Ann Surg Oncol (2024) 31:1643–1652
https://doi.org/10.1245/s10434-023-14631-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

REVIEW ARTICLE – BREAST ONCOLOGY

Prevention of Seroma Formation and Its Sequelae After Axillary Lymph Node Dissection: An Up-to-Date Systematic Review and Guideline for Surgeons

Merel A. Spiekerman van Weezelenburg, MD[1], Maikel J. A. M. Bakens, MD, PhD[1], Jean H. T. Daemen, MD, PhD[1], Loeki Aldenhoven, MSc[1], Elisabeth R. M. van Haaren, MD[1], Alfred Janssen, MD[1], Yvonne L. J. Vissers, MD, PhD[1], Geerard L. Beets, MD, PhD[2,3], and James van Bastelaar, MD, PhD[1]

[1]Department of Surgery, Zuyderland Medical Centre, Sittard-Geleen, The Netherlands; [2]Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]GROW School for Oncology and Developmental Biology, University of Maastricht, Maastricht, The Netherlands

ABSTRACT

Introduction. Seroma formation after axillary lymph node dissection (ALND) remains a troublesome complication with significant morbidity. Numerous studies have tried to identify techniques to prevent seroma formation. The aim of this systematic review and network meta-analysis is to use available literature to identify the best intervention for prevention of seroma after standalone ALND.

Methods. A literature search was performed for all comparative articles regarding seroma formation in patients undergoing a standalone ALND or ALND with breast-conserving surgery in the last 25 years. Data regarding seroma formation, clinically significant seroma (CSS), surgical site infections (SSI), and hematomas were collected. The network meta-analysis was performed using a random effects model and the level of inconsistency was evaluated using the Bucher method.

Results. A total of 19 articles with 1962 patients were included. Ten different techniques to prevent seroma formation were described. When combining direct and indirect comparisons, axillary drainage until output is less than 50 ml per 24 h for two consecutive days results in significantly less CSS. The use of energy sealing devices, padding, tissue glue, or patches did not significantly reduce the incidence of CSS. When comparing the different techniques with regard to SSIs, no statistically significant differences were seen.

Conclusions. To prevent CSS after ALND, axillary drainage is the most valuable and scientifically proven measure. On the basis of the results of this systematic review with network meta-analysis, removing the drain when output is < 50 ml per 24 h for two consecutive days irrespective of duration seems best. Since drainage policies vary widely, an evidence-based guideline is needed.

Keywords Axillary lymph node dissection · Seroma · Drain · Axillary padding · Energy devices · Tissue glue

Axillary lymph node dissection (ALND) is notorious for its complications, including surgical site infections, neuropathic pain, lymphedema, and seroma formation.[1] The introduction of sentinel lymph node biopsies (SLNB) resulted in fewer lymph node dissections. The AMAROS trial showed that axillary radiotherapy after a positive SLNB was equal to ALND for patients with breast cancer regarding survival, and the MSLT-II trial showed that immediate complete lymph node dissections did not improve melanoma-specific survival.[2–5] However, ALND remains an important treatment modality for some patients. Therefore, reducing surgical morbidity after these procedures remains pivotal.

Seroma formation is one of the most frequent complications after ALND, with an incidence of up to 90%.[1,6] As addressed by van Bemmel et al. in 2011, many studies address different techniques to prevent seroma formation,

First Received: 6 September 2023
Accepted: 6 November 2023
Published online: 1 December 2023

M. A. Spiekerman van Weezelenburg, MD
e-mail: m.spiekermanvanweezelenburg@zuyderland.nl

but no single intervention proved to be completely successful.[6] In the past decade, more research has been performed regarding this topic.

One major disadvantage in the current literature is that the majority of studies do not differentiate between ALND as a standalone procedure or ALND in combination with mastectomy.[7,8] The extent of the dissection is a proven risk factor for developing seroma, and therefore, patients undergoing ALND with mastectomy are more prone to develop seroma than after ALND as a standalone procedure or in combination with breast-conserving surgery.[9] Results of these trials suggest that flap fixation after mastectomy alone seems to be the most promising solution for seroma in these procedures; this could possibly be effective for ALND as a standalone procedure as well.[7,9,10] However, for ALND, flap fixation of the axillary dead space could cause other difficulties, and as such may compromise mobility of the ipsilateral arm.[11,12]

The aim of this systematic review is to identify the most effective measures for the prevention of seroma formation after a standalone ALND, using a network meta-analysis (NMA) to indirectly compare different techniques. The ultimate goal is to create a surgical guideline for surgeons performing ALND.

PATIENTS AND METHODS

Design

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,[13] including the network meta-analysis extension.[14] Prior to initiation, a local protocol for study selection and the NMA was drafted.

Eligibility Criteria

Articles were eligible for inclusion if: (1) it was a comparative study, (2) it compared any measure meant to prevent seroma formation after ALND, and (3) it had overall seroma or CSS incidence as outcome measure. Articles were excluded if ALND was combined with a mastectomy (modified radical mastectomy, MRM) only, or if there was no distinction in ALND procedures with or without mastectomy. If there was a clear distinction between ALND with and without mastectomy, the article was included and only the standalone ALND group was included. In addition, articles were excluded if older than 25 years (published before April 1998) or not written in English.

Search and Selection

The search was performed by two authors (MS and MB). The initial search for this systematic review was developed for PubMed and adjusted for EMBASE and Cochrane Library databases. The last search was performed on 24 April 2023. A full, detailed description of all searches is presented in Supplementary Material A–C. Search outcomes were imported in Rayyan (Rayyan Systems Inc., Cambridge, USA, http://rayyan.qcri.org), in which duplicates were removed. Titles and abstracts were first assessed, after which full texts were screened for eligibility. Study selection was performed in a blinded, standardized manner by two authors (MS and MB).

