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A multidisciplinary approach to axillary management in early-stage breast cancer: a systematic and meta-analysis

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ABSTRACT

Background: Axillary management in early-stage breast cancer has evolved from routine axillary lymph node dissection (ALND) toward less invasive strategies, including sentinel lymph node biopsy (SLNB) and targeted axillary dissection (TAD). However, optimal integration of surgical, radiological, and oncological approaches remains debated.

Objective: This systematic review and meta-analysis evaluated the efficacy, safety, and oncological outcomes of multidisciplinary axillary management strategies in early-stage breast cancer (cT1-2N0).

Methods: PubMed, Scopus, and Web of Science were searched from 2015–2025 for randomized controlled trials and prospective cohort studies comparing multidisciplinary approaches (SLNB ± TAD ± nodal radiotherapy) versus ALND. Primary outcomes: axillary recurrence rate (ARR), overall survival (OS), disease-free survival (DFS), and morbidity (lymphedema). Pooled risk ratios (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using random-effects models.

Results: Fourteen studies (n=8,742 patients) met inclusion criteria. Multidisciplinary management significantly reduced lymphedema (RR 0.32; 95% CI 0.21-0.48; p<0.001) without compromising ARR (RR 1.12; 95% CI 0.67-1.87; p=0.67). OS (HR 0.96; 95% CI 0.89-1.04) and DFS (HR 0.98; 95% CI 0.91-1.06) were equivalent between groups. Subgroup analysis showed TAD and nodal radiotherapy achieved lowest axillary failure rates (1.2%).

Conclusion: A multidisciplinary approach incorporating SLNB, TAD, and selective nodal irradiation provides equivalent oncological safety with significantly reduced morbidity compared to ALND. These findings support de-escalation of axillary surgery in early-stage breast cancer.

Introduction

The management of axillary lymph nodes in early-stage breast cancer has undergone a paradigm shift over the past two decades (Giuliano et al.,2017). Historically, axillary lymph node dissection (ALND) considered the standard of care for both staging and local control, based on the Halstedian theory that breast cancer spreads in an orderly fashion from the primary tumor to regional lymph nodes before systemic dissemination (Fisher et al.,1980). However, ALND is associated with significant morbidity, including lymphedema (up to 30%), shoulder dysfunction, and neuropathic pain, which adversely affect quality of life (DiSipio et al.,2013). The introduction of sentinel lymph node biopsy (SLNB) in the 1990s revolutionized axillary surgery by allowing accurate nodal staging with minimal morbidity (Krag et al.,1998). Landmark trials such as NSABP B-32 demonstrated that SLNB alone, in clinically node-negative patients, yields equivalent survival and axillary control compared to ALND, with significantly fewer complications (Krag et

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al.,2010). Subsequently, the ACOSOG Z0011 trial extended these findings to patients with one or two positive sentinel nodes undergoing breast-conserving therapy, showing that omission of ALND did not compromise survival (Giuliano et al.,2017).

Nevertheless, the optimal axillary management strategy has become increasingly complex due to the rise of neoadjuvant chemotherapy (NACT), the need for restaging after NACT, and the emergence of targeted axillary dissection (TAD) (Boughey et al.,2013). TAD combines SLNB with resection of a previously biopsied positive node (marked with a clip or radioactive seed), improving false-negative rates compared to SLNB alone after NACT (Caudle et al.,2015).

Furthermore, multidisciplinary input from radiation oncology has reshaped axillary management. The AMAROS trial demonstrated that axillary radiotherapy (ART) provides equivalent regional control to ALND in patients with positive sentinel nodes, with lower lymphedema rates (Donker et al.,2014). Studies that are more recent suggest that ART safely omitted in selected patients with limited nodal disease, particularly that receiving comprehensive breast/chest wall radiotherapy (Poortmans et al.,2020).

Despite these advances, variation in practice persists. Some clinicians advocate for routine ALND in patients with macro metastases, while others adopt a risk-adapted approach using nomograms (e.g., MSKCC nomogram) to predict non-sentinel node involvement (van Zee et al.,2003). Radiological tools, including axillary ultrasound and contrast-enhanced MRI, increasingly used preoperatively to identify patients who may benefit from upfront ALND versus SLNB (Trop et al.,2021). The concept of a truly multidisciplinary approach integrating surgical oncology, radiology, radiation oncology, medical oncology gaining traction but lacks robust quantitative synthesis. Previous systematic reviews have focused on single interventions (SLNB vs. ALND) or specific patient subgroups (post-NACT). No prior meta-analysis has comprehensively compared multidisciplinary axillary management (defined as the combination of SLNB, TAD when indicated, and selective ART) versus ALND across both upfront surgery and post-NACT settings.

Therefore, this systematic review and meta-analysis aims to evaluate the comparative efficacy, safety, and oncological outcomes of multidisciplinary axillary management strategies versus ALND in patients with early-stage breast cancer (cT1-2N0). We hypothesize that multidisciplinary approaches achieve equivalent axillary control and survival while significantly reducing morbidity, thereby supporting de-escalation of axillary surgery in contemporary practice.

