REVIEW

Editorial Process: Submission:02/01/2022 Acceptance:08/02/2022

Comparing Early-Stage Breast Cancer Patients with Sentinel Lymph Node Metastasis with and without Completion Axillary Lymph Node Dissection: A Systematic Review and Meta-Analysis

Naeimeh Heiranizadeh[1]*, Mohammad Rafiei Shahamabadi[1], Hamid Reza Dehghan[2], Jamal Jafari-Nedooshan[1], Saeid Kargar[1], Mohammad Zare[1], Abdolhamid Amooei[1], Seyed Mostafa Shiryazdi[1], Mohammad Ali Broomand[3], Mohammad Taghi Moravej[2], Zahra Sadri[4]

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

Asian Pac J Cancer Prev, **23 (8)**, 2561-2571

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

*[1]Department of General Surgery, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran. [2]Research Center for Health Technology Assessment and Medical Informatics, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [3]Department of Radiation Oncology, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran. [4]Clinical Research Development Center of Shahid Sadoughi University of Medical Sciences, Yazd. *For Correspondence: hrdcsadri@yahoo.com*

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 beast 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 ti¬tles 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., randomiza¬tion, 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 in¬specting the forest plots and estimating the I2 statistic, which is used to calculate the percentage of statistical hetero¬geneity 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

substantial statistical heterogeneity were investigated and reported.

Heterogeneity was also investigated using Cochran's Q statistic, which confirmed heterogeneity of the included studies.

Sensitivity analyses

A sensitivity analysis was performed by re-running the analyses without studies that were deemed to have a high risk of bias.

Analyses

The data from the selected papers were meta-analyzed by calculating HR and 95% CI for the studies using a random effects inverse-variance model. Cohort and clinical trials studies were meta-analyzed together and separately. The primary outcomes for this meta-analysis were OS and DFS, while the secondary outcome was axillary recurrence.

Results

After searching the databases, 169 papers were found; however, 115 papers remained after removing the duplicates. After examining the titles and abstracts of these 115 papers, only ten ones remained. After reading full-text of each article, four studies underwent further investigation. After 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 (Figure 1).

Of the 27 papers included in this study, 18 were cohort studies (six of which were included in the meta-analysis), and nine were clinical trials (five of which were included in the meta-analysis). The supplementary information for each paper is provided in Tables 1, 2, 3, and 4.

In this paper, the Funnel plot diagram was not used because its power for showing true asymmetry, when the number of systematic review articles is less than 10, is very low (Sterne et al., 2008).

Meta-Analyses

The results of the pooling of the hazard ratio (HR) showed no significance difference in OS (hazard ratio [HR]: 0.98; confidence interval [CI]: 0.89-1.07; P-value: 0.650) (see Figure 2), DFS (HR: 1.02; CI: 0.89-1.16; P-value: 0.797) (Figure 3), and axillary recurrence (HR: 0.794; CI: 0.551-1.145;P-value:0.217) (Figure 4) between SLNB-positive early-stage breast cancer patients with or without completion ALND. The effect sizes were very small (OS: 0.98, DFS: 1.02, and axillary recurrence: 0.79). In the present study, the P-value of heterogeneity for OS, DFS, and axillary recurrence was 0.376, 0.095, and 0.251, respectively, while the I^2 value was 7.2%, 40.8%, and 27.7%, respectively. These results showed a low heterogeneity in OS and a moderate heterogeneity in DFS and axillary recurrence.

Table 1. Characteristics of the Nine Randomized Controlled Trials Included in the Systematic Review and Meta-Analysis