Data Collection and Outcome Measures

Data collection was performed by one author (MS) and cross-checked for validity by a second author (LA). General study information was collected, including year of publication, number of participants, and study design. Patient characteristics gathered included age, BMI, neoadjuvant treatment, and concomitant surgery. The primary outcome was CSS, which is defined as seroma requiring intervention due to infection, patient's discomfort, or delayed wound healing. Secondary outcomes collected were overall seroma, surgical site infections (SSI), and hematoma.

Bias Assessment for Individual Studies

Bias assessment was performed using the Cochrane tool for Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) and the revised Cochrane Risk of Bias tool for randomized trials (RoB2).[15,16] ROBINS-I assesses observational trials and categorizes in low, intermediate, serious, or critical risk of bias. RoB2 assesses randomized trials and categorizes in low risk, some concerns, or high risk of bias. The risk of bias was visualized for all trials using the Robvis tool.[17]

Statistical Analysis

The NMA was performed using the MetaXL software (MetaXL, Version 5.3, EpiGear International Pty Ltd). Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate effects for categorical outcomes, which are presented in a league table. ORs are presented in a way that a value > 1 indicates a preference for the treatment described in the column of the league table. Transitivity was assessed by evaluating inconsistency across the network using the weighted pooled H-statistic. A value < 3 indicated minimal presence of inconsistency.

RESULTS

Search Results

A detailed overview of the search results is depicted in Fig. 1. In total, the search resulted in 2071 articles. After removal of duplicates, 1762 articles were screened, 85 were analyzed on the basis of full text, and 19 articles were eligible for inclusion. These results are summarized in Table 1.

Methods

Nine of the included studies describe a randomized controlled trial (RCT).[18–26] In addition, six prospective cohorts,[27–32] one retrospective cohort,[33] and three combined retrospective and prospective cohorts were included.[34–36] Inclusion periods were all between 1995 and 2021.

Participants

In total, the 19 articles included 1962 patients. Follow-up ranged from 3 weeks to 1 year postoperatively. The mean age ranged from 48 years to 65 years and BMI from 23 kg/m^2 to 30 kg/m^2. Only six articles reported the number of patients undergoing neoadjuvant chemotherapy (NAC). This was between 14% and 43% of the patients included.

Described Techniques

A variation of techniques is described by the different studies. Nine studies report on different wound closure techniques, including axillary padding, application of tissue glue, or use of a sealant patch.[19,21,23–26,28,30,35] Six studies show results of different drain policies (no drain, 24-h drainage, drainage until < 50 ml per 24 h, or drainage until < 50 ml per 24 h for two consecutive days and progressive

