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Axillary surgery in early breast cancer: real-world analysis of the INSEMA-trial at three certified university breast cancer centers in Germany regarding the omission of sentinel lymph node biopsy

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ABSTRACT

Background: Recent trials such as INSEMA and SOUND have demonstrated the oncological safety of omitting sentinel lymph node biopsy in selected patients with hormone receptor-positive, HER2-negative early breast cancer. However, the implications for adjuvant treatment decisions in routine clinical practice remain unclear.
Methods: We conducted a retrospective multicenter cohort study from university breast cancer centers, analyzing 867 patients diagnosed between 2020 and 2024 who met INSEMA criteria: cT1, G1-2, age ≥50 years, clinically node-negative, undergoing breast-conserving surgery. We evaluated the incidence of pathologically positive lymph nodes, frequency of postoperative upgrades in tumor stage or grading, and potential impact on adjuvant therapy decisions, including indications for CDK4/6 inhibitors, secondary axillary surgery or radiation.
Results: Sentinel lymph node biopsy revealed occult lymph node metastases in 14.3 % (n = 124) of patients, with a false-negative rate of 10.5 % when micrometastases and isolated tumor cells were excluded. In 11.6 % of cases, nodal positivity led to relevant therapeutic changes, including chemotherapy, axillary radiation, or potential adjuvant CDK4/6 inhibitor therapy. Moreover, 18.8 % of patients would have required secondary axillary surgery due to postoperative upgrades in tumor characteristics. The number needed to operate to prevent one invasive recurrence with CDK4/6 inhibitors varies significantly based on age and clinical tumor size, ranging from 1:333 (maximum) to 1:111 (minimum).
Conclusion: While omission of sentinel lymph node biopsy appears safe in selected patients, our real-world data suggest that axillary staging retains clinical relevance for guiding personalized treatment, unless other prognostic tests like gene expression profiles are used.

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1. Introduction

Management of the axilla in early-stage breast cancer has evolved significantly in recent years, driven by evidence suggesting that extensive axillary surgery can be safely de-escalated in select patient populations without compromising oncological outcomes [1–3]. Recently, not only axillary lymph node dissection (ALND), but also the less invasive standard of care, sentinel lymph node biopsy (SLNB) for clinically unsuspicious axillary lymph nodes, has experienced a de-escalation. Two landmark trials, Intergroup-Sentinel-Mamma (INSEMA) and Sentinel node vs. Observation after axillary UltraSouND (SOUND), have contributed pivotal data supporting this shift. Several other studies are currently investigating a complete de-escalation of axillary surgery (Table A1).

The INSEMA trial was a large, multicenter, randomized phase III study evaluating the omission of SLNB in patients with early breast cancer (eBC [cT1–T2, clinically and sonographically node-negative, and undergoing breast-conserving surgery]). The study demonstrated that omitting SLNB in these patients did not lead to inferior disease-free survival (DFS), but rather reduced surgical morbidity and improved quality of life (QoL) [4].

Similarly, the SOUND trial enrolled patients with small (cT1) invasive breast cancer who were both clinically and sonographically node-negative (cN0), comparing outcomes between patients undergoing standard SLNB and those with axillary observation alone. The results supported the safety of omitting SLNB in this low-risk group, further bolstering the case for less invasive axillary staging in appropriate candidates [5].

Ultimately, the investigators of both studies concluded that foregoing SLNB is oncologically safe in a patient population ≥50 years of age with hormone receptor positive (HR+) Her2neu negative (HER2−) breast cancer of stage cT1, G1-2 and no suspicious lymph nodes in clinical and sonographical examination. Based on the evidence presented, the American Society of Clinical Oncology (ASCO), the AGO Breast Committee (German Gynecological Oncology Group, AGO) and the German national S3 guideline recommend the safe omission of SLNB in this well-defined patient population [6–9].

However, it is also important to consider that knowledge of lymph node involvement may have a significant impact on the patient's adjuvant therapy. A potential treatment recommendation, namely the use of the CDK4/6 inhibitor (CDK4/6i) ribociclib in all patients with HR + HER2− eBC with lymph node involvement, could be withheld from patients if SLNB is not performed [10]. Real-world analyses from Germany estimated that 33–43 % of all patients in this cohort are potential candidates for ribociclib [11,12]. It is noteworthy that ribociclib has only received approval in the United States since September 2024 and in the European Union since November 2024, thereby not be taken into consideration in the INSEMA and SOUND trials, whose primary completion dates were in 2024 and 2017, respectively. The indication for radiotherapy of the lymphatic drainage channels or adjuvant chemotherapy for luminal-B-carcinomas is also significantly influenced by the presence of axillary lymph node infiltration.

Given this pivotal role of nodal status in treatment decisions, it remains essential to validate de-escalation strategies in diverse clinical settings. Building upon these findings, our real-world data analysis investigates the outcomes of patients who met INSEMA recommendations to omit SLNB and underwent SLNB in clinical routine prior to INSEMA era. The primary endpoints of this study are.

