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Review Article

The efficacy and oncological safety of minimally invasive axillary procedures in patients with node-positive breast cancer receiving neoadjuvant chemotherapy: A network meta-regression and trial sequential analysis

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ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) can downstage axillary nodes in breast cancer, prompting debate over the optimal axillary management after NAC. While axillary dissection (ALND) provides detailed assessment of node status, minimally invasive methods such as sentinel lymph node biopsy (SLNB), marked lymph node biopsy (MLNB) and targeted axillary dissection (TAD) are showing promise. This meta-analysis aims to assess the efficacy and safety of these strategies.

Methods: A systematic search of Medline, Embase and Cochrane Central was conducted and relevant RCTs were identified. Random-effects meta-analysis, meta-regression and trial sequential analysis (TSA) were conducted for diagnostic outcomes (identification rates [IFR], false negative rates [FNR] and negative predictive value [NPV]) and survival outcomes (overall survival [OS], disease-free survival [DFS]) to compare SLNB, MLNB and TAD with ALND.

Results: Twenty-eight studies (SLNB, n = 3392; MLNB, n = 1130; TAD, n = 946) investigated diagnostic outcomes and nine studies investigated survival outcomes (n = 5647). The pooled IFR, FNR and NPV of TAD was 96.8 %, 4.7 % and 93.2 %, respectively, and all values were superior to SLNB (91.9 %, 13.7 % and 84.8 %; meta-regression, $p < 0.001$) (SLNB vs. MLNB concordance = 73 %). The FNR of SLNB decreased with the number of nodes removed (≥3 nodes, 8.1 %) but remained inferior to TAD ($p = 0.001$). The IFR of SLNB in the ycN0 group was statistically lower than all patients (ycN0/+), 85.8 % vs. 91.9 % ($p < 0.001$). Pooled hazard ratios for DFS in SLNB/TAD, SLNB and TAD were 0.90 (95%CI, 0.77–1.04; $p = 0.45$), 0.89 (95%CI, 0.74–1.08; $p = 0.25$) and 0.91 (95%CI, 0.64–1.29; $p = 0.58$) (TSA 2.08>threshold). Indirect comparison between TAD and SLNB demonstrated no significant difference in DFS (HR 0.98; 0.64–1.32; 95%CI, $p = 0.95$).

Conclusion: Targeted axillary dissection is the optimal minimally invasive axillary technique in terms of diagnostic accuracy. De-escalation of axillary surgery following NAC does not negatively impact DFS in patients with node-positive breast cancer

1. Introduction

Neoadjuvant chemotherapy (NAC) is widely administered to patients with locally advanced and operable breast cancer with involved axillary nodes and produces an axillary pathological complete response (pCR) in 20–41 % of patients [1]. The optimal strategy to stage and treat patients with nodal metastasis after NAC remains uncertain [2,3]. While axillary lymph node dissection (ALND) clears all nodes from level 1 and 2 and is accurate in defining post-NAC nodal status, it produces significant morbidity and as nodes are frequently down-staged post-NAC, a search for the optimal minimally invasive axillary procedure post-NAC has explored a number of alternative procedures.

The role of minimally invasive techniques remains controversial in both patients that do (ycN0) or do not (ycN+) achieve a clinical response

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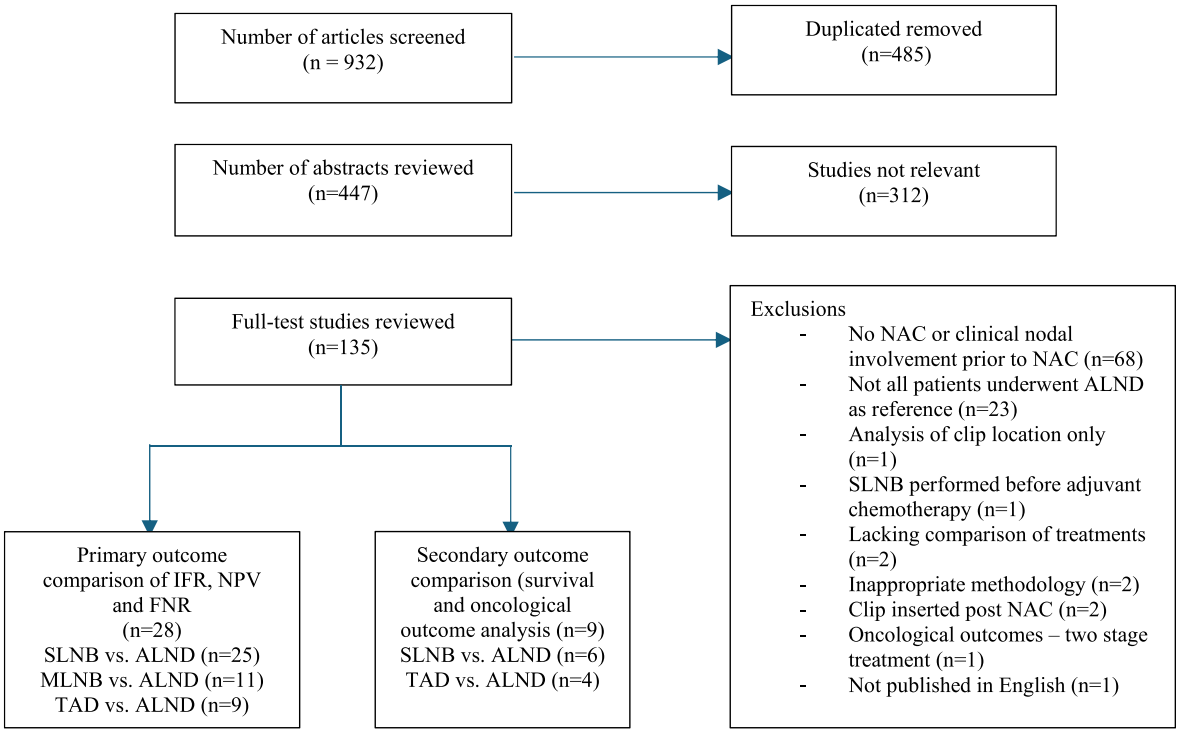

Fig. 1. PRISMA-flow diagram.

to NAC. Poor clinical prediction of pathological response and suboptimal identification rates of sentinel nodes can lead to false reassurance in such axillary sampling procedures [4]. With a view to reduce the false negative rate (FNR), a marked lymph node biopsy (MLNB) strategy has evolved whereby the positive node is clipped and removed without SLNB [5,6]. Since then the targeted axillary dissection (TAD) approach has emerged which combines MLNB with SLNB [7].

Previous studies (e.g. ACOSOG, SENTINA and SN FNAC) have reported a FNR of SLNB of up to 14.2 % even in ycN0 patients following NAC [8–10]. Both MLNB and TAD demonstrate promise in reducing the FNR and boast high identification rates; however, relevant studies and meta-analysis are marked by notable heterogeneity (e.g, ycN0 vs. ycN + or ypN0 vs. ypN1) and the incorporation of selection bias [1,11–15]. There is a need to synthesise the existing high-quality evidence to guide the optimal axillary strategy that accounts for clinical nodal response, pathological nodal status, cancer-type and the number of retrieved nodes.

