Omission of Axillary Surgery in Early Breast Cancer with Negative Lymph Nodes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Objective: To evaluate whether omitting axillary surgery impacts clinical outcomes in early-stage breast cancer with clinically negative nodes. **Methods**: A systematic review and meta-analysis of randomized clinical trials (RCT) comparing no axillary surgery versus standard axillary surgery - sentinel lymph node biopsy (SLNB) or axillary dissection (AD) was conducted in accordance with PRISMA guidelines and registered in PROSPERO. Primary outcomes were overall survival (OS), disease-free survival (DFS), and axillary recurrence (AR). **Results**: Seven RCTs including 8,806 patients were analyzed (2,915 no-surgery; 5,891 axillary-surgery). Two trials compared omission with SLNB and five with AD. No significant differences were observed in OS (OR = 1.02; 95% CI 0.86–1.20; p = 0.84) or DFS (OR = 0.80; 95% CI 0.63–1.00; p = 0.05). Axillary recurrence was lower with axillary surgery (OR = 0.18; 95% CI 0.10–0.31; p < 0.01). **Conclusion**: Omission of axillary surgery does not compromise survival outcomes in early-stage breast cancer with clinically negative nodes, although it is associated with a higher rate of axillary recurrence.

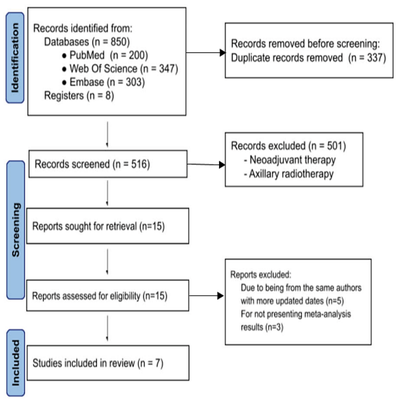
Introduction

Axillary lymph node status remains a critical prognostic factor in breast cancer. Surgical staging has progressed from Halsted's radical mastectomy to axillary lymph node dissection and subsequently to sentinel lymph node biopsy, which provides accurate staging with reduced morbidity and is feasible after neoadjuvant chemotherapy. Recent randomized trials indicate that omission of axillary surgery may be safe in selected early-stage patients with clinically and ultrasonographically negative axillae. This systematic review and meta-analysis assesses the impact of omitting axillary surgery on clinical outcomes.

Methods and Materials

We conducted a systematic review and meta-analysis of randomized clinical trials comparing no axillary surgery with standard axillary interventions (sentinel lymph node biopsy or axillary dissection). This study followed PRISMA guidelines and was registered in PROSPERO (CRD420250653779). Searches were conducted in PubMed, Web of Science, and Embase through June 2025. Outcomes assessed included overall survival, disease-free survival, and axillary recurrence. Meta-analyses were performed using RevMan 5.4. Risk of bias was assessed using the RoB 2 tool.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses



Results

Seven randomized controlled trials including 8,806 patients (2,915 without axillary surgery; 5,891 with axillary intervention) were analyzed, with follow-up ranging from 5 to 25 years. Five trials compared omission of axillary surgery with axillary lymph node dissection and two with sentinel lymph node biopsy. Meta-analysis showed no significant differences in disease-free survival (OR = 0.80; 95% CI, 0.63–1.00; p = 0.05) or overall survival (OR = 1.02; 95% CI, 0.86–1.20; p = 0.84) between groups. Subgroup analyses of the Reimer and Gentilini trials comparing omission with SLNB also showed similar outcomes for both endpoints. Axillary recurrence was higher in patients without surgery (OR = 0.18; 95% CI, 0.10–0.31; p < 0.01), although absolute rates remained low (<2%), and in the Reimer and Gentilini trials, recurrence still favored SLNB (OR = 0.36; 95% CI, 0.17–0.77; p = 0.008). Overall, the included studies demonstrated low to moderate risk of bias.

Table 1. Characteristics of included studies.

	N	Axillary surgery	Age	Tumor size	Breast surgery	Axillary evaluation	Adjuvant therapy	Follow-up
INSEMA (Reimer et al, 2024)	4,858	SLNB	>18 years	T1/T2	Breast-Conserving Surgery	US	Whole-breast RT (no axillary RT); CT in ~10–13%; presumed HT (95% HR+); no data on HER2 therapies	6 years
SOUND (Gentillini et al, 2023)	1,405	SLNB	Any age	T1	Breast-Conserving Surgery	US	RT in >97% (mostly whole-breast); CT in ~18–20%; HT in ~98% of HR+; trastuzumab in ~94–98% of HER2+	5 years
INT 09/98 (Agresti et al, 2024)	517	ALND	<65 years	T1/T2	Breast-Conserving Surgery	Clinical Exam	RT to breast/chest wall ± nodes; CT in 100%; HT in 56% (tamoxifen); no HER2 data	21 years
Martelli et al, 2014	219	ALND	65-80 years	T1	Breast-Conserving Surgery	Clinical Exam	RT in 63% (post-BCS); no CT; HT with tamoxifen (97%); no HER2 data	15 years
AXIL95 (Avril et al, 2012)	607	ALND	>45 years	T1a/T1b	Breast-Conserving Surgery	Clinical Exam	RT to breast/chest wall ± supraclavicular; CT in ~74%; HT in 75% (tamoxifen); no HER2 data	5 years
IBCSG 10-93 (Rudenstam et al, 2005)	473	ALND	>60 years	T1	Breast-Conserving Surgery	Clinical Exam	RT in ~33% (post-BCS); no CT; tamoxifen 5y (96%; 80% HR+); no HER2 data	6 years
NSABP B04 (Fisher et al, 2002)	727	ALND	Any age	T1/T2/T3	Mastectomy	Clinical Exam	No RT; no CT; no HT; surgery-only trial	21 years

