

OUTCOME OF SENTINEL LYMPH NODE BIOPSY POST NEOADJUVANT CHEMOTHERAPY IN CLINICALLY NODE NEGATIVE BREAST CANCER PATIENTS, CAN SENTINEL LYMPH NODE BIOPSY BE OMITTED IN SELECTED PATIENTS?

Albash Sarwar^{*1}, Sarah Iqbal², Maha Kamran³, Ayesha Bushaira⁴, Dr. Zill-E-Huma⁵,
Dr. Abid Ejaz⁶, Muhammad Amar Akram⁷

^{*1}Trained in General Surgery (CPSP), Shaukat Khanum Memorial Cancer Hospital and Research Center, Pakistan

²GP Surgical Oncology, Burjeel Cancer Institute, Abu Dhabi, UAE

³Department of Surgery, Mayo Hospital, Lahore, Pakistan

⁴Department of Biotechnology, University of Okara, Punjab, Pakistan

⁵Department of Environmental Sciences, Fatima Jinnah Women University, Rawalpindi Pakistan

⁶Department of Botany, University of Sargodha, Sargodha, Punjab, Pakistan

⁷Department of Plastic Surgery, Mayo Hospital, Lahore, Pakistan

¹albashsarwar@gmail.com, ²sarahiqbal31@gmail.com, ³drmaha3053@gmail.com,

⁴ayeshabushaira7350@gmail.com, ⁵humashah690@gmail.com, ⁶abid155yahoo.com,

⁷amar_u100@yahoo.com

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Corresponding Author: *

Albash Sarwar

Abstract

Background: Sentinel lymph node biopsy (SLNB) remains an important component of axillary staging in clinically node-negative (cN0) breast cancer following neoadjuvant chemotherapy (NAC). However, the increasing frequency of pathological complete response (pCR), particularly in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (TNBC), has prompted interest in response-guided de-escalation of axillary surgery to minimize treatment-related morbidity without compromising oncological safety.

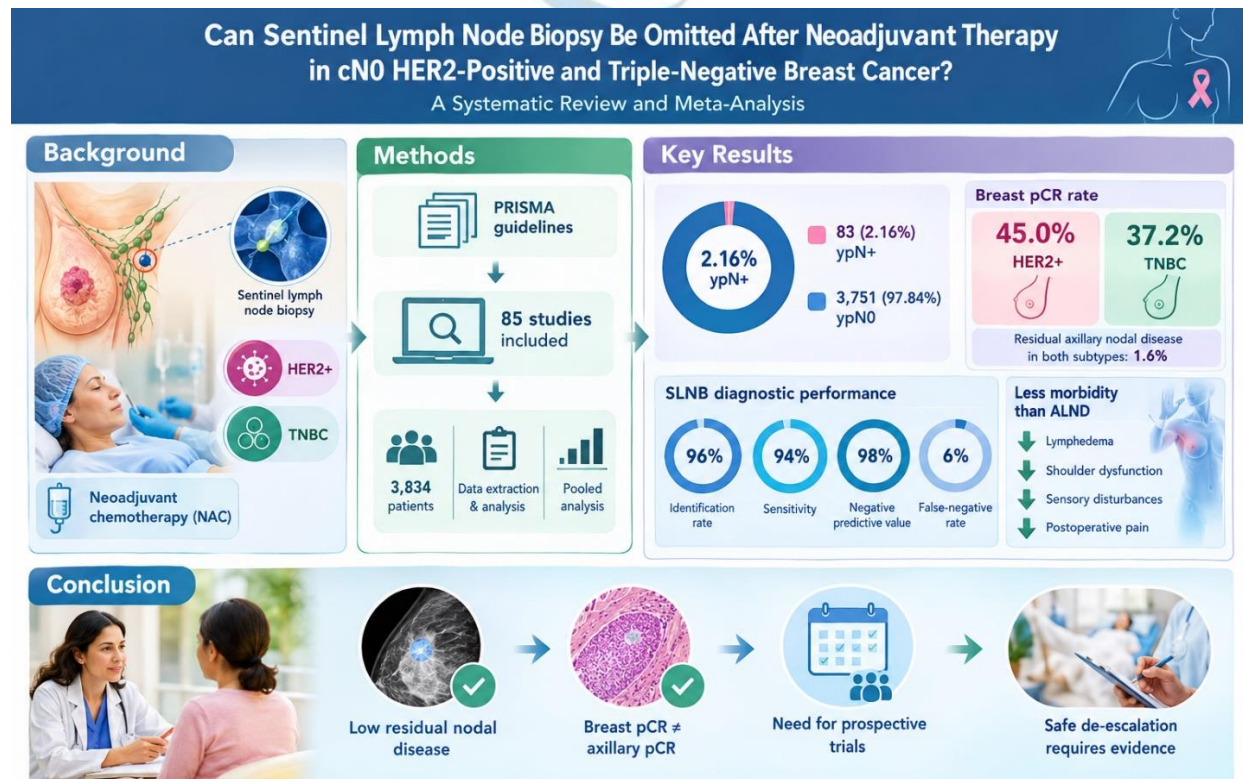
Methods: This systematic review evaluated the diagnostic performance of SLNB, the prevalence of residual axillary nodal disease, the association between breast pCR and axillary pathological response, and the feasibility of selectively omitting SLNB after neoadjuvant systemic therapy. The review followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Eligible prospective and retrospective studies involving patients with cN0 invasive breast cancer were assessed for pathological nodal outcomes, SLNB identification rates, diagnostic accuracy, recurrence, survival, and treatment-related morbidity. Quantitative synthesis was reported for studies providing relevant outcome data.

Results: Eighty-five reports were included in the systematic review, of which five studies contributed to the pooled analysis of 3,834 patients with HER2-positive or TNBC. Residual axillary nodal disease (ypN+) was identified in

83 patients (2.16%; 95% confidence interval [CI]: 1.70–2.63%), whereas 3,751 patients (97.84%) had ypN0 disease. Breast pCR rates were 45.0% in HER2-positive breast cancer and 37.2% in TNBC, while residual axillary nodal disease was reported in 1.6% of patients in each subtype. The pooled SLNB identification rate was 96% (95% CI: 95-97%), with sensitivity of 94% (95% CI: 92-97%), a negative predictive value of 98% (95% CI: 98-99%), and a false-negative rate of 6% (95% CI: 3-8%). The reviewed evidence also indicated lower morbidity following SLNB than axillary lymph node dissection, particularly regarding lymphedema, shoulder dysfunction, sensory disturbances, and postoperative pain.

Conclusion: The low prevalence of residual axillary disease in selected cN0 patients with HER2-positive and triple-negative breast cancer supports further investigation of response-adapted axillary management following neoadjuvant systemic therapy. Nevertheless, breast pCR cannot be considered a reliable substitute for pathological confirmation of axillary status, and the presence of residual nodal disease in a small proportion of patients remains clinically relevant. Routine omission of SLNB cannot be recommended on the basis of these findings alone; prospective trials with standardized response assessment and adequate long-term oncological follow-up are required to establish the safety of this strategy.

Advanced Research



Graphical abstract for outcome of sentinel lymph node biopsy post neoadjuvant chemotherapy in clinically node negative breast cancer patients

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women worldwide and is one of the leading causes of breast cancer-related morbidity and mortality. Survival has improved greatly with the development of new systemic treatments, surgical procedures and multidisciplinary management, and there is a clear trend towards de-escalation of treatment, that is, reducing the morbidity of treatment while maintaining oncological safety. Axillary lymph node status is one of the most significant prognostic factors of breast cancer, contributing to the disease's staging, treatment, or prognosis. Therefore, the correct diagnosis of axillary lymph node status is a crucial aspect of breast tumour management. Historically, axillary lymph node dissection (ALND) has been the "gold-standard" staging procedure for the axilla, but because of the high morbidity associated with lymphoedema, pain, sensory deficits and impaired shoulder function, less intrusive procedures have slowly taken the place of routine axillary clearance in many practice settings (Mattson et al., 2016; Knopf et al., 2026).

