

CADONOT: Comparing axillary dissection or not in breast cancer surgery

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ARTICLE INFO

Keywords:

Sentinel lymph node biopsy
Axillary lymph node dissection
Breast cancer
Breast neoplasm

ABSTRACT

Introduction: Sentinel lymph node biopsy (SLNB) is the gold standard for the axillary evaluation of clinically node-negative early breast cancer. The ACOSOG Z0011 study demonstrated the safety of omitting axillary dissection for limited SLNB disease, with other trials confirming SLNB alone or with axillary radiotherapy (AR) as non-inferior.

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<https://doi.org/10.1016/j.breast.2025.104453>

Received 1 January 2025; Accepted 18 March 2025

Available online 20 March 2025

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Mastectomy
Segmental mastectomy
Radiotherapy

Methods: We followed PRISMA guidelines and registered at PROSPERO. Using Medline, Embase, and Cochrane, we reviewed randomized controlled trials (2010–2024). Outcomes, including 5-, 8-, and 10-year OS, DFS, recurrence rates, and lymphedema, were analyzed with R software and assessed for bias (Cochrane RoB) and evidence quality (GRADE). The focus was ALND vs. SLNB, alone or with AR, in cT1-T3 BC with 1–2 metastatic SLNs.

Results: Thirteen articles from seven randomized controlled trials (RCTs) were included, covering 7338 women with a follow-up period of 2.8–10 years. SLNB was associated with a 65 % lower risk of lymphedema than ALND, with no significant differences in the 5-, 8-, or 10-year OS, DFS, or recurrence rates. A meta-analysis comparing micrometastasis and macrometastasis showed no impact on outcomes, indicating that ALND may be unnecessary in either case. Recurrence rates also did not differ between SLNB and ALND, reinforcing SLNB's significantly lower lymphedema risk of SLNB.

Conclusions: This systematic review and meta-analysis support SLNB as a safe and effective alternative to ALND in early-stage BC with 1–2 positive SLNs, providing comparable survival and recurrence outcomes, with fewer complications.

1. Introduction

In the early 1990s, sentinel lymph node biopsy (SLNB) was introduced for early-stage breast cancer (BC) in clinically node-negative (cN0) patients, using blue dye and radioisotope markers [1–4]. Over time, axillary dissection (AD) has been gradually substituted for patients with negative SLNB results, establishing SLNB as the standard procedure and significantly reducing the risk of severe complications associated with AD, particularly lymphedema [5,6].

More recently, several randomized studies have demonstrated that AD could be omitted in cN0 cases with limited SLNB disease [7–10]. The ACOSOG Z0011 trial confirmed that 10-year overall survival was non-inferior for those treated with SLND alone compared with ALND in women with T1 or T2 and 1–2 sentinel lymph nodes with metastases in upfront breast-conserving surgery [7].

Despite this, several criticisms arose after the publication of the Z0011 study, such as reduced statistical power and short follow-up, which motivated clinicians and researchers to conduct further trials [8].

Such sequential studies have demonstrated the non-inferiority of SLNB compared to AD in this setting, even in cases of patients undergoing mastectomy or with extra nodal extension (ECE). In 2023, an update from the SINODAR-ONE trial in women with T1-T2 breast cancer who had undergone mastectomy suggested that the SLNB and ALND groups provided similar 5-year recurrence-free survival rates (94.1 vs 95.7 %, $p = 0.821$) [9].

The first results of the SENOMAC trial published in 2024 [12]—a non-inferiority randomized clinical trial comparing SLNB and ALND—focused on women with T1-T3 breast cancer and 1–2 sentinel node macrometastasis (metastasis size >2 mm) demonstrated that the hazard ratio (HR) for 5-year recurrence or death between the SLNB and ALND groups was 0.89 (95 % CI, 0.66 to 1.19; $p < 0.001$), confirming non-inferiority (defined as $HR < 1.4$, one-sided $p < 0.025$) [9].

Despite the publication of these studies, many surgeons continue to recommend axillary dissection (AD) [10]. Moreover, prior reviews lacked analyses of the impact of macro- versus micrometastasis on outcomes, which is a critical predictor of recurrence [11]. Recent studies have also faced criticism [12], with authors suggesting that the quality of evidence warrants closer scrutiny because past reviews are poorly conducted and insufficiently updated [11,13].

Given this context and the availability of new publications in the literature [8,9], it is essential to reassess the current practice of offering SLNB to women with breast cancer who have no more than two metastatic sentinel lymph nodes [11,13,14], which aims to provide insights into whether there remains a gap that could be addressed with an additional clinical trial.

