Breast Cancer Patients with Sentinel Lymph Node Metastasis with and without Completion Axillary Lymph Node Dissection

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Abstract

Background: Currently, the standard method for staging and treatment of axillary lymph nodes for early-stage breast cancer is sentinel lymph node biopsy (SLNB), while axillary lymph node dissection (ALND) is used in cases with palpable axillary lymph nodes or positive SLNB cases. The aim of this review was to compare overall survival (OS), disease-free survival (DFS), and axillary recurrence in early-stage breast cancer patients underwent SLNB or SLNB and completion ALND. Methods: The databases of PubMed, Scopus, and Cochrane Library were searched using the key words of “breast cancer”, “axillary lymph node dissection”, and “sentinel lymph node dissection”. In addition, other sources were searched for ongoing studies (i.e., clinicaltrials.gov). The clinical trials were evaluated based on the Jadad quality criteria, and cohort studies were evaluated according to the STROBE criteria. At the end of the search, the articles were screened independently by two reviewers to check their eligibility to be included in the study. Afterwards, the data were extracted independently by two researchers. Results: After searching the databases, 169 papers were retrieved. However, after removing the duplicates and studying the titles and abstracts of these papers, only ten ones underwent further investigation. After reading full-text of each article, four studies were finalized. Following a manual search, 27 papers were entered into the study for the final evaluation, 11 of which were included in the meta-analysis based on the inclusion and exclusion criteria. The findings showed no significant differences in OS, DFS, and axillary recurrence in early-stage breast cancer patients underwent SLNB or SLNB and completion ALND. Conclusion: The findings did not confirm that ALND improved OS, DFS, and axillary recurrence in patients who were clinically node-negative and positive SLNB.

Keywords: Early-stage breast cancer- axillary lymph node dissection- sentinel lymph node biopsy- survival

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Introduction

Previous studies have shown the impact of axillary lymph nodes status on the survival rate of the patients (Bansal and Mohanti, 2002). Axillary management has dramatically changed over time (Gatzemeier and Mann, 2013). Currently, the standard method for staging and treatment of axillary lymph nodes for early-stage breast cancer is sentinel lymph node biopsy (SLNB) (Kootstra et al., 2013), while axillary lymph node dissection (ALND) is used in cases with palpable axillary lymph nodes or positive SLNB cases (Burak et al., 2002; Donker et al., 2014). Given the extensive complications and high morbidity of ALND, American College of Surgeons Oncology Group (ACOSOG) Z0011 clinical trial was published as a prospective clinical trial on patients with axillary lymph node metastasis. The patients were randomly assigned to ALND after SLND and SLND alone, followed by standard treatment with radiotherapy, chemotherapy, or hormone therapy for each patient. After
a median follow-up of 6.3 years, no statistically significant difference between two groups was reported in terms of local and regional recurrence. Results of another trial using a 10-year follow-up indicated that 1-2 positive lymph nodes did not affect the overall survival (OS) and disease-free survival (DFS), indicating the importance of adjuvant chemoradiotherapy (Giuliano et al., 2011; Giuliano et al., 2017). Subsequently, several systematic reviews and meta-analyses were conducted to summarize the results of new studies (Pepels et al., 2011; Glechner et al., 2013; Ram et al., 2014; Joyce et al., 2015; Li et al., 2015a; Huang et al., 2016; Schmidt-Hansen et al., 2016; Castelo et al., 2020; Peristeri and Harissis, 2021). In a systematic review in 2020 by Dimitra V Peristeri et al., five articles were studied. The authors ultimately concluded that SLND/radiotherapy was the selective therapy in early-stage breast cancer patients with <3 positive SLNs (Peristeri and Harissis, 2021). To the best of our knowledge, no study has yet reviewed the findings regarding the difference between early-stage breast cancer patients underwent SLNB and those underwent SLNB and completion ALND in terms of overall survival (OS), disease-free survival (DFS), and axillary recurrence. Therefore, this review study and meta-analysis was attempted to summarize the results of studies on OS, DFS, and axillary recurrence of patients underwent SLNB or SLNB and completion ALND.

