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Giacomo Montagna, Sara Myers, Massimo Ferrucci, Monica Morrow, and Walter P. Weber oversaw the protocol.
Varadan Sevilimedu analyzed data.
All authors interpreted the data.
All authors participated in drafting the manuscript and reviewing iterations of the manuscript, and approved the final draft for submission.
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Oncological outcomes with and without axillary lymph node dissection in patients with residual micrometastases after neoadjuvant chemotherapy (OPBC-07/microNAC): an international, retrospective cohort study

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Abstract

Background: Despite lack of outcome data, axillary lymph node dissection (ALND) is increasingly being omitted in patients with positive sentinel lymph nodes (SLNs) after neoadjuvant chemotherapy (NAC), particularly in those with low-volume residual disease. We investigated oncological outcomes in patients with ypN1mi disease treated with and without ALND.

Methods: Patients age ≥18 years with clinical T1–4 N0–3 breast cancer at diagnosis treated with NAC followed by surgery who were found to have residual micrometastases at frozen section or on final paraffin sections determined by sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), or the MARI (marking axillary lymph nodes with radioactive iodine seeds) procedure were retrospectively collected from 84 centers in 30 countries. The primary endpoint was the 3-year rate of any axillary (isolated or combined with local or distant) recurrence stratified by type of axillary surgery. This study is registered with ClinicalTrials.gov NCT06529302.

Findings: Between 01/01/2013–31/05/2023, 1,585 female patients with ypN1mi disease were analyzed, of whom 804 (50·7%) underwent ALND and 781 (49·3%) did not. Out of 1585, 238 (15%) self-identified as Asian, 65 (4·1%) as Black, 200 (13%) as Hispanic, 968 (61%) as White, and 114 (7·2%) as unknown race and ethnicity, 925 (58%) had cT2 tumors, 1054 (66%) were node positive and 1267 (80%) received nodal RT. The 3-year rate of any axillary recurrence was 1·3% (95%CI 0·65–2·4%) with no statistical difference by extent of axillary surgery. However, patients with triple-negative disease treated without ALND had significantly higher rates of any axillary recurrence as compared to those treated with ALND (8·7% [95%CI 4·4–15%] versus 2·4% [95%CI 0·65–6·5%], p=0·018). On multivariable analysis, triple-negative biology (hormone receptor positive/HER2 negative [referent]: hazard ratio [HR] 3·83 [95%CI 1·72–8·52%]) and omission of nodal RT (receipt of nodal RT [referent]: HR 2·62 [95%CI 1·19–5·73%]) but not omission of ALND (ALND [referent]: HR 0·86 [95%CI 0·37–2·00%]) were independently associated with an increased risk of axillary recurrence.

Interpretation: Overall, these results do not support ALND for all patients with ypN1mi on SLN biopsy treated with nodal RT; however, tumor biology should be taken into account when considering ALND omission.

Keywords

axillary lymph node dissection; sentinel lymph nodes; neoadjuvant chemotherapy; residual micrometastases; triple-negative breast cancer

Introduction

In the upfront surgery setting, randomized clinical trials have demonstrated no benefit of axillary lymph node dissection (ALND) in patients with micro- and macrometastases in 1 or 2 sentinel lymph nodes (SLNs).[1–3] In the neoadjuvant chemotherapy (NAC) setting, omission of ALND in patients with nodal complete pathological response (pCR) or residual isolated tumor cells (ITCs) after NAC does not affect oncological outcomes,[4–9] but whether this is the case for patients with residual micro- and macrometastases is currently unknown.

Several studies have demonstrated that the residual nodal burden in patients with a positive SLN after NAC is higher than in the upfront surgery setting, with additional positive lymph nodes (LNs) at completion ALND found in 24–59% of patients with residual micrometastases (ypN1mi)[10–12] and 60–64% in patients with residual macrometastases.[11–13]

Despite lack of oncological outcome data from randomized trials, several real-world studies have shown that ALND is increasingly being omitted in favor of regional nodal irradiation (RNI), particularly in patients with ypN1mi disease.[14–16] We conducted a multicentric international retrospective cohort study to evaluate oncological outcomes in patients with ypN1mi disease treated with and without completion ALND, focusing on the differences between tumor subtypes.

Methods

Study design and participants

The OPBC-07/microNAC cohort study (ClinicalTrials.gov identifier: NCT06529302) retrospectively analyzed institutional databases from 84 cancer centers in 30 countries (the majority of centers are within the Oncoplastic Breast Consortium [OPBC] network). Institutional review board approval was obtained for each site in the United States (USA), with informed consent waived due to use of de-identified data. The University Hospital of Basel (Switzerland) acted as a coordinating center for the non-USA sites and as the central ethics committee. The study received ethical approval from the Ethics Committee of Northwestern and Central Switzerland (ID 2024–00186), as well as from the local, regional or national institutional review boards of participating centers, whenever required by regulations. A data use agreement was executed between Memorial Sloan Kettering Cancer Center (MSKCC) and other North American institutions, and between MSKCC and the University Hospital of Basel, Switzerland, which served as the OPBC coordinating center. The study followed the STROBE [*Strengthening the Report of Observational Studies in Epidemiology*] guidelines.[17] Data cleaning for the OPBC sites was initiated at the OPBC coordinating center and completed at MSKCC. For all other sites, data cleaning was conducted at MSKCC where the statistical analysis was carried out.

Patients age 18 years or older with clinical T1–4N0–3 breast cancer at diagnosis treated with NAC between 01/01/2013–31/05/2023 who were found to have micrometastases (metastasis measuring greater than 0·2 mm and/or > 200 cells but not greater than 2·0 mm in size) at frozen section (FS) or on final paraffin sections determined by sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), or the MARI (marking axillary lymph nodes

with radioactive iodine seeds) procedure were selected. Downstaging to clinical N0 after NAC was required for patients who presented with palpable disease.