Importantly, NAC is capable of achieving pathological complete response (pCR) in a significant number of patients, thus eradicating metastatic deposits in the axillary lymph nodes. The probability of pCR is different among patients and is particularly high in those with human epidermal growth factor receptor-2-positive (HER2-positive) breast cancer and triple-negative breast cancer (TNBC) due to the efficacy of current systemic treatment and targeted therapy (Alamoodi et al., 2023; Julian et al., 2001).

For clinically node-negative patients, SLNB has been demonstrated to be a safe and effective tool to determine residual axillary disease following NAC. Meta-analyses have shown that adequate identification rates and low false-negative rates can be achieved for cN0 patients prior to treatment. However, only a few patients initially diagnosed with node-positive disease have been a cause of concern for the accuracy of SLNB

(Kuehn et al., 2013; Boughey et al., 2013; Boileau et al., 2015).

A major finding that supports this idea is the good correlation between pathological response at the breast and at the axilla. Patients who achieve breast pathological complete response after neoadjuvant chemotherapy have a very high probability of axillary pathological complete response, especially those with HER2-positive disease and TNBC. In the same way, Barron et al. reported the rate of residual node positivity as only approximately 1.6% among clinically node-negative patients with HER2-positive or triple-negative breast cancer who achieved breast pCR. Moreover, pooled analysis of 3,834 clinically node-negative patients with HER2+ or TNBC who underwent breast pCR after neoadjuvant therapy showed that the overall rate of residual nodal disease was only 2.16%, which may be lower than the accepted false-negative rate of SLNB itself (Barron et al., 2018; Weiss et al., 2021).

The results have led to an important clinical question to be raised regarding the need for SLNB in certain patients who respond well to neoadjuvant treatment. When the risk for residual axillary disease is very small, the risk of SLNB-related morbidity might be greater than the potential benefits. Therefore, several prospective studies in progress are exploring the safety and feasibility of not performing SLNB in highly selected patients. ASICS, EUBREAST-01, and ASLAN are ongoing trials that aim to demonstrate the safety of omitting axillary surgery in patients with complete or near-complete response after neoadjuvant treatment who have HER2+ and triple-negative breast cancer, respectively (McIntosh et al., 2026; Tasoulis et al., 2024).

In addition to clinical examination, image-guided biopsy procedures and breast magnetic resonance imaging (MRI) have enhanced the assessment of treatment response after neoadjuvant treatment. At present, MRI is considered to be the most reliable imaging method for the assessment of residual disease in the breast, especially in HER2-positive and triple-negative breast cancers.

Although imaging technology has advanced, radiological assessment cannot currently achieve the same degree of certainty as pathological assessment, and at the current stage, there is not sufficient evidence to recommend routine use of SLNB outside of investigational studies (Davis & McCarty, 1997; Marinovich et al., 2013).

SLNB is currently the standard approach to axillary staging after neoadjuvant chemotherapy (NAC) in clinically node-negative (cN0) breast cancer patients, but there is increasing evidence that selective omission of SLNB may be possible in carefully selected patients, such as those with HER2-positive or triple-negative breast cancer, who achieve an excellent pathological response. However, there is still a need for strong clinical evidence of the prevalence of residual nodal disease after NAC and patient selection criteria before the widespread use of such an approach. Therefore, the present study sought to determine the benefits of SLNB after neoadjuvant chemotherapy in patients with clinically node-negative breast cancer and the validity of the available pathological response data to support the potential for SLNB omission in selected patients with an excellent treatment response.

Methodology

Study Design

The aim of this study was to conduct a systematic review of the outcomes after sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NAC) in patients with clinically node-negative (cN0) breast cancer and to examine the evidence for the possibility of omitting SLNB in well-selected cases with excellent response to neoadjuvant treatment. The review focused on the prevalence of residual axillary nodal disease after NAC, the role of SLNB in diagnosis, pathological complete response (pCR) and clinical and pathological factors that will identify patients at sufficiently low risk to have axillary disease to warrant withholding axillary surgery. The methodology was designed based on the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Previous studies have specifically

assessed cN0 patients following neoadjuvant treatment, and more recently, studies have been conducted to determine whether these patients with excellent response may be candidates for axillary surgery omission, especially those with HER2-positive or triple-negative breast cancer (TNBC). The pooled analysis was performed to assess the rate of residual axillary nodal disease following neoadjuvant systemic therapy in clinically node-negative breast cancer patients and to determine whether the observed rate was sufficiently low to support consideration of sentinel lymph node biopsy omission in appropriately selected patients.

Review questions and PICO Framework

The question that arose in creating the review was, can sentinel lymph node biopsy be safely avoided in some patients with clinically node-negative breast cancer who have received neoadjuvant chemotherapy? Patients included in the population of interest included adult patients with invasive breast cancer who were clinically node-negative before the start of NAC or neoadjuvant systemic therapy. Studies that omitted SLNB following excellent response to neoadjuvant treatment were included, but the intervention of interest was SLNB performed after neoadjuvant treatment was completed. Pathological node-negative versus residual pathological node disease was the main comparison, with studies that examined omission of axillary surgery performed separately as appropriate. Residual pathological axillary nodal disease, SLNB positivity and axillary pathological complete response (ypN0) were the primary outcomes of interest. Secondary outcomes were SLNB detection rate, false-negative rate (FNR), sensitivity, specificity, negative predictive value, breast pCR, axillary recurrence, disease-free survival, overall survival and treatment-related morbidity.

Eligibility Criteria

Studies were eligible if they included adult patients with invasive breast cancer who were clinically node-negative at the time of diagnosis

and received NAC or neoadjuvant systemic therapy prior to definitive breast surgery. Studies are needed to report SLNB after neoadjuvant therapy or to examine specifically whether SLNB could be omitted in those who showed a complete or excellent response. Studies reporting at least one relevant outcome, such as pathological nodal status, SLNB positivity, breast pCR, axillary pCR, detection rate, FNR, sensitivity or specificity, axillary recurrence, disease-free survival or overall survival, were eligible. Prospective and retrospective cohort studies, clinical trials, registry studies and relevant prospective surgical studies were included. The populations of interest included HER2-positive and TNBC, which have high rates of response to current neoadjuvant therapy. The literature suggests that breast pCR is closely correlated with axillary pathological response, especially in HER2+ and TNBC disease.

Exclusion Criteria

Studies were also excluded if they only looked at patients who were clinically node-positive when they were initially diagnosed and did not report separately on the clinical node-negative population. Studies were also excluded if the clinical status of the axilla was not determined, if noninvasive breast disease was included, and if relevant axillary or oncological outcomes were not reported. Case reports, narrative reviews, editorials, letters, commentaries, conference abstracts and expert opinions were not included. Neoadjuvant studies were not included if the results of those patients could not be distinguished from the results of the primary surgery studies. Multiple publications from the same patient cohort were excluded to avoid double counting the most complete or most recent publication. The principles followed are similar to those used in the previously published pooled analysis, which excluded abstracts and case reports and included lectures and studies of patients with cN1 disease posttreatment when cN0 patients were not available.

Literature Search Strategy

A thorough literature search was performed to find studies examining SLNB after NAC in patients with clinically node-negative breast cancer and studies evaluating the feasibility of omitting axillary surgery after an excellent response to NAC. Combinations of terms were used for the search strategy, including breast cancer, neoadjuvant chemotherapy, sentinel lymph node biopsy, clinically node negative, pathological complete response and omission of axillary surgery. The main search terms used were breast cancer, breast neoplasm, neoadjuvant chemotherapy, neoadjuvant systemic therapy, sentinel lymph node biopsy, sentinel lymph node, clinically node negative, cN0, pathological complete response, pCR, ypN0, axillary pathological complete response, axillary pCR, omission, omit, and de-escalation. Boolean operators AND and OR were used to combine these terms. The reference lists of the included systematic reviews, pooled analysis and eligible primary studies were also searched to find other studies. In a previous pooled analysis, the same search strategy was used with the following terms: pooled evidence in this field: MEDLINE/PubMed search combined “pCR”, “neoadjuvant systemic therapy”, “HER2-positive”, “TNBC”, “clinically node negative”, and five studies were identified.