No	Author	Year	Country	(N)	T.Surgery	STROBE criteria (22/22)
1	Ling et al.(Ling et al., 2020)	2019	USA	161	SLND, ALND for positive SLND	18
2	Gondo et al.(Gondo et al., 2020)	2020	Japan	152	BCS and ALND	20
3	Haffty et al.(Haffty et al., 2019)	2019	USA	701	BCS, Mastectomy	15
4	Arisio et al. (Arisio et al., 2019)	2019	Italy	617	ALND, SLND Only	18
5	Joo et al.(Joo et al., 2019)	2019	South Korea	1697	Total Mastectomy	21
6	Li et al.(Li et al., 2015b)	2015	China	289	SLND, ALND, partial ALND	19
7	Kobayashi et al.(Kobayashi et al., 2015)	2014	Japan	158	BCS	20
8	Schulze et al.(Schulze et al., 2006)	2005	Germany	135	ALND following SLNB results, SLND, Mastectomy, BCS	19
9	Domenech et al.(Domènech et al., 2007)	2007	Spain	97	SLNB	19
10	Kuijt et al.(Kuijt et al., 2007)	2006	Netherland	2561	SLNB, ALND, BCS, Mastectomy	19
11	Bilimoria et al.(Bilimoria et al., 2009)	2009	USA	97314	SLNB followed by ALND, SLND alone	20
12	Langer et al.(Langer et al., 2009)	2008	Switzer-land	355	SLNB, ALND	21
13	Setton et al.(Setton et al., 2012)	2011	USA	326	SLNB, BCS, Mastectomy	20
14	Fu et al.(Fu et al., 2014)	2014	USA	214	SLNB followed by ALND, SLND alone, ALND alone	18
15	Park et al.(Park et al., 2014)	2013	South Korea	2581	SLNB followed by ALND, SLND alone	18
16	Yi et al.(Yi et al., 2010)	2010	USA	26968	SLNB followed by ALND, SLND alone	19
17	Yi et al.(Yi et al., 2013)	2013	USA	861	SLNB followed by ALND, SLND alone	19
18	Crawford et al.(Crawford et al., 2013)	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