In patients that achieve pCR following NAC, SLNB has proved to have acceptable short-term axillary recurrence rates, although to this date, a meta-analysis has not been performed [16,17]. Comparison of survival and recurrence outcomes must also be investigated in patients undergoing TAD and in patient groups stratified by response to NAC.

The primary aim of the present meta-analysis was to determine the diagnostic outcomes (identification rate, false negative rate and negative predictive value) of minimally invasive axillary strategies in patients with nodal involvement prior to NAC. The secondary aim was to determine survival and oncological outcomes of minimally invasive strategies as compared to ALND.

2. Methodology

This meta-analysis considers the efficacy and safety of minimally invasive axillary techniques following the administration of NAC in patients with node-positive disease. The inclusion criteria were patients undergoing either SLNB, MLNB or TAD where ALND was used as the reference comparative treatment. Primary outcomes were diagnostic outcomes including the identification rate (IFR), false negative rate (FNR) and negative predictive value (NPV) of the minimally invasive strategies. Secondary outcomes were overall survival (OS), disease free survival (DFS), axillary-recurrence-free survival (ARFS), distant metastasis-free survival (DMFS) and breast cancer specific survival (BCSS).

2.1. Literature search

A systematic search of MEDLINE (OVID), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted from their date of inception to May 1st, 2024. The following query key-words were employed: "neoadjuvant chemotherapy", "targeted axillary dissection", "TAD", "sentinel lymph node biopsy", "SLNB", "axillary lymph node dissection", "ALND", "marked node", “clipped node”, "axillary staging", "false-negative rate", "identification rate", "negative predictive value”, “survival", "recurrence”.

2.2. Eligibility and exclusion criteria

Studies investigating diagnostic outcomes (IFR, FNR and NPV) were only included if they followed a clearly defined study protocol to investigate the diagnostic accuracy of the minimally invasive axillary technique whereby ALND was used as a reference. Therefore, retrospective studies without a clearly defined study protocol were excluded. Other exclusion criteria were as follows:

- Studies including patients with distal metastasis, male breast cancer or inflammatory breast cancer.
- Studies reporting axillary procedures performed prior to NAC administration.
- Studies reporting clip insertion, if applicable, post-NAC.
- Studies using an alternative to ALND as the reference.
- Studies not published in English.

All studies comparing survival/oncological outcomes between axillary strategies were considered; however, those reporting univariate survival analysis were not included in pooled analysis. Studies

Table 1
Diagnostic outcomes (IFR, FNR and NPV) of SLNB, MLNB and TAD compared to ALND (reference) in all patients with nodal involvement prior to NAC.

Author	Year	Study Type	Number	IFR (%) (95%CI)	SLNB Sampling	+ve node locatisation	Definition ax-pCR	Ax-pCR (%)	FNR (%) (95%CI)	NPV (%) (95% CI)
SNLB vs. ALND										
Boileau [8]	2015	P, S	127	87.6 (82.2–93.0)	Tc and/or blue	–	ypN0	35	8.4 (2.4–14.4)	86 (74–94)
Boughey [20]	2013	P, M	637	92.7 (90.5–94.6)	Tc and/or blue	–	ypN0/itc+	41.0	12.6 (9.9–16.0)	82 (77–86)
Caudle [7]	2016	P; S	118	95.2 (89.8–98.2)	Tc and/or blue	–	ypN0	37.0	10.1 (4.2–19.8)	86 (73–94)
Chen [21]	2024	P, S	73	94.8 (87.2–98.6)	Tc and blue	–	NR	58.9	13.3 (3.8–30.7)	91.5 (79.6–97.6)
Enokido [22]	2016	R, S	130	90.9 (85.0–95.1)	Tc and/or blue	–	ypN0	52	21.0 (11.7–33.2)	84.0 (74.1–91.2)
Flores-Funes [23]	2019	P; S	23	82.6 (61.2–95.1)	Tc	–	ypN0	52.5	15.0 (0.0–41.0)	85.0 (61.0–100.0)
Ge [24]	2014	P, S	43	84.3 (71.4–93.0)	Tc and/or blue and/or Carbon	–	NR	27.9	19.4 (7.5–37.5)	66.7 (41.0–86.7)
Kang [25]	2011	R, S	66	95.7 (78.1–99.1)	Tc and/or blue	–	ypN0	ycN0	17.1 (7.2–32.1)	70.8 (48.9–87.4)
Kida [26]	2015	P, S	66	92.4 (83.2–97.5)	Blue	–	NR	29.0	16.1 (5.5–33.7)	85.7 (69.7–95.2)
Kuemmel [12]	2022	P; M	270	90.0 (85.8–93.3)	Clip ± wire	–	ypN0	60.3	23.9 (12.6–38.8)	92.0 (85.1–96.5)
Martinez [15]	2022	P, S	75	NR		–	NR	43.0	2.5 (0.00–13.2)	97.2 (85.5–99.9)
Ozmen [27]	2010	R, S	71	92.2 (83.8–97.1)	Tc + blue	–	ypN0	28	13.7 (5.7–26.3)	74.1 (53.7–88.9)
Park [28]	2013	R, S	169	94.9 (90.6–97.7)	Tc	–	ypN0/itc+	40.8	22.0 (14.3–31.4)	75.8 (65.7–84.2)
Pinero-Madrona [29]	2015	P, M	38	84.4 (70.5–93.5)	Tc ± blue	–	NR	NR	43.5 (23.2–65.5)	56.5 (34.5–76.8)
Shen [30]	2007	P, S	56	92.8 (83.9–97.6)	Tc and/or blue	–	NR	28.6	25.0 (12.7–41.2)	61.5 (40.6–79.8)
Simons [14]	2022	P; M	228	86.4 (81.3–90.6)	Tc and/or blue	–	ypN0	35.4	17.9 (12.4–24.5)	72.8 (63.5–80.4)
Siso [13]	2023	P, M	116	95.0 (90.8–97.2)	Tc and blue		ypN0	39.2	22.5 (13.5–33.9)	73.8 (60.9–84.2)
Yagata [31]	2013	P, S	81	85.3 (76.5–91.7)	Tc + blue	–	ypN0	37	15.7 (7.0–28.6)	79 (63–90)
Yang [32]	2023	P, S	38	100 (89.1–100.0)	ICG + MB	–	ypN0	15.8	9.4 (3.2–24.2)	NR
Zetterlund [33]	2017	P, M	152	77.9 (71.5–83.6)	Tc and/or Blue	–	ypN0	39.5	14.1 (7.7–23.0)	82.2 (71.5–90.2)
MLNB vs. ALND										
Caudle [7]	2016	P; S	191	97.5 (94.2–99.2)	–	Clip and Iodine Seed	ypN0	37.0	4.2 (1.4–9.5)	93.4 (0.85–0.98)
Chen [21]	2024	P, S	73	94.8 (87.2–98.6)	–	Clip + Tatto	NR	58.9	11.1 (2.4–29.2)	92.7 (80.1–98.5)
Donker [34]	2015	P; S	97	97.0 (91.5–99.4)	–	Iodine seed	ypN0	26.3	7.1 (2.4–15.9)	83.3 (65.3–94.4)
Flores-Funes [23]	2019	P; S	23	95.7 (78.1–99.9)	–	Clip + Wire	pN0	34.8	0.0 (0.00–0.15)	1.00 (0.74–1.00)
Koolen* [35]	2017	P; S	93	97.6 (93.2–99.5)	–	Iodine seed	ypN0	19.4	7.4 (1.2–14.0)	84.4 (71.8–96.9)
Kuemmel [12]	2022	P; M	203	77.8 (74.0–82.0)	–	Clip ± wire	ypN0	60.3	7.2 (3.1–13.6)	92.0 (85.1–96.5)
Martinez [15]	2022	P, S	75	100 (95.6–100.0)	–	Clip + Seed	NR	43.0	0.0 (0.0–9.0)	100.0 (92.0–100.0)
Simons [14]	2022	P; M	206	94.1 (90.3–96.8)	–	Iodine Seed	ypN0	35.4	7.0 (3.8–11.6)	86.3 (77.9–92.4)
Siso [13]	2023	P, M	116	96.0 (92.5–98.1)	–	Clip + IOUS	ypN0	39.2	12.7 (6.0–22.7)	
Straver [36]	2010	P; S	15	100.0 (78.2–100.0)	–	Iodine Seed	NR	26.7	0 (0.00–0.218)	100.0 (39.8–100.0)
Yang [32]	2023	P. S	38	100 (89.1–100.0)	–	Clip + Tattoo	ypN0	15.8	18.8 (8.9–35.3)	NR
TAD vs. ALND										
Caudle [7]	2016	P, S	85	NR	Tc and/or blue	Clip + Seed	ypN0	37.0	2.0 (0.1–10.7)	97.2 (85.5–99.9)
Chen [21]	2024	P, S	73	94.8 (87.2–98.6)	Tc and blue	Clip + Tatto	NR	58.9	10.0 (2.1–26.5)	93.5 (82.1–98.6)
Flores-Funes [23]	2019	P; S	23	95.7 (78.1–99.9)	Tc	Clip + Wire	ypN0	34.8	0.0 (0.00–0.15)	100 (74–100)
Martinez [15]	2022	P, S	75	100 (95.6–100.0)	NR	Clip + Seed	NR	43.0	0.0 (0.0–9.0)	100.0 (92.0–100.0)
Siso [13]	2023	P, M	116	NR	Tc and blue	Clip + IOUS	ypN0	39.2	7.0 (2.3–15.7)	90.0 (78.2–96.7)
Kuemmel [12]	2022	P; M	77	86.9 (81.8–91.0)	Tc and/or blue	Clip ± wire	ypN0	62.8	4.3 (0.5–14.8)	93.9 (79.8–99.3)
Simons [14]	2022	P; M	208	98.2 (95.6–99.5)	Tc and/or blue	Iodine Seed	ypN0	35.4	3.5 (1.38–7.16)	92.8 (85.4–97.1)
Yang [32]	2023	P, S	38	100 (89.1–100.0)	ICG + MB	Clip + Tattoo	ypN0	15.8	6.25 (1.7–20.2)	NR
Wu [37]	2023	P; M	152	94.9 (91.3–97.4)	Tc and/or blue	Clip + Wire	ypN0	46.1	12.2 (6.0–21.3)	87.5 (78.2–93.8)