The concomitant presence of ITCs in other SLNs was allowed. Race and ethnicity were self-reported. Patients with inflammatory breast cancer, stage IV disease, those who had ALND as a primary procedure, and those who received neoadjuvant endocrine therapy were excluded. Patients with isolated tumor cells (ITCs) only or macrometastases in any SLNs at FS or final pathology were ineligible.

Estrogen receptor (ER)-positive and progesterone receptor (PR)-positive disease was defined as ≥ 1% expression. Human epidermal growth factor receptor 2 (HER2) status was classified by immunohistochemistry (IHC) and fluorescence in situ hybridization analysis (FISH). HER2-negative cases were defined as those with an IHC score of 0 or 1+/2+ with negative FISH results. HER2-positive tumors were defined as those with an IHC score of 3+ or positive FISH.

Procedures

The SLNB procedure included removal of all LNs that were either blue (isosulfan blue dye, patent blue or methylene blue), green (indocyanine green), radioactive (technetium Tc 99m), or palpable abnormal. For patients with cN0 at presentation, single tracer was allowed, while for patients with cN+ disease, use of dual-tracer mapping was mandatory. TAD consisted of SLNB with single or dual-tracer mapping plus image-guided localization of the initially biopsy-proven and clipped node. The MARI procedure consisted of selective removal of the pathologically proven metastatic LN, which was marked with an iodine seed before NAC. Details of the surgical procedures, pathology assessment, and radiation therapy specific to each site are provided in the appendix p 1–84.

NAC regimens, adjuvant systemic therapy, and regional nodal irradiation (RNI) were administered following national guidelines.

Outcomes

The primary endpoint was the rate of any axillary recurrence (isolated or combined with local and distant recurrence within 30 days) stratified by type of axillary surgery. Secondary endpoints included the rates of locoregional recurrence (LRR), and any invasive recurrence (defined as locoregional or distant) as well as the proportion of additional positive LNs (stratified by tumor subtype) among patients who underwent ALND. We initially planned to analyze the rate of isolated axillary recurrence as a second primary endpoint and to conduct a multivariable analysis looking at factors associated with isolated axillary recurrence. However, given the extremely low number of events (n=7), this was not possible, and the rate of isolated recurrence was analyzed as a secondary endpoint; this decision had no impact on the remainder of the statistical analysis. In addition, it was initially planned to report 5-year rates, but given the median follow-up, 3-year rates and exploratory 5-year estimates were reported.

Statistical analysis

The determination of the sample size was pragmatic and based on the number of patients available at the participating sites. Clinicopathologic and demographic characteristics were compared between surgical groups using the Wilcoxon rank sum test or t-test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. The mean number of SLNs was calculated excluding patients who underwent the MARI technique. The rate of additional positive LNs at completion ALND was compared between tumor subtypes using the Chi-Square test. An exploratory correlation analysis was conducted between the number of SLNs with micrometastases and the number of additional positive LNs found at ALND, using Pearson's correlation. Follow-up data were obtained from the date of surgery. Cumulative incidence of axillary recurrence (isolated or combined with local or distant recurrence) and any invasive recurrence (locoregional or distant) was assessed using a competing risk analysis (appendix p 88). Three-year cumulative incidence rates were compared between patients treated with and without completion ALND in the overall cohort and within tumor subtypes, using Gray's test. The assumption of proportionality was made through preliminary visual inspection of the cumulative incidence curves. Sensitivity analysis for this assumption is provided in the appendix p 97. Exploratory 5-year cumulative incidence rates were also calculated. A p-value < 0·05 was considered statistically significant. A multivariable mixed-effect competing risk model was used to study the association between the risk of any axillary and any invasive recurrence and clinicopathological and treatment features selected a priori. Robust covariance estimates were used in order to account for the clustering effect induced by each individual institution participating in the study. Type I error rate was adjusted to 0·025 using Bonferroni correction to accommodate multiple hypothesis testing. To account for selection bias, we conducted a propensity-matched analysis, matching groups by age, race/ethnicity, clinical stage, tumor subtype, type of breast surgery, and receipt of RNI. We also performed two sensitivity analyses. The first, to take into account possible inter-institutional variability, was limited to patients treated in high-volume centers. The second, to take into account possible mis-classification, was limited to patients who had ≤ 1 non-SLN removed prior to ALND and ≥ 10 lymph nodes removed at ALND). These analyses are provided in the appendix p 92–93. An exploratory analysis limited to patients with TNBC who received adjuvant capecitabine was also conducted. Statistical analysis was performed using R 4·4·2 (R Core Development Team, Vienna, Austria).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between 01/01/2013–31/05/2023, 1,585 female patients with residual micrometastases detected on SLNB, TAD, or MARI, from 84 centers in 30 countries were identified (Fig. 1). Of 1,585 patients, 804 (50·7%) were treated with completion ALND and 781 (49·3%) without. The baseline characteristics of the cohort stratified by surgical group are presented in Table 1. The median age was 48 years (interquartile range [IQR] 41–58). The majority of

patients had cT2N+ disease at presentation and 1,267 of 1,585 (80%) received RNI. Out of 1,585 tumors, 808 (51%) were hormone receptor (HR) positive/HER2 negative, 493 (31%) were HER2 positive, and the remainder 284 (18%) triple negative. Patients treated with completion ALND were more likely to be non-White (338 of 804 [42%] versus 279 of 781 [36%], p < 0·001), present with cN+ disease (582 of 804 [72%] versus 472 of 781 [60%], p < 0·001), have micrometastases detected intraoperatively on FS (502 of 804 [62%] versus 377 of 394 [17%], p < 0·001), and receive breast (368 of 369 [99%] versus 377 of 394 [96%], p = 0·002) and chest wall irradiation (379 of 433 [88%] versus 311 of 387 [80%], p = 0·004), but not RNI (652 of 804 [81%] versus 615 of 781 [79%], p = 0·22).