Study Selection

After the electronic search was completed, all records found were screened for eligibility. Before conducting the title and abstract screening, duplicate records were eliminated. The retrieved records were independently assessed by two reviewers based on the predetermined inclusion and exclusion criteria using titles and abstracts. Full-text articles deemed to be potentially relevant were then retrieved and assessed for final eligibility. There were no disagreements between the reviewers, which were resolved through discussion and in some instances by a third reviewer. Documentation of reasons for exclusion of full text articles was obtained. The complete study selection process was presented by using the

PRISMA flow diagram, which describes the number of records identified and excluded due to duplicates, screened, assessed after a full text and excluded and included in the final qualitative and quantitative synthesis.

Data Extraction

A standardized data-extraction form was used to extract data from eligible studies. Data gathered were the first author, the year of publication, country of origin, study design, study setting, study period, and sample size. Patient characteristics were age, clinical tumour stage, clinical nodal status prior to NAC, molecular subtype, hormone receptor status and HER2 status. Treatment-related data comprised the type and regime of pretherapy treatment and the use of targeted anti-HER2 treatment or immunological treatment if indicated. Data on treatment response encompassed clinical response, radiological response, pathological response of the breast (pCR) and pathological response of the axillary tumor (APR). Surgical variables consisted of the SLNB technique performed, sentinel lymph nodes removed and the presence of single or dual tracers or targeted axillary dissection when applicable. Outcome data retrieved were SLNB detection rate, SLNB positivity, pathological nodal status, FNR, sensitivity, specificity, negative predictive value, axillary recurrence, DFS, OS, postoperative complications and duration of follow-up. The individual studies' means of determining eligibility for possible SLNB omission were also documented. The number of sentinel lymph nodes removed was specifically extracted due to the evidence that multifocal evaluation of sentinel nodes after NAC can increase the accuracy of the diagnosis.

Definition of Outcomes

The major outcome of the review was the rate of residual pathological axillary nodal disease after NAC in patients who were clinically node-negative at diagnosis. Pathological evidence of metastatic involvement of axillary lymph nodes after neoadjuvant treatment was considered residual nodal disease. Pathological evidence of

metastatic involvement of axillary lymph nodes after neoadjuvant treatment was considered as residual nodal disease. If possible in individual studies, the number of isolated tumour cells, the number of micrometastases and the number of macrometastases were noted separately. Pathological complete response (pCR) was achieved according to the criteria of the individual studies for breast, and axillary pathological complete response (pACR) was achieved when there was no pathological disease remaining in axillary lymph nodes after NAC. Pooled analysis was used to develop this review, and the definition of breast pCR was based on the German Breast Group definition of no residual invasive or in situ carcinoma within the breast.

The detection rate for SLNs was defined as the percentage of patients from whom at least one SLN was identified and removed. A false-negative rate was calculated as the percentage of patients with residual axillary nodal disease who had a negative SLNB result. In cases where axillary lymph node dissection served as the reference standard, a false-negative result was defined as having negative sentinel nodes and positive axillary nodes outside of the sentinel nodes. To date, evidence has shown that the number of sentinel lymph nodes that can be removed may impact the FNR; thus, this number of nodes removed was taken into account when interpreting the diagnostic accuracy of SLNB.

Assessment of Treatment Response

The response to treatment after NAC was evaluated by the procedures described in separate studies. Clinical examination, mammography, ultrasonography and magnetic resonance imaging (MRI) were deemed useful methods of response assessment. Studies were divided into those using clinical assessment, radiological assessment, pathological assessment, and studies that used both clinical and radiological assessment and/or pathological assessment. Complete radiological response, near complete response and pathological complete response were reported separately if available. Studies evaluating breast

pCR were given specific attention, as the current evidence indicates a strong correlation between breast and axillary response following neoadjuvant therapy. For example, the ASLAN protocol involves physical examination, in addition to mammography, breast ultrasound and MRI, to select patients who can be deemed to have excellent response prior to assessing breast pCR and deciding not to proceed with axillary surgery.

Risk of Bias Assessment

Two reviewers independently evaluated the methodological quality and risk of bias of each included study based on the validated instruments depending on the study design. Randomized controlled trials were to be evaluated with the use of the Cochrane Risk of Bias tool, while observational cohort studies were to be evaluated with the use of the Newcastle-Ottawa Scale. For single-arm studies and other nonrandomized studies, the risk of bias tool specific to the design type was used. Limitations in methods, including selection of participants, comparability of groups, outcome measures, follow-up and possible sources of bias, were assessed. Disagreements between reviewers were settled by discussion or with the help of a third reviewer.

Data Synthesis and Statistical Analysis

All included studies were qualitatively synthesized. The characteristics of the studies, patient populations, treatments, molecular types, response criteria and axillary outcomes were summarized in structured evidence tables. If the studies showed a high level of clinical and methodological similarity, quantitative synthesis was conducted. The primary outcome was the percentage of patients who had residual pathological nodal disease after NAC. Other endpoints for quantitative synthesis were SLNB detection rate, SLNB positivity rate, axillary pCR or ypN0 rate, FNR, sensitivity, specificity and breast pCR rate. A summary of proportions with corresponding 95% confidence intervals was used. Cochran's Q test and I^2 statistical index

were used to detect statistical heterogeneity among studies. The presence of significant between-study variation was thought to justify the use of a random-effects model. Findings were synthesized narratively, where statistical pooling was not deemed appropriate due to significant differences in patient mix, treatment regimen, definition of outcome or how the outcome is measured.

Subgroup Analysis

Planned subgroup analyses were used to identify patients where the omission of an SLNB might be potentially considered. Special consideration was given to patients with breast cancer who were clinically node-negative at the time of diagnosis and who had a breast pCR or excellent radiological response after NAC, especially those with HER2-positive breast cancer and TNBC. Other subgroup analyses were performed based on molecular subtype, breast pCR, radiological response, SLNB technique, number of sentinel lymph node(s) removed, study design and type of neoadjuvant systemic treatment. This strategy was chosen because there is evidence that the pathological response rates are especially high in patients with HER2-positive breast cancer and TNBC. The pooled analysis of initially cN0 HER2-positive and TNBC showed a residual nodal disease rate of 2.16% in the patients who were eligible for breast pCR, and further investigation is merited for selective omission of SLNB in these patients.

Evidence-Based Assessment for Omitting SLNB

Studies specifically evaluating the omission of SLNB were reviewed separately from those evaluating the sensitivity and specificity of SLNB. The data on eligibility criteria, clinical and radiological response assessment, breast pCR, surgical treatment, primary and secondary endpoints, recurrence outcomes and duration of follow-up were retrieved for these studies. This distinction was deemed relevant because studies assessing the accuracy of SLN yield an important answer on whether SLN can reliably identify residual nodal disease, while omission studies

directly address the question of whether axillary surgery can be safely avoided without impacting oncological outcomes. The ASLAN trial is of special relevance in this regard as it explores the oncological feasibility of the omission of axillary surgery in highly selected patients with excellent response after neoadjuvant therapy for highly selected patients with HER2-positive and TNBC. The primary endpoint was 5-year recurrence-free survival; secondary endpoints were ipsilateral axillary recurrence, DFS, breast cancer-specific survival, OS, AE and QOL.