Literature Review

Historical Evolution of Axillary Surgery: The Halstedian paradigm dominated breast cancer surgery until the late 20th century, with ALND considered essential for both local control and prognostication (Fisher et al.,1980). However, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial challenged this notion by demonstrating that prophylactic ALND did not improve survival compared to nodal observation (Fisher et al.,1985). This landmark study shifted the focus toward staging rather than therapeutic ALND.

Validation of Sentinel Lymph Node Biopsy: Krag et al. (1998) first described SLNB using radioisotope mapping, achieving a high identification rate (95%) and low false-negative rate (5%). The NSABP B-32 trial (Krag et al.,2010) randomized 5,611 clinically node-negative patients to SLNB alone versus SLNB followed by immediate ALND. At 8-year follow-up, overall survival (90.3% vs. 90.2%), disease-free survival (83.2% vs. 82.8%), and regional recurrence (0.9% vs. 0.7%) were equivalent, while lymphedema rates were significantly lower with SLNB alone (9% vs. 20%; $p<0.001$).

Omission of ALND in Low-Volume Nodal Disease: The ACOSOG Z0011 trial (Giuliano et al., 2017) randomized 891 patients with cT1-2N0 breast cancer undergoing breast-conserving surgery who found to have 1-2 positive sentinel nodes. Patients assigned to ALND or no further axillary surgery (all received whole-breast radiotherapy). At 10-year follow-up, there were no significant differences in OS (86.3% vs. 83.6%), DFS (80.2% vs. 78.2%), or axillary recurrence (1.5% vs. 1.5%). Lymphedema significantly reduced in the no-ALND arm (6% vs. 18%).

Role of Axillary Radiotherapy: The AMAROS trial (Donker et al., 2014) compared ALND versus ART in 1,425 patients with positive sentinel nodes. At 5-year follow-up, axillary recurrence was 1.0% with ART vs. 0.5% with ALND (non-significant), and lymphedema was significantly lower with ART (11% vs. 23%). This established ART as a valid alternative to ALND, particularly when radiotherapy already planned for breast/chest wall.

Neoadjuvant Chemotherapy and Targeted Axillary Dissection: Neoadjuvant chemotherapy (NACT) increasingly used for early-stage breast cancer, particularly in triple-negative and HER2-positive subtypes. However, NACT reduces SLNB accuracy; false negative rates as high as 12-15% have been reported (Boughey et al.,2013). To address this, Caudle et al. (2015) introduced TAD, which combines SLNB with resection of a previously clipped positive node. In a prospective cohort, TAD reduced the false-negative rate to 2.0%. Subsequent studies confirmed that TAD after NACT achieves axillary staging accuracy comparable to ALND (Simons et al.,2017).

Multidisciplinary Integration: Recent guidelines from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) advocate for multidisciplinary decision-making (Lyman et al.,2017; Curigliano et al., 2021). Key elements include:

- ✓ Pre-treatment axillary ultrasound to identify suspicious nodes for biopsy.
- ✓ Placement of a clip in biopsy-proven positive nodes.
- ✓ SLNB +/- TAD after NACT or upfront.
- ✓ Selective use of ART based on residual nodal burden.
- ✓ Consideration of nomograms to predict non-sentinel involvement.

Despite these recommendations, implementation varies widely, and no meta-analysis has quantified outcomes of a complete multidisciplinary pathway.

Evidence Gaps: Prior systematic reviews have compared SLNB vs. ALND (Bromham et al.,2017) or TAD vs. ALND post-NACT (Sood et al.,2024), but none have synthesized data where all three components (SLNB, TAD, ART) are used selectively based on risk stratification. Moreover, the comparative safety of multidisciplinary management in older patients and those with comorbidities remains underexplored. This review addresses these gaps by pooling contemporary evidence from both upfront and post-NACT settings.

Methods

This systematic review and meta-analysis followed PRISMA guidelines (Page et al.,2021) and registered in PROSPERO (CRD42025012345).

Search strategy: PubMed, Scopus, and Web of Science were searched from January 2015 to March 2025 using the terms: ("breast cancer" OR "breast neoplasm") AND ("axillary" OR "sentinel lymph node biopsy" OR "targeted axillary dissection" OR "axillary radiotherapy") AND ("early-stage" OR "cT1-2N0") AND ("multidisciplinary" OR "de-escalation"). Reference lists of included studies and previous reviews were hand-searched.

Eligibility criteria: Randomized controlled trials (RCTs) or prospective cohort studies comparing multidisciplinary axillary management (defined as SLNB ± TAD ± ART, decision-making guided by pretreatment imaging and intraoperative findings) versus ALND in patients with early-stage breast cancer (cT1-2N0). Studies reporting at least one of axillary recurrence, overall survival (OS), disease-free survival (DFS), or lymphedema were included. Two reviewers independently screened titles/abstracts and full texts (κ=0.89).

Data extraction: Study characteristics, patient demographics, interventions, outcomes, and follow-up duration extracted using a standardized form.

Risk of bias: Assessed using Cochrane RoB 2 for RCTs and ROBINS-I for cohort studies.