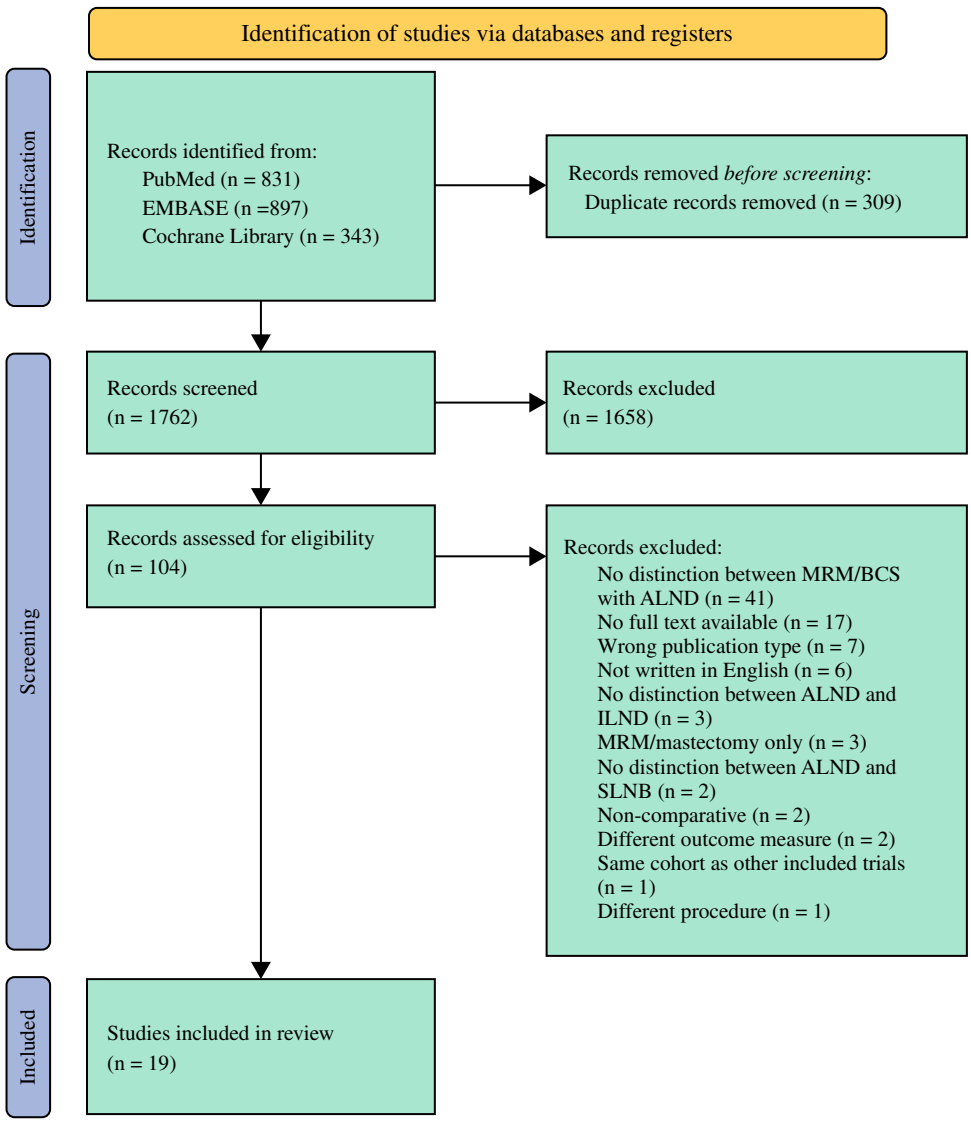

FIG. 1 PRISMA flow diagram of the article selection procedure

TABLE 1 Evidence table of all included studies, with study and patients' characteristics and outcome measures

References	Study details		Patients' characteristics				Incidence of outcome measures			
	Study design	Intervention groups	Number of participants	Mean age (years)	Mean BMI (kg/m^2)	NAC (n, %)	CSS (n, %)	Overall seroma (n, %)	SSI (n, %)	Bleeding complication (n, %)
Andeweg et al. (2011)[34]	Prospective versus retrospective cohort	24-h drain Drain removed < 50 ml per 24 h but no later than 7 days	18* 23*	57 ± 11 55 ± 9.8	–	–	7 (39) 4 (17)	–	7 (39) 6 (26)	–
Baas-Vrancken Peeters et al. (2005)[18]	RCT	24-h drain Drain removed < 50 ml per 24 h but no later than 7 days	16* 12*	58 ± 14 60 ± 14	–	–	10 (63) 8 (67)	–	–	–
Cavallaro et al. (2011)[27]	Prospective cohort	Harmonic Conventional	47 45	54 ± 12 52 ± 8.9	27 ± 4.3 25 ± 5.1	–	4 (8.5) 7 (16)	–	0 (0) 1 (2.2)	3 (6.4) 4 (8.9)
Classe et al. (2006)[19]	RCT	Axillary padding Axillary drainage	47 51	60 ± 10 58 ± 11	25 ± 5 25 ± 4	–	6 (13) 6 (12)	8 (17) 9 (18)	1 (2.1) 1 (2.0)	–
Conversano et al. (2017)[28]	Prospective cohort	Padding + sealant Axillary drainage	49 100	–	29 ± 7.2 28 ± 8.1	22 (45) 23 (23)	15 (31) 33 (33)	–	3 (6.1) 14 (14)	–
Divino et al. (2000)[29]	Prospective cohort	No drain Drain	20 62	62 57	–	–	8 (20) 4 (6)	–	–	–
Frich et al. (2021)[20]	RCT	Drain removed < 50 ml per 24 h for 2 days Progressive drain removal	30* 28*	63 ± 14 63 ± 17	27 ± 6.8 30 ± 7.8	–	9 (30) 9 (32)	13 (43) 11 (39)	7 (23) 3 (11)	–
Garbay et al. (2012)[30]	Prospective cohort	Axillary padding Axillary drainage	114 185	56 58	–	14 (12) 25 (14)	10 (8.8) 43 (23)	13 (11) 43 (23)	1 (0.9) 3 (1.6)	–
Ko et al. (2009)[21]	RCT	Fibrin glue Conventional	50 50	49 ± 8.7 48 ± 7.7	24 ± 9 23 ± 2	–	10 (20) 12 (24)	–	3 (6.0) 2 (4.0)	3 (6.0) 2 (4.0)
Koplin et al. (2017)[31]	Prospective cohort	Drain removed < 50 ml per 24 h but no later than 8 days Drain removed < 50 ml per 24 h for 2 days	117* 104*	57 ± 13 63 ± 15	28 ± 5 28 ± 5	–	40 (34) 6 (5.8)	–	2 (1.7) 0 (0)	1 (0.9) 1 (1)
Matthey-Gié et al. (2016)[22]	RCT	Harmonic Drain removed < 50 ml per 24 h for 2 days	27* 31*`	60 ± 15 62 ± 13	26 ± 4 27 ± 5	–	9 (30) 7 (22)	–	1 (4) 1 (3)	1 (4) 1 (3)
Neuss et al. (2008)[23]	RCT	Fibrin glue Conventional	29 29	58** 57**	28** 29**	–	5 (17) 1 (3.4)	–	2 (6.9) 1 (3.4)	1 (3.4) 0 (0)

Table 1 (continued)