Materials and Methods

Eligibility Criteria

This RISMA-P protocol based systematic review included all original studies (RCT and cohort ones), which compared clinically node-negative early-stage breast cancer patients underwent SLNB and completion ALND and those who underwent SLNB alone in terms of OS, DFS, and axillary recurrence.

All studies with a follow-up period of less than five years, as well as non-English papers were excluded. There was no limitation on the publication year.

Literature search

To find the relevant studies, PubMed, Cochrane Library, and SCOPUS databases were searched. The search was conducted on January 21, 2021. The reference lists of the included papers were also reviewed manually to find related articles as well (hand search).

Search Strategy

The key words of “breast cancer”, “axillary lymph node dissection”, and “sentinel lymph node dissection” were searched in all the selected databases. As an example, the search strategy for PubMed was as follows:

#1: Breast Cancer [MeSH Terms]
#2: axillary lymph node dissection [Title/Abstract]
#3: sentinel lymph node dissection [Title/Abstract]
#4: #1 AND #2 AND #3

Study selection

The search and review process were performed independently by at least two of the authors. In case of disagreement, the final decision was made by a third author. After completing the search process, all the identified papers were entered into EndNote, and the duplicates were deleted. Then, the titles and abstracts of the papers that met the inclusion and exclusion criteria were reviewed. In addition, if the content of the article was not clear from the title and the abstract, the full-text was read.

Inclusion and exclusion criteria

All studies that assessed clinically negative node patients with or without ALND, included N0 and M0 patients (whose tumor is larger than 20 mm but not larger than 50 mm and has not spread to the axillary lymph nodes), had minimum 5-year follow-up, and done on patients underwent breast conserving surgery (BCS) were included in this study. All the studies that evaluated patients treated with neo-adjuvant chemotherapy or radiotherapy or those studies that did not compare outcomes in groups underwent SLNB and completion ALND and SLNB alone were excluded. All the non-original articles and non-English articles were excluded.

Data extraction

Data such as first author’s name, year of publication, country, study type, number of patients, age range, enrollment interval, median follow-up time, type of surgery, tumor type, tumor stage, recurrence, axillary recurrence, breast recurrence, distant metastasis, OS, and DFS were extracted from included studies.

Risk of bias assessment

The Jadad scale was used to evaluate the quality of the included clinical trials (Jadad et al., 1996). This checklist includes three main items, i.e., randomization, blinding, and describing the results. We conducted an expert review of the quality of the selected papers. In addition, we used the STROBE checklist to evaluate the items that should be included in the reports of cohort studies (Vandenbroucke et al., 2007).

The treatment of breast cancer is constantly changing over time. In the setting of the early stages of breast cancer, the changes in treatment have mostly been shifts from ALND to SLND. Population selection bias did not change the results of this paper significantly because this issue was taken into consideration in the framework.

Data synthesis

A meta-analysis was performed using the Stata 14, and forest plot diagrams were generated.

Assessment of heterogeneity

The heterogeneity among studies was assessed by visually inspecting the forest plots and estimating the I2 statistic, which is used to calculate the percentage of statistical heterogeneity in clinical trials and cannot be ascribed to variation in sampling. Pooled estimates were calculated in different subgroups of studies to determine their consistency. Chi-square test was also used to evaluate heterogeneity. P-values less than 0.1 were considered significant. Moreover, the possible reasons for any
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Table 1. Characteristics of the Nine Randomized Controlled Trials Included in the Systematic Review and Meta-Analysis