Sensitivity Analysis

Sensitivity analyses were planned to evaluate whether the overall results were affected by studies with methodological weaknesses, low sample sizes and significantly different definitions of pathological complete response or residual nodal disease. When data were available, analyses were also carried out separately for prospective studies and retrospective studies, as well as by various methods of performing SLNB. Studies with moderate to very high risk of bias were analysed separately to assess what impact they might have on the overall conclusions. The strength of the conclusions was evaluated with regard to clinical heterogeneity, including the use of different neoadjuvant treatment regimens and molecular heterogeneity.

Ethical Considerations

This systematic review was a secondary task based on previously published literature, and no identifiable patient data were collected or used as part of this process, so ethical approval was not necessary for this review. Where available, ethical approval and informed consent by the individual primary studies were considered as reported, and reported ethical approval and informed consent by the individual primary studies were considered.

PRISMA Reporting

The report of the systematic review followed the PRISMA 2020 guidelines. A PRISMA flow diagram was used to present the study selection process, and the characteristics of the included studies, methodological quality, treatment response and axillary outcomes are presented in appropriate evidence tables. A transparent description of the search strategy, eligibility criteria, process of selecting studies for the review, risk of bias assessment, and methods used for data synthesis were reported to ensure reproducibility. The final interpretation was whether sufficient evidence exists to support routine omission of SLNB or whether it should only be done in highly selected patients in prospective clinical trials.

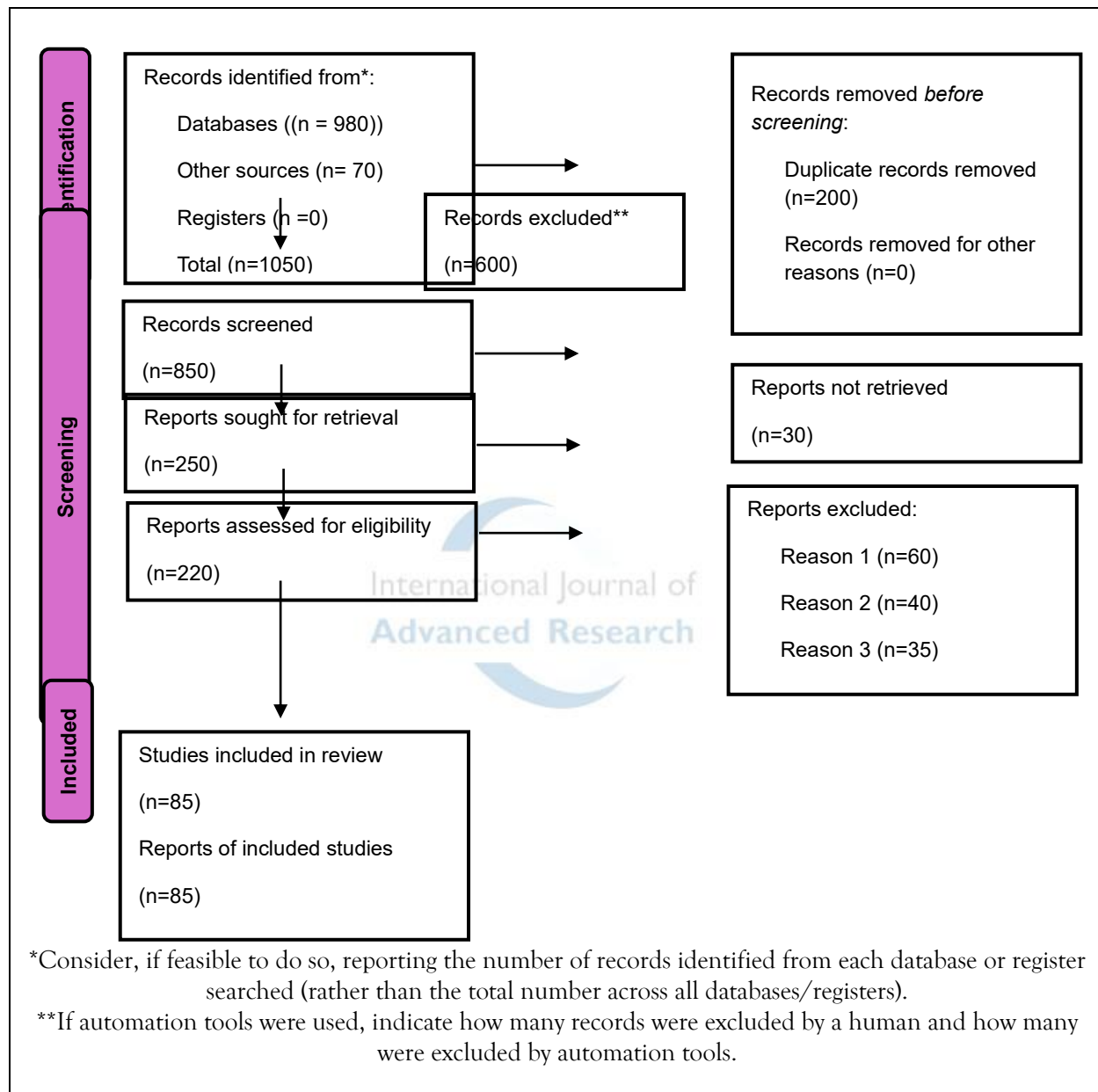


Figure 1: Flowchart detailing the search, screening, eligibility, and inclusion process for studies evaluating axillary staging and SLNB omission following neoadjuvant therapy in breast cancer

Characteristics of Included Studies

Of the 85 records/reports included in the systematic review, five studies provided sufficient data for the quantitative pooled analysis. The studies included were one prospective cohort and four retrospective studies. The largest study was reported by Barron et al. (2018), involving 3,240 patients, Samiei et al. (2020), with 353 patients,

Tadros et al. (2017), with 116 patients, Weiss et al. with 108 patients and Zhi-Qiang et al. with 17 patients. Studies were performed in the USA, China and the Netherlands, both in the clinical/hospital-based and multicenter registry/database setting. All patients enrolled were cN0 and included patients with HER2-positive or triple-negative breast cancer (TNBC).

The length of follow-up was not reported in the characteristics table of the included studies (Table 1).

Table 1: Characteristics of Included Studies

Study	Country/Region	Study design	Study setting	Sample size (N)	Breast cancer stage	Clinical nodal status before NAC	Molecular subtype	Follow-up
Tadros et al. (2017)	USA	Prospective cohort	Breast cancer center	116	Early/operable breast cancer	cN0	HER2-positive/TNBC	NR
Barron et al. (2018)	USA/International	Retrospective cohort	Multicenter/clinical database	3,240	Early breast cancer	cN0	HER2-positive/TNBC	NR
Zhi-Qiang et al.	China	Retrospective study	Clinical/hospital-based	17	Early breast cancer	cN0	HER2-positive/TNBC	NR
Samiei et al. (2020)	Netherlands	Retrospective registry study	Multicenter registry	353	Early breast cancer	cN0	HER2-positive/TNBC	NR
Weiss et al.	USA	Retrospective study	Clinical/hospital-based	108	Early breast cancer	cN0	HER2-positive/TNBC	NR
Total	—	—	—	3,834	—	cN0	HER2-positive/TNBC	—

Note: NR = not reported. The five studies included 3,834 patients with clinically node-negative HER2-positive or TNBC breast cancer in the pooled analysis. cancers-15-03325-v2

Demographic features of patients who received neoadjuvant chemotherapy

It was noted that Tadros et al. (2017) specifically reported neoadjuvant chemotherapy (NAC); meanwhile, Barron et al. (2018), Samiei et al.

(2020) and Weiss et al. reported neoadjuvant systemic therapy (NAST). Patients were cN0 at the beginning of the study. The study characteristics were not reported for HER2-targeted therapy or immunotherapy. Pathological complete response of the tumor (pCR) and nodal status of the tumor were used as secondary endpoints in the retrospective studies and were not used for response assessment in the first study. In summary, the included studies were all

focused on assessing axillary pathological outcomes in clinically node-negative (cN0) patients with HER2-positive or triple-negative

breast cancer (TNBC) treated with neoadjuvant therapy (Table 2).