References	Study details		Patients' characteristics				Incidence of outcome measures			
	Study design	Intervention groups	Number of participants	Mean age (years)	Mean BMI (kg/m^2)	NAC (n, %)	CSS (n, %)	Overall seroma (n, %)	SSI (n, %)	Bleeding complication (n, %)
Piñero-Madrona et al (2016)[24]	RCT	Tachosil® Conventional	44 47	53 ± 2.1 57 ± 1.7	27 ± 0.8 28 ± 0.9	15 (34) 9 (14)	7 (16) 22 (47)	–	1 (2.3) 3 (6.4)	0 (0) 3 (6.4)
Sanguinetti et al. (2010)[36]	Matched cohorts	Harmonic Conventional	35 35	–	–	–	–	3 (8.6) 5 (14)	0 (0) 0 (0)	0 (0) 0 (0)
Spiekerman van Weezelenburg et al. (2022)[35]	Prospective versus retrospective cohort	Hemopatch® Conventional	20 42	63 ± 12 58 ± 16	30 ± 6.4 27 ± 3.8	5 (25) 10 (24)	6 (30) 18 (43)	10 (50) 28 (67)	3 (15) 2 (4.8)	–
Taflampas et al. (2009)[25]	RCT	BioGlue® COSEAL® Conventional	15 23 39	55 ± 11 59 ± 12 56 ± 12	29 ± 4.7 29 ± 7.2 28 ± 5.3	–	–	3 (20) 3 (13) 3 (7.7)	3 (20) 7 (30) 9 (23)	–
Taylor et al. (2013)[32]	Prospective cohort	No drain Drain	115 50	57 ± 12 56 ± 9.4	–	–	40 (35) 13 (26)	–	6 (5.2) 2 (4.0)	2 (1.7) 0 (0)
Weber et al. (2018)[26]	RCT	Tachosil® Conventional	72 70	59 ± 17 58 ± 17	26 ± 4.9 26 ± 5.8	21 (29) 21 (30)	25 (33) 18 (25)	–	4 (5.3) 5 (6.8)	–
Wienerroither et al. (2022)[33]	Retrospective cohort	Ligature Conventional	35 36	65 ± 13 62 ± 12	27 ± 5.5 28 ± 5.9	35 (43) 50 (34)	24 (69) 15 (42)	–	4 (11) 3 (8.3)	–

*Only selected patients were included in these results (WLE + ALND and ALND alone). MRM and ILND patients were excluded.

**Median instead of mean

BMI body mass index, *NAC* neoadjuvant chemotherapy, *CSS* clinically significant seroma, *SSI* surgical site infection, *RCT* randomized controlled trial.

drain removal). In the drainage until < 50 ml per 24 h group, thresholds varied between 30 ml and 50 ml per day. In the drainage until < 50 ml per 24 h for two consecutive days group, only 50 ml thresholds were described. Progressive drain removal is described as removing the drain 1–2 cm a day, as opposed to immediate drain removal.[18,20,29,31,32,34] The remaining four studies report on the use of different surgical energy devices in the prevention of seroma formation.[22,27,33,36] The network structure is presented in Fig. 2. The weighted pooled H-statistic of 1.021 indicated minimal presence of inconsistency.

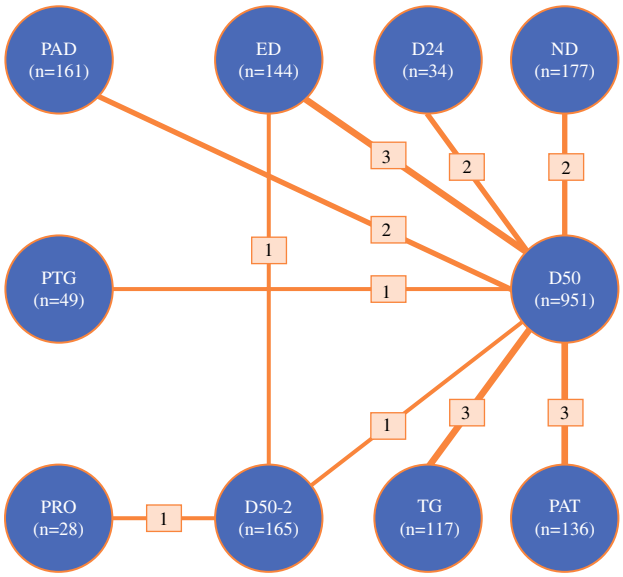

FIG. 2 Network structure of the direct comparisons. *PAD* Padding, *ED* Energy devices, *D24* 24 hour drainage, *ND* No drain, *PTG* Padding + tissue glue, *D50* Drainage until <50ml/24h, *PRO* Progressive drain removal, *D50-2* Drainage until <50ml/24h for two consecutive days, *TG* Tissue glue, *PAT* Patches

Risk of Bias Assessments

All included articles were assessed for their individual bias. A summary of these results is shown in Fig. 3 for randomized trials and in Fig. 4 for non-randomized trials. Only one trial was rated as low risk of bias. All other articles were considered to have some concerns/a moderate risk of bias (14 articles) or even high/serious risk of bias (4 articles). In most cases, this elevated risk was caused by lack of blinding in the randomized trials. Blinding was one of the main concerns in the non-randomized trials as well. In addition, confounders could also induce bias in the non-randomized trials. For bias in selection of reported results, only one of the articles referred to a preregistered protocol or statistical analysis plan. Therefore, these are indicated as moderate risks as well.

Clinically Significant Seroma

The results of the NMA for clinically significant seroma are presented in Table 2. As previously described, the three main domains of interventions are drain policies, surgical energy devices, and wound closure techniques. In general, the only two techniques with statistically significant differences in OR for CSS are progressive drain removal and drain removal if drain output is below 50 ml per 24 h for