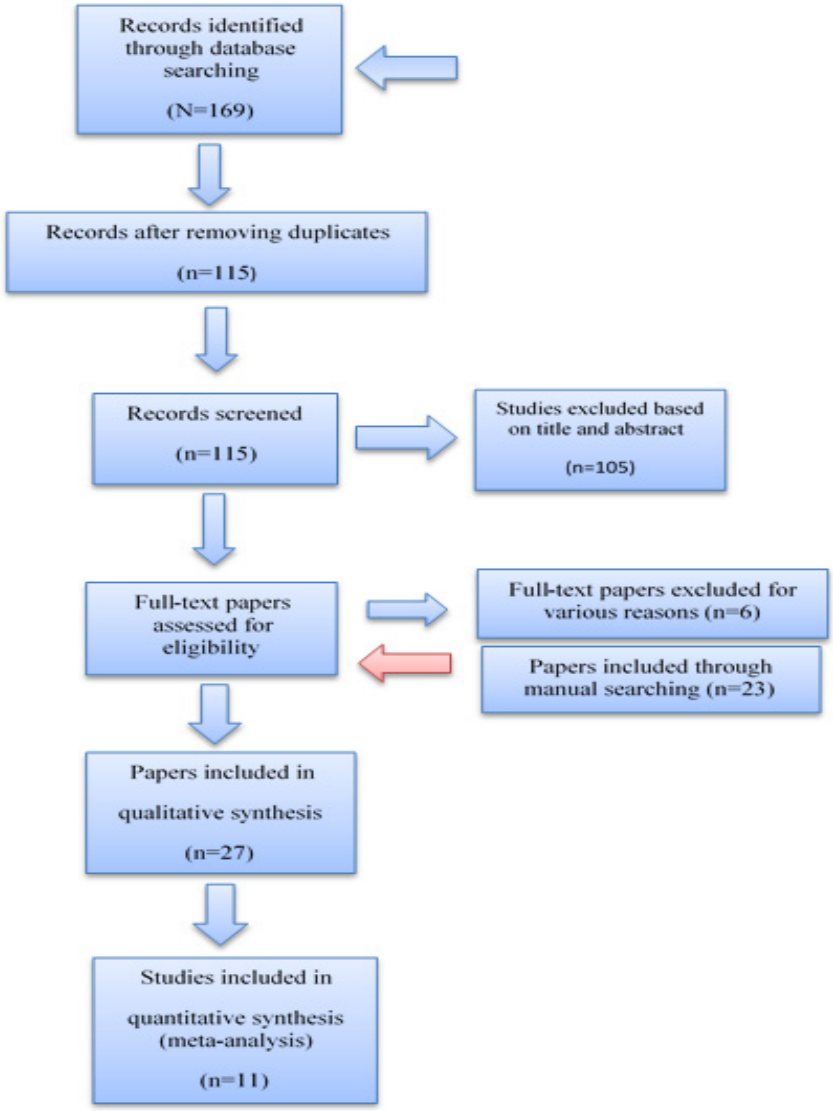

Figure 1. PRISMA Flow Diagram

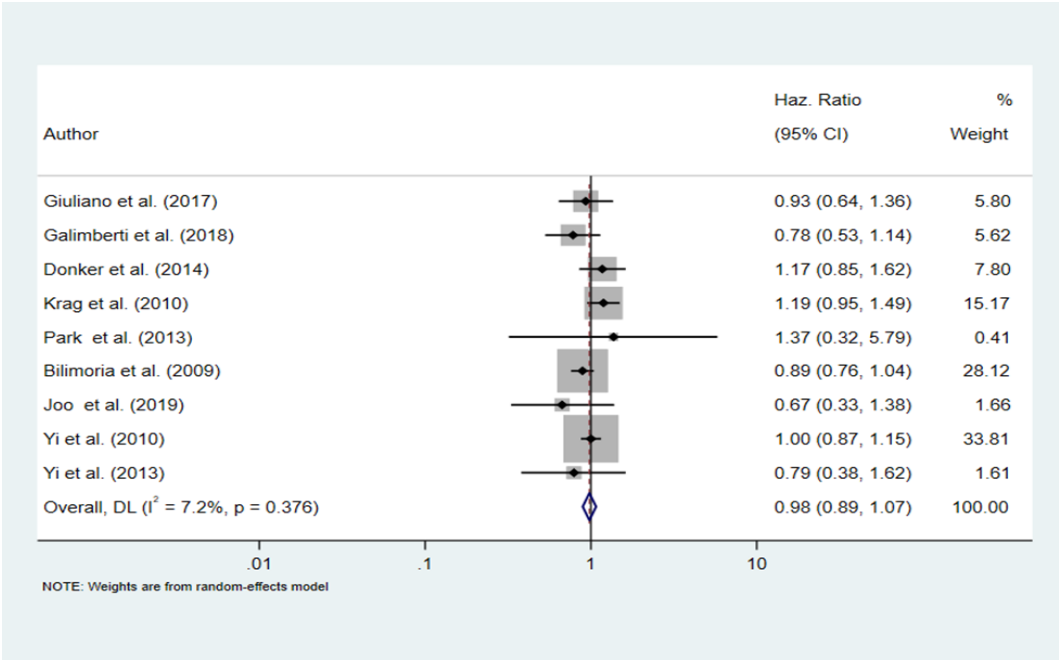

Figure 2. Meta-Analysis for OS Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau²

Table 2. Characteristics of 18 Retrospective and Follow-up Studies Included in Systematic Review and Meta-Analysis

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 Radical 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 resault 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.(Solá 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