1. Incidence of pathologically positive lymph nodes: Among patients with clinically and sonographically negative lymph nodes, we evaluate the prevalence of pathological nodal involvement in SLNB, analysing the dependency on relevant criteria (e.g. tumor size, patient age, grading and Ki67) and its subsequent impact on treatment recommendations, particularly with regard to the initiation of adjuvant therapies such as CDK4/6i, radiation of lymphatic drainage pathways or chemotherapy.
2. The number needed to operate (NNO): The number of patients who would require SLNB to prevent an invasive recurrence based on the new indication for adjuvant therapy with CDK4/6i.
3. Secondary axillary surgery: We assess how often patients would require a secondary SLNB due to a postoperative upgrade in tumor classification—either from cT1 to ≥ pT2 or from histologic grading G1-2 in the biopsy to G3 after tumor excision or a secondary ALND because of SLN positivity if SLNB would have been omitted according to the INSEMA criteria.

This analysis aims to bridge the gap between trial data and clinical practice, offering insights into the potential trade-offs of omitting SLNB and highlighting the implications for surgical planning and staging accuracy for personalized treatment strategies in eBC.

2. Materials and methods

The conception, methodology, analysis, and writing of the paper for this real-world analysis were conducted in accordance with the European society of medical oncology (ESMO) guidance for reporting oncology real-world evidence (GROW) [13].

2.1. Data collection

This analysis was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of the University of Lübeck (file number: 2024-657), University of Kiel (file number: D 406/25) and University of Hamburg (file number: D 406/25).

Patients diagnosed with HR+/HER2-eBC who met the criteria for omitting SLNB as recommended by the ASCO cT1, G1-2, ≥50 years of age, clinically and sonographically unsuspicious axillary lymph nodes, breast conserving surgery [BCS]) were identified and enrolled in this retrospective study at three certified German university breast cancer centers (University Medical Center Hamburg, University Medical Center Schleswig-Holstein, Campus Kiel, and Campus Lübeck). Data were collected from patients diagnosed with eBC who received surgical treatment between January 1st, 2020 and December 31st, 2024.

Patient characteristics were obtained from routine clinical documentation. Data extracted included tumor biology of biopsy and surgical specimens (BC subtype, receptor status, Ki67 index, grading), clinical and pathological TNM classification (sonographically estimated tumor size and histologically determined tumor size, pathologically determined lymph node infiltration after SLNB). Hormone receptor positivity was defined as an expression level ≥10 %, indicating a definitive endocrine sensitivity. In addition, patients with positive lymph nodes were followed up after BCS plus SLNB for secondary ablative therapy, ALND, regional lymph node irradiation, gene expression testing or BRCA1/2 testing, adjuvant chemotherapy, or administration of CDK4/6i or PARP inhibitor (PARPi).

We also calculated how many patients would hypothetically have an indication for extended endocrine therapy with a CDK4/6i or the PARPi olaparib from today's perspective to meet current recommendations, as three compounds were approved for oral maintenance therapy during our observation period (olaparib: EMA in August 2022 and FDA in March 2022 [14,15], abemaciclib: EMA in April 2022 and FDA in March 2023 [16,17] and ribociclib: EMA in November 2024 and FDA in September 2024, respectively [10,18]).

2.2. Statistics

The data analysis was conducted using Excel 2503 and Statistical Package for Social Sciences (IBM SPSS Statistics, Version 29.0.2.0, Armonk, NY, USA: IBM Corp). The results were used to create a Venn and Sankey diagram using Power Point 2503 and the website http

s://sankeymatic.com.

Statistical correlations within the entire cohort (including both SLNB-positive and SLNB-negative patients) were assessed using a two-sided Chi-squared test, with statistical significance defined as $p < 0.05$. Variables analyzed included patient age, histopathological upgrade to G3, presence of at least pT2 stage in the tumor specimen, and menopausal status between ≥50 and ≤ 55 years. Within the false-negative rate (FNR) cohort (SLN-positive subgroup), the correlation between preoperative tumor size (in millimeters) and sentinel node status was likewise evaluated using the Chi-squared test. Proportion confidence intervals were calculated using the 95 % Wilson score method.

2.3. Validity and potential bias

The internal validity of this retrospective analysis is supported by standardized data collection at three certified university breast cancer centers and by clearly defined inclusion criteria (HR+/HER2-eBC, meeting ASCO, AGO and S3-guideline criterias for omission of SLNB). The use of routinely documented clinical data minimizes the risk of recall bias, as no patient-reported or memory-based data were collected.

A potential selection bias is considered low, as in Germany, breast cancer patients represent the largest group of oncology patients treated in certified breast cancer centers [19]. Moreover, the inclusion of patients from three independent university hospitals increases the heterogeneity of the study population and enhances generalizability. Therefore, the risk of limited representativeness is minimized, and external validity is deemed adequate for comparable certified clinical settings.