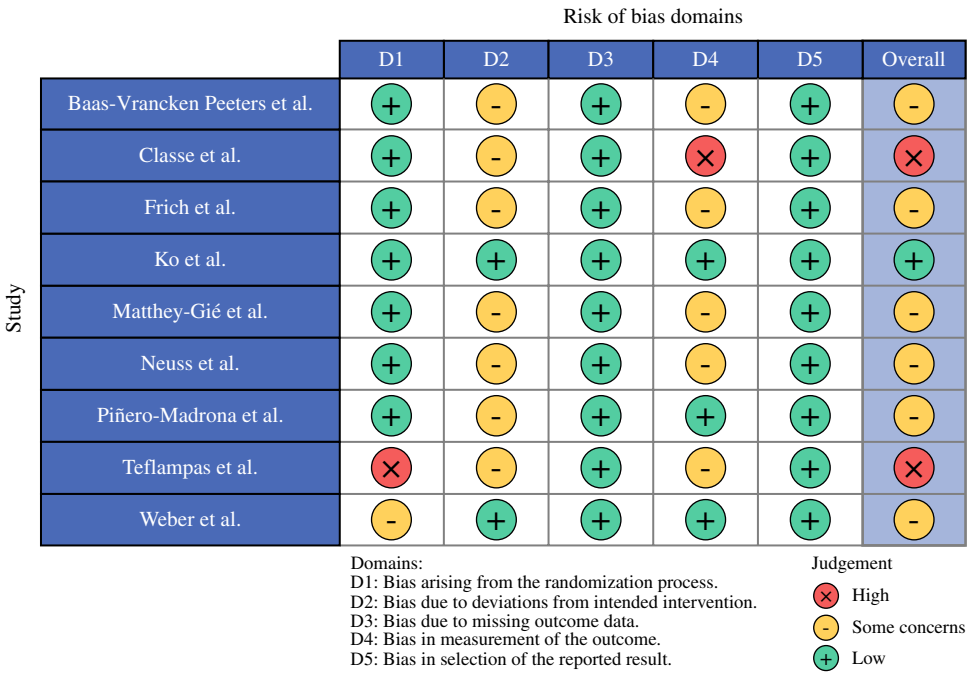

FIG. 3 Bias assessment of the individual randomized trials using the RoB2-tool

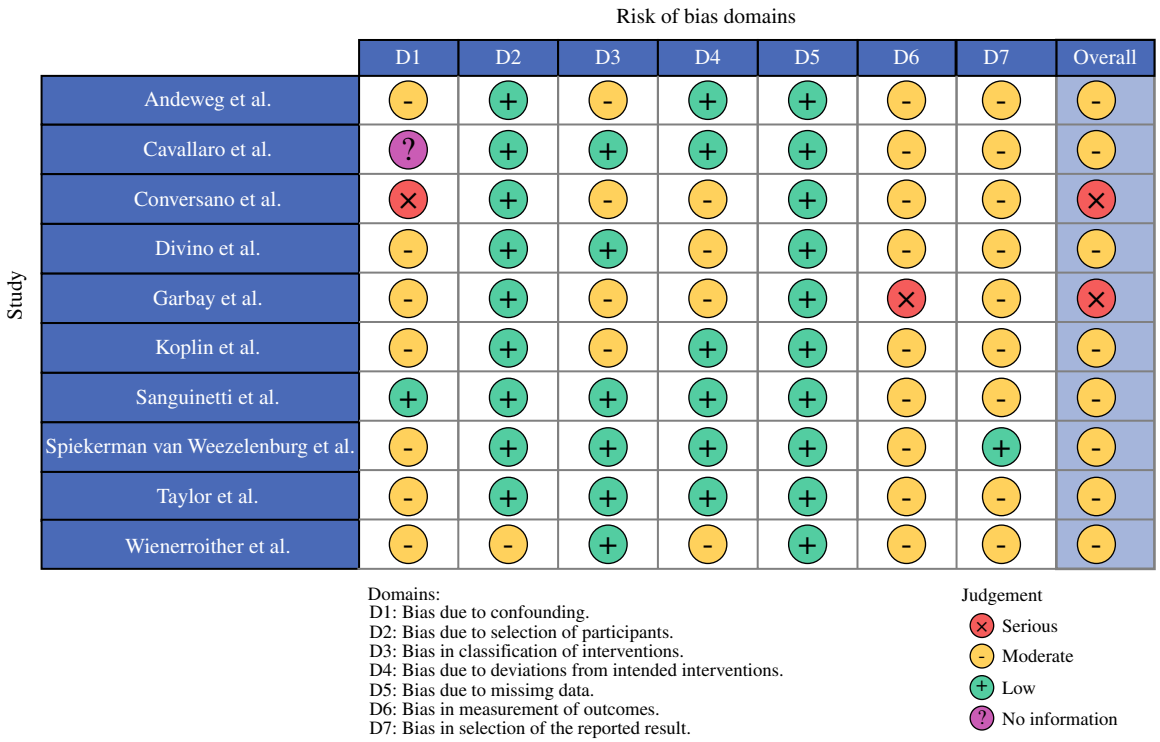

FIG. 4 Bias assessment of the individual non-randomized trials using the ROBINS-I-tool

TABLE 2 League table presenting the combined direct and indirect comparisons between different surgical measures for preventing CSS after ALND

D24									
2.78 (0.48-16.05)	PAT								
0.54 (0.05-6.40)	0.20 (0.02-2.26)	ND							
12.69 (1.88-85.80)	4.57 (0.69-30.07)	**23.31 (1.80-301.38)**	PRO						
1.00 (0.10-9.68)	0.36 (0.04-3.41)	1.84 (0.11-31.34)	**0.08 (0.01-0.85)**	TG					
3.09 (0.54-17.59)	1.11 (0.20-6.15)	5.67 (0.50-64.67)	0.24 (0.04-1.58)	3.09 (0.33-28.97)	PAD				
1.71 (0.30-9.72)	0.62 (0.11-3.40)	3.15 (0.28-35.79)	0.36 (0.08-1.59)	1.71 (0.18-16.03)	0.56 (0.10-3.02)	ED			
1.85 (0.43-7.95)	0.66 (0.16-2.76)	3.39 (0.36-31.93)	**0.15 (0.03-0.73)**	1.85 (0.24-14.04)	0.60 (0.15-2.45)	1.08 (0.27-4.39)	PTG		
14.03 (2.97-66.3)	**5.05 (1.10-23.10)**	**25.77 (2.57-258.21)**	1.11 (0.36-3.36)	**14.04 (1.73-114.26)**	**4.55 (1.05-20.49)**	**4.09 (1.65-10.14)**	**7.60 (2.36-24.48)**	D50-2	
1.65 (0.47-5.83)	0.60 (0.18-2.01)	3.03 (0.37-25.25)	**0.13 (0.03-0.55)**	1.66 (0.25-10.95)	0.54 (0.16-1.78)	0.62 (0.24-1.63)	0.90 (0.43-1.87)	**0.15 (0.06-0.37)**	D50