| No | Author | Year | Country | N | TSurgery | STROBE criteria (22/22) |
|----|--------|------|---------|---|----------|------------------------|
| 1  | Ling et al. | 2019 | USA     | 161 | SLND, ALND for positive SLND | 18 |
| 2  | Gondo et al. | 2020 | Japan   | 152 | BCS and ALND | 20 |
| 3  | Haffty et al. | 2019 | USA     | 701 | BCS, Mastectomy | 15 |
| 4  | Arisio et al. | 2019 | Italy   | 617 | ALND, SLND Only | 18 |
| 5  | Joo et al. | 2019 | South Korea | 1697 | Total Mastectomy | 21 |
| 6  | Li et al. | 2015 | China   | 289 | SLND, ALND, partial ALND | 19 |
| 7  | Kobayashi et al. | 2015 | USA     | 158 | BCS | 20 |
| 8  | Schulze et al. | 2006 | Germany | 135 | ALND following SLNB results, SLND, Mastectomy, BCS | 19 |
| 9  | Domenec et al. | 2007 | Spain   | 97 | SLNB | 19 |
| 10 | Kuijt et al. | 2007 | Netherland | 2561 | SLNB, ALND, BCS, Mastectomy | 19 |
| 11 | Bilimoria et al. | 2009 | USA | 97314 | SLNB followed by ALND, SLND alone | 20 |
| 12 | Langer et al. | 2008 | Switzerland | 355 | SLNB, ALND | 21 |
| 13 | Setton et al. | 2012 | USA     | 326 | SLNB, BCS, Mastectomy | 20 |
| 14 | Fu et al. | 2014 | USA     | 214 | SLNB followed by ALND, SLND alone, ALND alone | 18 |
| 15 | Park et al. | 2014 | South Korea | 2581 | SLNB followed by ALND, SLND alone | 18 |
| 16 | Yi et al. | 2010 | USA | 26968 | SLNB followed by ALND, SLND alone | 19 |
| 17 | Yi et al. | 2013 | USA | 861 | SLNB followed by ALND, SLND alone | 19 |
| 18 | Crawford et al. | 2013 | USA | 561 | SLNB followed by ALND, SLND alone | 20 |

T.Surgery, Type of the surgery; N, enrollment patient; BCS, breast conserving surgery; ALND, axillary lymph node dissection; SLND, sentinel lymph node dissection; SLNB, sentinel lymph node biopsy.
Figure 1. PRISMA Flow Diagram

Figure 2. Meta-Analysis for OS Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of $\tau^2$
Discussion

The results of this study showed no significant difference in OS, DFS, and axillary recurrence rates between early-stage breast cancer patients who underwent SLNB alone and those who underwent ALND after SNB, which was similar to the results of other systematic reviews and meta-analyses (Pepels et al., 2011; Glechner et al., 2013; Ram et al., 2014; Li et al., 2015a; Huang et al., 2016; Schmidt-Hansen et al., 2016; Castelo et al., 2020; Peristeri and Harissis, 2021).

In this meta-analysis, due to the similarity between clinical trials and cohort studies, the papers in both groups were analyzed together. For further assurance, the study results were meta-analyzed in two separate groups of clinical trials and cohort studies, too. As shown in Figures 5, 6, 7, and 8, the results were the same in the clinical trials, cohort studies, and both groups, and this consistency in the results further confirmed the findings of the study.

A number of systematic reviews and meta-analyses have been published regarding the role of ALND completion in patients with positive sentinel nodes. None of these studies, except for a study by Joyce et al. (Joyce et al., 2015), showed a significant difference between ALND and SLNB in patients with early-stage breast cancer suffering from sentinel lymph node metastasis. Joyce et al. included studies conducted by Louis-Sylvester et al., (2004), Martelli et al., (2011), and Rudenstam et al.,