R – retrospective; P – prospective; S – single centre; M – Multicentre.

comparing survival/oncological outcomes were excluded if two-stage axillary strategies were described.

2.3. Study selection and data points and extraction

Title and abstract screening were conducted independently by three reviewers (JL, HB and EM) following deduplication. In cases where there was disagreement regarding the suitability of trials for full-text review, a third party (MD) was consulted to resolve any discrepancies. A comprehensive overview of the screening process is provided in the PRISMA flow diagram (Fig. 1).

Detailed review of the full texts to confirm eligibility based on inclusion and exclusion criteria was then performed. The data were extracted using a predefined extraction sheet, which can be provided upon reasonable request. Following extraction, the reviewers compared the data, addressing any inconsistencies through discussion. If necessary, a third party (MD) was consulted to resolve any discrepancies and reach consensus.

2.4. Data points

Data was sought for general information (e.g. year of publication, study design, sample size), the cohort examined (ycN0/+ or ypN0/+), the SLNB sampling method and the technique to localise the marked node, if applicable. Primary outcomes were reported. The FNR was defined as the number of false negatives (FN) divided by the sum of FN and true positives (TP). The NPV was defined as the number of true negatives (TN) divided by the sum of TN and FN. Secondary outcomes (survival and oncological outcomes) were considered and hazards ratios were reported with 95 % confidence intervals.