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.,

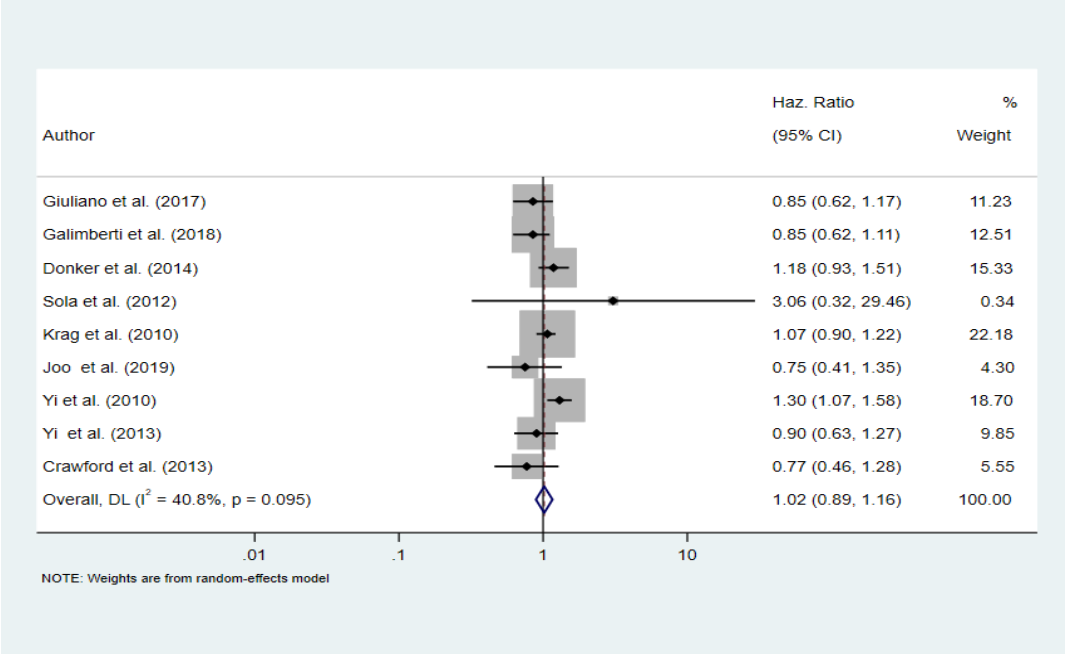

Figure 3. Meta-Analysis for DFS Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau^2

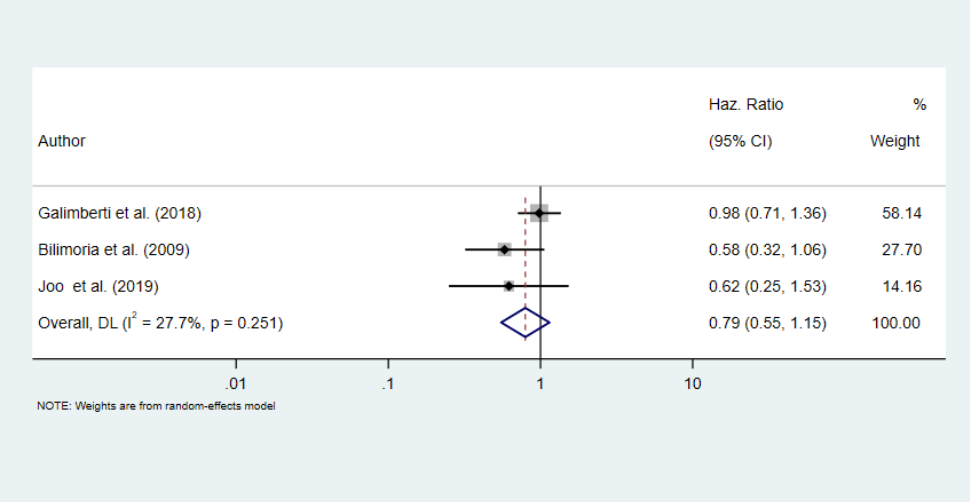

Figure 4. Meta-Analysis for Axillary Recurrence Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau^2