There were some small differences in terms of axillary staging between the two surgical groups; patients who underwent completion ALND had fewer SLNs and non-SLNs removed during SLNB compared to patients in the non-ALND group (mean number of nodes removed; 3·0 [range 0–20] versus 3·1 [range 0–12] and 0·5 [range 0–9] versus 1·0 [range 0,11], respectively, both p<0·001), but significantly more SLNs with micrometastases (1·2 [range 0–6] versus 1·1 [1–4], p <0·001)(Table 1). Among the 804 patients who underwent ALND, additional positive nodes were found in 245 (30·5%) of cases, consisting of ITCs in 20/245 (8%), micrometastases in 123/245 (50%), and macrometastases in 102/245 (42%) patients. The number of additional positive LNs is shown in Fig. 2A. The likelihood of finding additional positive lymph nodes at ALND varied by tumor subtype (Fig. 2B). There was a weak positive correlation between the number of SLNs with micrometastases and the number of additional positive LNs found at ALND (estimate: 0·16, p<0·001).

The median follow-up was 3·1 years (IQR 1·8–5·2). During the follow-up there were 7 isolated axillary recurrences, 34 any axillary recurrences, and 251 any invasive recurrences (appendix p 96). The 3-year rate of any axillary recurrence (isolated or combined with local or distant recurrence) for the entire cohort was 2% (95% confidence interval [CI] 1·3–2·9%) (Fig. 3A), while the 3-year rate of isolated axillary recurrence was 0·33% (95% CI 0·13–0·74%). The rate of any axillary recurrence was statistically different across tumor subtypes (Fig. 3B). There were no statistically significant differences between patients treated with and without ALND for 3-year rates of any axillary recurrence (1·7% versus 2·3%; p=0·92) (Fig. 3C) or isolated axillary recurrence (0·13% versus 0·53%; p=0·67). The 3-year rates of LRR and any invasive (locoregional or distant) recurrence in the entire cohort were 4.1% (95% CI 3·1–5·3%) and 14% (95% CI 12–16%), respectively, with no significant difference in outcome between patients treated with and without ALND (4·1% versus 4·2%, p=0·55 and 15% versus 13%, p=0·60). 3-year rates of any invasive recurrence were statistically different across subtypes (Supplementary Figure 1).

The 5-year rate of any and isolated axillary recurrence was 2·7% (95% CI 1·8–3·8%) and 0·49% (95% CI 0·19– 1·1%), respectively (with no significant differences between groups [ALND versus no-ALND], 3·1% versus 2·3%; and 0·46% versus 0·53%, respectively). The 5-year rate of any invasive recurrence was 21% (95% CI 18–23%), with no significant difference between groups (ALND versus no-ALND, 21% versus 20%, respectively).

On multivariable analysis, undergoing ALND was not independently associated with the risk of any axillary or any invasive recurrence, while triple-negative subtype, omission of

RNI, and more advanced clinical T category were independently associated (Table 2). In the TNBC group there were 92 any invasive recurrence events, of which 15 were axillary (3 isolated, 6 combined axillary and supraclavicular, 1 locoregional, and 5 synchronous locoregional and distant). When comparing TNBC patients treated with (n = 157) and without ALND (n = 127), those without ALND had significantly higher rates of any axillary recurrence (8·7% versus 2·4%, p = 0·018)(Fig. 3D), but similar rates of any invasive recurrence (35% versus 32%, p = 0·86)(appendix p 88). An exploratory analysis limited to the 131 of 284 (46%) patients with TNBC who received adjuvant capecitabine showed similar results: the 3-year rate of axillary recurrence in this group was 4·1% (1·5–8·8%) and was significantly lower among those who underwent ALND as compared to those who did not (0% versus 10%, p=0·017).

Discussion

This large multicenter cohort study provides evidence that ALND may not confer oncological benefit for most patients with residual micrometastases post-NAC. Although current guidelines recommend completion ALND for all patients with residual micro- and macrometastases after NAC,[18,19] in the present study, ALND was omitted for almost half of the patients. This accords with data from the National Cancer Database which found that ALND was omitted for 40–69% of patients with ypN1mic disease treated between 2012–2021.[20] Similarly, of 242 patients with a positive SLN after NAC treated in the ISPY2 trial between 2011–2021, ALND was omitted in 144 (60%) of them.[16] In our study, clinicopathological factors associated with performing an ALND included higher nodal stage at presentation and detection of micrometastases on FS. Patients who underwent ALND also had fewer sentinel and non-sentinel lymph nodes removed, and had more sentinel lymph nodes with micrometastases; however, these differences were very small and not clinically meaningful. These findings show that surgeons are selecting patients who they believe are at high risk of recurrence and for whom the morbidity of ALND may be justified. In addition, in our study, compared to patients who did not undergo ALND, those who did were more likely to be non-White and to be treated in North America, suggesting a more stringent use of ALND in the United States, where the population is more ethnically diverse.