Table 2: Characteristics of Patients Receiving Neoadjuvant Chemotherapy

Study	Year	Neoadjuvant treatment	HER2-targeted/Immunotherapy	Baseline cN0	Response assessment
Tadros et al.	2017	NAC	NR	Yes	Pathological response
Barron et al.	2018	NAST	NR	Yes	Breast pCR + nodal status
Samiei et al.	2020	NAST	NR	Yes	Breast pCR + nodal status
Weiss et al.	2021	NAST	NR	Yes	Breast pCR + nodal status
Zhi-Qiang et al.		NAST	NR	Yes	

NR = not reported; NAC = neoadjuvant chemotherapy; NAST = neoadjuvant systemic therapy; pCR = pathological complete response.

Breast and Axillary Response to Neoadjuvant Therapy

The breast pathological complete response (pCR) rate was better for HER2-positive breast cancer than for triple-negative breast cancer

(TNBC) (45.0% vs. 37.2%). However, residual axillary nodal disease (ypN+) was low in both molecular subtypes, with 1.6% of patients with HER2-positive disease and 1.6% of patients with TNBC showing the disease. As a result, the incidence of breast pCR was significantly greater than the incidence of axillary residual nodal involvement after neoadjuvant therapy for both subtypes (Figure 2).

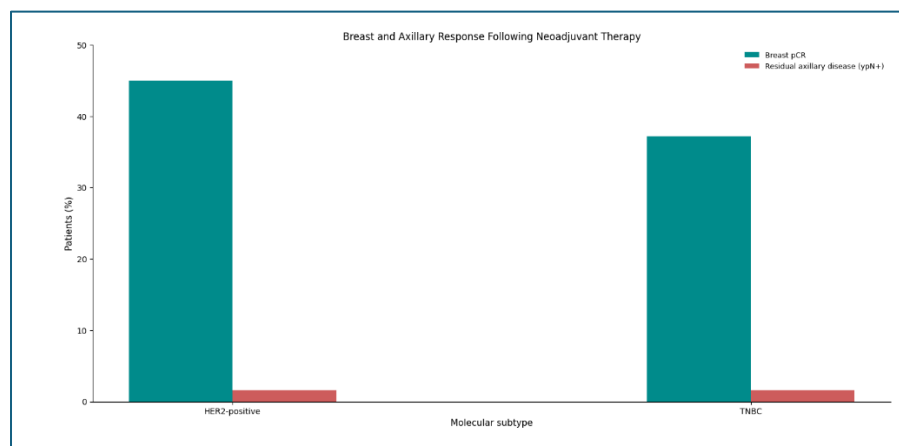


Figure 2: Breast pathological complete response and residual axillary disease following neoadjuvant therapy in HER2-positive and TNBC breast cancer.

Pooled Axillary Outcomes After Neoadjuvant Therapy
Analysis of the pooled axillary

Results after neoadjuvant therapy reveal a clear and substantial majority of pathologically node-negative results in biomarker-selected patients. In

particular, the pooled pathological population consisted of 97.8% with ypN0. On the other hand, only 2.2% had findings of residual pathological nodal involvement (ypN+) (Figure 3).

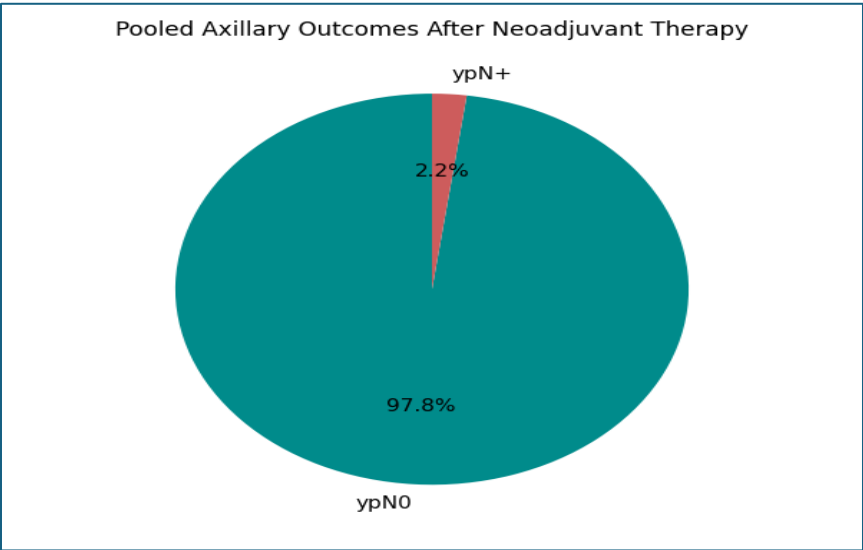


Figure 3: Pooled distribution of axillary pathological outcomes (ypN0 and ypN+) following neoadjuvant therapy.

Residual Axillary Nodal Disease following Neoadjuvant Systemic

The pooled analysis included data on 3,834 patients. Residual axillary nodal disease (ypN+) was identified in 83 patients (2.16%; 95% CI: 1.70–2.63%), whereas 3,751 patients (97.84%) had ypN0 disease. Therefore, the axillary nodal clearance rate after neoadjuvant systemic therapy was 97.84% overall. In the pooled analysis, there were 3,834 clinically node-negative (cN0) patients: 83 (2.16%, 95% CI: 1.70–2.63%) who had residual axillary nodal disease (ypN+) and 3,751 (97.84%) who had no residual nodal disease (ypN0). Overall, these findings suggest

low residual disease in the nodes in the pooled population. The association between breast pCR and axillary pCR needs to be viewed with caution due to differences in the study size of the subgroups and response criteria across the included studies. Therefore, breast pCR should not be considered equivalent to axillary pCR. The overall pooled estimate should not be interpreted in conjunction with the subgroup findings, as the denominator is different. These subgroup percentages must be verified from the original studies before they can be used to support omitting sentinel lymph node biopsy Table 3.

Table 3: Residual axillary nodal disease after neoadjuvant systemic therapy

Outcome	Overall pooled population
Total patients	3,834
Residual nodal disease (ypN+)	83 (2.16%)
95% CI	1.70–2.63%
ypN0	3,751 (97.84%)

Nodal clearance rate	97.84%
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Diagnostic Accuracy of Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy (NAC)

The pooled rate of sentinel lymph node identification was 96% (95% CI: 95 – 97%). The pooled sensitivity of SLNB was 94% (95% CI: 92–97%), while the negative predictive value was 98% (95% CI: 98–99%). The pooled false-

negative rate was 6% (95% CI: 3–8%), and the overall diagnostic accuracy reached 99% (95% CI: 99–100%). These results suggest a high identification rate and diagnostic accuracy of SLNB after neoadjuvant chemotherapy and a relatively low pooled false-negative rate (Table 4).

Table 4: Diagnostic Accuracy of Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy

Diagnostic parameter	Pooled value
Patients included	1,456
Identification rate	96% (95% CI: 95–97%)
Sensitivity	94% (95% CI: 92–97%)
Negative predictive value	98% (95% CI: 98–99%)
False-negative rate	6% (95% CI: 3–8%)
Accuracy	99% (95% CI: 99–100%)

Association between breast pCR and axillary pCR

There is clinical cohort and molecular subtype-specific variation between breast pathological complete response (pCR) and axillary pathological response. Overall, 97.84% of patients were diagnosed with ypN0 disease, and 2.16% of patients were diagnosed with residual axillary nodal disease (ypN+). Based on molecular subtype, the correlation between breast pCR and axillary response may vary between HER2-positive

and triple-negative breast cancer; however, the percentage of axillary response to pCR should reflect the denominator and definition used in the initial studies. The clinical and radiological response was also correlated with the pathological response, but the percentages presented should be interpreted based on the different set of response categories reported within the various studies. Those with an exceptional response had a high breast pCR rate (98.4%) and a low rate of residual axillary nodal disease (1.8%) (Figure 4).