(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

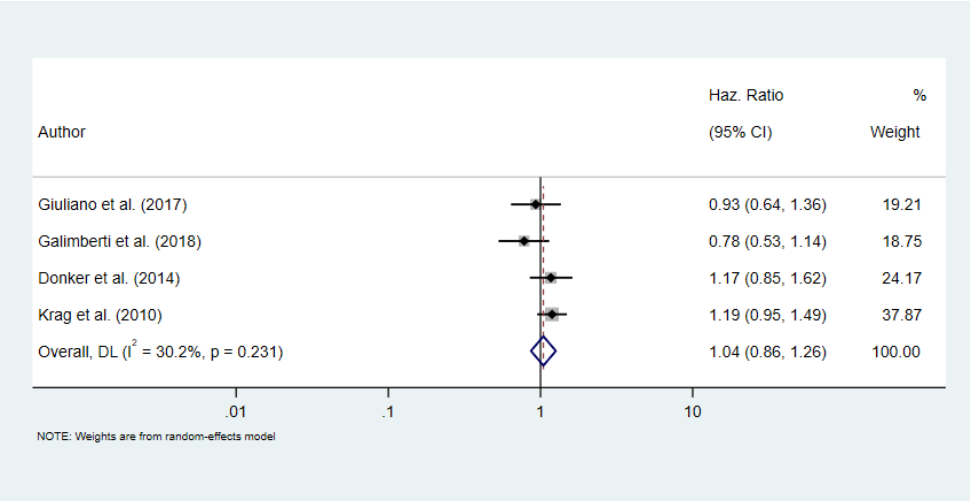

Figure 5. Meta-Analysis for OS in RCT Subgroup Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau^2

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

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) B (453)	0.98	0.71	1.36
Bilimoria et al.	2009	USA	A (77097) B (20217)	0.58	0.32	1.06
Joo et al.	2019	South Korea	A (1539) B (158)	0.62	0.25	1.53

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

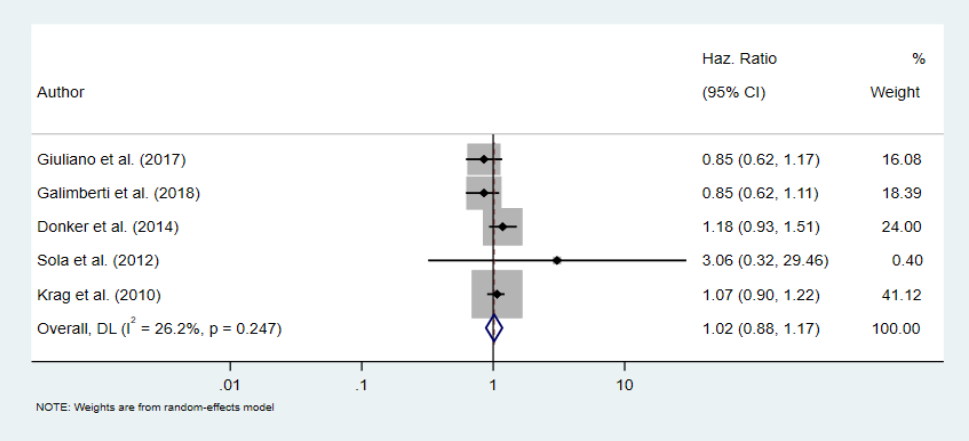

Figure 6. Meta-Analysis for DFS in RCT Subgroup Pooling of Hazard Ratios Using Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau^2

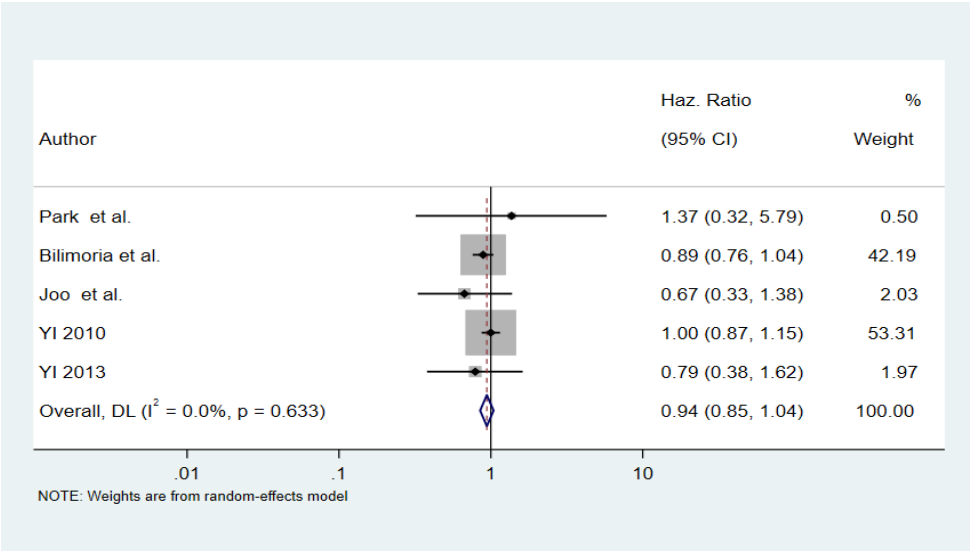

Figure 7. Meta-Analysis for OS in Cohort Subgroup Pooling of Hazard Ratios Using the Random Effects Inverse-Variance Model with DerSimonian-Laird estimate of tau^2