Due to the retrospective design, there is a risk of information bias, particularly through incomplete, misclassified, or inconsistently documented data. These potential sources of bias were addressed through rigorous data review and standardized evaluation procedures to minimize their impact.

3. Results

3.1. Descriptive statistics

A total of 867 cases of early breast cancer (n = 386 Kiel, n = 342 Lübeck, n = 139 Hamburg) that met the INSEMA criteria were retrospectively identified over a 5-year observation period at the participating certified breast cancer centers. Between 2020 and 2024, a total of 4545 patients with primary breast cancer were surgically treated at the three certified breast cancer centers (Kiel: 1855; Lübeck: 1798; Hamburg: 892). Of this cohort, 99 patients were pre- or perimenopausal. Taken together, these numbers show that 19.5 % of all primary surgical cases at the three centers could be potential candidates for omission of SLNB according to ASCO/AGO criteria, based on the INSEMA and SOUND trials (867 out of a total of 4545 breast cancer cases from 2020 to 2024, excluding 99 pre- or perimenopausal patients).

Among the 867 cases with preoperative axillary ultrasonography showing no lymph node involvement (cN0) 124 patients had histopathologically positive lymph node(s) (pN+), resulting in a retrospective FNR of 14.3 % (95 % CI 12.1–16.8). Within the SLN-positive cohort (cN0 → pN+), there was one case with isolated tumor cells (pN0[i+]), 32 cases with micrometastases (pN1mi), 89 cases with pN1 status, and two cases with pN2 status (Fig. 1). The FNR, excluding micrometastases and isolated tumor cells, is therefore 10.5 % (95 % CI 8.6–12.7). These patients had a mean age of 65.4 years (SD 9.4; 95 % CI 64.7–66.0; range 50–87 years, median 65.0) with a mean preoperative tumor size upon ultrasound of 10.8 mm (median: 10 mm; SD 4.2; 95 % CI 10.5—11.1; range 2–20 mm) and a postoperative histopathologically determined tumor size of 19.8 mm (median: 14 mm; SD 31.0; 95 % CI 17.7–21.9; range 1–422 mm).

3.2. Correlation of SLN status with patient characteristics

The number of patients by age group was: 305 patients between the ages of 50 and 60, 275 between 61 and 70, 236 between 71 and 80, and 51 patients older than 80 years. The FNR for macrometastatic SLN involvement was significantly associated with age group (p = 0.002), indicating a higher probability of SLN positivity at the younger age (Table 1). In our cohort, 99 patients were pre- or perimenopausal. These patients do not fulfill the criteria for omission of SLNB in accordance with current ASCO, S3 and AGO recommendations. However, the FNR were similar in the pre-/perimenopausal and postmenopausal groups (Table 1).

3.3. Postoperative upgrade of the histopathological characteristics with potential therapeutic implications

Among the entire cohort of 867 cases diagnosed with cT1 stage, 83.9 % had a pathological tumor stage pT1. However, 15.3 % had a final tumor size >2 cm (≥pT2) (Fig. 2). A total of 23 patients (2.7 %) exhibited an upgrade in their tumor grading to G3 as determined by the

Fig. 1. Sankey diagram depicting the pre- and postoperative distribution of nodal stages (N-stage) in the real-world cohort (n = 867) collected between 2020 and 2024.

Table 1
Characteristics of patients included in the analysis.