Therefore, the present systematic review with meta-analyses aimed at assessing the 5-, 8-, and 10-year overall survival (OS), disease-free survival (DFS), recurrence rates, and lymphedema in randomized clinical trials comparing ALND and SLNB with or without AR in women with T1-T3 and cN0 BC, presenting with 1–2 metastatic sentinel lymph nodes

(SLN). As secondary objectives, this review also provided meta-analyses on the influence of micrometastasis and macrometastasis on outcomes.

2. Methods

2.1. Protocol registration and rationale of review

This systematic review was registered with PROSPERO (CRD42024585305). This study aimed to identify randomized controlled trials (RCTs) that compared the outcomes of different axillary treatments in women with lymph node-positive early breast cancer (BC). Therefore, our research question was as follows: “In randomized controlled trials (RCTs), what are the efficacy (OS, DFS, and axillary recurrence) and lymphedema outcomes of SLNB alone compared to ALND or AR in women with cN0 early breast cancer presenting 1–2 positive SLNs?”.

2.2. Data sources and searches

Three databases were screened for studies: Medline, Embase, and the Cochrane Central Register of Controlled Trials [30]. Manuscripts published between January 2010 and April 2024 with no language restrictions were considered for review.

2.3. Study selection

Two independent reviewers screened the initial results of the research strategy based on the title and abstract and included papers that were in accordance with the systematic review protocol. Disagreements between the two reviewers were discussed with experienced breast surgeons to achieve a consensus.

2.4. Data extraction

The following data were extracted: author, year of publication, number of study sites, baseline population characteristics (age), inclusion and exclusion criteria, sample size, study arms, tumor characteristics (size, macro-and micrometastasis, number of positive sentinel nodes, number of removed sentinel nodes), radiotherapy, adjuvant chemotherapy, lymphedema, recurrence, OS, and DFS. For the last two outcomes, data were collected based on Kaplan-Meier curves, including those reported by the authors. When there was no information, PlotDigitizer was used to estimate the proportion of events given a time in the graph (plotdigitizer.com). Two independent reviewers extracted data in duplicate and resolved any inconsistencies by consulting breast surgeons.

2.5. Outcomes, data synthesis, and analysis

The outcomes of interest in this review were [1] axillary recurrence

Table 1

Characteristics of the seven studies reported by thirteen papers.

Study name	Publication Year	Author	Study arms	Inclusion criteria	Exclusion criteria	Period	Country	Sample size
AMAROS	2014 and 2022	Donker et al. and Bartels et al.	RT + SLNB versus ALND	T1–2 primary, unifocal, invasive breast cancer, with no palpable lymphadenopathy, tumors of up to 3 cm diameter. In 2008 to adjust to developments in clinical practice, the eligibility criteria were broadened to include tumors up to 5 cm diameter or multifocal disease, or both. Furthermore, sentinel nodes with only isolated tumor cells were no longer regarded as sentinel node positive.	Previous malignancy, neoadjuvant systemic treatment for the primary breast cancer, or treatment of the axilla by surgery or radiotherapy.	2001–2010	Multicentric	4806 randomly assigned (RT: 2404/ALND: 2402) Included for analysis, (ITT defined by author) (RT: 681/ALND: 744)
SENOMAC	2 articles in 2024	Both are Boniface et al.	SLNB versus ALND	cN0 breast cancer with a tumor stage of T1, T2, or T3 (tumor size, T1, ≤ 20 mm; T2, 21–50 mm. and T3, > 50 mm in the largest dimension) and one or two sentinel-node macrometastasis (metastasis size, > 2 mm in the largest dimension)	Extraaxillary regional or distant metastases, a history of invasive breast cancer, breast cancer in both breasts if one of the breasts met exclusion criteria, medical contraindications against radiation therapy or systemic	2015–2021	Multicentric	2766 randomly assigned (SLNB: 1382/ALND: 1384) Included for analysis, (Per protocol population, defined by author): (SLNB: 1335/ALND: 1205)
IBCSG-23-01	2014 and 2018	Both are Galimbert et al.	SLNB versus ALND, patients could be submitted to BCS if tumor ≤ 5 cm, and one or more micrometastatic (≤ 2 mm) foci in the SNs, but no macrometastatic disease.	Clinically palpable axillary lymph node(s) and a primary tumor ≤ 5 cm who, after sentinel node biopsy, had one or more micrometastatic (≤ 2 mm) sentinel lymph nodes with no extracapsular extension. In 2006, to broaden eligibility by allowing patients with one or more positive SNs (formerly only one); multicentric/multifocal tumors (formerly only unicentric), and largest lesion size ≤ 5 cm (formerly ≤ 3 cm).	Not clearly reported, otherwise, lactating or pregnant women.	2001–2010	Multicentric	934 randomly assigned (SLNB: 469/ALND: 465) Included for analysis: (SLNB: 464/ALND: 467)
ACOSOG Z0011	2011, 2016 and 2017	There are 3 papers published by Giuliano et al.	SLNB versus ALND	Women with clinical T1 or T2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases.	Women were ineligible if they had 3 or more positive SLNs, matted nodes, or gross extranodal disease, or if they received neoadjuvant hormonal or chemotherapy	1999–2004	USA	891 randomly assigned (SLNB: 446/ALND: 445) Included for analysis, (Intention to treat, defined by author): (SLNB: 436/ALND: 420)
OTOASOR	2017	Savolt et al.	RNI (regional nodal irradiation) versus ALND, all patients received breast surgery	cT ≤ 3 cm, cN0 primary invasive breast cancer	Not clearly reported		Hungary	526 randomly assigned after positive SLN (RT: 265/ALND: 261). The analysis set was: (RT: 230/ALND: 244).
AATRM	2013	Sola et al.	Clinical follow-up (SLNB) versus ALND All patients received postoperative adjuvant systemic therapy	Newly diagnosed breast cancer at an early stage (T < 3.5 cm, clinical N0, M0) who had undergone surgical	Pregnant or lactating women, those older than 75 years, and those ineligible for	2001–2008	Spain	247 patients were ultimately recruited. The analysis set was:

(continued on next page)

[2], overall survival [3], disease free, and [4] lymphedema.

We tabulated the studies (Tables 1 and 2) and calculated the pooled relative risk based on the number of events described in each study. OS, DFS, and recurrence outcomes were assessed among the 5-, 8-, and 10-year horizons, when possible. Meta-analyses were conducted using R software with a random-effects model. Heterogeneity was assessed using the I^2 method.

Additionally, to explore the impact of micro-or macrometastasis on outcomes, previous meta-analyses included studies in descending order of % of micrometastasis reported in the studies (from 100 % to 0 % micrometastasis). Finally, macrometastasis-only studies were also meta-analyzed and compared with the pooled overall population results.

2.6. Quality of evidence and risk of bias

RCTs were also assessed for risk of bias using the Cochrane tool (RoB, Risk of Bias v2). A modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of evidence. (www.gradeworkinggroup.org). This tool was applied to the longest follow-up reported; therefore, if there was overall survival for 5 and 10 years, the last one was chosen. This tool was applied to OS, DFS, recurrence rates, and lymphedema.

3. Results

Initially, 2462 papers were identified. After removing duplicate studies, 1790 reports were excluded by title or abstract reading, and 31 articles were selected for full-text reading. This step allows the reviewers to include an additional study published during the review process [15]. Finally, 13 articles from seven RCTs were included in the review (Fig. 1).

This review included 7338 women included in the studies between the 1999 and 2020 recruitment periods. The women with BC had a mean

age of 53–61 years and were followed up for 2.8–10 years. The study population comprised 3637 women who were allocated to ALND and 3701 who were not exposed to ALND (SLNB or Intervention Group).

In Tables 1 and it can be observed that most studies included women with an average of one positive SLN and, when reported, it could be seen that the group exposed to ALND had on average, more than 15 positive lymph nodes (besides positive SLN). Overall, two trials focused on the micrometastasis-only population, and one study focused on macrometastasis. Most studies included both micro-and macrometastasis. Additional interventions, such as radiotherapy and adjuvant chemotherapy, varied significantly between studies (Table 2).

3.1. Recurrence

The recurrence rates were similar between the SLNB and ALND groups. The 5-year local recurrence (Fig. 2) was not significantly different between the ALND and SLNB arms (RR = 1.48, 95 %CI 0.84 to 2.60), as was the 8-year regional recurrence (RR = 1.38, 95 %CI 0.78 to 2.45) and 10-year regional recurrence (RR = 2.18, 95 %CI 0.98 to 4.84). The 5-year systemic recurrence was not different between the groups (RR = 1.29, 95 %CI 0.48 to 3.47) (Supp figures).

3.2. Disease free survival

The DFS was also similar between the ALND and SLNB study arms. The 5-year DFS (Fig. 3) provided a pooled RR of 1.0 (95 %CI 0.98 to 1.02). The 8-year DFS (RR = 1.02, 95 %CI 0.98 to 1.07) and 10-year DFS (RR = 1.0, 95 %CI 0.95 to 1.06) also showed no statistical differences between the two surgical modalities (Supplementary figures).