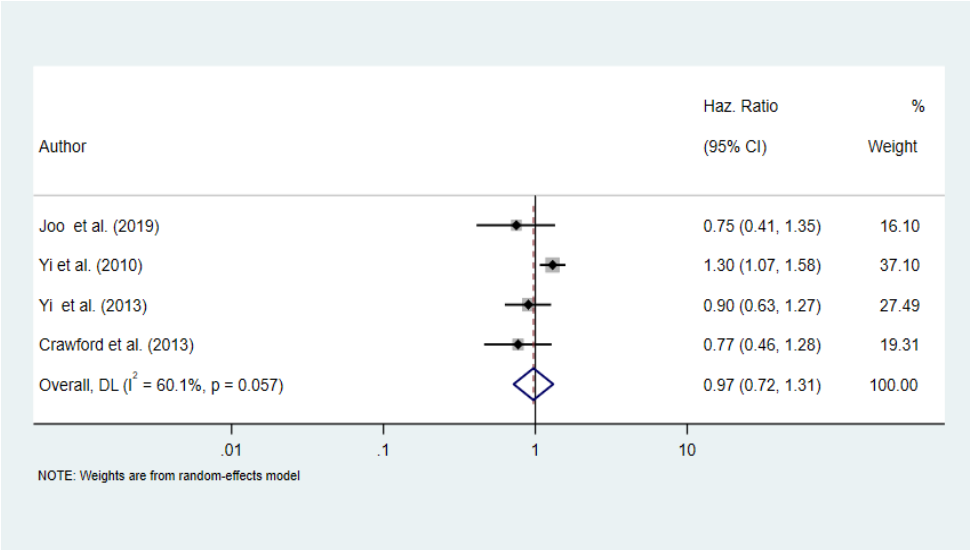

Figure 8. Meta-Analysis for DFS in Cohort Subgroup Pooling of Hazard Ratios Using the Random Effects Inverse-Variance Model with DerSimonian-Laird Estimate of tau^2

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 in 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.

Acknowledgements

We are thankful of Clinical research Development Center of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, for contributing us to perform this study.

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.

References

Arisio R, Borella F, Porpiglia M, et al (2019). Axillary Dissection vs. no Axillary Dissection in Breast Cancer Patients With Positive Sentinel Lymph Node: A Single Institution Experience. *In Vivo*, **33**, 1941-7.

Bansal M, Mohanti BK (2002). Sentinel lymph node biopsy, axillary dissection and breast cancer: Radiation oncologist's viewpoint. *Nat Med J India*, **15**, 154-7.

Bilimoria KY, Bentrem DJ, Hansen NM, et al (2009). Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. *J Clin Oncol*, **27**, 2946-53.

Burak Jr WE, Hollenbeck ST, Zervos EE, et al (2002). Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. *Am J Surg*, **183**, 23-7.

Canavese G, Bruzzi P, Catturich A, et al (2016). Sentinel Lymph Node Biopsy Versus Axillary Dissection in Node-Negative Early-Stage Breast Cancer: 15-Year Follow-Up Update of a Randomized Clinical Trial. *Ann Surg Oncol*, **23**, 2494-500.

Castelo M, Hu SY, Dossa F, et al (2020). Comparing observation, axillary radiotherapy, and completion axillary lymph node dissection for management of axilla in breast cancer in patients with positive sentinel nodes: a systematic review. *Ann Surg Oncol*, **2020**, 1-13.

Crawford JD, Ansteth M, Barnett J, et al (2013). Routine completion axillary lymph node dissection for positive sentinel nodes in patients undergoing mastectomy is not associated with improved local control. *Am J Surg*, **205**, 581-4; discussion 4.

Domènech A, Benitez A, Bajén MT, et al (2007). Patients with breast cancer and negative sentinel lymph node biopsy without additional axillary lymph node dissection: a follow-up study of up to 5 years. *Oncology*, **72**, 27-32.