	Number of patients	Number of patients with isolated tumor cells, micro- or macrometastatic SLN (pN0(i+), pN1mi, pN1/2)	FNR within the respective subgroup in % (CI 95 %[b])	p-value[a]	Number of patients with macrometastatic SLN (pN1/2)	FNR within the respective subgroup in %	p-value[a]
Total	***n* = 867 (100 %)**	***n* = 124** (100 %)	**14.3**		***n* = 91** (100 %)	**10.5**	
Histological subtype				0.118			0.152
No special type	648 (75.7)	96 (77.4)	14.8 (12.3–17.6)		72 (79.1)	11.1 (8.6–13.3)	
Invasive lobular	156 (18.0)	23 (18.5)	14.7 (9.6–20.9)		17 (18.7)	10.9 (6.7–16.2)	
Other	59 (5.1)	3 (2.4)	5.1 (1.3–13.9)		2 (2.2)	3.4 (0.9–11.4)	
Unknown	4 (0.5)	2 (1.6)	50.0 (15.0–85.0)		0.0	0.0	
Ki67				**0.022**			0.099
<20 %	694 (80.0)	90 (72.5)	13.0 (10.7–15.7)		67 (73.6)	9.7 (7.8–11.9)	
≥20 %	172 (19.8)	34 (27.4)	19.8 (18.9–27.6)		24 (26.4)	14.0 (12.9–20.5)	
Unknown	1 (0.1)	0.0	0.0 (0.0–70.8)		0.0	0.0 (0.0–70.8)	
Clinical tumor size				**<0.001**			**<0.001**
≤5 mm	86 (9.9)	2 (1.6)	2.3 (0.5–7.8)		2 (2.2)	2.3 (0.5–7.8)	
6–10 mm	355 (40.9)	31 (25.0)	8.7 (6.3–13.9)		21 (23.1)	5.9 (3.3–7.8)	
11–15 mm	294 (33.9)	55 (44.4)	18.7 (15.6–23.7)		43 (47.3)	14.6 (11.0–17.7)	
16–20 mm	131 (15.1)	36 (29.0)	27.5 (20.4–35.7)		25 (27.5)	19.1 (14.0–26.7)	
Unknown	1 (0.1)	0.0	0.0 (0.0–70.8)		0.0	0.0 (0.0–70.8)	
Pathological tumor size				**<0.001**			**0.001**
1–10 mm	241 (27.8)	12 (9.7)	5.0 (3.3–7.9)		11 (12.1)	4.6 (3.7–8.9)	
11–20 mm	366 (42.2)	76 (61.3)	20.8 (17.6–25.7)		52 (57.1)	14.2 (11.4–16.6)	
21–30 mm	83 (9.6)	24 (19.4)	28.9 (19.0–38.1)		18 (19.8)	21.7 (13.3–30.5)	
31–40 mm	12 (13.8)	6 (4.8)	50.0 (23.2–69.7)		4 (4.4)	33.3 (10.2–47.2)	
>40 mm	40 (4.6)	6 (4.8)	15.0 (6.8–27.7)		6 (6.6)	15.0 (6.8–27.7)	
Unknown	1 (0.1)	0.0	0.0 (0.0–70.8)		0.0	0.0 (0.0–70.8)	
Age				0.364			**0.002**
50–60 years	305 (35.2)	50 (40.3)	16.4 (13.2–20.6)		37 (40.7)	12.1 (8.3–15.9)	
61–70 years	275 (31.7)	38 (30.6)	13.8 (9.3–18.4)		28 (30.8)	10.2 (6.4–13.2)	
71–80 years	236 (27.2)	27 (21.8)	11.4 (9.3–17.6)		21 (23.1)	8.9 (7.0–13.9)	
≥81 years	51 (5.9)	9 (7.3)	17.6 (8.3–30.0)		5 (5.5)	9.8 (2.1–15.7)	
Grading (tumor specimen)				0.296			0.246
G1	321 (37.0)	40 (32.3)	12.5 (8.8–16.2)		33 (36.3)	10.2 (6.7–14.3)	
G2	523 (60.3)	79 (63.7)	15.1 (13.– 18.4)		55 (60.4)	10.5 (8.1–13.6)	
G3	23 (2.7)	5 (4.0)	21.7 (7.1–39.4)		3 (3.3)	13.0 (2.6–26.8)	
Menopausal status				0.801			0.842
Pre-/ perimenopausal	99 (11.4)	15 (12.1)	15.2 (9.3–22.4)		10 (11.0)	10.1 (4.8–18.5)	
Postmenopausal	753 (86.9)	107 (86.3)	14.2 (12.5–17.4)		81 (89.0)	10.8 (9.1–13.4)	
Unknown	15 (1.7)	2 (1.6)	18.2 (1.4–30.0)		0.0	0.0 (0.0–20.6)	

[a] chi-square test, two sided, statistically significance <0.05.
[b] Calculation of the confidence interval according to Wilson.

Fig. 2. Sankey diagram depicting the pre- and postoperative distribution of tumor stages (T-stage) in the real-world INSEMA cohort (n = 867) collected between 2020 and 2024.

histopathological assessment of the tumor specimen. The FNR was numerically higher in patients with G3 tumors compared to G2 and G1 cases, but these differences did not reach statistical significance.

Considering the postoperative grading and T-stage upgrade, 163 patients (18.8 %; 95 % CI 16.4–21.4) might have required a secondary SLNB if the procedure had been omitted initially.

Of the 124 patients with a false negative result of axillary lymph nodes (cN0 → pN+), seven patients (5.6 %; 95 % CI 2.7–11.1) had an indication for the CDK4/6i abemaciclib based on the histopathological findings of the tumor specimen. One patient (0.8 %; 95 % CI 0.1–4.4) had an indication for diagnostic gBRCA testing, in accordance with the OlympiA trial, to evaluate the potential use of the PARP inhibitor olaparib in the case of a confirmed *gBRCA1/2* mutation.

Regarding the CDK4/6i ribociclib, among the 124 patients with a false negative result, 91 (73.4 %; 95 % CI 65.0–80.4) would qualify for treatment due to their positive axillary nodal status (pN+). In contrast, 16 patients (12.9 %; 95 % CI 8.0–20.0) would have fulfilled the ribociclib criteria even without knowledge of their histopathological SLN status, according to the NATALEE trial: one patient with pT2 stage and an OncotypeDX Recurrence Score of 29, four patients with pT3 stage, and seven patients with pT2 stage and Ki-67 $\geq$ 20 %.