D24 24-h drainage, *PAT* patches, *ND* no drain, *PRO* progressive drain removal, *TG* tissue glue, *PAD* padding, *ED* energy devices, *PTG* padding + tissue glue, *D50-2* drainage until < 50 ml per 24 h for two consecutive days, *D50* drainage until < 50 ml per 24 h

Results are presented as OR (95% CI): an OR < 1 indicates a preference for the technique described in the column, statistically significant differences are bold. Statistical significance was defined as a confidence interval not containing 1

two consecutive days. Regarding different drain policies, no drains and drainage for 24 h is significantly worse than both long-term drainage options. When compared with drainage until output is < 50 ml per 24 h, progressive drain removal (OR 0.13, 95% CI 0.03–0.55) and drainage until output is < 50 ml per 24 h for two consecutive days (OR 0.15, 95% CI 0.06–0.37) are significantly better. Comparing progressive drain removal and drain removal until output is < 50 per

24 h for two consecutive days did not show a statistically significant difference (OR 1.11, 95% CI 0.36–3.36).

Energy devices are significantly worse than removing drains when output is < 50 ml per 24 h for 2 days (OR 4.09, 95% CI 1.65–10.14). All wound closure techniques are significantly worse than removing drains when output is below < 50 per 24 h for 2 days (patches: OR 5.05, 95% CI 1.10–23.10; tissue glue: OR 14.04, 95% CI 1.73–114.26; axillary padding: OR 4.55, 95% CI 1.05–20.49; and padding + tissue glue: OR 7.60, 95% CI 2.36–24.48). Progressive drain removal is also significantly better than tissue glue (OR 0.08, 95% CI 0.01–0.85) and axillary padding + tissue glue (OR 0.15, 95% CI 0.03–0.73).

Surgical Site Infections

Secondarily, all techniques were compared regarding SSI incidence, as described in Table 3. None of the techniques show superiority in this outcome measure. Specifically, shorter drainage periods (24-h drainage) or no drainage periods did not show reduced OR for SSI when compared with more conservative drainage policies.

DISCUSSION

In this systematic review, current literature is used to identify the most effective measures for preventing seroma formation after standalone ALND. The necessity for developing a surgical guideline is highlighted by the incidence of CSS in this article, which varies between 3% and 67%. Postoperative drainage remains the most effective way to reduce seroma-related complications after ALND. However, it is striking that drain policies vary widely across different studies. In this NMA, no drains or drains for 24 h are inferior to volume-controlled drainage. This is in accordance with a previously conducted systematic review by Droeser et al.[37]

One of the main concerns of long-term drainage was the incidence of surgical site infections.[34] The results show no significant increase in infections in patients undergoing drainage for a longer duration. In addition, none of the other techniques seem to reduce the incidence of SSI after ALND. Therefore, with proper drain care, infections should not be one of the limiting factors when implementing longer drainage periods.

Remarkably, within the volume-controlled drainage group, multiple policies are described as well. Some surgeons remove drains when drain output is less than 50 ml in one day, whereas others will wait for drain output < 50 ml for two consecutive days. The latter is prone to result in longer drainage periods after surgery. However, results of this study show significantly less seroma formation after ALND when adhering to a more conservative drainage policy. These findings are supported by Shima et al., who concluded that early drain removal in ALND combined with mastectomy or breast-conserving surgery did not result in fewer cases with seroma.[38]

One of the studies described two different techniques to remove drains: progressively with 1–2 cm a day or immediately when drain output was low for two consecutive days. These techniques did not show a significant difference in a direct comparison by Frich et al.,[20] which indicates complete drain removal is a safe technique.

TABLE 3 League table presenting the combined direct and indirect comparisons between different surgical measures for preventing SSI after ALND

D24									
1.77 (0.33-10.58)	PAT								
1.36 (0.17-11.23)	0.77 (0.10-5.86)	ND							
20.69 (0.55-783.04)	11.70 (0.32-422.97)	15.16 (0.35-649.10)	PRO						
1.34 (0.28-6.49)	0.76 (0.18-3.29)	0.98 (0.16-6.21)	0.06 (0.00-2.12)	TG					
2.54 (0.28-23.12)	1.43 (0.17-12.12)	1.86 (0.17-20.64)	0.12 (0.00-5.57)	1.89 (0.27-13.39)	PAD				
2.50 (0.25-24.82)	1.42 (0.15-13.04)	1.83 (0.15-22.01)	0.28 (0.03-2.39)	1.86 (0.24-14.52)	0.99 (0.08-12.92)	ED			
4.50 (0.70-28.82)	2.55 (0.44-14.88)	3.30 (0.41-26.61)	0.22 (0.01-8.14)	3.35 (0.71-15.78)	1.77 (0.20-15.87)	1.80 (0.19-17.51)	PTG		
8.16 (0.29-226.68)	4.61 (0.17-121.92)	5.98 (0.19-189.99)	0.39 (0.09-1.71)	6.07 (0.26-143.61)	3.22 (0.10-108.89)	1.63 (0.38-6.87)	1.81 (0.07-49.76)	D50-2	
1.80 (0.48-6.81)	1.02 (0.31-3.38)	1.32 (0.26-6.78)	0.09 (0.00-2.57)	1.34 (0.58-3.38)	0.71 (0.12-4.16)	0.60 (0.12-3.08)	0.40 (0.11-1.47)	0.37 (0.05-2.47)	D50