In the present study, additional positive LNs were found in 30·5% (245/804) of patients undergoing completion ALND. In the ongoing prospective ALLIANCE A011202 trial, which randomized patients with residual disease in the SLNs to completion ALND with RNI or RNI alone, the proportion of additional positive LNs at ALND among patients with ypN1mi disease was 38·4%.[12] This difference is likely due to the fact that nearly 70% of patients in the ALLIANCE A011202 trial had HR-positive/HER2-negative tumors, which have higher rates of positive LNs.[21]

In this cohort of patients, where 80% received RNI, we found no difference in the rates of any axillary or any invasive recurrence based on ALND use, with the exception of TNBC patients who had significantly higher rates of axillary recurrence after ALND omission (8·7% versus 2·4%, p=0·018). On multivariable analysis, factors associated with an increased risk of any axillary recurrence included TNBC and omission of RNI, which were associated with a near 4-times and a 2·6-times increase in risk, respectively. Importantly,

despite the higher risk of any axillary recurrence observed in the TNBC groups, the risk of any invasive recurrence was similar between patients treated with and without ALND.

To our knowledge, this is the first study to show a significant benefit of ALND in reducing the risk of axillary recurrence in patients with TNBC with residual nodal disease after NAC. This group of patients, that likely harbors micrometastatic disease beyond the regional lymph nodes, is at increased risk of early locoregional and distant recurrence,[22] and randomized trials have demonstrated a benefit of escalating adjuvant systemic therapy with capecitabine[23] and olaparib in BRCA carriers.[24] While breast conservation has been shown to be oncologically safe,[25] de-escalation of axillary surgery translated into an increased risk of axillary recurrence in the first 3–5 years after surgery, despite the fact that the majority of these patients (75%) received RNI. From a mechanistic perspective, it is plausible that, even in patients without additional positive lymph nodes left behind at the time of surgery, circulating tumor cells may preferentially home to residual regional lymphatic structures preserved in the setting of ALND omission,[26] which could explain the increased risk of axillary recurrence in this population. It should, however, be noted that despite additional positive lymph nodes being found in 22% of patients with TNBC who underwent ALND (Fig. 2B), the absolute difference in any axillary recurrence rate by use of ALND in this group was small (6·3%). Therefore, even in case of residual disease, most patients did not experience axillary recurrence, and since synchronous locoregional and distant recurrences represented a minority of cases, many of these patients were still treated with curative intent. In addition, only about a quarter of patients with TNBC received adjuvant immunotherapy, and despite statistical significance, caution should be taken when interpreting these findings, as the increased use of effective post-neoadjuvant systemic therapy may impact the association between ALND omission and the risk of axillary recurrence in the future. However, an exploratory subgroup analysis among patients with TNBC who received adjuvant capecitabine still showed a benefit of ALND in reducing the risk of any axillary recurrence. As patients treated with pembrolizumab were a small minority (77/284, 27%) and had a short follow-up, we are unable to run a subgroup analysis for this group.

Conversely, with short-term follow-up, omission of ALND was not detrimental for selected patients with HR-positive and HER2-positive tumors who received adjuvant therapies for a significant period of time after surgery. However, in contrast to TNBC, HR+/HER2− tumors tend to recur over a longer period of time (10–15 years),[22] and therefore caution should be taken when interpreting these results, as longer follow-up is needed to establish the safety of ALND omission in this group of patients. Nonetheless, surgical de-escalation trials in the upfront surgery setting have demonstrated that axillary recurrence in patients with HR+/HER2− tumors tends to occur early,[1,3] and smaller studies in the NAC setting suggest a similar pattern.[7]

These data provide evidence supporting de-escalation of axillary surgery in patients with ypN1mi disease, for whom highly effective adjuvant systemic treatment is available, but not in the high-risk scenario of TNBC with incomplete response to NAC. Prospective studies[12,27,28] are awaited to guide clinical management in these high-risk patients.

To our knowledge, this is the largest real-world study to compare outcomes in patients with residual micrometastases treated with and without ALND, and the first to identify a benefit of ALND among patients with TNBC. However, our study has several limitations that require consideration. Firstly, this is a retrospective observational study, including patients treated over a period of 10 years, during which systemic therapy recommendations for patients with residual disease after NAC changed. As a consequence, only a minority of the included patients with TNBC received adjuvant capecitabine and immunotherapy, which could have led to overestimation of the benefit of ALND. However, an exploratory analysis limited to patients who received capecitabine confirmed the benefit of ALND even in this subgroup of patients. Secondly, as the surgeons' decision to omit ALND was based on a lower baseline risk in addition to patient choice, selection bias needs to be taken into account and these findings are not generalizable to all patients with ypN1mi disease. However, propensity-score-matched analysis, matching patients for all baseline differences, showed consistent results. Omission of ALND in favor of RNI in patients with ypN+ disease is being investigated in randomized trials which will report in the upcoming years.[12,29] However, our results are important to inform current surgical decisions, as there is a large group of patients with ypN1mi disease who likely does not benefit from ALND. In addition, the ongoing randomized controlled trials are unlikely to answer subtype specific questions. Only 12·5% of patients enrolled in the ALLIANCE A011202 trial had TNBC,[12] and although the OPBC-03/TAXIS trial is still accruing patients, only 7% were reported to have TNBC.[28] Thirdly, despite our study's pooled analysis from 84 centers, sample size determination was based on the number of cases available at the participating sites. Fourthly, the median follow-up was relatively short (3·1 years). Although longer follow-up is planned, prior NAC studies suggest that axillary recurrence tends to be an early event.[7] It is therefore anticipated that these findings will be re-affirmed with more prolonged follow-up. Another limitation is the lack of standardized pathological assessment and centralized review, which could have introduced potential misclassification bias; nonetheless, the two sensitivity analyses conducted showed consistent results. It should also be highlighted that the applicability of these findings to regions with limited access to RNI, systemic therapy, dual tracer mapping, and TAD/MARI techniques is unclear, and caution should be taken when extrapolating these findings to low-resource settings. Lastly, due to the retrospective nature of the study, we were unable to collect lymphedema rates and patient-reported outcomes, which should be the focus of future prospective trials.