Donker M, van Tienhoven G, Straver ME, et al (2014). 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*, **15**, 1303-10.

Fu Y, Chung D, Cao MA, et al (2014). Is axillary lymph node dissection necessary after sentinel lymph node biopsy in patients with mastectomy and pathological N1 breast cancer? *Ann Surg Oncol*, **21**, 4109-23.

Galimberti V, Cole BF, Viale G, et al (2018). Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year

follow-up of a randomised, controlled phase 3 trial. *Lancet Oncol*, **19**, 1385-93.
Gatzemeier W, Mann GB (2013). Which sentinel lymph-node (SLN) positive breast cancer patient needs an axillary lymph-node dissection (ALND)–ACOSOG Z0011 results and beyond. *Breast J*, **22**, 211-6.
Giuliano AE, Ballman K, McCall L, et al (2016). Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. *Ann Surg*, **264**, 413-20.
Giuliano AE, Ballman KV, McCall L, et al (2017). Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*, **318**, 918-26.
Giuliano AE, Hunt KK, Ballman KV, et al (2011). Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*, **305**, 569-75.
Glechner A, Wöckel A, Gartlehner G, et al (2013). Sentinel lymph node dissection only versus complete axillary lymph node dissection in early invasive breast cancer: a systematic review and meta-analysis. *Eur J Cancer*, **49**, 812-25.
Gondo N, Sawaki M, Hattori M, et al (2020). Utility of regional nodal irradiation in Japanese patients with breast cancer with 1-3 positive nodes after breast-conserving surgery and axillary lymph-node dissection. *Mol Clin Oncol*, **13**, 48-53.
Haffty BG, McCall LM, Ballman KV, et al (2019). Impact of Radiation on Locoregional Control in Women with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy and Axillary Lymph Node Dissection: Results from ACOSOG Z1071 Clinical Trial. *Int J Radiat Oncol Biol Phys*, **105**, 174-82.
Huang T-W, Kuo KN, Chen K-H, et al (2016). Recommendation for axillary lymph node dissection in women with early breast cancer and sentinel node metastasis: A systematic review and meta-analysis of randomized controlled trials using the GRADE system. *Int J Surg*, **34**, 73-80.
Jadad AR, Moore RA, Carroll D, et al (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clin Trials*, **17**, 1-12.
Joo JH, Kim SS, Son BH, et al (2019). Axillary Lymph Node Dissection Does Not Improve Post-mastectomy Overall or Disease-Free Survival among Breast Cancer Patients with 1-3 Positive Nodes. *Cancer Res Treat*, **51**, 1011-21.
Joyce D, Manning A, Carter M, et al (2015). Meta-analysis to determine the clinical impact of axillary lymph node dissection in the treatment of invasive breast cancer. Breast cancer research and treatment, 153, 235-40.
Kobayashi R, Shiraishi K, Iwase S, et al (2015). Omission of axillary lymph node dissection for clinically node negative early-stage breast cancer patients. Breast Cancer, 22, 657-63.
Kootstra JJ, Dijkstra PU, Rietman H, et al (2013). A longitudinal study of shoulder and arm morbidity in breast cancer survivors 7 years after sentinel lymph node biopsy or axillary lymph node dissection. *Breast Cancer Res Treat*, **139**, 125-34.
Krag DN, Anderson SJ, Julian TB, et al (2010). Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*, **11**, 927-33.
Kuijt GP, van de Poll-Franse LV, Voogd AC, et al (2007). Survival after negative sentinel lymph node biopsy in breast cancer at least equivalent to after negative extensive axillary dissection. *Eur J Surg Oncol*, **33**, 832-7.
Langer I, Guller U, Hsu-Schmitz SF, et al (2009). Sentinel lymph node biopsy is associated with improved survival compared to level I & II axillary lymph node dissection in node negative breast cancer patients. *Eur J Surg Oncol*, **35**, 805-13.
Li C, Zhang P, Li R, et al (2015a). Axillary lymph node dissection versus sentinel lymph node biopsy alone for early breast cancer with sentinel node metastasis: A meta-analysis. *Eur J Surg Oncol*, **41**, 958-66.
Li J, Jia S, Zhang W, et al (2015b). Partial axillary lymph node dissection inferior to the intercostobrachial nerves complements sentinel node biopsy in patients with clinically node-negative breast cancer. *BMC Surg*, **15**, 79.
Ling DC, Iarrobino NA, Champ CE, et al (2020). Regional Recurrence Rates With or Without Complete Axillary Dissection for Breast Cancer Patients with Node-Positive Disease on Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy. *Adv Radiat Oncol*, **5**, 163-70.
Louis-Sylvestre C, Clough K, Asselain B, et al (2004). Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. *J Clin Oncol*, **22**, 97-101.
Martelli G, Miceli R, Daidone MG, et al (2011). Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. *Ann Surg Oncol*, **18**, 125-33.
Park HS, Chae BJ, Song BJ, et al (2014). Effect of axillary lymph node dissection after sentinel lymph node biopsy on overall survival in patients with T1 or T2 node-positive breast cancer: report from the Korean Breast Cancer Society. *Ann Surg Oncol*, **21**, 1231-6.
Pepels MJ, Vestjens JH, De Boer M, et al (2011). Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review. *Breast Cancer Res Treat*, **125**, 301-13.
Peristeri DV, Harissis HV (2021). Axillary lymph node dissection vs sentinel biopsy only among women with early-stage breast cancer and sentinel node metastasis: A systematic review and meta-analysis. *Breast J*, **27**, 158-64.
Ram R, Singh J, McCaig E (2014). Sentinel node biopsy alone versus completion axillary node dissection in node positive breast cancer: systematic review and meta-analysis. *Int J Breast Cancer*, **2014**.
Roy P, Leizorovicz A, Villet R, et al (2018). Systematic versus sentinel-lymph-node-driven axillary-lymph-node dissection in clinically node-negative patients with operable breast cancer. Results of the GF-GS01 randomized trial. *Breast Cancer Res Treat*, **170**, 303-12.
Rudenstam CM, Zahrieh D, Forbes JF, et al (2005). Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol*, **24**, 337-44.
Sávolt Á, Péley G, Polgár C, et al (2017). Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol*, **43**, 672-9.
Schmidt-Hansen M, Bromham N, Hasler E, et al (2016). Axillary surgery in women with sentinel node-positive operable breast cancer: a systematic review with meta-analyses. *SpringerPlus*, **5**, 1-13.
Schulze T, Mucke J, Markwardt J, et al (2006). Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node