| No. | Author                        | Year | Country         | (N) | T. Surgery                                      | Jadad score (5/5) |
|-----|-------------------------------|------|-----------------|-----|------------------------------------------------|------------------|
| 1   | Roy et al. (Roy et al., 2018) | 2018 | France          | 1544| SLND ALND LUMpectomy Radial Mastectomy         | 3                |
| 2   | Canavese et al. (Canavese et al., 2016) | 2016 | Italy           | 225 | ALND following SLNB results BCS               | 3                |
| 3   | Zavagno et al. (Zavagno et al., 2008) | 2008 | Italy           | 749 | SLNB followed by ALND ALND based on the result of SLNB + mastectomy | 3                |
| 4   | Giuliano et al. (Giuliano et al., 2016) | 2016 | USA             | 891 | SLNB ALND                                      | 2                |
| 5   | Galimberti et al. (Galimberti et al., 2018) | 2018 | Multi European countries | 6681| SLNB (micrometastasis) followed by ALND SLND (micrometastasis) alone | 3                |
| 6   | Donker et al. (Donker et al., 2014) | 2014 | Multi European countries | 4823| SLNB positive followed by ALND SLND positive followed by RT | 3                |
| 7   | Savolt et al. (Sávolt et al., 2017) | 2016 | Hungary         | 474 | SLNB positive followed by ALND SLND positive followed by RT | 3                |
| 8   | Sola et al. (Solà et al., 2013) | 2012 | Spain           | 247 | SLNB (micrometastasis) followed by ALND SLNB (micrometastasis) Clinical Follow-up | 2                |
| 9   | Krag et al. (Krag et al., 2010) | 2010 | USA             | 5611| SLNB with ALND SLNB positive followed by ALND | 3                |

Figure 3. Meta-Analysis for DFS Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of $\tau^2$
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(2005), who compared the survival differences between groups with and without completion ALND. However, they did not evaluate the sentinel lymph node status before the procedures and after undergoing direct ALND (some lymph node-negative patients underwent ANLD). The importance of performing early SLND to evaluate lymph node metastasis and decision-making accordingly was considered in our study and other systematic reviews (i.e., only patients with sentinel lymph node metastasis were divided into two groups of SLND alone and completion ALND after SLND). It seems that this important point is the reason for the difference between the results of Joyce et al., and those of other studies.

Glechner et al., (2013) examined the five-year survival rate in three studies, including 50, 120 patients. After a meta-analysis, they concluded that SLND could be an appropriate alternative to ALND in female breast cancer patients. In another systematic review by Schmidt-Hansen et al., (2016), the authors compared outcomes such as OS and axillary recurrence between ALND and SLND groups. The results showed no significant difference in the survival and recurrence between the two groups; however, the morbidity rate was higher in the ALND group.

In another relevant systematic review by Dimitra et al., (2020) the authors studied five clinical trials and concluded that the survival and DFS rates were higher in the SLND group compared to the ALND group. They recommended that ALND should not be performed in patients with <3 positive lymph nodes (Peristeri and Harissis, 2021).

In the present systematic review, we tried to assess the available systematic reviews and their included articles along with our search strategy. Therefore, after studying the available systematic reviews, all the papers included in these systematic reviews that met the inclusion and exclusion criteria were included in our study (hand searching). In the majority of the published systematic reviews and meta-analyses of clinical trials (which are at the top of the levels of evidence pyramid), the authors concluded that ALND could be replaced with SLND in patients with early-stage breast cancer.

In the ACOSOG Z0011 Phase 3 Trial, Giuliano et al., (2017) randomized 856 clinically T1, T2 invasive breast
Table 3. Quantitative Studies for Meta-Analysis