Table 1 (continued)

Study name	Publication Year	Author	Study arms	Inclusion criteria	Exclusion criteria	Period	Country	Sample size
SINODAR-ONE	2022 and 2023	Both are Tinterri et al.	(chemo or hormone therapy, according to the guidelines used at each center). SLNB with further adjuvant therapy versus ALND The 2022 publication focus on SLNB vs ALND. The 2023 was focused on patients undergoing mastectomy with one to two metastatic sentinel lymph nodes	excision (mastectomy or breast-conserving surgery) as the primary treatment. All had micrometastatic SN. Patients were included after removal of ≥ 10 axillary level I/II nonsentinel nodes followed by adjuvant therapy. Other inclusion criteria: Age ≥ 40 and ≤ 75 years Invasive BC (cytology/core biopsy assessment) Unilateral lesion Tumor size ≤ 5 cm (cT1–2) (ultrasound/mammography assessment) Clinically negative axillary nodes (NO) (ultrasound assessment) No more than two SLNs proven metastatic (histological assessment) Involved SLNs with macrometastasis (≥ 2 mm) No distant metastasis (MO) No neoadjuvant therapy No previous invasive BC	follow-up were excluded. Ongoing pregnancy or breast-feeding Inflammatory BC In situ BC Synchronous contralateral BC Comorbidity possibly preventing adjuvant therapy Disease, comorbidity, or psychological conditions preventing compliance to regular follow-up Previous neoplasm within the 3 years preceding randomization (except for in situ carcinoma of the cervix, basaloma, and spinocellular carcinoma of the skin)	2015–2020	Italy	(SLNB: 112/ ALND: 121). The ITT population was composed of 879 patients, who were randomly assigned in 1:1 fashion (SLNB: 440/ALND: 439)

Legend: SLNB: sentinel lymph node biopsy, SN: sentinel node, BC: breast cancer, ALND: axillary lymph node dissection, RT: radiotherapy.

Table 2
Clinical characteristics of patients included in the studies.

Study name and authors	Sample size (Experimental/ALND)	Age (mean in years)	Follow-up (years)	Micro and macrometastasis	Tumor size (mean in mm)	Mean number of <u>positive sentinel lymph nodes</u> ^a	Mean number of <u>sentinel lymph nodes removed</u>	% of residual disease	% of ≥3 lymph nodes positive besides sentinel	Adjuvant chemotherapy	Description of RT
AMAROS Donker et al., 2014 and Bartels et al., 2022	RT + SLNB: 681/ALND: 744	RT + SLNB: 55/ALND: 56	6.1 in Donker et al. and 10.0 in Bartels	Micrometastasis RT + SLNB: 28/ALND: 29 % Macrometastasis RT + SLNB: 61/ALND: 59 %	Median (IQR) RT + SLNB: 18 [13–23]/ALND: 17 [13–22]	RT + SLNB/ALND 1 SN: 75/78 % 2 SN: 20/17 % 3 SN: 4/4 % ≥4 SN: 1/1 %	RT + SLNB/ALND 1SN: 43/45 % 2SN: 32/27 % 3SN: 15/17 % ≥4SN: 10/11 %	Not reported	AR/ALND# 0 LN: 38/67 % 1-3 LN: 35/25 % ≥4 LN: 25/8 %	Adjuvant systemic treatment was applied at the discretion of the treating multidisciplinary team	25 fractions of 2 Gy
SENOMAC Boniface et al., 2024 for both studies	SLNB: 1335/ALND: 1205	61/60	3.9	One sentinel node with macrometastasis RS: 85/ALND: 83 % Two sentinel nodes with macrometastasis RS: 14/ALND: 16 %	SLNB/ALND: 24.4/24.2	2 per patient	SLNB/ALND 1-2: 70/71 % 3-4: 26/25 % >4: 4/4 %	Not reported	Mean number SLNB/ALND: 2.3/15.5	65 %, ACT type not reported	88 % received RT in accordance with national guidelines
IBCSG-23-01 Galimberti et al., 2014 and 2018	SLNB: 467/ALND: 464	SLNB: 54/ALND: 53	In 2014 was 5 years, in 2018 was 9.7 years	Only micrometastasis were included, but there were 2 % in each group with tumors sizing >2 mm	≤50	Not reported. Formally one positive SN was included, but “one or more positive sentinel nodes” were included.	Not reported.	Not reported.	Not reported.	96 % received adjuvant chemotherapy	98 % received RT.
ACOSOG Z0011 Giuliano et al., 2011, 2016 and 2017	SLNB: 436/ALND: 420	SLNB: 54/ALND: 56	median 9.3 (~10- year)	Micrometastasis SLNB: 37.5 % and ALND: 44.8 %	Median SLNB: 16/ALND: 17	The inclusion criteria were 1 or 2 SLN. If three, it was excluded.	The inclusion criteria were 1 or 2 SLN. If three, it was excluded.	Not reported	Median (IQR) SLNB: 2 (1–4) ALND: 17 (13–22)	Nearly 96 % received adjuvant chemotherapy.	Nearly 96 % received radiotherapy.
OTOASOR Savolt et al., 2017	RT: 230/ALND: 244	RT: 55/ALND: 54.7	8.0	Micrometastasis RT: 33/ALND: 7.4 %	Not reported	RT: 1.17 (range 1–4)/ALND: 1.36 (range: 1–4)	RT: 1.95 (range 1–5)/ALND: 1.83 [1–5]	Not reported	ALND: 14.3 (range: 7–32) RT is not applicable	Adjuvant systemic therapies were administered in accordance with our institutional protocols	100 % of patients in RT group received radiotherapy. (25 fractions of 2Gy over 5 weeks)
AATRM Sola et al., 2013	SLNB: 112/ALND: 121	SLNB: 53.2/ALND: 55.3	5.1	All patients had micrometastasis	SLNB: 17.8/ALND: 15.8	Not reported	Not reported	Not reported	Not reported	92 % of all patients received postoperative adjuvant systemic therapy (chemotherapy or hormone therapy) and 7.9 % received only hormone therapy.	89.7 % received radiotherapy.
SINODAR ONE Tinterri et al., 2022 Tinterri et al., 2023	SLNB: 440/ALND: 439	SLNB: 56.2/ALND: 56.1	A minimum of 5-year follow-up is expected (2.8 years in 2023)	Overall, less than 1 % of the population had micrometastasis in Tinterri et al., 2022. Seven percent had micro and macro metastasis. In 2023 study, 100 % of patients present macrometastasis.	SLNB: 18.0/ALND: 19.6	Overall, the median number of positive SLN was 1 (IQR = 1 to 1)	Not reported	Not reported	Only 5 % of the population had more than 3 non-sentinel positive lymph nodes.	Adjuvant therapy was given to 90 % of all enrolled patients.	Radiotherapy was given to 71 % of all enrolled patients.