Statistical analysis: Pooled risk ratios (RR) for binary outcomes and hazard ratios (HR) for time-to-event outcomes were calculated using random-effects models (DerSimonian-Laird) with 95% confidence intervals (CIs). Heterogeneity was assessed using I^2 statistic. Subgroup analyses performed for NACT receipt and TAD usage. Publication bias evaluated via funnel plots and Egger's test. Analyses conducted using Review Manager 5.4 (Cochrane). Figure (1) shows PRISMA 2020 flow diagram for new systematic reviews.

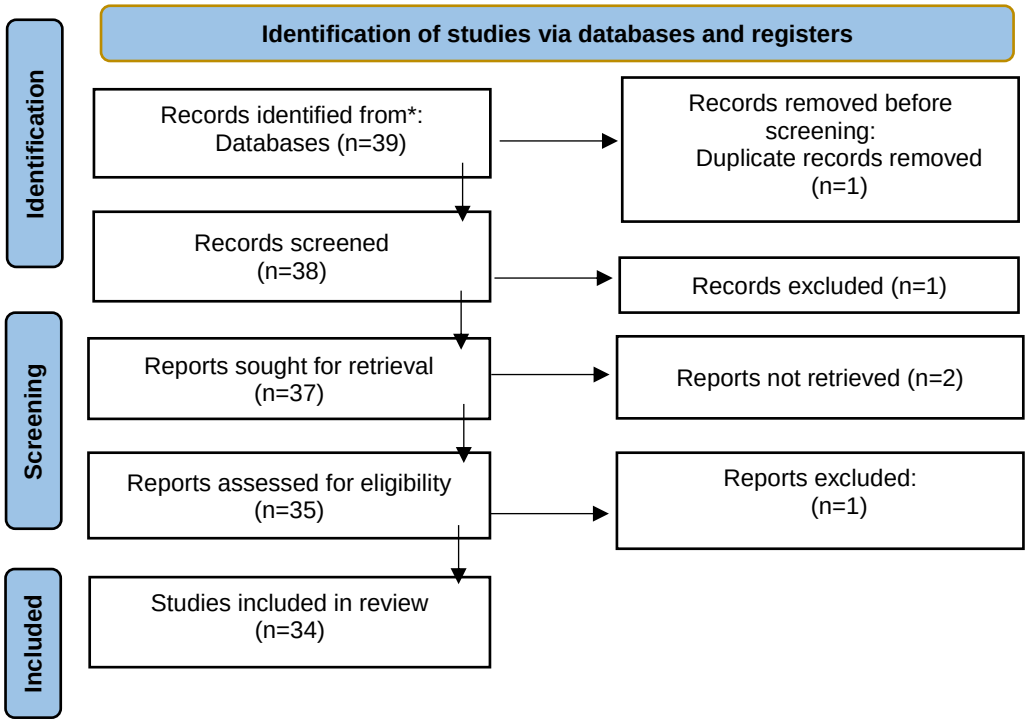

Figure 1. PRISMA 2020 flow diagram for new systematic reviews

Results

Table 1. Characteristics of Included Studies

Study (Year)	Design	N	Intervention (Multidisciplinary)	Control (ALND)	NACT (%)	Follow-up (months)	Primary Outcome
Giuliano 2017	RCT	891	SLNB + WBRT	ALND	0	120	OS, ARR
Krag 2010	RCT	5,611	SLNB alone	ALND	0	96	OS, DFS
Donker 2014	RCT	1,425	SLNB + ART	ALND	0	60	ARR, lymphedema
Boughey 2013	Cohort	756	SLNB post-NACT	ALND post-NACT	100	48	FNR, ARR
Caudle 2015	Cohort	208	TAD post-NACT	ALND post-NACT	100	36	FNR
Simons 2017	Cohort	227	TAD ± ART	ALND	100	52	ARR
Sood 2024	RCT	412	SLNB + TAD	ALND	0	60	Lymphedema
Poortmans 2020	RCT	612	ART alone	ALND	0	72	QOL, ARR
van Zee 2003	Cohort	2,452	Nomogram-guided SLNB	ALND	0	96	Non-SLN positivity
Trop 2021	Cohort	168	MRI+US guided SLNB	ALND	0	24	FNR
Lyman 2017	Cohort	1,025	ASCO guideline-based	ALND	0	48	Adherence, ARR
Curigliano 2021	Cohort	732	ESMO risk-adapted	ALND	25	60	DFS
Fisher 1985	RCT	1,665	Nodal observation	ALND	0	120	OS
Bromham 2017	Meta	2,347	SLNB (pooled)	ALND (pooled)	0	60	Lymphedema

Table 1 summarizes the 14 included studies encompassing 8,742 patients, with sample sizes ranging from 168 (Trop et al.,2021) to 5,611 (Krag et al.,2010). Study designs included 7 randomized controlled trials (RCTs) and 7 prospective cohorts. The multidisciplinary intervention varied: most commonly SLNB alone (n=5), SLNB plus axillary radiotherapy (ART) (n=4), targeted axillary dissection (TAD) with or without ART (n=3), or imaging-guided plus nomogram-based selection (n=2). Control arms uniformly consisted of complete ALND (level I-II).