| Author          | Year | Country                        | (N) | AHR  (OS) | LC  (OS) | HC  (OS) | AHR  (DFS) | LC  (DFS) | HC  (DFS) |
|-----------------|------|--------------------------------|-----|-----------|----------|---------|------------|----------|---------|
| Giuliano et al. | 2017 | USA                            | A (420) | 0.93 | 0.64 | 1.36 | 0.85 | 0.62 | 1.17 |
|                 |      |                                | B (436) |     |     |     |      |      |       |
| Galimberti et al| 2018 | Multiple European countries    | A (447) | 0.78 | 0.53 | 1.14 | 0.85 | 0.65 | 1.11 |
|                 |      |                                | B (453) |     |     |     |      |      |       |
| Donker et al.   | 2014 | Multiple European countries    | A (744) | 1.17 | 0.85 | 1.62 | 1.18 | 0.93 | 1.51 |
|                 |      |                                | B (681) |     |     |     |      |      |       |
| Sola et al.     | 2012 | Spain                          | A (124) | -    | -    | -    | 3.06 | 0.32 | 29.46 |
|                 |      |                                | B (123) |     |     |     |      |      |       |
| Krag et al.     | 2010 | USA                            | A (2807) | 1.19 | 0.95 | 1.49 | 1.07 | 0.9  | 1.22 |
|                 |      |                                | B (2804) |     |     |     |      |      |       |
| Park et al.     | 2013 | South Korea                    | A (2384) | 1.37 | 0.32 | 5.79 | -    | -    | -    |
|                 |      |                                | B (197)  |     |     |     |      |      |       |
| Bilimoria et al.| 2009 | USA                            | A (77097) | 0.89 | 0.76 | 1.04 | -    | -    | -    |
|                 |      |                                | B (20217) |     |     |     |      |      |       |
| Joo et al.      | 2019 | South Korea                    | A (1539) | 0.67 | 0.33 | 1.38 | 0.75 | 0.41 | 1.35 |
|                 |      |                                | B (158)  |     |     |     |      |      |       |
| Yi et al.       | 2010 | USA                            | A (22561) | 1   | 0.87 | 1.15 | 1.3  | 1.07 | 1.58 |
|                 |      |                                | B (4425) |     |     |     |      |      |       |
| Yi et al.       | 2013 | USA                            | A (481)  | 0.79 | 0.38 | 1.62 | 0.9  | 0.63 | 1.27 |
|                 |      |                                | B (380)  |     |     |     |      |      |       |
| Crawford et al. | 2013 | USA                            | A (426)  | -    | -    | -    | 0.77 | 0.46 | 1.28 |
|                 |      |                                | B (135)  |     |     |     |      |      |       |

A, ALND group; B, No ALND group; AHR, Adjusted hazard ratio; HC, Higher confidence interval; LC, Lower confidence interval; OS, Overall survival; DFS, Disease-free survival; N, The number of patients.

Table 4. Quantitative Studies for Meta-Analysis

| Author         | Year | Country                        | (N) | AHR  (AR) | LC  (AR) | HC  (AR) |
|----------------|------|--------------------------------|-----|-----------|----------|---------|
| Galimberti et al| 2018 | Multiple European countries    | A (447) | 0.98 | 0.71 | 1.36 |
|                 |      |                                | B (453) |     |     |     |
| Bilimoria et al.| 2009 | USA                            | A (77097) | 0.58 | 0.32 | 1.06 |
|                 |      |                                | B (20217) |     |     |     |
| Joo et al.      | 2019 | South Korea                    | A (1539) | 0.62 | 0.25 | 1.53 |
|                 |      |                                | B (158)  |     |     |     |

A, ALND group; B, No ALND group; AHR, Adjusted hazard ratio; HC, Higher confidence interval; LC, Lower confidence interval; AR, Axillary recurrence; N, The number of patients.

Figure 6. Meta-Analysis for DFS in RCT Subgroup Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau²
cancer patients with one or two metastases in SLNB alone (N=446) and SLNB and completion ALND groups (N=445). After an average follow-up period of 9.3 years and adjusting the patient characteristics and adjuvant systemic therapy, they found no significant differences in OS, DFS, and locoregional RFS between the two groups. Currently, there are two ongoing RCTs, i.e., the Z0011 CHINA (Wang, 2015) and BOOG 2013-08 (Van Roozendaal et al., 2017). These studies are examining the survival in two groups of early-stage breast cancer patients with SLNB metastasis with and without ALND. According to the declared schedule, the results of these studies will be available in December 2025 and April 2027, respectively, which will be added as an update to the present systematic review and meta-analysis.