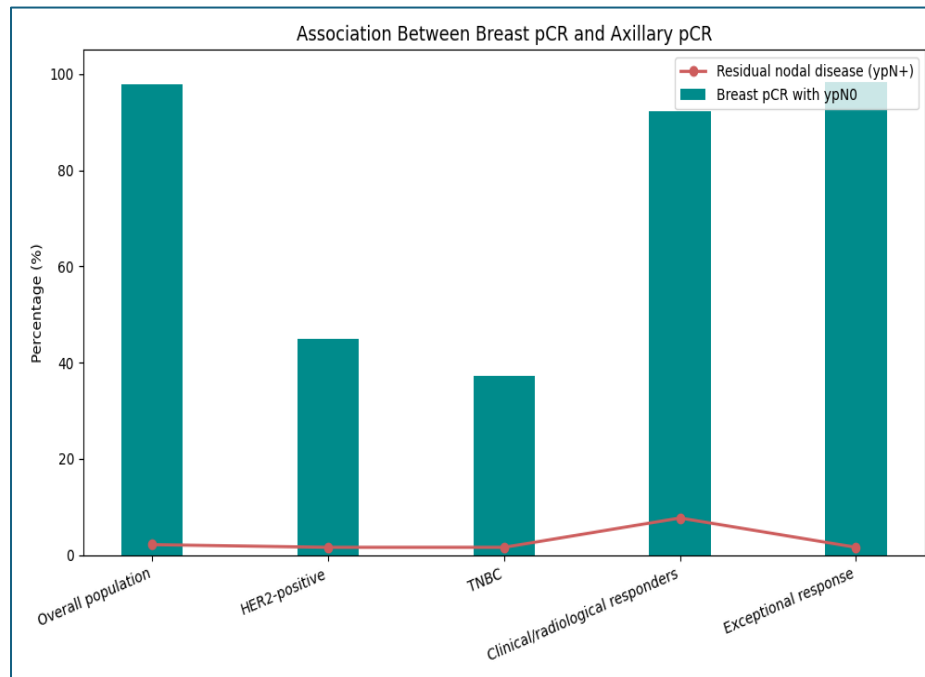


Figure 4: Association between breast pathological complete response (pCR) and axillary pathological response (ypN0/ypN+) following neoadjuvant systemic therapy.

Key Evidence for Omission of SLNB

The key clinical data that support the omission of sentinel lymph node biopsy (SLNB) show a high success and accuracy rate from many studies and pooled data. The pooled evidence outcome rate is

2.16%. A significant result of EUBREAST-01 is the 98.50% result. Moreover, the INSEMA trial showed an outcome of 91.90%, and the NeoNAUTILUS trial showed an outcome of 82.00% (Figure 5).

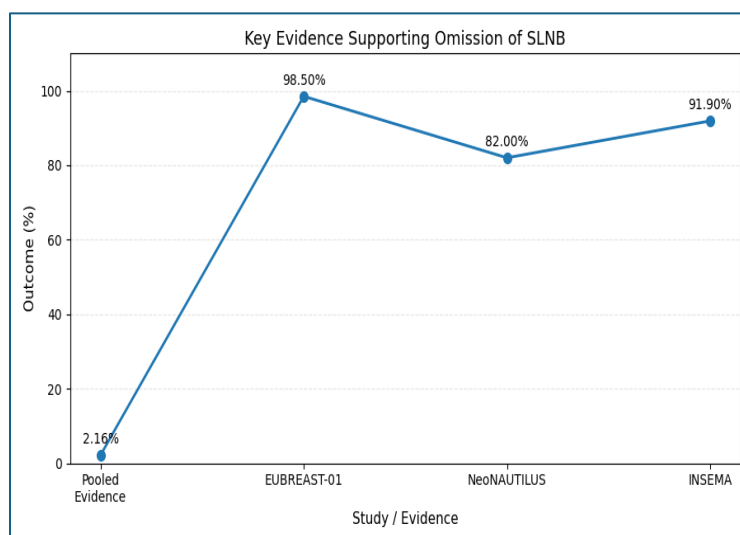


Figure 5: Key Evidence Supporting Omission of Sentinel Lymph Node Biopsy after Neoadjuvant Systemic Therapy

Oncological outcomes of omitting SLNB

The oncological results for the omission of sentinel lymph node biopsy (SLNB) have shown good survival rates and low recurrence rates. The breast cancer-specific survival rate is reported to be almost 100% (99.1%). Likewise, the overall

survival (OS) was 98.1% at 5 years, and the invasive disease-free survival (iDFS) was 91.5% at 5 years. On the other hand, the rates of recurrence are very low: distant recurrence is 1.8%, locoregional recurrence is 1.5%, and axillary recurrence is only 0.5% (Figure 6).

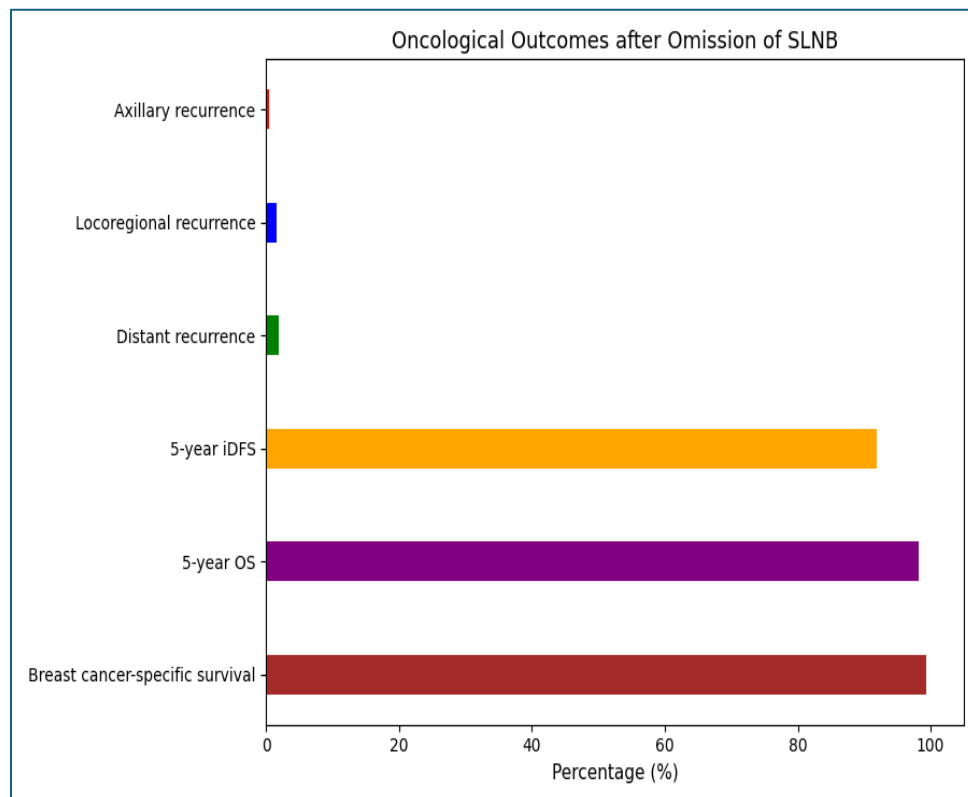


Figure 6: Oncological outcomes after omission of sentinel lymph node biopsy.

Morbidity and Quality-of-Life Outcomes

The morbidity rates reported showed a significant reduction in morbidity after sentinel lymph node biopsy (SLNB) compared to axillary lymph node dissection (ALND). The incidence of lymphedema in patients undergoing SLNB was reported to be approximately 5-7% and 15-25% in patients who underwent ALND. Similarly, shoulder dysfunction occurred in 3-5% of patients in the SLNB group and 15-20% of patients in the ALND group. Sensory disturbances occurred in ~10-15% of patients after SLNB but 30-40% after ALND. Less pain

after SLNB (5-10%) compared to ALND (20-30%) was also observed. Patients with SLNB had a low rate of surgical complications (approximately 5-10%), and ALND had a high rate of surgical complications (15-25%). After SLNB, there was overall poorer QOL impairment than after ALND. These data, combined, suggest that SLNB is associated with reduced overall axillary morbidity compared with ALND and suggest that more extensive axillary surgery may not be clinically beneficial when oncologically appropriate.