dissection. *J Surg Oncol*, **93**, 109-19.
Setton J, Cody H, Tan L, et al (2012). Radiation field design and regional control in sentinel lymph node-positive breast cancer patients with omission of axillary dissection. *Cancer*, **118**, 1994-2003.
Solá M, Alberro JA, Fraile M, et al (2013). 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*, **20**, 120-7.
Sterne JA, Egger M, Moher D (2008). Addressing Reporting Biases. In 'Cochrane Handbook for Systematic Reviews of Interventions', Eds pp 297-333.
Van Roozendaal L, Vane M, van Dalen T, et al (2017). Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial (BOOG 2013-08). *BMC Cancer*, **17**, 1-8.
Van Zee KJ, Manasseh D-ME, Bevilacqua JL, et al (2003). A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol*, **10**, 1140-51.
Vandenbroucke JP, Von Elm E, Altman DG, et al (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*, **4**, e297.
Vieni S, Graceffa G, La Mendola R, et al (2016). Application of a predictive model of axillary lymph node status in patients with sentinel node metastasis from breast cancer. A retrospective cohort study. *Int J Surg*, **35**, 58-63.
Yi M, Giordano SH, Meric-Bernstam F, et al (2010). 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*, **17**, 343-51.
Yi M, Kuerer HM, Mittendorf EA, et al (2013). Impact of the american college of surgeons oncology group Z0011 criteria applied to a contemporary patient population. *J Am Coll Surg*, **216**, 105-13.
Zavagno G, De Salvo GL, Scalco G, et al (2008). A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg*, **247**, 207-13.