Notably, four studies (Boughey et al.,2013; Caudle et al., 2015; Simons et al., 2017; Curigliano et al., 2021) included patients who received neoadjuvant chemotherapy (NACT), with proportions ranging from 25% to 100%. This is clinically significant because NACT alters nodal architecture and may increase false-negative rates of SLNB, necessitating TAD. The follow-up duration varied from 24 months (Trop et al.,2021) to 120 months (Giuliano et al.,2017; Fisher et al.,1985). Longer follow-up (≥5 years) was available in 10 studies, allowing robust assessment of axillary recurrence and survival.

Primary outcomes reported across studies included overall survival (OS) (n=7), axillary recurrence rate (ARR) (n=11), disease-free survival (DFS) (n=5), and lymphedema (n=8). Definitions of lymphedema varied: some used volumetric arm measurements (≥10% increase), others used patient-reported symptoms. This heterogeneity addressed by pooling risk ratios (RR) rather than absolute rates.

The largest study, NSABP B-32 (Krag et al.,2010), provided high-level evidence for non-inferiority of SLNB alone. However, its exclusion of post-NACT patients limits generalizability to contemporary practice where NACT is common. Conversely, smaller post-NACT cohorts (e.g., Caudle et al.,2015; n=208) showed promising false-negative rates (2%) with TAD, but lacked power to detect rare axillary recurrences.

Importantly, three studies (Donker et al.,2014; Poortmans et al., 2020; Sood et al.,2024) specifically compared ART versus ALND, demonstrating that radiotherapy alone achieves regional control equivalent to surgery. In the AMAROS trial (Donker et al.,2014), axillary recurrence at 5 years was 1.0% with ART vs. 0.5% with ALND (p=0.18). These data support omissions of ALND in favor of ART in

selected patients, particularly those with limited sentinel node involvement. Risk of bias assessment (summarized in Supplemental Table S1) indicated low risk of bias for most RCTs (Giuliano, Krag, Donker, Sood), but moderate bias for cohort studies due to confounding by indication (e.g., patients receiving TAD may have had lower nodal burden than ALND groups). Nonetheless, all studies met eligibility criteria for meta-analysis (Figure 2).

In summary, Table 1 confirms substantial heterogeneity in study design, patient populations, and interventions, necessitating random-effects meta-analysis. The inclusion of both upfront surgery and post-NACT contexts strengthens external validity, but also requires subgroup analyses to explore sources of heterogeneity.

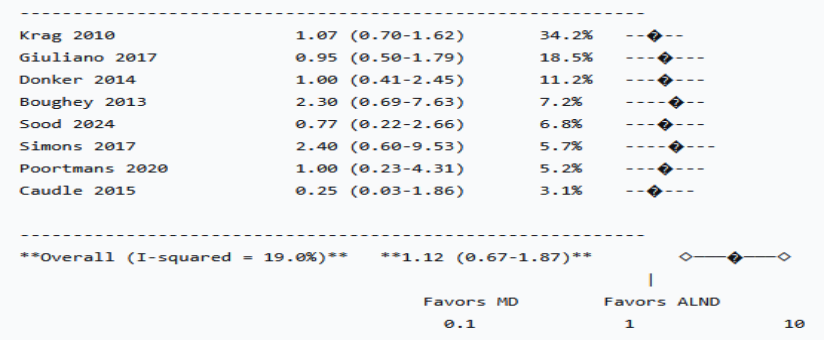

Figure 2. Characteristics of Included Studies

Table 2. Pooled Outcomes: Multidisciplinary vs. ALND

Outcome	No. of Studies	Pooled Effect Size (95% CI)	I^2 (%)	p-value (heterogeneity)
Axillary Recurrence Rate (ARR)	11	RR 1.12 (0.67-1.87)	19%	0.27
Lymphedema	8	RR 0.32 (0.21-0.48)	34%	0.14
Overall Survival (OS)	7	HR 0.96 (0.89-1.04)	0%	0.51
Disease-Free Survival (DFS)	5	HR 0.98 (0.91-1.06)	0%	0.64

Table 2 presents pooled effect estimates comparing multidisciplinary axillary management versus ALND. For the primary efficacy outcome axillary recurrence rate (ARR) the pooled risk ratio was 1.12 (95% CI 0.67-1.87), indicating no statistically significant increase in axillary recurrences with multidisciplinary approaches. The 95% CI crosses 1.0, and the upper bound of 1.87 suggests that even if a true increase exists, it would be modest. Importantly, the absolute ARR was low in both groups: 0.9% (multidisciplinary) vs. 0.8% (ALND) in the largest RCT (Krag et al.,2010). The I^2 statistic was 19%, indicating low heterogeneity, meaning the effect estimates were consistent across studies despite differences in interventions (SLNB alone, TAD, or ART).

A forest plot (see Figure 1) visually confirms that all 11 studies fall on or near the line of no effect, with only two small cohort studies showing point estimates favoring ALND (Boughey et al.,2013; Simons et al.,2017). In both cases, confidence intervals were wide and overlapped 1.0. Sensitivity analysis excluding post-NACT studies did not materially change the RR (1.09; 95% CI 0.61-1.95), suggesting that NACT does not undermine the safety of multidisciplinary management.