In patients with residual micrometastases selected for ALND omission, rates of axillary and invasive recurrence did not significantly differ based on extent of axillary surgery, with the exception of patients with TNBC. Omission of RNI and TNBC biology were independently associated with an increased risk of axillary recurrence. Overall, these results provide evidence supporting de-escalation of axillary surgery in HR-positive/HER2-negative and HER2-positive tumors with residual micrometastases. However, omission of ALND in TNBC patients who fail to achieve nodal pCR appears to increase risk of axillary recurrence, and can therefore not be endorsed on the basis of these results. Longer follow-up of this cohort is planned to support the safety of ALND omission in patients with residual micrometastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

Data collected for the study including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to others on acceptance of an official request to Memorial Sloan Kettering Cancer Center, NY, USA (montagng@mskcc.org), after Institutional Review Board approval for release. The study protocol is available in the appendix p 103–113 of this article, and other related documents can also be made available to others on request to Memorial Sloan Kettering Cancer Center.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for studies published in English from inception to March 30, 2025, on oncological outcomes after omission of axillary lymph node dissection (ALND) in patients with residual nodal disease after neoadjuvant chemotherapy (NAC). Searches were intentionally broad and included the terms “breast cancer” AND “node positive” AND “neoadjuvant chemotherapy” AND (“axillary surgery” OR “sentinel lymph node biopsy” OR “targeted axillary dissection” OR “axillary lymph node dissection”) AND “residual nodal disease”. We identified two population-based studies, five retrospective studies, and one prospective multi-institutional registry. Collectively, all studies showed low rates of axillary recurrences with no apparent benefit of ALND as compared to less extensive axillary surgery, but were limited by selection bias, small sample size, and short-term follow-up. Despite a substantial knowledge gap on the safety of ALND omission in patients with persistent nodal disease after NAC, ALND is currently being omitted in up to 69% of patients with residual micrometastases.

Added value of this study

To our knowledge, this is the first international multi-institutional study to compare oncological outcomes after omission of ALND in a large cohort of patients with residual micrometastases. We aimed to include both high-volume centers and small breast units in the private, public, and academic settings to increase the applicability of our findings. Results indicate that axillary recurrence after ALND omission was rare, with the exception of patients with TNBC who were at increased risk of regional recurrence when treated with less-extensive axillary surgery.

Implications of all the available evidence

With the exception of patients with TNBC, 3-year axillary recurrence rates were low and did not significantly differ based on ALND use. This study does not support ALND for all patients with ypN1mic disease treated with nodal RT but it underscores the importance of tumor biology when considering de-escalation of axillary surgery in the post-NAC setting. Future research should focus on the impact of ALND omission post-NAC based on tumor biology.

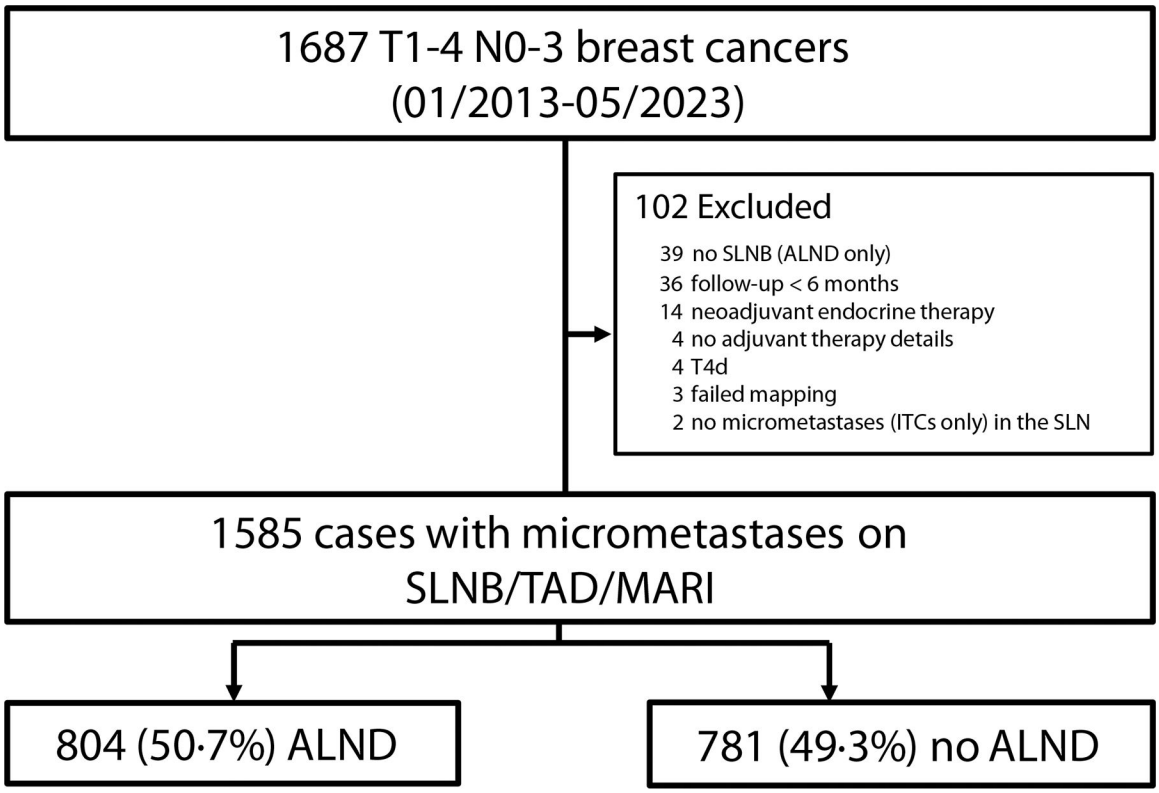

Figure 1: Flow diagram

SLNB=sentinel lymph node biopsy, ALND=axillary lymph node dissection, TAD=targeted axillary dissection, MARI=marking axillary lymph nodes with radioactive iodine seeds