Legend: SLNB: sentinel lymph node biopsy, SLN: sentinel lymph node, ALND: axillary lymph node dissection, RT: radiotherapy, IQR: inter quartile range, LN: lymph node.

^a (as mean number was not available in all studies, we collected exactly as reported). # (The % does not sum 100 % because the authors reported that “Additional metastatic lymph nodes in the axillary radiotherapy group were found in a group of patients who crossed over from axillary radiotherapy to axillary lymph node dissection and are thus not representative of the number of additional nodes in the whole group”).

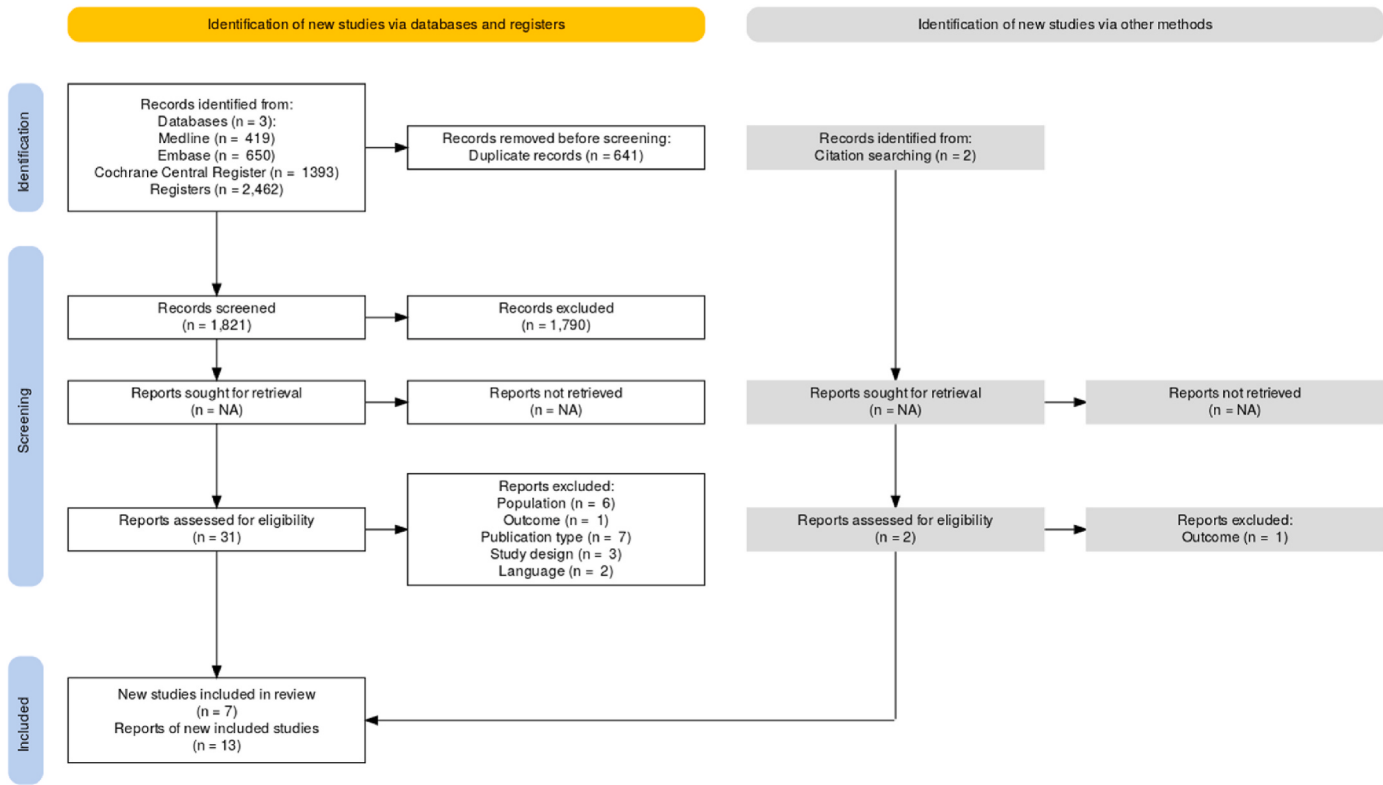


Fig. 1. Prisma flow diagram.

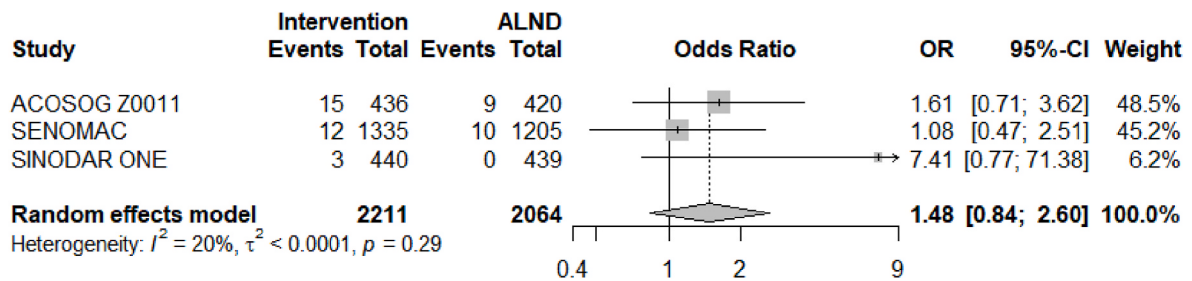


Fig. 2. Five-year local recurrence.

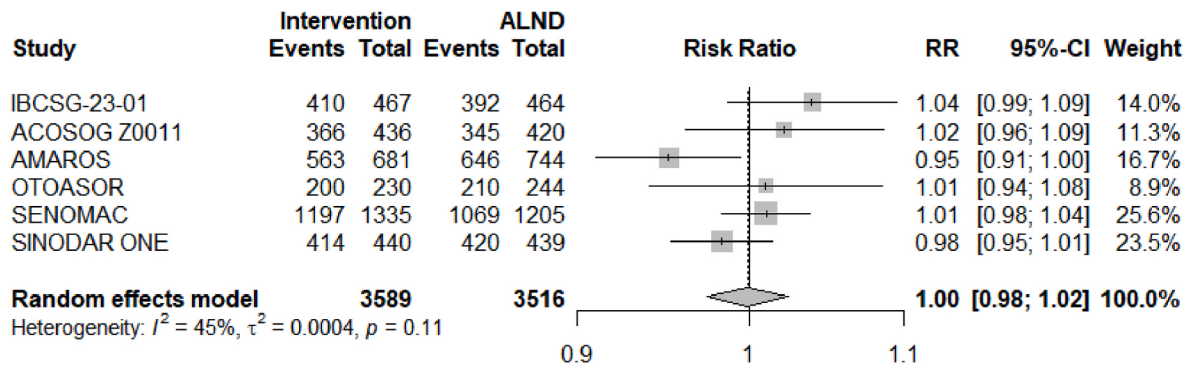


Fig. 3. Five-year disease-free survival.
Events: number of patients that are without recurrence.