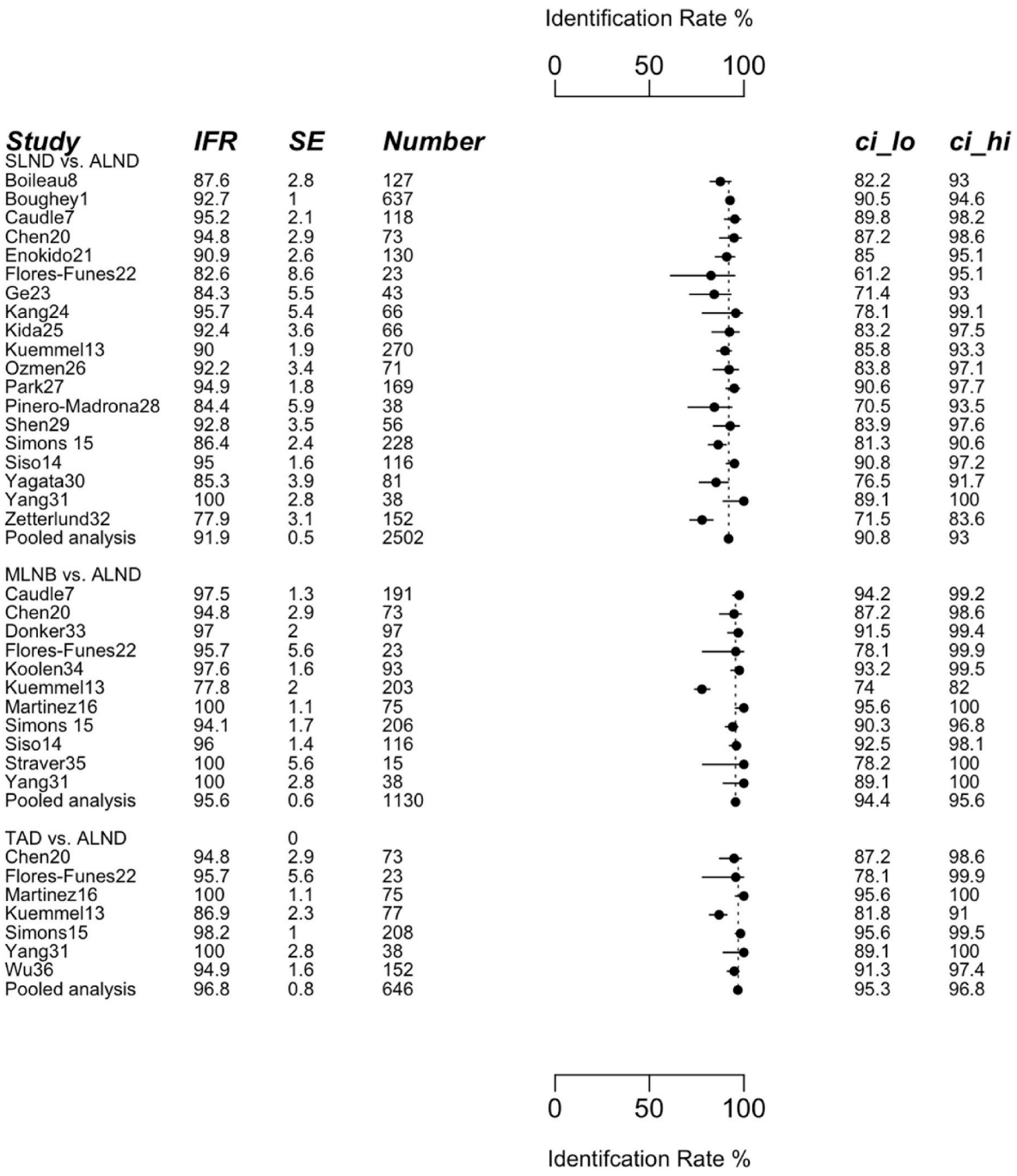

Fig. 2. IFR of SLNB, MLNB and TAD compared to reference ALND.

2.5. Statistical analysis

A random-effects meta-analysis was performed in R (R Foundation for Statistical Computing) using the 'metafor' and 'gemtc' packages, guided by I^2 statistics, and was conducted for diagnostic outcomes (IFR, FNR and NPV) of SLNB, MLNB and TAD [18]. The pooled diagnostic outcomes were reported for each axillary strategy and these were compared. Heterogeneity was reported using Tau (τ) and I^2 and funnel plots were inspected for asymmetry to indicate publication bias. A meta-regression using the 'metafor' statistical package was performed and adjusted for relevant variables (SLNB localisation technique, TAD localisation technique and year of study). Analysis was repeated in patient subgroups (ycN0, ycN+, triple-negative breast cancer [TNBC], HER2-positive).

For survival and oncological outcomes, hazards ratios, confidence intervals and standard errors were log-transformed, and the weight of each study was calculated using the inverse of the variance. Pooled HRs were then calculated. Network maps were generated to visualise all direct comparisons made using the 'netmeta' package. Line thickness corresponds with the number of studies assessing a particular direct comparison and the size of nodes correlates with the number of participants receiving a particular intervention. Direct comparisons were reported between minimally invasive strategies and ALND and indirect comparisons were conducted where possible. Trial sequential analysis was performed using the 'Sequential' and 'gsDesign' packages in 'R Studio'. The O'Brien Fleming approach was selected due to its conservative thresholds in cases of where robust evidence may be lacking [19]. Meta-regression was also conducted to adjust for pathological response

Table 2
Pooled diagnostic outcomes (IFR, FNR and NPV) of SLNB, MLNB and TAD compared to reference ALND.

	Diagnostic Outcome		
	IFR (95%CI)	FNR (95%CI)	NPV (95%CI)
All patients with nodal involvement (cN+)			
• SLNB	91.9 (90.8–93.0)	13.7 (12.4–15.0)	84.8 (83.5–86.2)
• MLNB	95.6 (94.4–96.8)	7.0 (5.4–8.6)	90.4 (88.4–92.3)
• TAD	96.8 (95.3–98,6)	4.7 (3.2–6.2)	93.2 (91.4–95.1)
ycN0			
• SLNB	85.8 (83.5–88.2)	14.1 (11.8–16.4)	85.3 (82.9–87.7)
• TAD	NR	11.1 (1.4–34.7)	94.4 (81.3–99.3)
ycN+			
• SLNB	84 (0.69–0.93)	19.4 (7.5–37.5)	45.5 (16.8–76.6)
• TAD	NR	8.3 (0.2–38.5)	90.0 (55.5–99.8)

and year of study.

3. Results

3.1. Diagnostic outcomes

The PRIMSA-flow diagram demonstrating study selection is summarised in Fig. 1. Overall, 28 studies (prospective (23), retrospective (5); single centre (19) and multi-centre (9)) were included to investigate the diagnostic outcomes (IFR, FNR and NPV) and included 3756 patients (SLNB, 3392; MLNB, 1130; TAD, 946). A total of seven (n = 889) studies investigated the ycN0 subgroup and two studies (n = 57) investigated the ycN+ subgroup. Of the studies investigating diagnostic outcomes, five studies investigated specifically the HER2-positive group and two studies TNBC. Six studies investigated the number of resected SLN and the FNR. The studies that investigated IFR, FNR or NPV in all patients with nodal involvement prior to NAC are displayed in Table 1 and study heterogeneity is reported (Supplementary Fig. 1).

3.1.1. Identification rate

The pooled IFR (Fig. 2, Table 2) of SLNB, MLNB and TAD in all patients were 91.9 % (range 77.9–95.7; 95%CI, 90.8–93.0), 95.6 % (range, 77.8–100; 95%CI, 94.4–96.8), and 96.8 % (range, 86.9–100; 95%CI, 95.3–98.3), respectively. The IFR of SLNB was significantly lower than that of MLNB ($p < 0.001$) and TAD ($p < 0.001$); although there was no significant difference between MLND and TAD ($p = 0.234$). Across 6 studies that reported the concordance between sentinel nodes and the clipped node, the mean concordance was 73 % (n = 569) [7,12,14,15,23,38,39].

3.1.2. False negative rate

The pooled FNR (Fig. 3, Table 2) of SLNB, MLNB and TAD were 13.7 % (range 2.5–43.5; 95%CI, 12.4–15.0), 7.0 % (range, 0–18.8; 95%CI, 5.4–8.6), and 4.7 % (range, 0–12.2; 95%CI, 3.2–6.2), respectively. Both MLNB ($p < 0.001$) and TAD ($p < 0.001$) had a significantly lower FNR compared to SLNB. TAD had the lowest FNR (4.7 %) which was significantly lower than MLNB ($p = 0.039$). Results from the meta-regression confirmed a superior FNR with TAD ($p < 0.001$) and MLNB ($p < 0.001$) compared to SLNB (F statistic = 12.7) with 40.7 % of the variation in FNR among all studies being explained by the axillary technique.

In studies (n = 6) investigating the relationship between the number of nodes in the SLNB and the FNR, the pooled FNR was: 1 node, 22.1 % (95%CI,14.1–30.0), 2 nodes, 20.1 % (95%CI, 13.5–26.6) and ≥3 nodes, 8.1 % (95%CI, 5.4–10.8 %) (Supplementary Table 1). The FNR was significantly lower with ≥3 nodes compared to 1 ($p = 0.001$) or 2 nodes ($p < 0.001$), although this remained significantly higher than the FNR of TAD ($p = 0.034$). There was no significant difference between the FNR between 1 and 2 nodes ($p = 0.705$).