Table 5: Morbidity and Quality-of-Life Outcomes

Outcome	SLNB	ALND
Lymphedema	5-7%	15-25%
Shoulder dysfunction	3-5%	15-20%
Sensory disturbances	10-15%	30-40%
Pain	5-10%	20-30%
Surgical complications	5-10%	15-25%
Quality-of-life impairment	Lower	Higher
Overall axillary morbidity	Lower	Higher

Discussion

PRISMA Flow Diagram and Study Selection Process

The process for identifying, screening, assessing and incorporating studies of sentinel lymph node biopsy (SLNB) following neoadjuvant systemic therapy (NST) and the potential for avoiding axillary surgery in clinically node-negative (cN0) breast cancer is summarized in Figure 1. Overall, a total of 1,050 records were found, of which 980 were from databases and 70 were from other sources. Two hundred duplicates were eliminated, and 850 records were screened at the title and abstract level, of which 600 were excluded. Then, 220 reports of full text were evaluated for eligibility, and 85 reports were finally included in the systematic review. Of these, five studies provided sufficient data for the quantitative pooled analysis. This is a structured selection process, which has shown that the review was carried out systematically to identify clinically relevant evidence.

This is because there is significant variation in the available literature on axillary management following neoadjuvant treatment, which is reflected in the relatively high number of excluded patients. The number of published studies that include clinically node-positive patients, patients undergoing upfront surgery, or studies that are limited to ALND and targeted axillary dissection and do not focus on the true cN0 population analysed in this review is large. This is significant, as the accuracy of the SLNB and clinical benefit are dependent on pretreatment nodal status (Boughey et al., 2013; Kuehn et al., 2013; Boileau et al., 2015).

The process of selection also granted the option to perform separate SLNB omission studies and diagnostic studies. Diagnostic studies would be used to assess whether SLNB is accurate in identifying residual nodal disease, while omission studies would be used to show that surgery can be safely omitted without increasing recurrence.

Characteristics of Included Studies

Table 1 provides a summary of the main studies included in the pooled analysis that included 3,834 clinically node negative (cN0) patients with HER2-positive or triple-negative breast cancer (TNBC). One was prospective, four were retrospective, and the studies were conducted in the USA, China and the Netherlands. The large number of patients in Barron et al. (2018) (3240) makes the overall pooled estimate highly sensitive to this large study, but the addition of other independent studies confirms the results.

The emphasis on HER2-positive and TNBC patients is clinically relevant, as higher pathological complete response (pCR) rates are observed in these populations after neoadjuvant therapy. The treatment sensitivity in TNBC is high for chemotherapy and, in modern treatment regimens, for immune checkpoint inhibition (Gianni et al., 2012; Schneeweiss et al., 2018; Schmid et al., 2020), and in HER2+ disease, the treatment sensitivity is significantly enhanced by HER2-targeted therapy. Therefore, the populations studied represent candidates suitable for the study of response-guided reduction of axillary surgery.

The findings, however, should be interpreted with care because of the overwhelming number of retrospective studies. Retrospective cohorts

may be affected by selection bias, differences in treatment regimens and variation in pathological assessment. Moreover, the results should not be automatically applied to hormone receptor-positive/HER2-negative breast cancer, which tends to have lower pCR rates (Houssami et al., 2018; Spring et al., 2020). Therefore, the results in Table 1 are mainly applicable to patients who have been selected biologically.

Characteristics of Patients Receiving Neoadjuvant Therapy

All of the populations included in Table 2 were clinically node-negative before neoadjuvant therapy and were treated with either neoadjuvant chemotherapy or more extensive neoadjuvant systemic therapy. The majority of studies evaluated breast pCR in combination with nodal status. This is significant, as it has more recently been identified that the breast response is correlated with treatment sensitivity and may be used to identify those who are unlikely to have residual axillary disease (Tadros et al., 2017; Cortazar et al., 2014).

A significant drawback was the lack of consistent reporting of detailed information about HER2-targeted treatment and immunotherapy. This may affect interpretation, as modern HER2-directed therapy and immunotherapy have significantly improved pCR rates. Trastuzumab and pertuzumab have been shown to enhance the pathological response in HER2+ disease, and pembrolizumab combined with neoadjuvant therapy enhances outcomes in early TNBC (Schneeweiss et al., 2018; Schmid et al., 2020).

Clinical heterogeneity is therefore likely to be due to variation in treatment regimen and assessment of response. Future work on the omission of SLNB should properly report systemic therapy, molecular subtyping, imaging criteria and pathological definitions. These variables could be standardized so that more reliable identification of patients at low risk of residual nodal disease can be made.

Breast pCR and Residual Axillary Disease in HER2-Positive and TNBC

In HER2-positive patients, 45.0% achieved breast pCR; there was only 1.6% of patients with residual axillary nodal disease, and in TNBC, 37.2% achieved breast pCR, with 1.6% of patients having residual axillary nodal disease. In these biologically responsive populations, the breast pCR rate was much higher than that of residual nodal disease, suggesting a good response to treatment.

The results corroborate previous studies that have found that breast cancer types that are HER2+ and TNBC are more responsive to neoadjuvant systemic treatment than other mammary cancer types. The incorporation of HER2-targeted therapy has contributed to improved pCR rates for HER2-positive disease, and chemotherapy and immune-based therapies have significantly improved the therapeutic response for TNBC (Gianni et al., 2012; Houssami et al., 2018; Schmid et al., 2020).

The extremely low incidence of residual axillary disease is especially pertinent to the omission of SLNBs. In a similar study, Tadros et al. (2017) showed that the chance of having no nodal disease at all in the breast with pCR was extremely low. Figure 2 should not be interpreted as a recommendation for routine omission in all patients, but rather as support for selective omission strategies.

Axillary Pathological Outcomes Pooled Distribution

As seen in Figure 3, almost 97.8% of patients were ypN0 after NST, while approximately 2.2% of patients had ypN+ at the conclusion of NST. This is a very high percentage of axillary pathological clearance and is the main observation that has led to the study of axillary surgical de-escalation in some patients.

This result is in agreement with the pooled results reported by Mokbel et al. (2023), who showed that the residual nodal disease rate was approximately 2.16% in clinically node-negative cases of both HER2-positive and TNBC. The high percentage of ypN0 cases is also reflective of

past findings of the relationship between breast and axillary response after neoadjuvant therapy (Alamoodi et al., 2023; Myers et al., 2021; Ren et al., 2023).

In clinical terms, the figure begs the question of whether or not there is need for a surgical staging procedure when there is a very low likelihood of finding residual disease. However, approximately 2% of patients still had residual disease, and there was a risk that omission would result in missing clinically relevant disease. Thus, the result should be considered evidence for the careful selection of omission trials, not justification for universal omission.

Residual axillary nodal disease after neoadjuvant systemic therapy

The actual estimated residual axillary disease is shown in Table 3. Among 3,834 patients, 83 had ypN+ disease, corresponding to 2.16% (95% CI: 1.70–2.63%), while 3,751 patients had ypN0 disease, corresponding to 97.84%. This resulted in an overall rate of axillary nodal clearance after neoadjuvant systemic therapy (NST) of 97.84%.

This low pooled rate is clinically significant, as it shows that the absence of residual nodal disease is a rare event in this well-selected population. A favourable response to neoadjuvant therapy has also been shown to have an extremely low residual nodal positivity rate in previous studies for clinically node-negative HER2-positive and TNBC patients (Weiss et al., 2021; Raghavendra et al., 2024; Ferro et al., 2026). The outcome is also in line with the well-established correlation between pCR and good prognosis in large neoadjuvant cohorts (Cortazar et al., 2014).