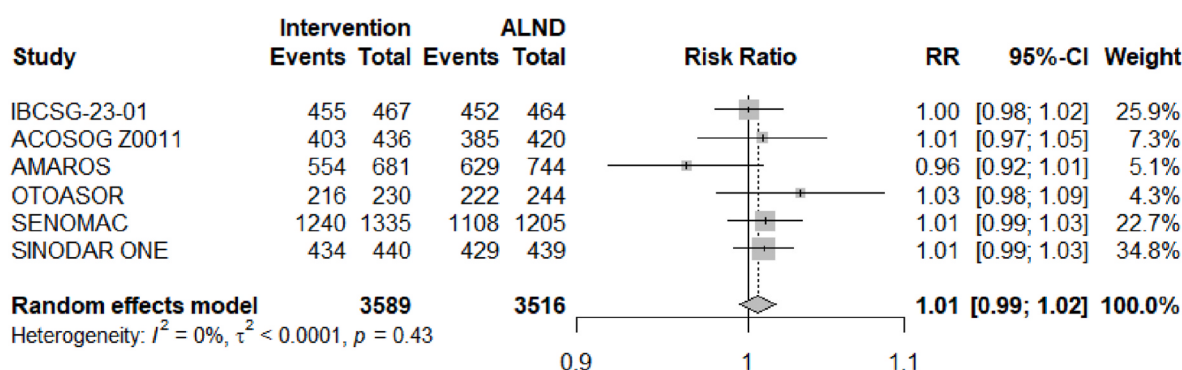


Fig. 4. Five-year overall survival.

Events: number of patients that are without recurrence.

3.3. Overall survival

OS was not considered statistically different between ALND and SLNB groups in 5-year (RR = 1.01, 95 %CI 0.99 to 1.02) (Fig. 4), 8-year (RR = 1.01, 95 %CI 0.99 to 1.04) or 10-year analyses (RR = 1.02, 95 %CI 0.98 to 1.06) (Supp figures).

3.4. Lymphedema

SLNB was associated with a 65 % lower rate of lymphedema than ALND (RR = 0.35, 95 %CI: 0.20–0.60) (Supplementary Figure).

3.5. Quality of the evidence

Using the GRADE tool [29], all evidence was rated as having low to moderate certainty (Supp). The reasons for grading down the trials, in many cases, included a significant number of withdrawals (after randomization, many patients were excluded) and per protocol sample was used in place of intention-to-treat population. Additionally, the protocol was designed to find papers with two or fewer positive SLN; however, some studies included an average of one positive SLN, ranging from 1 to 4. As many RCTs were designed to find non-inferiority between the compared arms, uncertainty due to imprecision might not be considered a drawback.

4. Discussion

In our review, we included seven randomized trials that compared ALND with observation [7,9,15–17] or axillary radiotherapy [18,19] for 1–2 positive SLN. No differences were observed in the main endpoints evaluated in this study, except for lymphedema, which was more common in AD cases.

The indications for axillary lymph node dissection (ALND) have steadily declined. This is because of its adverse effects such as lymphedema, reduced arm mobility, and sensory changes, and this approach would only be justifiable if the procedure significantly improved the outcome.

This updated systematic review with meta-analyses has shown that, based on the most recently published information, women with T1-T3 and 2 positive SLN BC exposed to SLNB had fewer lymphedema events, but similar survival, DFS, and recurrence rates at 5-, 8- and 10-years follow-up.

These reinforcing findings change previously published reviews that mentioned that ALND provided lower recurrence rates in comparison to SLNB [14] (HR for locoregional recurrence, 1.64; 95 %CI, 1.03 to 2.61) and Cardoso et al. [11] (RR for 10-year regional recurrence, 1.9; 95 %CI 1.03 3.45).

In our meta-analysis, all recurrence rates statistically crossed the null line in all periods of observation and recurrence types (local, regional, or

systemic). Updated results from the SENOMAC trial [15], a study that included more than 2700 patients, impacted the final pooled estimate for recurrence, if the correct statistical method (random effects model) and transparent data are considered [11,13].

The finding of micro-or macrometastasis can have different impacts on outcomes [20] and was explored in our analyses by two methods [1]: conducting a meta-analysis organizing the trials from 100 % micro-metastasis to 100 % macrometastasis [2]; meta-analyzing only macrometastasis and making inferences on the overall population. No trend favoring SLNB or ALND was found, considering both methods, suggesting that, despite being prognoses, they do not have any relevance in the decision of a possible need for ALND.