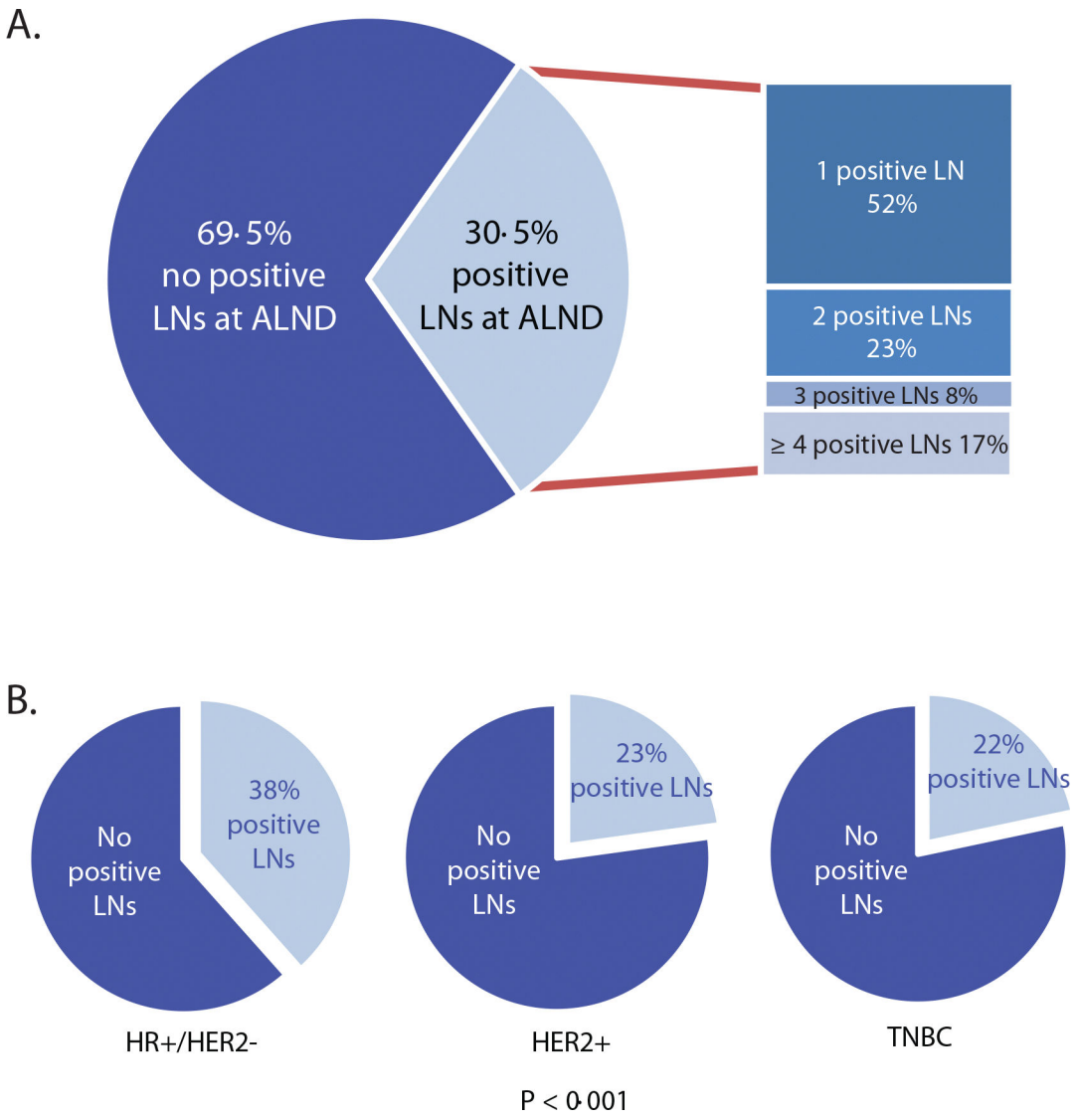

Figure 2: Proportion of patients with additional positive lymph nodes at axillary lymph node dissection by: (A) all patients undergoing ALND (n = 804); (B) stratified by tumor subtype