CT = Chemotherapy; HT = Hormone Therapy; RT = Radiotherapy

Figure 1. Assessment of the Risk of Bias for each of the three outcomes of the randomized clinical trials, conducted using the RoB 2 tool

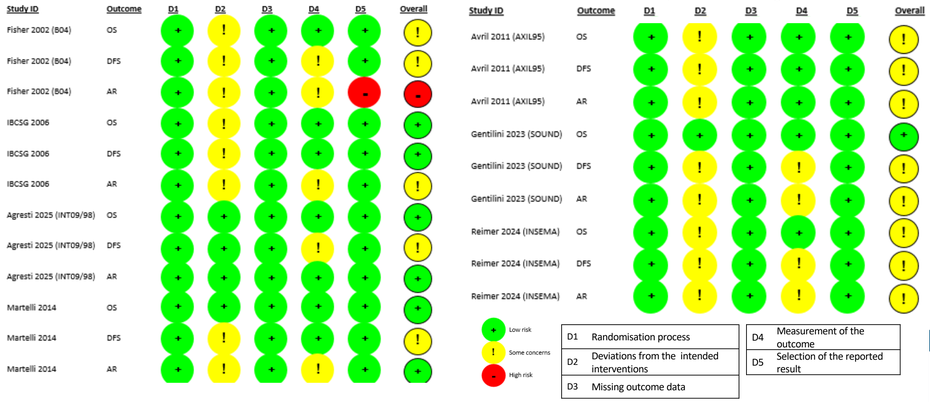


Figure 2. Forest plot of disease-free survival in patients comparing omission of axillary surgery to axillary surgery (ALND or SLNB)

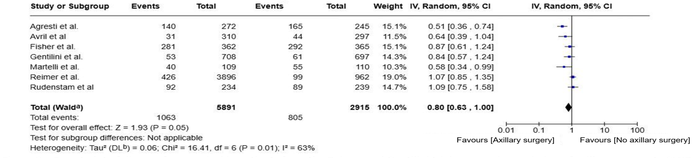


Figure 3. Forest plot of disease-free survival in patients from the Reimer and Gentilini trials comparing omission of axillary surgery to SLNB

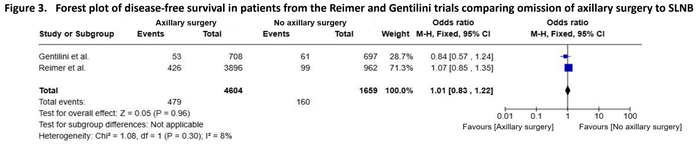


Figure 4. Forest plot of overall survival in patients comparing omission of axillary surgery to axillary surgery (ALND or SLNB)

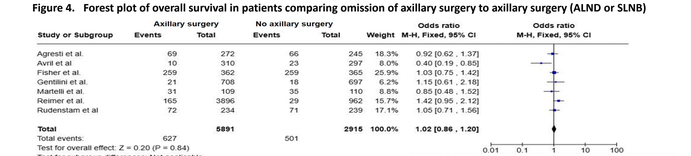


Figure 5. Forest plot of overall survival in patients from the Reimer and Gentilini trials comparing omission of axillary surgery SLNB.

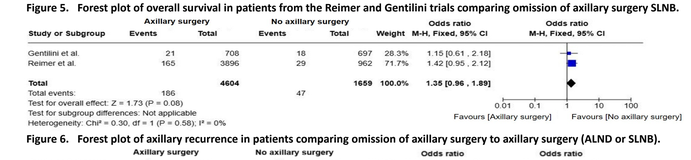


Figure 6. Forest plot of axillary recurrence in patients comparing omission of axillary surgery to axillary surgery (ALND or SLNB).

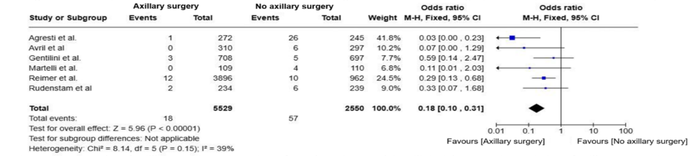


Figure 7. Forest plot of axillary recurrence in patients from the Reimer and Gentilini trials comparing omission of axillary surgery SLNB.



Conclusions

Axillary recurrence was slightly higher in patients without surgery but remained rare overall. Omitting axillary surgery did not compromise disease-free or overall survival. Special caution is needed for younger patients, HER2-positive, and triple-negative tumors. Ongoing trials will clarify applicability in broader populations.

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