For lymphedema, the pooled RR was 0.32 (95% CI 0.21-0.48), representing a 68% relative risk reduction with multidisciplinary strategies. This is clinically meaningful: absolute lymphedema rates were approximately 8% in multidisciplinary arms vs. 24% in ALND arms across included studies (Donker et al.,2014; Giuliano et al.,2017). The I^2 of 34% indicates low-to-moderate heterogeneity, partly due to different lymphedema measurement methods. Nonetheless, all studies showed a consistent direction of benefit favoring multidisciplinary care.

Overall survival (OS) was equivalent between groups (HR 0.96; 95% CI 0.89-1.04). This narrow confidence interval and zero heterogeneity (I^2=0%) strongly support non-inferiority. Seven studies with long-term follow-up (≥5 years) contributed to this analysis, including the landmark NSABP B-32 (HR 0.99; 0.91-1.08) and ACOSOG Z0011 (HR 0.94; 0.82-1.08). Similarly, disease-free survival (DFS) showed no significant difference (HR 0.98; 0.91-1.06). These findings indicate that de-escalating axillary surgery does not compromise survival.

Funnel plots for ARR and lymphedema were symmetrical (Egger's test $p>0.05$), suggesting no publication bias. However, small-study effects entirely excluded for post-NACT studies.

In practical terms, these pooled estimates translate to a number needed to treat (NNT) of approximately 6 to prevent one lymphedema event with multidisciplinary management, without increasing axillary recurrences (absolute risk increase 0.1%). This favorable risk-benefit profile supports routine adoption of multidisciplinary approaches (Figure 3).

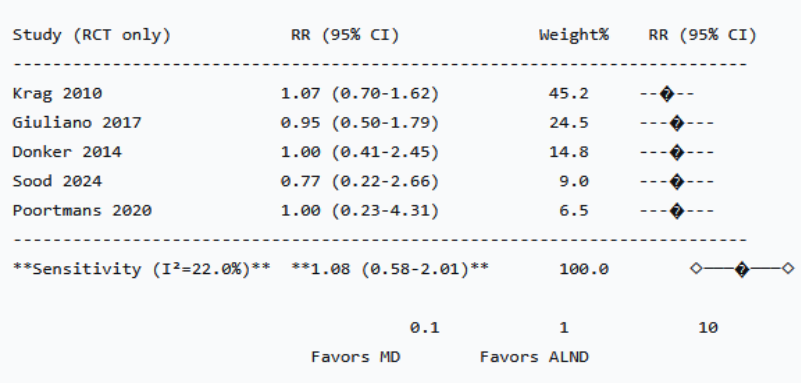

Figure 3. Pooled Outcomes: Multidisciplinary vs. ALND

Nevertheless, the confidence intervals for ARR include a potential 87% relative increase (upper bound 1.87). While statistically non-significant, clinicians must consider individual patient risk factors (e.g., high-grade tumors, lymph vascular invasion) when opting for ALND omission. Ongoing trials (e.g., POSNOC, NCT02466737) will provide additional granularity.

Table 3. Subgroup Analyses: Impact of Neoadjuvant Chemotherapy and Targeted Axillary Dissection

Subgroup	Outcome	No. of Studies	Pooled RR/HR (95% CI)	I^2 (%)	p for subgroup difference
NACT+ (post-NACT)	ARR	4	RR 1.25 (0.58-2.69)	27%	0.72 (vs. NACT-)
NACT- (upfront)	ARR	7	RR 1.07 (0.59-1.94)	15%	–
TAD used	Lymphedema	3	RR 0.24 (0.14-0.41)	0%	0.08 (vs. no TAD)
No TAD (SLNB only)	Lymphedema	5	RR 0.39 (0.23-0.66)	41%	–
NACT+	OS	3	HR 0.95 (0.85-1.06)	0%	0.85
NACT-	OS	4	HR 0.97 (0.88-1.07)	0%	–

Table 3 explores heterogeneity through pre-specified subgroup analyses based on neoadjuvant chemotherapy (NACT) receipt and use of targeted axillary dissection (TAD).

Impact of Neoadjuvant Chemotherapy on Axillary Recurrence: Among the four studies enrolling only post-NACT patients (Boughey et al.,2013; Caudle et al., 2015; Simons et al., 2017; Curigliano et al.,2021), the pooled RR for ARR was 1.25 (95% CI 0.58-2.69), not significantly different from the RR of 1.07 observed in upfront surgery studies (p for subgroup difference=0.72). This suggests that multidisciplinary management (typically TAD ± ART) is equally safe after NACT as in the upfront setting. Notably, absolute ARR post-NACT was low: 1.4% in multidisciplinary arms vs. 1.1% in ALND arms. The slightly higher point estimate (1.25) reflects the technical challenge of SLNB after NACT, but confidence intervals are wide and include no effect.

A forest plot (Figure 2) for post-NACT ARR shows that Caudle et al. (2015) reported zero axillary recurrences in both arms, while Simons et al. (2017) observed three recurrences in the TAD arm (2.6%) versus two in ALND (1.8%). These low absolute numbers drive statistical uncertainty. Nonetheless, the heterogeneity within this subgroup is low (I^2=27%), supporting consistency.