3.1.3. Negative predictive value

The pooled NPV (Fig. 4 and Table 2) of SLNB, MLNB and TAD were 84.8 % (95%CI, 83.5–86.2), 90.4 % (95%CI, 88.4–92.3), and 93.2 % (95%CI, 91.4–95.1), respectively. The NPV of TAD were higher than both MLNB and SLNB ($p < 0.001$). Results of the meta-regression confirmed a superior FNR in TAD ($p < 0.001$) and MLNB ($p < 0.001$) compared to SLNB (F statistic = 13.4) with 42.3 % of the variation in FNR among all studies being explained by the axillary technique.

3.1.4. ycN0/+ subgroups

The studies exploring the diagnostic outcomes of SLNB and TAD in the ycN0 subgroup and the pooled IFR is reported in Supplementary Table 2. No studies reported diagnostic outcomes in the MLNB ycN0/+ subgroups.

The IFR of SLNB in the ycN0 group was statistically lower than all patients (ycN0/+), 85.8 % vs. 91.9 % ($p < 0.001$) but there was no significant difference in IFR in TAD patients (ycN0 vs. ycN0/+).

The FNR of SLNB and TAD in the ycN0 subgroup were 14.1 % (95% CI, 11.8–16.4) and 11.1 % (95%CI, 1.4–34.7), respectively, and in both cases were statistically similar ($p = 0.754$ and $p = 0.181$) to the studies considering all patients (Supplementary Table 2). Two studies investigated the FNR in patients with ycN+, one reported a FNR with SLNB of 19.4 % (95%CI, 7.5–37.5) and one reporting the FNR with TAD of 8.3 % (95%CI, 0.2–38.5).

The pooled NPV was unchanged between all patients and ycN0 patients ($p = 0.754$).

3.1.5. TNBC and HER2-positive

Seven studies investigated the FNR of SLNB in HER2+ (n = 4), TNBC (n = 2) and non-luminal (n = 1) breast cancer subgroups, respectively. Five of the seven studies did not stratify patients by clinical response to NAC (e.g. ycN0/+) and anti-HER2 treatments. These studies had a pooled FNR of 10.7 % (95%CI, 5.7–15.7) and 8.4 % (95%CI, 1.5–15.2) for HER2-positive and TNBC respectively. There was no significant difference between these findings and those from the overall pooled outcomes for all cancer-types ($p > 0.05$). Interestingly, Bae et al. demonstrated a FNR of 0 % with SLNB in HER2-positive/TNBC who showed a complete response to NAC on MRI, compared to a FNR of 33.3 % in those who did not have an imaging CR [40]. Analysis of TAD in TNBC and HER2-positive patients was limited to one study investigating 25 ycN0/+ cancers (FNR, 0 %).

3.2. Survival and oncological outcomes

A total of nine studies investigated survival and oncological outcomes including 5647 patients, with 4 studies investigating ypN+, three studies ypN0 and three studies ypN0/+ (Table 3). Six studies compared SLNB versus ALND including 5034 patients and four studies compared TAD versus ALND including 2816 patients. No studies found any statistical significance in survival or oncological outcomes. No randomised controlled trials had been conducted. Pfob et al. reported grouped outcomes based on the number of sentinel nodes (<3 and ≥ 3) obtained and pathological response (ypN0/+) [41].

3.3. Disease-free survival

Six studies compared DFS between either SLNB (n = 3) or TAD (n = 3) with ALND using survival analysis (Table 3; Fig. 5a). The pooled HR for SLNB/TAD, SLNB and TAD compared to ALND were 0.90 (95%CI, 0.77–1.04; p=0.45), 0.89 (95%CI, 0.74–1.08; $p = 0.25$) and 0.91 (95% CI, 0.64–1.29; $p = 0.58$), respectively, illustrating no statistical difference in DFS and no compromise in outcome (Fig. 5b and c). Indirect comparison between TAD and SLNB demonstrated no significant difference (HR 0.98; 95%CI, 0.64–1.32; $p = 0.95$). TSA analysis demonstrated a Z-score beyond the level O'Brien Fleming threshold indicating sufficient cumulative evidence to draw such a conclusion (Fig. 5d).

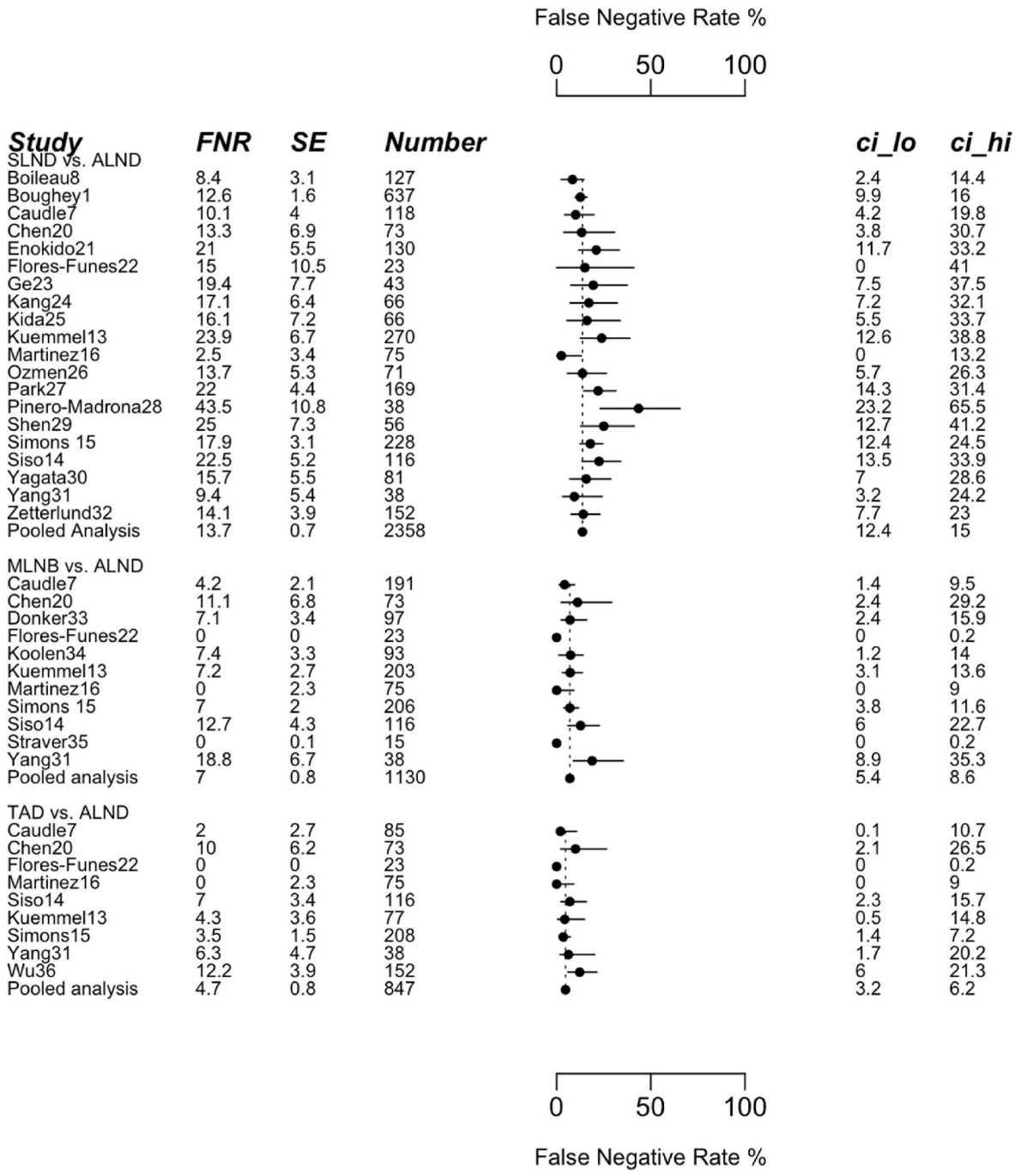

Fig. 3. FNR of SLNB, MLNB and TAD compared to reference ALND.