D24 24-h drainage, *PAT* patches, *ND* no drain, *PRO* progressive drain removal, *TG* tissue glue, *PAD* padding, *ED* energy devices, *PTG* padding + tissue glue, *D50-2* drainage until < 50 ml per 24 h for two consecutive days, *D50* drainage until < 50 ml per 24 h

Results are presented as OR (95% CI), an OR < 1 indicates a preference for the technique described in the column

For mastectomy and MRM, flap fixation reduces the incidence of CSS significantly.[9,10,39] This technique does not seem to be the solution for standalone ALND patients. Axillary padding was introduced by Classe et al. to omit drain use after ALND.[40] However, as indicated in the results of the NMA, axillary padding as well as other techniques to reduce dead space after surgery did not reduce CSS incidence to the same extent as it does after mastectomy. One thing worth mentioning is that none of the axillary padding groups included drain placement postoperatively. The combination of drain placement and axillary padding might be an option to reduce CSS after standalone ALND.

Limitations need to be discussed when interpreting the results of the current study. As shown in the bias assessment, there is a considerable risk of bias in almost all included studies. Among others, this is caused by the lack of blinding, which in most cases is impossible due to the nature of the intervention. In addition, there are few articles describing the same direct comparison. This is probably the main reason for the wide confidence intervals in the league table. Several results are based on indirect comparisons only. Lastly, the definition of CSS varies among studies. It is essential to describe a widely accepted definition, including the criteria used for performing seroma aspiration. It is becoming standard practice to only perform seroma aspirations when seromas are accompanied by signs of infection, delayed wound healing, or pain.

CONCLUSIONS

Current literature describes many different techniques to reduce seroma formation after axillary lymph node dissection in patients with breast cancer or melanoma. The only technique that consistently reduces the incidence of seroma formation, without increasing surgical site infection, is axillary drainage. The results of this systematic review support drain removal when drain output is < 50 ml per 24 h for two consecutive days irrespective of duration. Since drainage policies vary widely, an evidence-based guideline is needed.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at https://doi.org/10.1245/s10434-023-14631-9.

REFERENCES

1. Purushotham AD, Upponi S, Klevesath MB, Bobrow L, Millar K, Myles JP, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol*. 2005;23:4312–21.
2. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376:2211–22.
3. Bartels SAL, Donker M, Poncet C, Sauvé N, Straver ME, van de Velde CJH, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981–22023 AMAROS Trial. *J Clin Oncol*. 2023;41:2159–65.
4. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997;349:1864–7.
5. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med*. 2003;349:546–53.
6. van Bemmel AJM, van de Velde CJH, Schmitz RF, Liefers GJ. Prevention of seroma formation after axillary dissection in breast cancer: a systematic review. *Eur J Surg Oncol*. 2011;37:829–35.
7. Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. *J Breast Cancer*. 2012;15:373–80.
8. Carless PA, Henry DA. Systematic review and meta-analysis of the use of fibrin sealant to prevent seroma formation after breast cancer surgery. *Br J Surg*. 2006;93:810–9.
9. de Rooij L, van Kuijk SMJ, Granzier RWY, Hintzen KFH, Heymans C, Theunissen LLB, et al. Reducing seroma formation and its sequelae after mastectomy by closure of the dead space: a multi-center, double-blind randomized controlled trial (SAM-Trial). *Ann Surg Oncol*. 2021;28:2599–608.
10. van Bastelaar J, van Roozendaal L, Granzier R, Beets G, Vissers Y. A systematic review of flap fixation techniques in reducing seroma formation and its sequelae after mastectomy. *Breast Cancer Res Treat*. 2018;167:409–16.
11. Kottayasamy Seenivasagam R, Gupta V, Singh G. Prevention of seroma formation after axillary dissection–a comparative randomized clinical trial of three methods. *Breast J*. 2013;19:478–84.
12. ten Wolde B, van den Wildenberg FJ, Keemers-Gels ME, Polat F, Strobbe LJ. Quilting prevents seroma formation following breast cancer surgery: closing the dead space by quilting prevents seroma following axillary lymph node dissection and mastectomy. *Ann Surg Oncol*. 2014;21:802–7.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10:89.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162:777–84.
15. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
17. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth*. 2020;12:55–61.
18. Baas-Vrancken Peeters MJ, Kluit AB, Merkus JW, Breslau PJ. Short versus long-term postoperative drainage of the axilla after axillary lymph node dissection. A prospective randomized study. *Breast Cancer Res Treat*. 2005;93:271–5.
19. Classe JM, Berchery D, Campion L, Pioud R, Dravet F, Robard S. Randomized clinical trial comparing axillary padding with closed suction drainage for the axillary wound after lymphadenectomy for breast cancer. *Br J Surg*. 2006;93:820–4.