Based on the characteristics of the patients with a false negative result ($n = 124$), a retrospective therapeutic consequence was identified in 101 patients (11.6 % of the total cohort of $n = 867$; 95 % CI 9.6–14.0): secondary ALND in 1.7 %, axillary radiation therapy in 6.7 %, adjuvant chemotherapy in 2.0 %, and an indication for adjuvant CDK4/6i therapy in 10.8 % of cases (Fig. 3). It should be noted that the patients did in fact receive chemotherapy, axillary dissection and/or axillary radiotherapy, and that the indications for the respective CDK4/6i are only hypothetical, as they were gradually approved over the past few years.

3.4. Number needed to operate to prevent a recurrence in the context of a CDK4/6i indication

The indication of an adjuvant treatment with a CDK4/6i is decisively dependent on the status of the axillary node. The *number needed to operate* (NNO) to prevent a potentially avoidable invasive recurrence through a CDK4/6i is currently under discussion. Assuming a final absolute invasive disease-free survival (iDFS) benefit of 4.9 % from ribociclib, as demonstrated in the NATALEE trial [20] and a FNR consisting exclusively of macrometastases (10.5 %; 95 % CI 8.6–12.7), the NNO to prevent a single recurrence would be approximately 1 in 200 [95 % CI 8.6 (1:250)–12.7 (3:500)].

However, when focusing on the subgroup of patients aged 50–55 years with a preoperative tumor size (cT-stage) of 11–20 mm, the FNR increases to 17.2 % (15 cases with macrometastases out of a total of 87 cases). In this scenario, the corresponding NNO would be reduced to 1 in 125 [NNO CI 95 % 10.7 (1:200)–26.5 (13:1000)]. When calculating the NNO based on the FNR according to clinical tumor stage (cT), the NNO reaches its minimum value of 1:111 [FNR 19.1 %; CI 95 % 14.0 (7:1000)–26.7 (13:1000)] for a preoperative tumor size of 16–20 mm, whereas it is maximum at 1:333 [FNR 5.9 %; CI 95 % 3.3 (2:125)–7.8 (1:250)] for tumors measuring 6–10 mm.

4. Discussion

The axillary lymph node status remains one of the most important prognostic factors in early BC [21–23]. During the last decades the SLNB has been established not as a therapeutic, but as a staging procedure that may guide adjuvant treatment decisions. Recent studies showed that the omission of axillary SLNB in patients with clinically node negative eBC does not compromise clinical outcomes [4,5,24]. On the one hand, two phase III studies confirmed that there were no differences in disease free survival (DFS) between SLNB and no SLNB after a median follow-up of 5–6 years. On the other hand, adjuvant treatment did not differ