Meta-regression was performed to adjust for the pathological response (ypN0 vs. ypN+) and the year of study and demonstrated a HR of 0.87 (95%CI, 0.52–1.43; p = 0.58) for SLNB/TAD versus ALND.

3.4. Overall survival

Five studies compared OS between SLNB (n = 4) or TAD (n = 1) with ALND. Combined pooled analysis of SLNB/TAD had a HR for OS of 0.90 (95%CI, 0.65–1.24; p = 0.53). Meta-regression revealed a HR for OS of 0.65 (95%CI, 0.34–1.17; p = 0.16) for SLNB/TAD. The limited number of patients involved in investigating OS in TAD prevented a direct comparison between TAD and SLNB. TSA analysis demonstrated a Z-score of −0.86 which did not meet the O'Brien Fleming threshold.

4. Discussion

This meta-analysis evaluates the efficacy and safety of Sentinel Lymph Node Biopsy (SLNB), Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) as alternative less invasive strategies to Axillary Lymph Node Dissection (ALND) following neoadjuvant chemotherapy (NAC) in patients with node-positive breast cancer. Prior to this meta-analysis, two previous systematic reviews had been conducted on this subject [5,47]. The analysis by Simons et al. included two studies incorporating TAD and therefore subgroup-specific analysis and survival/oncological outcomes were not investigated [47]. The more recent study by Swarnkar et al. investigated FNR and did not consider IFR, NPV, survival/oncological outcomes or perform a subgroup analysis [5]. Whilst all strategies are valid diagnostic approaches to reduce

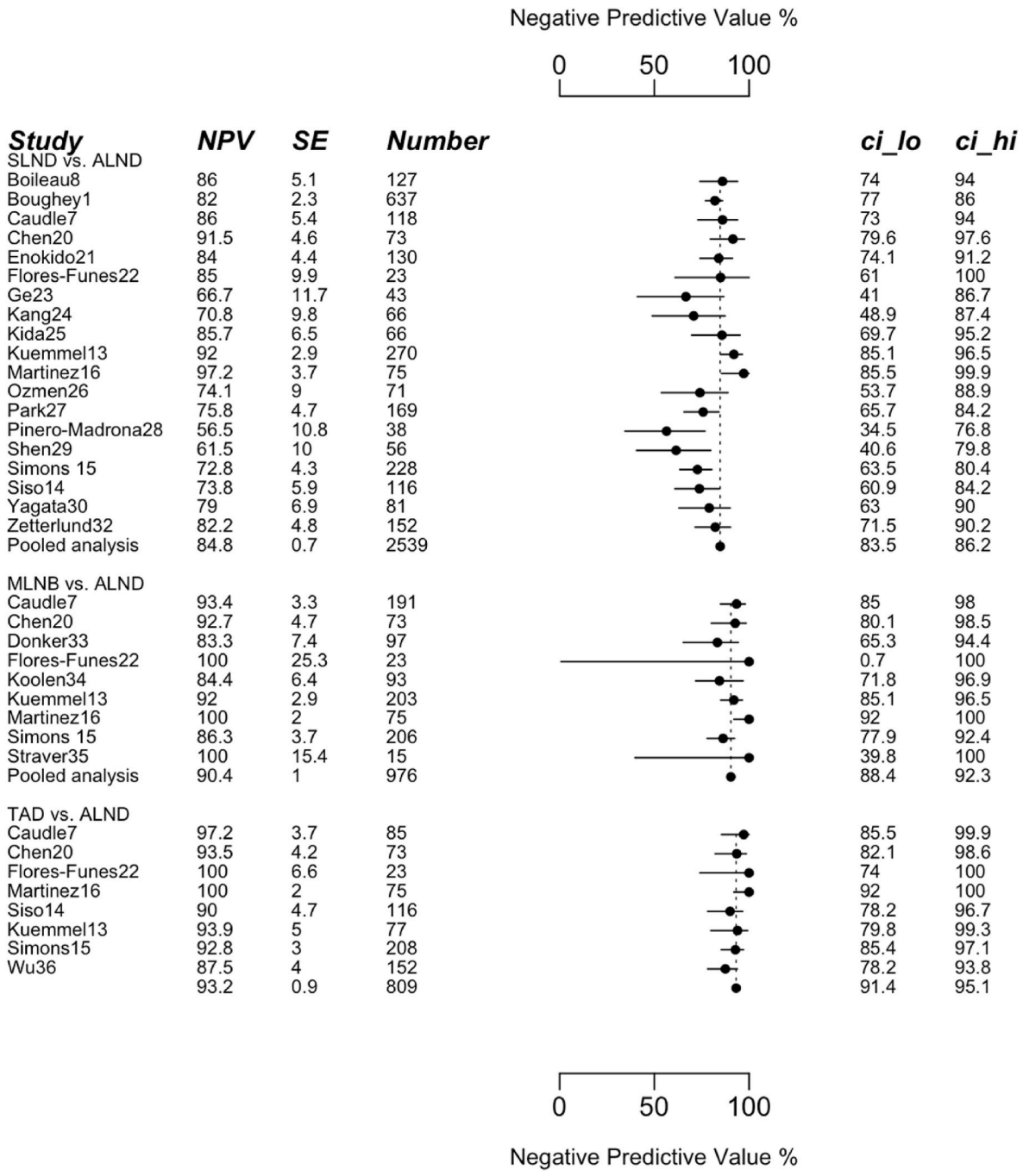

Fig. 4. NPV of SLNB, MLNB and TAD compared to reference ALND.

the morbidity associated with ALND, our findings present convincing evidence that TAD demonstrates superior diagnostic accuracy compared to SLNB and MLNB, with a higher IFR, a higher NPV and a lower FNR. Further analysis confirms the efficacy of TAD in subgroups defined by clinical response (e.g. ycN0) to NAC and breast cancer subtype (TNBC and HER2-positive). Our analysis revealed no evidence to suggest that SLNB or TAD would compromise overall or disease-free survival compared to ALND in this patient group.

The results of this study align with previous research, which has highlighted the limitations of SLNB in the post-NAC setting, particularly in terms of FNR. Studies such as the ACOSOG Z1071 and SENTINA trial reported FNRs as high as 14.2 % for SLNB after NAC, raising concerns about its reliability as a stand-alone staging procedure [20,9]. Our findings corroborate these concerns (overall FNR 13.7 %) and provide robust evidence that the FNR exceeds the empiric 10 % threshold proposed in the literature [48,49]. The identification rate was significantly higher (pooled FNR of 22.1 % and 20.1 %) when only 1 or 2 nodes were resected, highlighting the concern if a malignant node has not been marked pre-operatively and further sentinel nodes cannot be located [7–9].