20. Frich L, Hermann R, Berentzen Å, Ryder T. Randomized study of wound drainage on early complications after lymph node dissection for melanoma. *J Surg Res*. 2021;267:467–76.
21. Ko E, Han W, Cho J, Lee JW, Kang SY, Jung SY, et al. Fibrin glue reduces the duration of lymphatic drainage after lumpectomy and level II or III axillary lymph node dissection for breast cancer: a prospective randomized trial. *J Korean Med Sci*. 2009;24:92–6.
22. Matthey-Gie M, Gie O, Deretti S, Demartines N, Matter M. Prospective randomized study to compare lymphocele and lymphorrhea control following inguinal and axillary therapeutic lymph node dissection with or without the use of an ultrasonic scalpel. *Ann Surg Oncol*. 2016;23:1716–20.
23. Neuss H, Raue W, Koplin G, Schwenk W, Reetz C, Mall JW. Intraoperative application of fibrin sealant does not reduce the duration of closed suction drainage following radical axillary lymph node dissection in melanoma patients: a prospective randomized trial in 58 patients. *World J Surg*. 2008;32:1450–5.
24. Piñero-Madrona A, Castellanos-Escrig G, Abrisqueta-Carrión J, Canteras-Jordana M. Prospective randomized controlled study to assess the value of a hemostatic and sealing agent for preventing seroma after axillary lymphadenectomy. *J Surg Oncol*. 2016;114:423–7.
25. Taflampas P, Sanidas E, Christodoulakis M, Askoxylakis J, Melissas J, Tsiftsis DD. Sealants after axillary lymph node dissection for breast cancer: good intentions but bad results. *Am J Surg*. 2009;198:55–8.
26. Weber WP, Tausch C, Hayoz S, Fehr MK, Ribi K, Hawle H, et al. Impact of a surgical sealing patch on lymphatic drainage after axillary dissection for breast cancer: the SAKK 23/13 multicenter randomized phase III trial. *Ann Surg Oncol*. 2018;25:2632–40.
27. Cavallaro G, Polistena A, D'Ermo G, Basile U, Orlando G, Pedulla G, et al. Usefulness of harmonic focus during axillary lymph node dissection: a prospective study. *Surg Innov*. 2011;18:231–4.
28. Conversano A, Mazouni C, Thomin A, Gaudin A, Fournier M, Rimareix F, Bonastre J. Use of low-thrombin fibrin sealant glue after axillary lymphadenectomy for breast cancer to reduce hospital length and seroma. *Clin Breast Cancer*. 2017;17:293–7.
29. Divino CM, Kuerer HM, Tartter PI. Drains prevent seromas following lumpectomy with axillary dissection. *Breast J*. 2000;6:31–3.
30. Garbay J-, Thoury A, Moinon E, Cavalcanti A, Di Palma M, Karsenti G, et al. Axillary padding without drainage after axillary lymphadenectomy—a prospective study of 299 patients with early breast cancer. *Breast Care*. 2012;7:231–5.
31. Koplin G, Mall JW, Raue W, Böhm S, Hoeller U, Haase O. Quantity-guided drain management reduces seroma formation and wound infections after radical lymph node dissection: results of a comparative observational study of 374 melanoma patients. *Acta Chir Belg*. 2017;117:238–44.
32. Taylor J, Rai S, Hoar F, Brown H, Vishwanath L. Breast cancer surgery without suction drainage: the impact of adopting a 'no drains' policy on symptomatic seroma formation rates. *Eur J Surg Oncol*. 2013;39:465.
33. Wienerroither V, Hammer R, Kornprat P, Schrem H, Wagner D, Mischinger HJ, El-Shabrawi A. Use of LigaSure vessel sealing system versus conventional axillary dissection in breast cancer patients: a retrospective comparative study. *BMC Surg*. 2022;22:436.
34. Andeweg CS, Schriek MJ, Heisterkamp J, Roukema JA. Seroma formation in two cohorts after axillary lymph node dissection in breast cancer surgery: does timing of drain removal matter? *Breast J*. 2011;17:359–64.
35. Van Spiekerman Weezelenburg MA, De Rooij L, Aldenhoven L, Broos PPHL, Van Kuijk SMJ, Van Haaren ERM, et al. Evaluating HEmopatch in reducing seroma-related complications following axillary lymph node DIssection: a pilot study (HEIDI). *Breast Care*. 2022;17:567–72.
36. Sanguinetti A, Docimo G, Ragusa M, Calzolari F, D'Ajello F, Ruggiero R, Parmeggiani D, Pezzolla A, Procaccini E, Avenia N. Ultrasound scissors versus electrocautery in axillary dissection: our experience. *G Chir*. 2010;31:151–3.
37. Droeser RA, Frey DM, Oertli D, Kopelman D, Baas-Vrancken Peeters MJ, Giuliano AE, et al. Volume-controlled vs no/short-term drainage after axillary lymph node dissection in breast cancer surgery: a meta-analysis. *Breast*. 2009;18:109–14.
38. Shima H, Kutomi G, Sato K, Kuga Y, Wada A, Satomi F, et al. An optimal timing for removing a drain after breast surgery: a systematic review and meta-analysis. *J Surg Res*. 2021;267:267–73.
39. Velotti N, Limite G, Vitiello A, Berardi G, Musella M. Flap fixation in preventing seroma formation after mastectomy: an updated meta-analysis. *Updates Surg*. 2021;73:1307–14.
40. Classe J, Dupre PF, François T, Robard S, Theard JL, Dravet F. Axillary padding as an alternative to closed suction drain for ambulatory axillary lymphadenectomy: a prospective cohort of 207 patients with early breast cancer. *Arch Surg*. 2002;137(169):72 (**Discussion 173**).