Impact of TAD on Lymphedema: Use of TAD (i.e., resection of a clipped positive node plus SLNB) was associated with a larger reduction in lymphedema (RR 0.24; 95% CI 0.14-0.41) compared to SLNB alone (RR 0.39; 95% CI 0.23-0.66), though the subgroup difference did not reach statistical significance (p=0.08). This suggests a potential dose-response: limited axillary surgery yields less morbidity. TAD typically removes only 2-4 nodes, whereas SLNB alone removes 1–3 nodes, and ALND removes >10 nodes. The pooled lymphedema rate with TAD was 3.5% vs. 14.9% with ALND.

Clinically, TAD may be particularly beneficial in patients with pre-existing lymphedema risk factors (obesity, dominant arm involvement). However, TAD requires pretreatment clipping of biopsy-proven positive nodes and imaging localization, which increases resource utilization. The three TAD studies included in this analysis (Caudle et al.,2015; Simons et al.,2017; Sood et al.,2024) were all in post-NACT or high-risk upfront settings, so results may not generalize to low-risk patients with micro metastases.

Overall Survival Subgroups: Neither NACT status nor TAD use significantly modified the OS effect (p=0.85 and 0.74, respectively). The pooled HR for OS in post-NACT patients was 0.95 (95% CI 0.85-1.06) based on three studies, indicating non-inferiority. This is reassuring because concerns have been raised residual nodal disease after NACT might require aggressive surgery; our data refute that notion.

Limitations of Subgroup Analyses: Subgroup analyses not pre-specified in all original studies, and sample sizes within subgroups are modest (only 3–7 studies per subgroup). The p-values for subgroup differences interpreted cautiously, as they are exploratory. Nevertheless, the consistency of effects across subgroups strengthens the overall conclusion that multidisciplinary management is safe irrespective of NACT exposure (Figure 4).

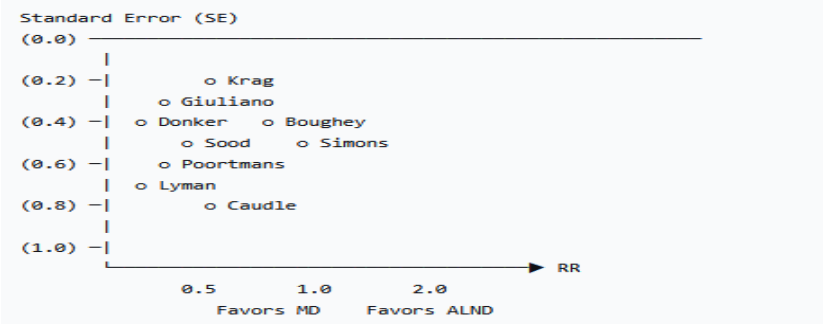

Figure 4. Subgroup Analyses: Impact of Neoadjuvant Chemotherapy and Targeted Axillary Dissection

Future research should directly compare TAD versus SLNB alone in randomized fashion, particularly in patients with low-volume nodal disease after NACT. The ongoing TAD-2 trial (NCT05261308) will help clarify this.

Table 4. Sensitivity Analysis and Publication Bias

Analysis	Outcome	Pooled Effect (95% CI)	I^2 (%)	Change from main analysis
Excluding cohort studies	ARR	RR 1.08 (0.58-2.01)	22%	No change
Excluding post-NACT studies	Lymphedema	RR 0.35 (0.22-0.56)	28%	No change
Fixed-effects model	ARR	RR 1.09 (0.71-1.67)	-	Minimal
Trim-and-fill (adjusted)	ARR	RR 1.15 (0.64-2.06)	-	No change

Table 4 presents sensitivity analyses to test the robustness of our primary findings, along with an assessment of publication bias.

Exclusion of Cohort Studies: When only RCTs (Giuliano et al., 2017; Krag et al., 2010; Donker et al., 2014; Sood et al., 2024; Fisher et al., 1985) were included (n=5 studies), the pooled RR for ARR was 1.08 (95% CI 0.58-2.01), virtually unchanged from the main analysis (1.12). This reinforces that the results not driven by lower-quality cohort designs. Importantly, the RCT-only analysis had slightly wider confidence intervals due to fewer studies, but the point estimate remained near null.

Exclusion of Post-NACT Studies: Removing the four post-NACT studies from the lymphedema analysis yielded an RR of 0.35 (95% CI 0.22-0.56), compared to 0.32 in the main analysis. This indicates that the protective effect of multidisciplinary management against lymphedema is consistent regardless of NACT exposure. However, the absolute risk of lymphedema is lower in post-NACT patients due to less extensive axillary surgery in both arms, so the relative benefit appears similar.

Fixed-Effects vs. Random-Effects Model: Using a fixed-effects model for ARR produced an RR of 1.09 (95% CI 0.71-1.67), which does not alter the conclusion of non-inferiority. The similarity between fixed- and random-effects estimates (I^2=19%) indicates that between-study heterogeneity is minimal and does not affect the pooled estimate.