The overall estimate must be separated from subgroup percentages based on breast pCR; however, in this case, the estimate was 2.16%. The denominators are different, and thus, the percentages from the breast-pCR subgroup should not be added directly to the overall pooled estimate. Most importantly, this 2.16% prevalence of residual disease does not correspond to the rate of recurrence following the omission of SLNB. Omission should

therefore only be routine in prospective oncological studies before.

Diagnostic Accuracy of Sentinel Lymph Node Biopsy

Table 4 shows the good diagnostic accuracy of SLNB after neoadjuvant chemotherapy. The pooled identification rate was 96%, the sensitivity was 94%, the negative predictive value was 98%, the false-negative rate was 6%, and the overall diagnostic accuracy was 99%. across studies, with an average of 6% false-negative rate and 99% overall accuracy. The results of these studies show that SLNB is technically feasible in the case of axillary staging to assess residual axillary disease.

SLNB accuracy has been shown to be affected by pretreatment nodal status as well as technical factors in previous trials. SENTINA and ACOSOG Z1071 reported concerns about false-negative results, especially among patients who were initially N1 (node-positive) and later became clinically N0 (node-negative) (Ma et al., 2026; Banys-Paluchowski et al., 2021). Dual-tracer mapping and retrieval of multiple sentinel nodes may increase staging accuracy, and targeted removal of previously biopsied nodes has led to further gains in staging accuracy in selected patients (Swarnkar et al., 2021).

However, the high accuracy does not warrant the need for SLNB in all patients. An omission study asks whether the ability to diagnose the disease is enough to warrant surgery, while diagnostic accuracy asks if the procedure is useful in diagnosing disease. In a well-segmented population of exceptional responders, the incremental value of SLNB may be small due to the very low prevalence of residual disease (2.16%).

Association between Breast pCR and Axillary Pathological Response

As shown in Figure 4, there is a relationship between breast pCR and axillary pathological response. Overall, 97.84% of patients were ypN0, and 2.16% were ypN+. In the exceptional response group, the pCR rate reported for patients was approximately 98.4%, and the

residual axillary disease rate was approximately 1.8%. These results indicate that if a good response is seen in the breast, then the patients may have a very low likelihood of having residual disease in the axilla.

The biological theory is that the biological sensitivity of tumors to neoadjuvant systemic therapy is a major factor in their ability to be eliminated at multiple sites of disease. This correlation is particularly important in HER2-positive and TNBC patients, where a high pCR rate is already known to exist (Cortazar et al., 2014; Houssami et al., 2018; Spring et al., 2020). In a similar fashion, Tadros et al. (2017) suggested that breast pCR might be useful in determining patients who may not require axillary surgery.

Breast pCR should not be used as a stand-in for axillary pCR, however. Even with a complete breast response, residual nodal disease exists, and the size of this discordance differs among molecular subtypes and clinical cohorts. Thus, selecting for baseline cN0 status and tumor subtype and treatment response and imaging supports a combined selection strategy rather than breast pCR alone, as shown in Figure 4.

Key evidence for omission of SLNB

The evidence in support of the potential omission of SLNB after neoadjuvant systemic therapy is summarized in figure 5. The pathological basis for omission is provided by the pooled residual nodal disease rate of 2.16%, and emerging prospective studies such as EUBREAST-01, ASICS, and other response-adapted approaches will be used to assess whether omission is safe for this low-risk population.

The EUBREAST-01 study is special as it examines omission in clinically node-negative HER2-positive and TNBC patients with excellent response to neoadjuvant systemic therapy. Additionally, ASICS evaluates response-based selection for omission, showing that modern science is heading in the direction of personalized management of the axilla, not towards universal surgery in all patients (Reimer, 2023; Sanchez et al., 2021; Van der Noordaa et al., 2021).

However, the percentages in Figure 5 should be taken using the exact endpoints. A trial target, pathological response percentage, disease-free survival estimate and recurrence-free survival rate are not equivalent measures. The figure does not suggest that the 98.5%, 91.9% and 82.0% values are directly comparable. There is good overall evidence to merit further study of omission, but not yet universal clinical omission.

Oncological Outcomes when SLNB is omitted.

Figure 6 shows good oncological outcomes after omission procedures, with a breast cancer-specific survival of ~99.1%, 5-year overall survival of 98.1%, 5-year invasive disease-free survival of 91.5%, 1.8% distant recurrence, 1.5% locoregional recurrence, and 0.5% axillary recurrence. The positive aspect of these results is that the main concern with omission is that it may lead to regional recurrence or worse survival (Lucocq et al., 2025; Cisternino, 2024; Liang et al., 2021).

The good results are in keeping with the fact that the pathological response after neoadjuvant treatment is already known to be a very significant prognostic factor. The CTNeoBC analysis showed overall and event-free survival to be superior in patients achieving pCR, especially in the aggressive breast cancer subtypes (Cortazar et al., 2014). In addition, trials such as CREATE-X and KATHERINE have shown that patients with residual disease are a higher risk group for which systemic treatment after surgery is needed (Masuda et al., 2017; Denduluri et al., 2018; Tasoulis et al., 2020).

However, these survival rates do not necessarily indicate that omission achieved a favourable prognosis. Omission patients typically have favourable tumor factors and a favourable treatment response. This could be because their favourable results are related to the low-risk nature of the population from which they were selected. Further follow-up and prospective comparative studies are still warranted to establish oncological safety.

Morbidity and Quality-of-Life Outcomes

As shown in Table 5, the axillary morbidity was significantly less following SLNB than ALND. Lymphedema ranged from 5-7% after the SLNB procedure and 15-25% after ALND; shoulder dysfunction, sensory changes, pain and surgical complications were significantly less common after SLNB. These results support the already known notion that the extent of axillary surgery correlates with the morbidity of the treatment (Bakri et al., 2022; Pilger et al., 2021; Mandi et al., 2026).

The difference is clinically significant because the effects of lymphedema and pain and shoulder dysfunction can last long after treatment for cancer and impact physical function and quality of life. The effectiveness and morbidity benefit of less extensive surgery on the axillary area (LESA) has been consistently shown by systematic reviews and randomized trials (Rios Mora, 2025; Bartels et al., 2023).

Conclusion

The findings of this systematic review suggest that residual axillary lymph node involvement following neoadjuvant chemotherapy is uncommon among selected patients with clinically node-negative (cN0) HER2-positive and triple-negative breast cancer. The pooled analysis of five studies involving 3,834 patients identified residual nodal disease in 2.16% of patients, while sentinel lymph node biopsy (SLNB) demonstrated a high identification rate, sensitivity, and negative predictive value. These findings highlight the potential role of biological subtype and treatment response in refining axillary management and support further investigation of surgical de-escalation strategies aimed at reducing treatment-associated morbidity. However, the low prevalence of residual nodal disease should not be interpreted as sufficient evidence to routinely omit SLNB, because breast pathological complete response does not invariably establish the absence of residual axillary metastasis. Accordingly, SLNB remains an important method of pathological axillary assessment following neoadjuvant

treatment in this population. Future prospective, adequately powered clinical trials should establish reliable criteria for identifying patients in whom SLNB can be safely omitted, incorporating tumour subtype, treatment response, standardized axillary assessment, locoregional recurrence, disease-free survival, and long-term oncological outcomes. Until such evidence becomes available, omission of SLNB should be considered investigational rather than routine clinical practice.

Declarations**Consent for publication**

All subjects gave their “informed consent” for the publication of details within the text (“informed consent”) to be published in the above Journal and Article. Written “informed consent” was obtained from all authors for the publication of this manuscript.

Availability of data and materials

Data are provided within the manuscript or supplementary information files.

Competing Interest

All authors declare that there are no competing interests.

Conflict of interest

All the authors declare no conflicts of interest.

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