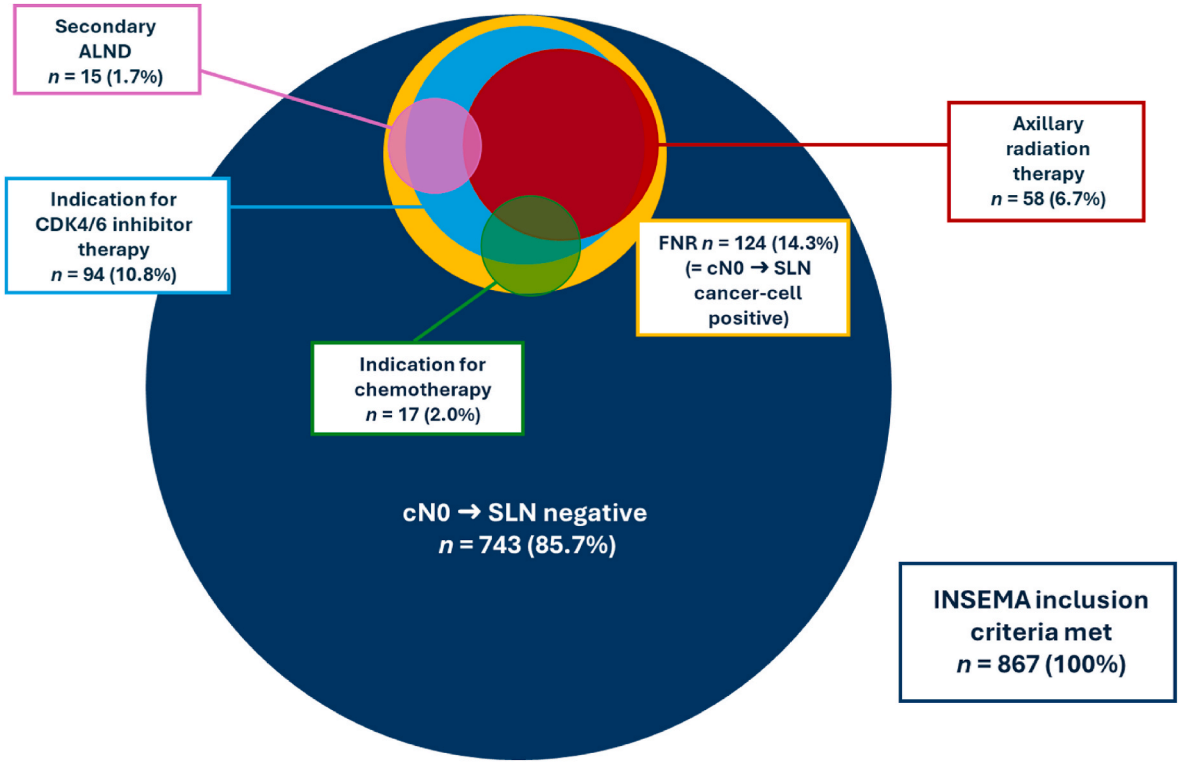

Fig. 3. Venn diagram illustrating the axillary FNR within the analyzed real-world INSEMA cohort and its therapeutic implications, including chemotherapy, irradiation of lymphatic drainage pathways, CDK4/6 inhibitors, and secondary axillary dissection.

significantly between the SLNB and non-SLNB patients except for adjuvant chemotherapy. Nevertheless, the incidence of axillary recurrence was numerically higher when no axillary surgery was performed, but still without impact on disease-free or overall survival [4,25,26].

Based on these findings the AGO Breast Committee in its revised guidelines (March 2025), the ASCO (April 2025) and the German national S3 guidelines (June 2025) implemented the omission of the SLNB in postmenopausal patients ≥50 years of age with small (≤2 cm), grade 1–2, HR + HER2-tumors with negative lymph node status upon ultrasound receiving breast-conserving surgery [6–8]. Characteristics of the updated Breast Committee guidelines (AGO, ASCO) and the German national S3 guideline are presented in Table 2.

The INSEMA study included adult BC patients with a clinical tumor size of ≤5 cm and negative nodal status according to clinical assessment and imaging (cN0), irrespective of grading and receptor status. However, approx. 90 % of the study collective fulfilled the criteria of the updated guidelines mentioned above [4]. The underrepresentation of HER2+ and triple-negative BC is likely due to the higher proportion of these patients receiving neoadjuvant chemotherapy and the potential implications of the lymph node status for further adjuvant therapy (de-) escalation [27]. Further, a preoperative tumor size >2 cm and higher grading (G3) were associated with a decreased iDFS in the INSEMA study. These findings are reflected in the aforementioned guidelines [4,6,8].

To the best of our knowledge our retrospective study is the largest analysis of the potential effects of the omission of SLNB in a real-world collective. The FNR in the patient group selected based on the above-mentioned criteria was 10.5 %, and therefore similar to the FNR reported in the INSEMA and SOUND trials (11.6 % and 8.7 %, respectively). In this context, it is important to mention that the estimated FNR of the SLNB itself is between 6 and 10 % [21]. When micrometases and isolated tumor cells were considered, the FNR increased to 14.3 % in our analysis and 15.0 % in the INSEMA trial [4]. Aside from that, the extent of lymph node involvement in our collective and in the INSEMA study were similar.

In our analysis, the probability of sentinel node involvement was higher in younger patients as well as those with larger tumors and higher Ki67. On the other hand, characteristics included in some of the above mentioned guidelines such as the menopausal status and the histological type did not affect the FNR. It is worth noting that the updated ASCO guidelines allow the omission of the SLNB only in patients with invasive ductal (NST) carcinoma, despite no apparent evidence for higher risk of axillary lymph node involvement in lobular carcinoma compared to NST carcinoma, neither from the INSEMA/SOUND trials nor in our real-world analysis [28,29]. Nevertheless, preoperative and postoperative tumor size often differs in lobular carcinomas [30]. This may lead to higher rates of postoperative tumor stage upgrade due to pathological tumor size in lobular carcinoma with a possible indication for a secondary SLNB.

Whereas the FNR significantly differed between subgroups with a Ki67 < 20 % and ≥20 %, this was only the case for FNR including macro-, micrometastases and isolated tumor cells and not when the FNR was calculated based solely on macrometastases.

Furthermore, there was no correlation between the menopausal status and lymph node involvement. In the updated guidelines from the ASCO as well as from Germany (AGO, S3) only postmenopausal patients are included in the recommendation for the omission of SLNB. This may be due to the fact that in postmenopausal patients the involvement of 1–3 lymph nodes has less impact on adjuvant therapy decisions than in premenopausal women [31,32].

In summary, in our real-world analysis we can confirm most of the recommendation criteria for the omission of the SLNB. However, the FNR was higher in younger patients (50–60 year old) and those with clinical tumor size >1 cm (cT1c) and the omission of SLNB should therefore be carefully discussed in this group.

