p*<0.0001	*p*=0.0004	
Donker	ALND vs. AR	N/A	23% vs. 11%		
			p<0.0001		
Ginliano	ALND vs. no ALND	39% vs. 9%	19% vs. 6%		8% vs. 3%
		p<0.0001	*p*<0.0001		*p*=0.0016
Savolt	ALND vs. no ALND	15.3% vs. 4.7%	*p*<0.05 (including lymphedema, pain, and dysfunction)		

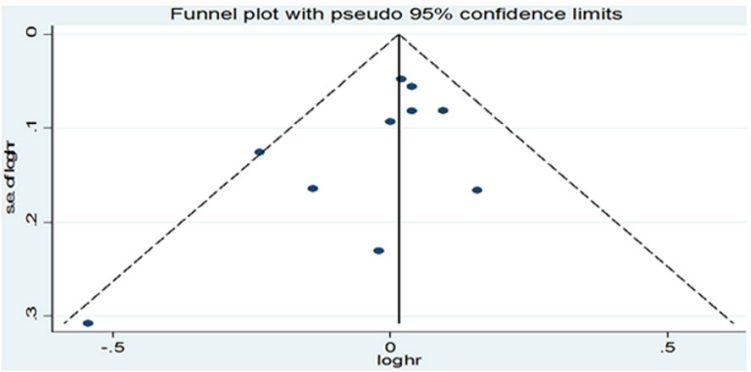

Figure 6. Funnel plot based on the risk radio (RR) of overall survival showing no publication bias among the included studies.

Figure 4). Considering that DFS might be influenced by the status of SLN, we performed subgroup analysis according to the status of SLN. The pooled HR also showed no significant difference between subgroups. This suggested that DFS in no-ALND and ALND groups was not significantly influenced by SLN status.

Comparison of local recurrence between no-ALND and ALND groups

for DFS showed that there was no significant difference between no-ALND and ALND groups (HR=0.96, 95%; CI: 0.80~1.15, P=0.644; ORs for local recurrence data were available for seven studies. Heterogeneity test indicated that a random-effect model was used. The

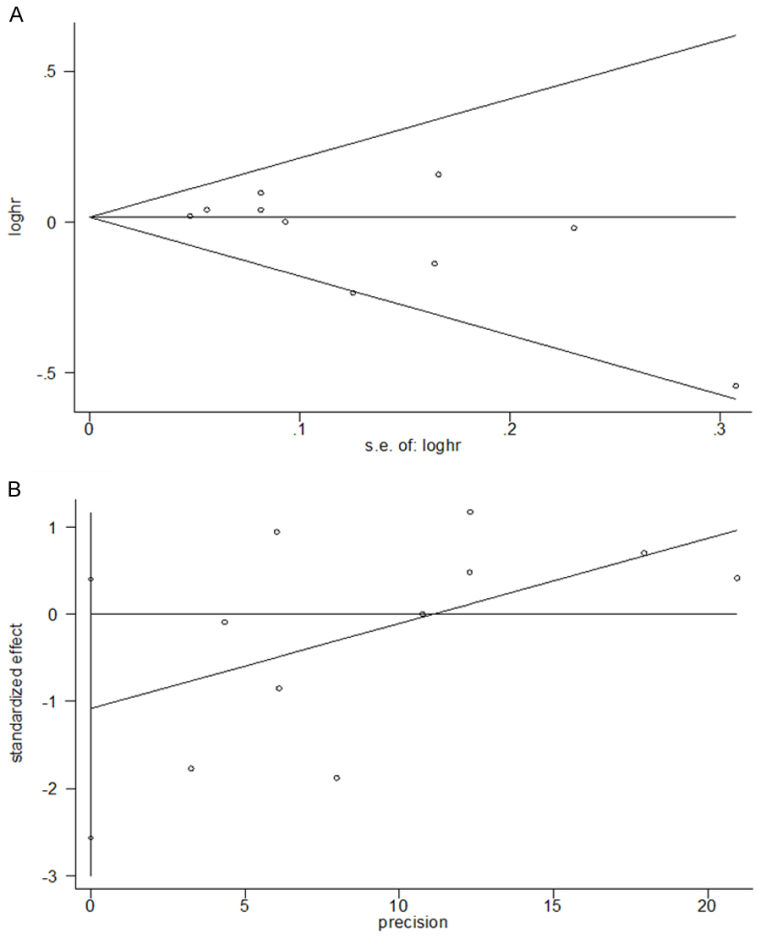

Figure 7. Begg's funnel plot with pseudo 95% A and Egger's publication bias plot B for overall survival. There was no evidence of bias in either plot.

pooled OR for local recurrence showed that there was no significant difference between no-ALND and ALND groups (OR=2.32, 95% CI: 0.91~5.89, P=0.78; **Figure 5**). Considering that local recurrence might be influenced by the status of SLN, we performed subgroup analysis according to the status of SLN. The subgroup analysis showed that patients with macro-metastasis had a higher recurrence rate (OR=5.96, 95% CI: 1.33~26.70, P=0.02). This suggested that ALND should be recommended for the patients with macro-metastasis of SLN.