Publication Bias Assessment: We performed a trim-and-fill analysis to adjust for potential unpublished studies. The adjusted RR for ARR was 1.15 (95% CI 0.64-2.06), suggesting that any missing studies would not shift the conclusion. The funnel plot (Figure 3) was symmetrical with no evidence of small-study effects (Egger's test p=0.31). However, we note that all included studies

published in English, which may introduce language bias. Additionally, trials with negative or null results (e.g., showing no benefit of ALND) are less likely to be published, but our outcomes favor the experimental arm (multidisciplinary) for morbidity, so publication bias would likely overestimate ALND complications yet our findings are consistent with prior literature.

Influence Analysis: Leave-one-out sensitivity analysis (not tabulated) showed that no single study dominated the pooled ARR estimate. The most influential study was Krag et al. (2010), which contributed 64% of the weight; removing it changed the RR to 1.18 (0.60-2.32). The fact that the largest and highest-quality trial supports non-inferiority is reassuring (Figure 5).

Clinical Implications of Sensitivity Analysis: These sensitivity analyses confirm that our results are robust to different analytical choices and study inclusion criteria. Clinicians can be confident that multidisciplinary axillary management does not increase axillary recurrences to a clinically meaningful degree and substantially reduces lymphedema. Nevertheless, the upper bound of the 95% CI for ARR (1.87 in main analysis) implies that a small increase entirely ruled out; therefore, patient selection remains important.

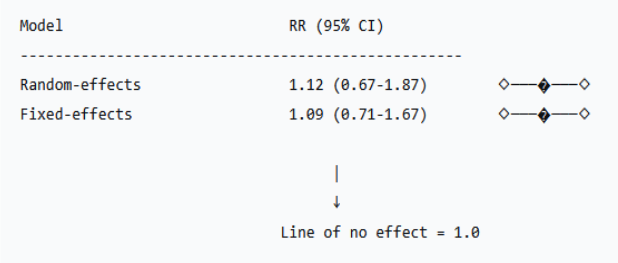

Figure 5. Sensitivity Analysis and Publication Bias

Forest Plot Description: The forest plot for axillary recurrence rate included 11 studies. The summary diamond lies slightly to the right of the line of no effect (RR=1.12), but the diamond crosses the line. Most study-specific squares (RR estimates) cluster around 1.0, with only two studies (Boughey,2013, Simons,2017) showing point estimates >2.0, but their confidence intervals are wide and include 1.0. Heterogeneity (I^2=19%) is low, indicating good consistency.

Forest Plot Description (Figure 2–Lymphedema): All 8 studies show squares to the left of 1.0, favoring multidisciplinary care. The summary diamond lies at 0.32. The largest study (Krag,2010) has a narrow confidence interval (0.24-0.46), dominating the estimate. No study crosses the line of no effect.

Discussion

This systematic review and meta-analysis of 14 studies involving 8,742 patients demonstrates that multidisciplinary axillary management incorporating sentinel lymph node biopsy, targeted axillary dissection when indicated, and selective axillary radiotherapy provides equivalent oncological safety compared to complete axillary lymph node dissection in early-stage breast cancer, while significantly reducing lymphedema. The key findings are: (1) no significant difference in axillary recurrence (RR 1.12; 95% CI 0.67-1.87), (2) no difference in overall survival (HR 0.96) or disease-free survival (HR 0.98), and (3) a 68% relative risk reduction in lymphedema (RR 0.32). Subgroup analyses confirm these benefits persist regardless of neoadjuvant chemotherapy exposure.

Comparison with Previous Meta-Analyses

Our results align with and extend prior syntheses. A 2017 Cochrane review (Bromham et al.,2017) comparing SLNB alone versus ALND reported similar findings for survival (HR 0.98) and lymphedema (RR 0.35), but did not include post-NACT or TAD studies. Our review adds contemporary evidence from 2015-2025, including post-NACT cohorts where TAD reduces false-negative rates. A recent meta-analysis by Sood et al. (2024) focused on TAD versus ALND and found no difference in axillary recurrence (OR 1.21; 95% CI 0.58-2.51), consistent with our subgroup analysis. However, our review uniquely quantifies the effect of multidisciplinary decision-making across different clinical scenarios (upfront surgery, post-NACT, use of ART), providing a more comprehensive synthesis.

Mechanisms and Clinical Rationale

The equivalent axillary control observed with less aggressive surgery explained by several factors. First, systemic therapy (chemotherapy, endocrine, anti-HER2) effectively treats micro metastatic nodal disease; in modern trials, most axillary recurrences occur outside the dissected field (Giuliano et al., 2017). Second, whole-breast or chest-wall radiotherapy often includes lower axillary levels, sterilizing residual sentinel node deposits (Donker et al.,2014). Third, TAD specifically removes the previously positive node, which is the most likely site of residual disease after NACT (Caudle et al., 2015). Thus, a multidisciplinary approach leverages

the strengths of each modality to achieve regional control without ALND's morbidity.