It remains an open question how patients with cT1 G1-G2 tumors and postoperative upgrade to either a higher tumor stage (≥pT2) or G3 should be counselled. The above-mentioned guidelines define the group of patients in whom the SLNB may be omitted based on clinical (preoperative) and not pathological (postoperative) criteria. In cases where the tumor size is ≥ 2 cm and/or the postoperative grade is 3, a secondary SLNB has to be discussed. According to the findings of our real-world study, 18.8 % of patients would have necessitated a subsequent surgical procedure. Cases involving secondary mastectomy were not considered, although they would also require a secondary SLNB according to the guidelines. The SentiNot-trial examined the feasibility of a secondary SLNB with superparamagnetic iron oxide (SPIO) as a tracer in patients undergoing BCS for DCIS with postoperative diagnosis of invasive carcinoma [33]. The injection of SPIO prior to the primary BCS and again when secondary SLNB was performed, showed a higher detection rate in comparison to the use of technetium-99. The application of SPIO in the context of SLNB omission may be a practicable procedure in eBC, especially for patients with higher probability of postoperative tumor upgrade, as cT1c tumors, lobular carcinoma or G2 with increased Ki67-index, but requires further studies. The implementation of the secondary SLNB due to postoperative grading and T-stage upgrade is currently not part of the revised guidelines mentioned and needs to be discussed individually based on the respective expected consequences for further therapy.

Another aspect that needs to be considered is the possible de-escalation of adjuvant radiotherapy in patients with low risk eBC. The APBI-trail has shown that there is no significant difference regarding the incidence of ipsilateral breast tumor recurrence comparing whole breast and partial breast irradiation in a collective similar to our study collective including mainly patients >50 years old with HR + HER2-tumors, grade 1–2, size <2 cm and negative nodal status [34]. The efficacy of partial breast irradiation is closely related to an adequate choice of patients [35]. In the INSEMA trial patients received adjuvant whole breast irradiation [4]. Currently, there is a lack of sufficient data regarding the safety of BCS and partial breast irradiation or even omission of radiotherapy in elderly patients who do not undergo SLNB [33,36].

In terms of systemic therapy, the standard of care for HR+, HER2− eBC has changed since the completion of the INSEMA trial. In particular, three agents have been approved for use in combination with endocrine adjuvant therapy in selected patients (olaparib, abemaciclib, ribociclib). All patients with macrometastatic SLN involvement may be offered adjuvant ribociclib treatment. Further, current AGO Breast Committee guidelines recommend the target volume of radiotherapy to include axillary level I and II and end 5 mm below the axillary vein in case of a positive SLN.

Indeed, in 101 (11.6 %) patients in our cohort, the histological confirmation of lymph node involvement resulted in further therapy

Table 2
Comparison of the recommendations from the updated guidelines from the AGO Breast Committee, German S3 national guideline and ASCO.

	AGO Breast Committee and German national S3 guideline	ASCO
Clinical tumor size	≤2 cm (cT1)	≤2 cm (cT1)
cN-stage (clinically plus ultrasound)	0	0 or only one suspicious node and biopsy is benign
Age (years)	≥50	≥50
Menopausal stage	postmenopausal	postmenopausal
Receptor stage	HR+/HER2-	HR+/HER2-
Grading	G1-2	G1-2
Surgical procedure	BCS	BCS
Radiation therapy	WBI	WBI (only for patients <65 years)
BC subtype		invasive ductal carcinoma
Number of tumor foci		unifocality

recommendations (1.7 % secondary ALND, 6.7 % axillary radiotherapy, 10.5 % ribociclib). These findings discover a relevant proportion of patients with indications for additional adjuvant systemic therapy beyond adjuvant chemotherapy. This observation contrasts with the INSEMA trial, which did not observe any discrepancy between the SLNB-omission and the SLNB group with respect to postoperative systemic treatment, excluding chemotherapy. It should be noted that the INSEMA trial completed prior to the introduction of adjuvant ribociclib [4]. The combination of ribociclib with an aromatase inhibitor improves the iDFS significantly [10,18]. Further retrospective analyses demonstrated that the number of patients with an indication for an extended endocrine therapy combined oral maintenance therapy might have doubled since the approval for adjuvant ribociclib in 2024 [11,12]. In 10.5 % of patients in our cohort, the omission of SLNB could have potentially led to undertreatment negatively affecting iDFS [10]. Given that previous analyses of the NATALEE trial [18] showed an absolute iDFS benefit, this results in a 'number needed to operate' of 200 to prevent one invasive event. It is worth noting, however, that the FNR reaches it's minumum in patients with larger tumors (16–20 mm). In this patient group, the NNO drops to 1:111.