pos=positive, LNs=lymph nodes, ALND=axillary lymph node dissection

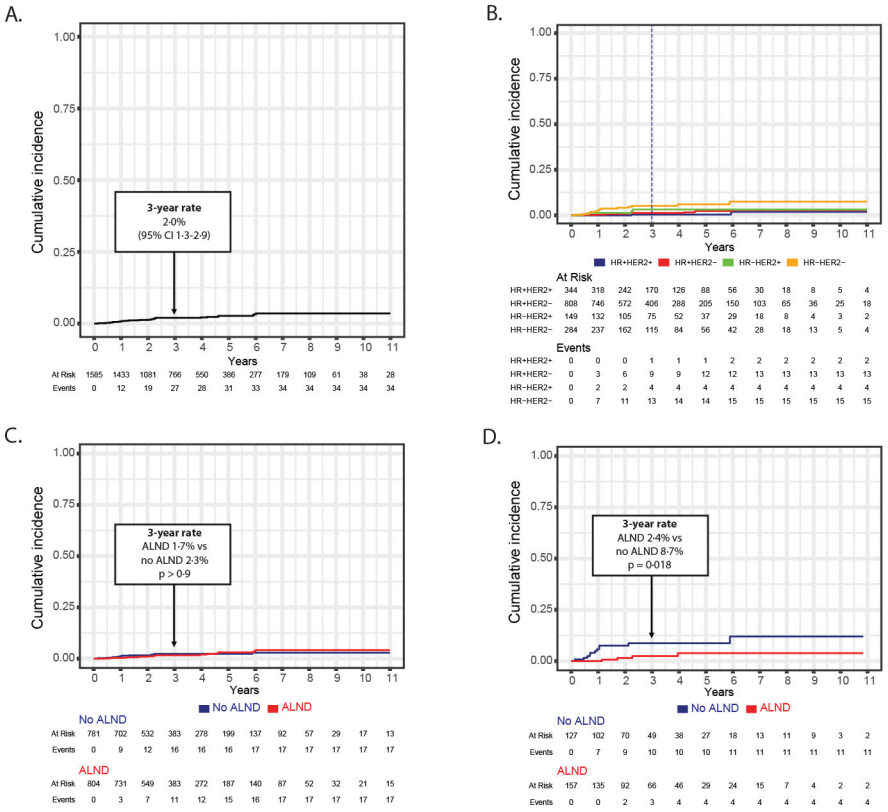

Figure 3: Competing risk analysis for: (A) any axillary recurrence (Overall Cohort); (B) any axillary recurrence (stratified by tumor subtype); (C) any axillary recurrence (stratified by axillary surgery); (D) any axillary recurrence among TNBC patients (stratified by surgical group)

CI=confidence interval, HR=hormone receptor, HER2=human epidermal growth factor receptor 2, ALND=axillary lymph node dissection

Table 1:

Clinicopathological features of the study cohort, stratified by surgical group

	Overall n=1,585	No ALND n=781	ALND n=804	*P-value* [a]
Age, years (median, IQR)	48 (41,58)	48 (40,59)	48 (41, 57)	0·89
Race/Ethnicity				**< 0·001**
Asian	238 (15)	96 (12)	142 (18)	
Black	65 (4·1)	23 (2·9)	42 (5·2)	
Hispanic	200 (13)	85 (11)	115 (14)	
White	968 (61)	502 (64)	466 (58)	
Other/Unknown	114 (7·2)	75 (9·6)	39 (4·9)	
Site location				**< 0·001**
North America	557 (35)	236 (30)	321 (40)	
Other	1,028 (65)	545 (70)	483 (60)	
Year of surgery				0·85
2013–2016	308 (19)	156 (20)	152 (19)	
2017–2019	428 (27)	208 (27)	220 (27)	
2020–2013	849 (54)	417 (53)	432 (54)	
Clinical T category at presentation				0·14
1	235 (15)	114 (15)	121 (15)	
2	925 (58)	476 (61)	449 (56)	
3	347 (22)	155 (20)	192 (24)	
4	76 (4·8)	36 (4·6)	40 (5)	
X	2 (0·1)	0 (0)	2 (0·2)	
Clinical N category at presentation				**< 0·001**
0	531 (34)	309 (40)	222 (28)	
1	889 (56)	412 (53)	477 (59)	
2	124 (7·8)	38 (4·9)	86 (11)	
3	41 (2·6)	22 (2·8)	19 (2·4)	
Tumor subtype				0·13
HR+/HER2−	808 (51)	402 (51)	406 (50)	
HR+/HER2+	344 (22)	184 (24)	160 (20)	
HR−/HER2+	149 (9·4)	68 (8·7)	81 (10)	
HR−/HER2−	284 (18)	127 (16)	157 (20)	
Histology				0·48
Ductal	1,434 (91)	711 (91)	723 (90)	
Lobular or mixed	108 (6·8)	54 (6·9)	54 (6·7)	
Other	37 (2·3)	14 (1·8)	23 (2·9)	
Occult or unknown	6 (0·4)	2 (0·3)	4 (0·5)	
Tumor differentiation				0·57
Well	76 (5·1)	37 (5·1)	39 (5·1)	

	Overall n=1,585	No ALND n=781	ALND n=804	*P-value* [a]
Moderately	682 (46)	343 (47)	339 (45)	
Poorly	729 (49)	346 (48)	383 (50)	
Unknown	98	55	43	
LVI				0·21
Present	469 (30)	218 (28)	251 (31)	
Type of breast surgery				0·059
BCS	763 (48)	394 (50)	369 (46)	
Mastectomy	820 (52)	387 (50)	433 (54)	
No breast surgery[b]	2 (0·1)	0 (0)	2 (0·2)	
Breast pCR (ypT0/is)				0·49
Yes	290 (18)	140 (18)	150 (19)	
Residual breast disease (size) (n = 1,295)				0·57
< 2 cm	815 (65)	401 (66)	414 (64)	
2–5 cm	85 (6·8)	42 (6·9)	43 (6·6)	
> 5 cm	355 (28)	163 (27)	192 (30)	
Unknown	40	35	5	
NAC regimen HER2− (n = 1,092)				**< 0·001**
AC-T	790 (72)	356 (67)	434 (77)	
AC-T + Carbo	83 (7·6)	44 (8·3)	39 (6·9)	
AC-T + Carbo + pembrolizumab	77 (7·1)	37 (7·0)	40 (7·1)	
Anthracycline-free regimen[c]	39 (3·6)	15 (2·8)	24 (4·3)	
Other	103 (9·4)	77 (15)	26 (4·6)	
NAC regimen HER2+ (n = 493)				0.99
AC-TH	21 (4·3)	10 (4·0)	11 (4·6)	
AC-THP	107 (22)	55 (22)	52 (22)	
TCH	110 (22)	55 (22)	55 (23)	
TCHP	114 (23)	60 (24)	54 (22)	
Other	141 (29)	72 (29)	69 (29)	
Axillary staging technique in cN+ (n = 1,054)				**< 0·001**
SLNB with dual tracer mapping	659 (62)	285 (60)	374 (64)	
TAD	330 (31)	143 (30)	187 (32)	
MARI	65 (6·2)	44 (9·3)	21 (3·6)	
Number of sentinel lymph nodes removed [d]				**0·024**
mean (range)	3·08 (0, 20)	3·14 (0, 12)	3·03 (0, 20)	
< 3	640 (42)	292 (40)	348 (44)	
≥ 3	880 (58)	445 (60)	435 (56)	
Number of non-sentinel lymph nodes removed (mean, range)	0·74 (0, 11)	0·97 (0, 11)	0·52 (0, 9)	**< 0·001**
Number of sentinel lymph nodes with micrometastases				**< 0·001**
mean (range)	1·17 (0, 6)	1·13 (1, 4)	1·22 (0, 6)	