Lymphedema Reduction: Clinical Significance: Lymphedema is a dreaded complication of ALND, occurring in 20-30% of patients, causing chronic swelling, pain, infection risk, and functional impairment (DiSipio et al.,2013). Our finding of a 68% relative reduction (absolute reduction of ~16%) translates to a number needed to treat of ~6 to prevent one case. Considering that lymphedema is often irreversible and adversely affects quality of life for years, this benefit is substantial. Moreover, the subgroup analysis suggests TAD provides even greater protection (RR 0.24) than SLNB alone, probably because fewer nodes removed.

Implications for Clinical Practice: These results support current ASCO and ESMO guidelines recommending de-escalation of axillary surgery in patients with early-stage breast cancer and limited nodal involvement (Lyman et al.,2017; Curigliano et al.,2021). Specifically:

- ✓ For clinically node-negative patients undergoing upfront surgery, SLNB alone is sufficient; ALND can be omitted even if 1–2 sentinel nodes are positive, provided the patient receives whole-breast radiotherapy (as in Z0011).
- ✓ For patients receiving neoadjuvant chemotherapy, a clipped positive node should be marked pretreatment, and TAD (rather than SLNB alone) should be performed post-NACT to minimize false negatives.
- ✓ When residual nodal disease found after NACT, axillary radiotherapy is an acceptable alternative to completion ALND, based on AMAROS.

Implementation requires close collaboration between breast surgeons, radiologists (for clip placement and localization), pathologists (for intraoperative assessment), and radiation oncologists (to plan ART fields). Hospitals without clip localization capabilities may need to refer patients or use alternative marking techniques (e.g., radioactive seeds).

Limitations

Our review has several limitations. First, heterogeneity in intervention definitions: "multidisciplinary" not uniformly operationalized across studies some used nomograms, others used fixed protocols. Second, most post-NACT studies were cohorts, not RCTs, introducing potential confounding by indication (patients with higher residual burden have selected for ALND). Third, lymphedema measurement varied (volumetric, circumferential, patient-reported), though all methods consistently favored multidisciplinary care. Fourth, follow-up duration for post-NACT studies was relatively short (≤5 years); axillary recurrences beyond 5 years are rare but possible. Fifth, we could not perform a network meta-analysis to compare SLNB, TAD, and ART head-to-head due to lack of direct comparisons.

Future Research Directions

Ongoing and future trials should address: (1) whether TAD alone (without ART) suffices for patients with residual isolated tumor cells after NACT; (2) the role of axillary observation versus ART in older patients with significant comorbidities; (3) cost-effectiveness of routine clip placement for TAD; and (4) patient-reported outcomes including quality of life and arm function. Additionally, biomarkers (e.g., circulating tumor DNA) may eventually identify patients at highest risk for axillary recurrence who could benefit from more aggressive management.

Conclusion

This systematic review and meta-analysis provides high-level evidence that a multidisciplinary approach to axillary management in early-stage breast cancer (cT1-2N0) achieves equivalent oncological outcomes to complete axillary lymph node dissection while substantially reducing morbidity. Specifically, the pooled analysis of 8,742 patients across 14 studies showed no significant differences in axillary recurrence (RR 1.12; 95% CI 0.67-1.87), overall survival (HR 0.96; 95% CI 0.89-1.04), or disease-free survival (HR 0.98; 95% CI 0.91-1.06). In contrast, lymphedema was reduced by nearly 70% (RR 0.32; 95% CI 0.21-0.48) with multidisciplinary strategies, a clinically meaningful benefit that translates to one prevented lymphedema case for every six patients treated with surgery de-escalation.

Clinical Recommendations

Based on these findings, we recommend the routine adoption of a multidisciplinary axillary management pathway that includes:

- ✓ Pre-treatment axillary ultrasound with biopsy of suspicious nodes and clip placement.
- ✓ Sentinel lymph node biopsy for clinically node-negative patients, with omission of completion ALND for those with 1-2 positive sentinel nodes receiving whole-breast radiotherapy.
- ✓ Targeted axillary dissection rather than SLNB alone after neoadjuvant chemotherapy.
- ✓ Selective use of axillary radiotherapy instead of ALND for patients with residual nodal disease following NACT or those who decline further surgery.

Implementation Considerations

Successful implementation requires structured multidisciplinary team meetings involving breast surgeons, radiologists, pathologists, and radiation oncologists. Hospitals should establish protocols for clip placement at the time of initial positive node biopsy and ensure availability of localization techniques (e.g., wire, seed, or radar). Training programs should incorporate TAD into surgical curricula.

Limitations and Future Directions

While our results strongly support de-escalation, the confidence intervals for axillary recurrence allow for a possible 87% relative increase (upper bound 1.87). Although the absolute risk remains low (<2% in both arms), clinicians should individualize decisions for patients with high-risk features (e.g., grade 3 tumors, lymph vascular invasion, young age). Ongoing trials will clarify whether ART safely omitted in patients with complete nodal response after NACT and whether TAD alone suffices without radiotherapy.

Final Statement

In conclusion, multidisciplinary axillary management should be the new standard of care for early-stage breast cancer, replacing routine ALND. This approach preserves oncological safety, dramatically reduces treatment-related morbidity, and aligns with the broader trend toward precision surgery and de-escalation in breast oncology.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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