Comparison of post-operative complications between no-ALND and ALND groups

The incidence of postoperative complications including lymphedema, sensory neuropathy, motor neuropathy and infection. in the no-ALND group was significantly lower than that in the ALND group (P<0.05 or 0.01, **Table 2**).

Publication bias analysis

Assessed by funnel plot, Begg's test (*P*=0.21) and Egger's test (*P*=0.13), the publication bias was not found (**Figures 6** and **7**).

Discussion

Breast cancer has become the most common female malignant tumor [3, 22]. ALND has been considered the standard management for patients with axillary lymph node metastasis [3, 23]. NSABP B-32 trail have clearly showed that breast cancer patients without SLN metastases can avoid ALND [24]. However, for patients with SLN positive and without palpable lymphadenopathy, ALND is still controversial. According to the AJCC guidelines [25], micrometastasis is defined as tumors with a maximum diameter from 0.2 to 2 mm, and macrometastasis as tumors with a diameter over 2 mm. Isolated tumor metastasis represents tumors with a maximum diameter less than 0.2 mm. ALND may cause many complications, such as lymphedema, seroma, pain, infection and reduced arm movement [4]. Moreover, the biological characteristics of primary tumor, such as hormone receptor [26, 27], Her-2 expression [28, 29], tumor growth rate [28, 29] (for example, the expression of Ki-67) has greatly reduced the value of axillary lymph node dissection in the prognosis and treatment of breast cancer. Studies have also shown that about 50% patients with positive SLN developed no lymph node metastasis [8]. They have therefore suggested that ALND is an excessive treatment for patients with early breast cancer and without palpable lymphadenopathy. In this meta study, we evaluated whether ALND should be omitted in these patients.

This study includes five RCTs [9-13] and three retrospective cohort studies [14-16], which contains breast cancer patients with cT1~2N0M0

and SLN positive who have not received any therapy for axillary before enrollment. Meta-analysis show that compared with no-ALND, ALND could not improve the OS and DFS. Moreover, omitting ALND did not affect local recurrence rate. However, ALND group has a higher rate of complication (such as lymphedema, sensory motor dysfunction, infection, etc). While AATRM [10] and IBCSG 23-01 [11] registered eligible patients with micrometastasis SLN, the remaining three RCTs [9, 12, 13] only recruit patients with cN0 and positive SLN without classified metastasis status. Subgroup analysis results revealed no significant difference in OS or DFS among patients with different node metastasis status (micrometastasis, macrometastasis, mix-metastasis (both micro- and macro) and more than 3 positive SLNs). Nevertheless, patients with macro-metastasis had a significant higher recurrence rate ($P<0.05$).

The current meta-analysis found that breast cancer patients with positive SLN and without palpable lymphadenopathy did not benefit from ALND. Our conclusion is consistent with previous studies by SINODAR ONE [30] and BOOG 2013-07 [31]. Furthermore, subgroup analysis showed that the number of metastatic lymph nodes did not affect patients' prognosis. Several reasons might exist. First, the patients in the selected RCTs and retrospective cohort studies are early breast cancer (cT1~2N0M0) whose clinical stage may range from I to IIA. Therefore, these patients may have a better prognosis compared with other advanced stages. Meanwhile, the systematic adjuvant therapy including chemotherapy, radiotherapy, endotherapy and trastuzumab may effectively improve the survival of these patients. Secondly, about 50% of the patients with ALND did not find additional lymph node metastasis [8]. Lastly, NSABP B-04 [3] has compared the outcome between ALND and AR in patients without SLNB and clinical axillary lymph node metastasis. A 25-year follow-up study has shown a local axillary recurrence rate of 4% in both groups. The outcome suggests that although axillary surgery may act as a approach to cure lymphadenopathy and minimize the recurrence rate, it doesn't improve patients' survival.

This review has several limitations. First, the criteria of tumor size in each study is different, which might cause a selection bias. For example, the tumor size of three studies [9, 11, 12] is less than 5 cm, whereas the criteria of AATRM [10] and OTOASOR [13] is less than 3.5 and 3 cm, respectively. Secondly, the criteria of SLN metastasis status might also make a bias. While AATRM [10] and IBCSG 23-01 [11] focus on the micro-metastasis, AMAROS [12] contains three SLN metastasis status including 60% patients with macrometastases, 30% patients with micrometastases, and 10% patients with isolated tumor metastases. Z0011 [9] only has patients with 1~2 positive SLN (including 40% micro-metastases). Third, the surgery in the selected studies include mastectomy and breast conserving surgery, and the SLNB management includes radioactive isotope, blue dye and the combination of both. Developed countries prefer to use radioactive isotope combined with blue dye. In contrast, developing countries tend to use only a single method, which might cause a higher false negative rate compared with the combined SLNB method. Such a different SLNB management strategy might have affected the result of our meta-analysis.