Marked Lymph Node Biopsy and TAD, have both been proposed within the last decade, although the role of both relative to SLNB are yet to be established in terms of standard of care [6,7,34]. With a higher IFR (95.6 % and 96.8 %, respectively) and a lower FNR (7.0 % and 4.7 %), the present data reveals that both are superior alternatives to SLNB which is consistent with the growing body of literature supporting the removal of a clipped node in this setting [7,39,32,34,50,51]. In fact, despite a high degree of nodal concordance between the marked and

Table 3
Survival and oncological outcomes of SLNB, MLNB and TAD compared to ALND (reference) in all patients with nodal involvement prior to NAC.

Author	Year	Study type	Number SLNB: ALND	Subgroup	SLNB Sampling	+ve node locatisation	Anlaysis	Median F/U (months)	OS, HR (95% CI)	DFS, (HR, 95% CI)	ARFS, (HR, 95%CI)	DMFS, (HR, 95%CI)	BCSS, (HR, 95%CI)
SLNB vs. ALND													
Almahariq [42]	2021	R, M	304:1313	ypN+	NR	–	CPHM	36:44	1.74 (1.34–2.25)	NR	NR	NR	NR
Chun [43]	2021	R; S	98:98	ypN+	Tc	–	CPHM (PSM)	71	1.07 (0.39–2.96)	NR	1.20 (0 0.41–3.54)	0.85 (0.42–1.72)	1.39 (0.40–4.81)
Kim [37]	2021	R, S	94:129	ypN0	Tc	–	CPHM	77	0.53 (0.16–1.75)	1.16 (0.56–2.39)	NR	NR	NR
Lim [44]	2023	R, M	314:163	ypN0	Tc ± blue	–	CPHM	65	0.244, (0.06–0.98	0.50, (0.29–0.86)	NR	NR	NR
Ling [44]	2019	R, S	53:108	ypN+	NR	–	CPHM (univariate)	24.7	NS	NS	NS	NS	NS
Pfob [41]	2024	R; M	205:2204	ypN0 <3 SLNs	NR	–	CPHM	24.7	NR	1.21 (0.72–2.0)	NR	NR	NR
			255; 2204	ypN0 ≥3 SLNs					NR	0.91 (0.53–1.60)	NR	NR	NR
			205:2204	ypN0/+ <3 SLNs					NR	0.97 (0.62–1.51)	NR	NR	NR
			255; 2204	ypN0/+ ≥3 SLNs					NR	0.86 (0.56–1.31)	NR	NR	NR
TAD vs. ALND													
Dux [45]	2023	R, M	35:107	ypN+	Tc and/or blue	Clip	CPHM (univariate)	34 months	NS	NS	NR	NR	NR
Kuemmel [46]	2023	P; M	119:80	ypN0/+	Tc and/or blue	Clip + Wire	CPHM	43.0	1.07 (0.31–3.70)	0.83 (0.34–2.05)	NR	NR	1.77 (0.39–8.03)
Pfob [41]	2024	R: M	34:2204	ypN0/+	NR	Clip	CPHM	24.7	NR	0.23 (0.03–1.64)	NR	NR	NR
Wu [37]	2023	P, M	85:152	ypN0/+	Tc and/or blue	Clip	CPHM	36.6	NR	1.59 0.33–7.69	NR	NR	NR

*NS – not significant, no HR reported; R – retrospective; P – prospective; S – single centre; M – Multicentre.

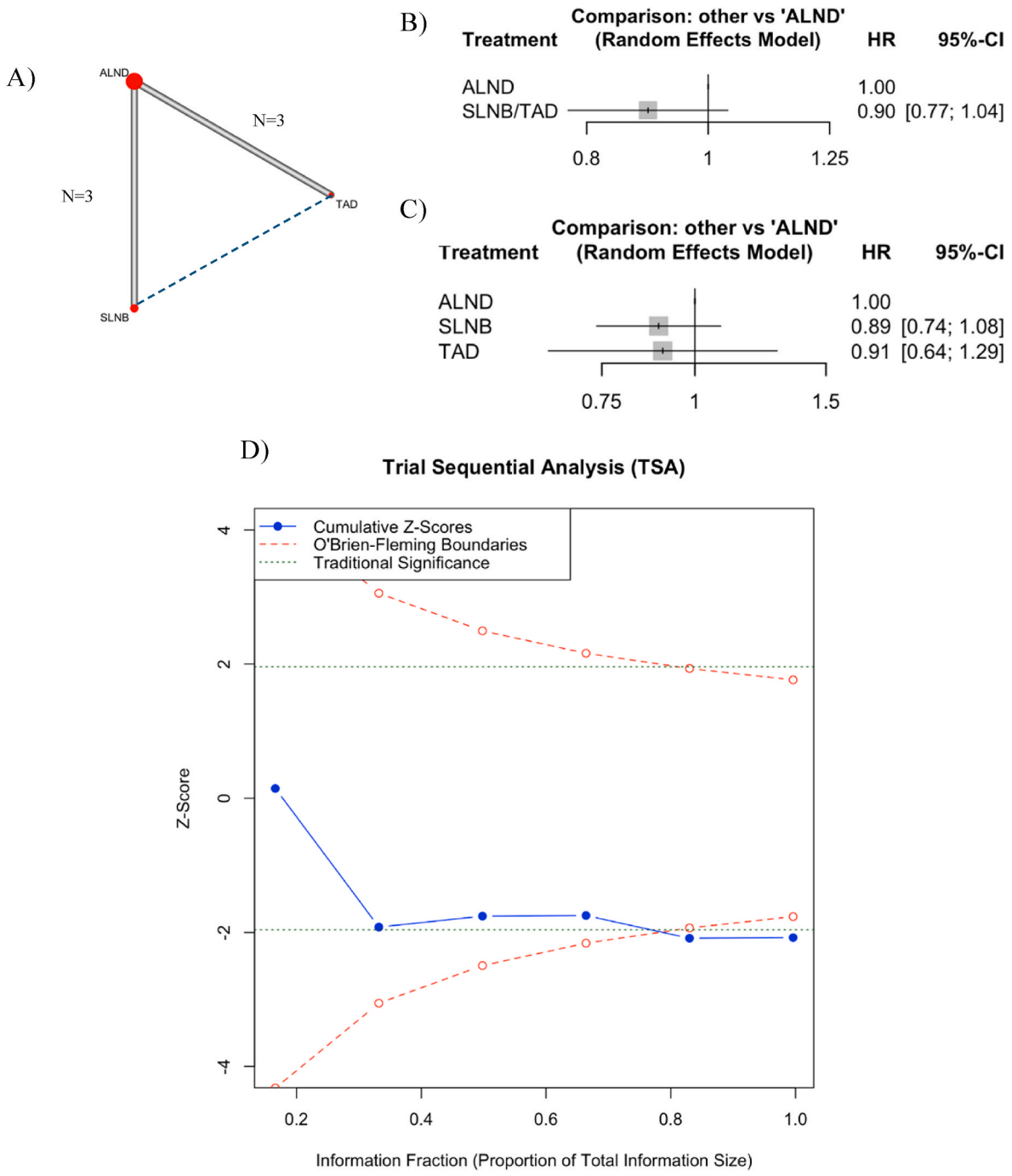

Fig. 5. A) Network plot of studies comparing DFS; B) and C) Direct comparisons of DFS between SLNB/TAD versus ALND D) TSA of studies comparing DFS.

sentinel nodes (73 %), TAD was superior to MLNB and to SLNB even when ≥3 sentinel nodes were retrieved (FNR, 8.1 %) [9,13,52,21]. Therefore, where a malignant node has been identified prior to NAC, the recommendation is that sentinel nodes should be removed alongside the marked node as part of TAD, in order to optimise diagnostic outcomes.