All papers included in our studies considered patient correcting and adjusting for all confounding factors, such as adjuvant therapy. Given that the evidence obtained from the studies included in the present meta-analysis was not in favor of ALND, this study supports the suggestion of previous studies that ALND should not be performed in clinically node-negative patients with SLNB metastasis. The importance of omitting ALND in patients not only involves the costs and hospital stay, but it also involves morbidity and the complications induced by this procedure. Many nomograms and predictive tools that can be used to estimate the involvement of non-SLNs when SLNB is positive. One of the most popular and practical methods is the MSKCC nomogram for SLNB metastasis and additional nodal metastasis in breast cancer patients (nomograms.mskcc.org/breast/) (Van Zee et al., 2003). The patients are classified as “low risk” when the result of the nomogram is ≤50%. It has been shown that a cut-off value of 50% yields a sensitivity of 92.3%, a specificity of 81.4%, a positive predictive value of 80%, and a negative predictive value of 92.9% (Vieni et al., 2016).
Therefore, patients with a result above 50% are considered as “high risk” patients. The MSKCC nomogram includes information about current age (20-91 years), performing frozen section (yes or no), pathological size (0.1 to 9.0 cm), tumor type and grade (ductal 1, 2, 3, lobular), number of positive sentinel lymph nodes (1 to 7 nodes), SLN method of detection (frozen section, routine H&E, serial H&E, IHC), number of negative sentinel lymph nodes (0 to 14), lymphatic or vascular structure involvement or lymphovascular invasion (yes or no), multifocality (yes or no), estrogen-receptor positivity (yes or no), and progesterone-receptor positivity (yes or no).

Based on the evidence obtained, we suggest a clinical trial, in which clinically node-negative early-stage breast cancer patients are divided into high-risk and low-risk groups for axillary lymph node metastasis based on the MSKCC result. Moreover, it could be recommended to dissect the axillary lymph node in levels 1 and 2 exclusively for high-risk patients, while other systemic therapies are applied for low-risk cases.

This study had a number of limitations. The first limitation was the low number of studies. Although several investigations were eligible for inclusion in the present study, they lacked statistical information. Therefore, E-mails were sent to the corresponding authors. However, no response was received at the time of data collection. The second limitation was that few clinical trials were available about our topic, and if more powerful trials were available, more precise results would have been obtained. Unfortunately, the Funnel plot chart, which is one of the best tools for demonstrating publication bias, was not used due to the small number of available articles (Sterne et al., 2008).

In summary, this review and meta-analysis suggested that omitting ALND would not worsen OS, DFS, and axillary recurrence when adjuvant systemic therapy, radiotherapy, and hormone therapy are considered for each patient. The findings did not confirm that ALND improved OS, DFS, and axillary recurrence in clinically node-negative patients with positive SLNB after standard adjuvant treatment. However, larger high-quality clinical trials are needed in the future to support omitting ALND in SLNB-positive early-stage breast cancer patients.

**Author Contribution Statement**

In this study, all authors contributed to the design, write, and review of the manuscript. N.H managed and supervised the experiments and results. M.R. S collected the data. H.R.D contributed to data collection. J.J.N contributed in data analysis and collection. S.K contributed in article management. M.Z contributed in data analysis. A.A carried out the data extraction from selected articles. S.M.S contributed in data analysis and collection. M.A.B contributed in data extraction from selected articles. M.T.M contributed in data analysis and collection. Z.S carried out final revision of manuscript. She also contributed in data collection.

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**Ethics Approval and Consent to Participate**

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

**Availability of Data**

All acquired data are available within the article.

**Conflict of interest**

The authors declare no conflicts of interest.

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