Conclusions

In conclusion, omitting ALND in early stage of breast cancer with positive SLN and without palpable lymphadenopathy has similar OS (HR=1.01, 95% CI: 0.96~1.07, $P=0.662$), DFS (HR=0.96, 95% CI: 0.80~1.15, $P=0.644$) and local recurrence (OR=2.32, 95% CI: 0.91~5.89, $P=0.78$), but caused significant lower incidence of postoperative complications when compared with ALND. Therefore, ALND could be omitted in patients with T1-2 primary breast cancer and without palpable lymphadenopathy.

Disclosure of conflict of interest

None.

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Samphao S, Eremin JM, El-Sheemy M, Eremin O. Management of the axilla in women with breast cancer: current clinical practice and a new selective targeted approach. Ann Surg Oncol 2008; 15: 1282-1296.
[3] Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002; 347: 567-575.
[4] Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Giuliano AE; American College of Surgeons Oncology Group. Surgical complications associated with sentinel lymph node dissection (slnd) plus axillary lymph node dissection compared with slnd alone in the american college of surgeons oncology group trial z0011. J Clin Oncol 2007; 25: 3657-3663.
[5] Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 2000; 88: 608-614.
[6] Kuehn T, Bembenek A, Decker T, Munz DL, Sautter-Bihl ML, Untch M, Wallwiener D. A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer 2005; 103: 451-461.
[7] Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. Cancer 2006; 106: 4-16.
[8] Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305: 569-575.
[9] Solá M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial aatrm 048/13/2000. Ann Surg Oncol 2013; 20: 120-127.
[10] Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (ibcsg 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013; 14: 297-305.
[11] Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (eortc 10981-22023 amaros): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15: 1303-1310.
[12] Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, Győrffy B, Kásler M, Mátrai Z. Optimal treatment of the axillary after positive sentinel lymph node biopsy in primary invasive breast cancer: otoasor trial, a randomized, single centre, phase iii, non-inferiority trial. Eur J Surg Oncol 2017; 43: 672-679.
[13] Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, Winchester DP, Winchester DJ. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol 2009; 27: 2946-2953.
[14] Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, Bedrosian I, Rourke L, Hunt KK. Trends in and outcomes from sentinel lymph node biopsy (slnb) alone vs. Slnb with axillary lymph node dissection for node-positive breast cancer patients: experience from the seer database. Ann Surg Oncol 2010; 17: 343-351.
[15] Bonneau C, Hequet D, Estevez JP, Pouget N, Rouzier R. Impact of axillary dissection in women with invasive breast cancer who do not fit the z0011 acosog trial because of three or more metastatic sentinel lymph nodes. Eur J Surg Oncol 2015; 41: 998-1004.
[16] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.
[17] Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-2834.
[18] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating

summary time-to-event data into meta-analysis. Trials 2007; 8: 16.
[19] Higgins JPT, Churchill R, Chandler J, Cumpston MS. Cochrane handbook for systematic reviews of interventions version 5.2.0 (Updated february. 2017). Cochrane, 2017. Available from Cochrane Community.
[20] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle–ottawa scale (nos) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric 2014; 18: 227-734.
[21] Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, Chen WQ, Shao ZM, Goss PE. Breast cancer in china. Lancet Oncol 2014; 15: e279-289.
[22] Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival--a bayesian meta-analysis. Ann Surg Oncol 1999; 6: 109-116.
[23] Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, Skelly JM, Harlow SP, Weaver DL, Mamounas EP, Costantino JP, Wolmark N; National Surgical Adjuvant Breast, Bowel Project. Morbidity results from the nsabp b-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 2010; 102: 111-118.
[24] Greene FL, Page DL, Fleming ID. AJCC cancer staging manual.8th ed. New York: Springer; 2017.
[25] Colleoni M, Rotmensz N, Peruzzotti G, Maisonneuve P, Mazzarol G, Pruneri G, Luini A, Intra M, Veronesi P, Galimberti V, Torrisi R, Cardillo A, Goldhirsch A, Viale G. Size of breast cancer metastases in axillary lymph nodes: clinical relevance of minimal lymph node involvement. J Clin Oncol 2005; 23: 1379-1389.
[26] Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: international consensus panel on the treatment of primary breast cancer. Seventh international conference on adjuvant therapy of primary breast cancer. J Clin Oncol 2001; 19: 3817-3827.
[27] Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ; Panel members. Thresholds for therapies: highlights of the st gallen international expert consensus on the primary therapy of early breast cancer. Ann Oncol 2009; 20: 1319-1329.
[28] Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003; 21: 3357-3365.
[29] Tinterri C, Canavese G, Bruzzi P, Dozin B. Sinodar one, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes. Breast 2016; 30: 197-200.
[30] van Roozendaal LM, de Wilt JH, van Dalen T, van der Hage JA, Strobbe LJ, Boersma LJ, Linn SC, Lobbes MB, Poortmans PM, Tjan-Heijnen VC, Van de Vijver KK, de Vries J, Westenberg AH, Kessels AG, Smidt ML. The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy: a dutch randomized controlled multicentre trial (boog 2013-07). BMC Cancer 2015; 15: 610.