Further analysis was conducted in subgroups defined by the clinical response to NAC. Hypothetically, the role of each axillary strategy may be dependent on the response to NAC, particularly where axillary disease may only be retrieved in the clearance tissue. Whilst few studies have reported diagnostic outcomes in patients who fail to achieve a clinical response to NAC (n = 2), many studies have reported outcomes in the ycN0 subgroup [21,25]. The IFR of SLNB was lower in ycN0 (85.8 % vs. 91.9 %, $p < 0.001$), which may be secondary to axillary scarring in NAC responders, and provides further cause for concern towards the use of SLNB [53]. The myriad of localisation techniques in TAD may overcome this limitation since no change in diagnostic outcome was observed in patients receiving TAD, regardless of NAC response [54]. However, the number of studies investigating the ycN+ group in isolation was low and further research is required to confirm the efficacy of SLNB, MLNB or TAD in this patient group.

In the context of TNBC and HER2-positive disease, axillary strategy becomes even more critical. These subtypes are characterized by aggressive biology and although pCR rates are higher than luminal subtypes, survival in those without a response is poor [55,56]. Recent studies have suggested that patients with TNBC or HER2-positive cancers who achieve a pCR actually have a low rate of axillary recurrence

and SLNB may be sufficient [57,58]. Certainty, the FNR of SLNB in both TNBC and HER2-positive were reassuring in the present analysis with pooled FNRs of 10.7 % (95%CI, 5.7–15.7) and 8.4 % (95%CI, 1.5–15.2), respectively. Nevertheless, the investigation of ycN + subgroups was minimal and limited to Bae et al. who reported a FNR of 33.3 % in this group compared to 0 % in ycN0 HER2-positive/TNBC patients confirmed with MRI [40].

The absence of a significant difference in OS or DFS between SLNB or TAD and ALND in our analysis suggests that minimally invasive techniques may be sufficient to guide further treatment decisions without compromising survival or oncological outcome. This aligns with the growing trend toward de-escalation of surgical treatment in breast cancer, particularly in the context of improved systemic therapies that enhance the overall response to NAC [11,59]. The trial sequential analysis suggests that sufficient evidence has been incorporated to draw such a conclusion. The network meta-analysis found no difference in survival or oncological outcomes in the indirect comparison between SLNB and TAD.

The ypN status post-NAC is a critical determinant of prognosis in breast cancer patients, influencing decisions regarding the extent of surgery and adjuvant therapy [54,60,61]. The meta-regression adjusted for ypN status and suggests that in patients with ypN0 status, indicative of a complete nodal response to NAC, minimally invasive approaches confer excellent survival outcomes. This finding is consistent with studies that have reported high OS rates in ypN0 patients, suggesting that the biological response to NAC, rather than the extent of surgical intervention, is a key driver of long-term outcomes [12,46,60,61].

For patients with ypN+ status, however, the optimal surgical approach remains a topic of debate. While ALND has traditionally been recommended to ensure complete removal of residual nodal disease, a number of studies have questioned the role of clearance in those with residual disease and suggested that SLNB may be sufficient [42,43,62]. It has been hypothesised that those with minimal nodal burden or those with a good response to NAC may benefit from SLNB without a negative long-term impact on survival or recurrence. The impact of TAD on ypN+ patients has never been investigated exclusively however and requires further research. Targeted removal of the marked node may offer further assurance against axillary recurrence and confer non-inferior long-term outcomes.

There are several limitations to the present meta-analysis. While the meta-analysis of diagnostic accuracy outcomes was conducted using mostly prospective studies (level of evidence 2a), the meta-analysis of survival/oncological outcomes incorporated mainly retrospective studies (level of evidence 3a). This reflects the current state of the evidence base and the need for a higher level of evidence. Secondly, there was inherent heterogeneity which was likely not addressed by the meta-regression. This arose from variation of the localisation method, different baseline cohort characteristics and distribution of cancer subtypes. Although there were statistically significant findings despite the heterogeneity, this aspect may reduce the generalisability of the findings to subgroups (e.g. different localisation methods, cancer subtypes). An additional limitation was the few studies that investigated key cancer-types (e.g TNBC and HER2-positive) and subgroups defined by the clinical and pathological response to NAC. Whilst evidence is in favour of minimally invasive techniques in ycN0, further studies are needed to investigate axillary strategy in patients with residual disease and in specific cancer-types. Lastly, the relatively short follow-up durations for oncological outcomes and the poor access to radiotherapy data limits the robustness of long-term conclusions, and more extended follow-up is required in future studies.

In conclusion, the findings support the ongoing de-escalation of axillary sampling and confirms that TAD is the optimal minimally invasive strategy in terms of diagnostic accuracy in node-positive patients undergoing NAC. Despite a high level of nodal concordance, SLNB and MLNB do not provide the same level of diagnostic reliability as TAD. The survival analysis suggests that SLNB and TAD are viable alternatives to ALND and do not compromise oncological safety. The role of these techniques in high-risk subtypes like TNBC and HER2-positive cancer and those without a response to NAC requires further investigation. Future research should also focus on large prospective randomized trials to confirm the long-term oncological safety of TAD.

The authors of the present study have no conflicts of interest to declare.

Contribution Author(s)

Conceptualisation: James Lucocq, Professor J Michael Dixon, Data Curation: James Lucocq, Professor J Michael Dixon, Formal Analysis: James Lucocq, Professor J Michael Dixon.

Funding acquisition: N/A.

Investigation: James Lucocq, Professor J Michael Dixon, Methodology: James Lucocq, Professor J Michael Dixon.

Project administration: James Lucocq, Professor J Michael Dixon.

Software: James Lucocq, Hassan Baig, Esther McNeill, Professor J Michael Dixon, Resources: James Lucocq, Hassan Baig, Esther McNeill, Professor J Michael Dixon, Supervision Professor J Michael Dixon, Validation James Lucocq, Professor J Michael Dixon, Visualisation James Lucocq, Writing – Original draft James Lucocq, Hassan Baig, Esther McNeill, Professor J Michael Dixon.

Writing – review and editing James Lucocq, Hassan Baig, Esther McNeill, Professor J Michael Dixon.

Declaration of interest statement

There are no conflicts of interest to declare by James Lucocq, Hassan Baig, Esther McNeill or Professor J Michael Dixon.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109689.

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