	Overall n=1,585	No ALND n=781	ALND n=804	*P-value* [a]
1	1293 (85)	654 (89)	639 (82)	
2	192 (13)	72 (9.8)	120 (15)	
≥ 3	33 (2.2)	10 (1.4)	23 (2.9)	
Number of concomitant SLNs, TAD or MARI nodes with ITCs (mean, range)	0·12 (0, 9)	0·10 (0, 4)	0·13 (0, 9)	0·34
Total number of lymph nodes removed (mean, range)	10 (1,47)	4 (1,18)	16 (2, 47)	**< 0·001**
Total number of positive lymph nodes removed (mean, range)	1·62 (1, 17)	1·22 (1, 6)	2·02 (1, 17)	**< 0·001**
Micrometastases detected on frozen section	637 (40)	135 (17)	502 (62)	**< 0·001**
Breast RT (n = 763)	745 (98)	377 (96)	368 (99)	**0·002**
Chest Wall RT (n = 820)	690 (84)	311 (80)	379 (88)	**0·004**
Regional nodal irradiation	1,267 (80)	615 (79)	652 (81)	0·22
Adjuvant endocrine therapy (n = 1152)	1,104 (96)	562 (96)	542 (96)	0·68
Adjuvant abemaciclib (n = 808)	19 (2·4)	9 (2·2)	10 (2·5)	0·83
Adjuvant anti-HER2 therapy (n = 493)	470 (95)	242 (96)	228 (95)	0·45
Adjuvant capecitabine (n = 1092)	188 (17·2)	77 (14·6)	111 (19·7)	0·02
Adjuvant olaparib	14 (0·9)	7 (0·9)	7 (0·9)	0·99

Data are expressed as frequency (column percentage) for categorical variables, and median (interquartile range) or mean (standard deviation) for continuous variables. Statistically significant values are indicated in bold.

HR=hormone receptor, HER2=human epidermal growth factor receptor 2, LVI=lymphovascular invasion, BCS=breast-conserving surgery, SLNB=sentinel lymph node biopsy, pCR=pathological complete response, MARI=**marking axillary lymph nodes with radioactive iodine seeds**, NAC=neoadjuvant chemotherapy, AC-T=doxorubicin hydrochloride (Adriamycin) and cyclophosphamide, followed by paclitaxel (Taxol), Carbo=Carboplatin, H=Herceptin, P=Perjeta, TAD=targeted axillary dissection, TC=Docetaxel and Carboplatin, ITCs=isolated tumor cells, RT=radiation therapy

[a]Results are from the Wilcoxon rank-sum test for continuous variables, and Fisher's exact test or the Chi-square test of independence for categorical variables

[b]Occult carcinoma

[c]Includes CMF (Cyclophosphamide, Methotrexate, Fluorouracil) and TC (Taxotere and Cyclophosphamide)

[d]MARI cases were excluded (n=65)

Table 2:

Multivariable analysis looking at the association between clinicopathological factors and the risk of A) any axillary recurrence and B) any invasive recurrence.

	Any Axillary recurrence		**Any Invasive recurrence**	
	Multivariable		**Multivariable**	
	Hazard ratio (95% CI)	**P**	**Hazard ratio (95% CI)**	**P**
Age*per 1-year increase*	0·97 (0·94, 1·00)	**0·025**	1·01 (1·00, 1·02)	0·11
ALND*ref: no ALND*	0·86 (0·37, 2·00)	0·73	1·05 (0·78, 1·41)	0·77
Breast surgery*ref: BCS*				
Mastectomy	0·74 (0·36, 1·50)	0·40	1·02 (0·77, 1·35)	0·88
cT category at presentation*ref: 1/x*				
2	6·19 (0·83, 46·1)	0·08	1·51 (1·04, 2·19)	0·03
3/4	11·1 (1·13, 108)	**0·039**	2·00 (1·32, 3·03)	**0·001**
cN category at presentation*ref: 0*				
1	1·77 (0·76, 4·09)	0·23	0·91 (0·68, 1·21)	0·50
2	1·09 (0·23, 5·21)	0·99	0·95 (0·61, 1·49)	0·82
3	3·07 (0·87, 10·9)	0·08	1·22 (0·64, 2·32)	0·54
Subtype*ref: HR+/HER2−*				
HER2+	0·81 (0·39, 1·68)	0·60	0·89 (0·66, 1·20)	0·45
TNBC	3·83 (1·72, 8·52)	< **0·001**	3·17 (2·30, 4·35)	< **0·001**
Regional nodal irradiation*ref: Yes*	2·62 (1·19, 5·73)	**0·016**	1·61 (1·20, 2·15)	**0·002**

CI=confidence interval, ALND=axillary lymph node dissection, BCS=breast-conserving surgery, HR=hormone receptor, HER2=human epidermal growth factor receptor 2, TNBC=triple-negative breast cancer