Other interesting findings deserve further attention. Our inclusion criteria were expected to include papers on ≤ 2 positive SLN, such as Z0011 [7], SENOMAC [15], and SINODAR-ONE [21] studies. However, few studies included an “average” of one positive SLN, such as in the AMAROS [22] and OTOASOR [19] trials. In the last one, OTOASOR included patients with 1–4 positive SLN (average of 1). Although there were no changes in the meta-analyses, this illustrates the challenges in clinical practice when surgeons face positive 1/1 or 2/2 SLN [23]. In the present review, we further characterized all SLN positivity information and the number of positive lymph nodes with metastasis in the ALND group. There is no evidence of benefits regarding the use of strict criteria for two SLN, such as those applied to Z0011 and other trials. However, this is still an open discussion, and even deep machine learning has been used to predict SLN metastasis based on preoperative information [24]. Using a predictive model with 75 % accuracy (70 % specificity, 78 % sensitivity and 0.74 area under the curve), HER2, Ki67 %, estrogen, and progesterone receptor expression showed statistically significant associations with SLN metastasis. While this is a hypothesis generator study, it is well known that tumor biology plays an important role in recurrence rates and outcomes [25]; therefore, these covariates (Ki67 and receptor profile) should be minimally better reported in further research.

Finally, despite recent evidence on the use of ALND and abemaciclib in HER2 negative [26], high-risk hormone receptor-positive BC, defined as the presence of at least four positive nodes or one to three positive nodes with additional high-risk features (i.e., tumor size ≥ 5 cm or grade 3), the risks and benefits should be outweighed [25] between SLNB benefits (similar OS, DFS, and recurrence rates in comparison to ALND) versus choosing ALND and abemaciclib in light of an additional 4-year 6.4 % absolute risk reduction in invasive disease-free survival, 19 % chance of treatment suspension due to toxicity, and 65 % increased risk of lymphedema (based on our meta-analysis of SLNB vs. ALND).

In patients with BRCA, the use of olaparib in the adjuvant setting is a known standard of care for high-risk disease, prolonging both disease-free survival and OS [27,28]. These patients were eligible if they had residual disease and a clinical and pathologic stage (CPS), estrogen receptor status, and histologic grade (EG) score ≥ 3 after neoadjuvant chemotherapy or at least four nodes involved in surgery prior to

adjuvant chemotherapy. Again, a possible loss of eligible patients may occur in this scenario.

Finally, this review has limitations. First, the quality of the review is directly proportional to the quality of the trials included: few studies showed a significant number of withdrawals, use of per-protocol population to assess outcomes, and lack of information in tumor biology, which is known to be a predictor of poor outcomes.

5. Conclusion

This systematic review with meta-analyses confirms that SLNB provides similar overall survival and disease-free survival outcomes to ALND, with a 65 % lower risk of lymphedema. Additionally, this study contradicts earlier reviews that suggested a lower recurrence risk with ALND as the updated analysis found no significant difference in recurrence rates between the two groups.

CRedit authorship contribution statement

André Mattar: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Marcelo Antonini:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Francisco Pimentel Cavalcante:** Conceptualization, Writing – original draft, Writing – review & editing. **Felipe Zerwes:** Writing – review & editing. **Eduardo de Camargo Millen:** Writing – review & editing. **Fabrizio Palermo Brenelli:** Writing – review & editing. **Antônio Luiz Frasson:** Writing – review & editing. **Patrícia Carvalho Baruel:** Writing – review & editing. **Lucas Miyake Okumura:** Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Leonardo Ribeiro Soares:** Writing – original draft, Writing – review & editing. **Marcelo Madeira:** Writing – review & editing. **Marina Diógenes Teixeira:** Writing – review & editing. **Andressa Gonçalves Amorim:** Writing – review & editing. **Larissa Chrispim de Oliveira:** Writing – review & editing. **Marcellus do Nascimento Moreira Ramos:** Writing – review & editing. **Gil Facina:** Writing – review & editing. **Ruffo de Freitas Junior:** Writing – review & editing. **Henrique Lima Couto:** Writing – review & editing. **Sabrina Monteiro Rondelo:** Writing – review & editing. **Renata Montarroyos Leite:** Writing – review & editing. **Renata Arakelian:** Writing – review & editing. **Luiz Henrique Gebrim:** Writing – review & editing. **Juliana Monte Real:** Writing – review & editing.

Ethics approval

Informed consent and ethics approval were not required as this systematic review was based on published studies.

Data availability

All data is available upon request.

Funding

This study did not receive any funding.

Declaration of competing interest

AM received honoraria from Roche, AstraZeneca, Novartis, Exact Sciences, and Eli Lilly. The other authors have no conflicts of interest to declare.

Acknowledgements

We would like to thank all the patients who participated in the included studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2025.104453>.

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