Although the INSEMA and SOUND trials refer to patients who did not receive neoadjuvant treatment, it remains to be seen for this particular cohort whether, and to what extent, omission of SLNB or ALND in cases with an initially node-negative axillary status or axillary pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) will increasingly be adopted in the future [37–39]. In addition to ensuring the oncological safety of surgical de-escalation, it is important to consider new surgical approaches, such as the marking of axillary lymph node metastases prior to NACT, in order to successfully implement already established de-escalating procedures such as targeted axillary dissection (TAD), which is currently being investigated within the framework of the AXSANA/EUBREAST-03/AGO-B-053 trial [40–43].

4.1. Limitations

Retrospective data analysis of a real-world collective has its limitations such as selection bias. All patients were selected based on the above-mentioned recommendations which reduces selection bias. In our investigation we cannot differentiate between therapy recommendations and actually implemented therapies.

5. Conclusions

Our real-world analysis regarding the omission of the SLNB in selected patients based on updated international guidelines confirms the FNR in the routine setting of 10.5 %. However, with the approval of adjuvant CDK4/6i therapy, there is a new standard of care, especially for node positive, HR + HER2− eBC, that needs to be taken into consideration when counselling patients. In our study the histopathological examination revealed an increase in tumor size >2 cm or a grade 3 diagnosis in 18.8 % of cases. At present, the guidelines do not offer any recommendations concerning the performance of a secondary SLNB in this particular circumstance. In addition, the safety of partial breast irradiation after SLNB-omission remains unclear and requires further studies.

The omission of SLNB in the SOUND and INSEMA studies was non-inferior to SLNB regarding the endpoints of DFS and OS but the decision to omit this procedure should be made on an individual basis and in an interdisciplinary setting.

Author contributions

Conceptualization: N.T., A.C.R., C.G., L.H., L.S., M.B.P., M.vM.; **Data curation**: N.T., A.C.R., C.G.; **Formal analysis**: N.T., A.C.R., C.G., L.S., M.B.P., M.vM.; **Funding acquisition**: None; **Investigation**: N.T., A.C.R., C.G., L.S., M.B.P., M.vM.; **Methodology**: N.T., A.C.R., C.G., L.S., M.B.P., M.vM.; **Project administration**: N.T., A.C.R., C.G.; **Resources**: N.T., A.C.R., C.G., L.S., M.B.P., M.vM.; **Software**: N.T., M.B.P.; **Supervision**: L.S., M.B.P., M.vM. A.R., B.S., N.M.; **Validation**: L.S., M.B.P., M. vM.; **Visualization**: N.T., A.C.R., C.G., L.H., N.K., L.S., M.B.P., M.vM.; **Writing – original draft**: N.T., A.C.R., C.G., N.K., L.S., M.B.P., M.vM.; **Writing – review and editing**: N.T., A.C.R., C.G., F.F., I.GN., L.H., F.K., N.K., H.DL., M.E., N.M., V.M., A.R., K.W.F.S., B.S., L.S., M.B.P., M.vM.

Ethical approval

This analysis was approved by the Ethical Committee of the University of Lübeck (file number: 2024-657; January 30, 2025), University of Kiel (file number: D 406/25; January 08, 2025) and University of Hamburg (file number: D 406/25; January 17, 2025).

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Appendices A.

Table A.1
Ongoing trials investigating the omission of sentinel lymph node biopsy in cN0 patients in both adjuvant and neoadjuvant treatment settings.

Trial	Inclusion criteria	Number of patients (*n*)	Results/current status
SOUND (NCT02167490) prospective, randomized	cT1, cN0, BCS, primary surgery	1405	5-Year-DFS 94.7 % vs. 93.9 % 5-Year-DDFS 97.7 % vs. 98.0 % 5-Year-OS 98.2 % vs. 98.4 %
INSEMA (NCT02466737) prospective, randomized	cT1-2, cN0, BCS, primary surgery	5154	5-Year-iDFS 91.7 % vs. 91.9 % 5-Year-OS 96.9 % vs. 98.2 %
NAUTILUS (NCT04303715) prospective, randomized	cT1-2, cN0, BCS, primary surgery	1734	Recruitment completed, results expected in December 2027
BOOG 2013–08 (NCT02271828) prospective, randomized	cT1-2, cN0, BCS, primary surgery or NACT	1730	Recruitment completed, results expected in 2025
EUBREAST-01 (NCT04101851) single-arm, prospective	cT1-3, cN0, BCS, TNBC or HER2+, pCR of the breast (ypT0/Tis), NACT	350	Recruitment ongoing, analysis planned for January 2028
ASLAN (NCT04993625) single-arm, prospective	cT1-3, cN0-1, BCS, ycT0, TNBC or HER2+, NACT	178	Recruitment completed, results expected in December 2028

Abbrevations: BCS = breast conserving surgery, NACT = neoadjuvant chemotherapy, TNBC = triple negative breast cancer, pCR = pathological complete remission, DFS = disease-free survival, DDFS = distant disease-free survival, iDFS = invasive disease-free survival.

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