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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Summary

Background Despite the paucity of outcome data, axillary lymph node dissection (ALND) is increasingly being omitted in patients with positive sentinel lymph nodes after neoadjuvant chemotherapy, particularly in those with low-volume residual disease. We investigated oncological outcomes in patients with breast cancer and residual micrometastases in the sentinel lymph nodes treated with or without ALND.

Methods OPBC-07/microNAC was a retrospective cohort study, using data obtained from the institutional databases of 84 cancer centres in 30 countries. Patients aged 18 years or older with clinical T1–4, N0–3 breast cancer at diagnosis treated with neoadjuvant chemotherapy followed by surgery between Jan 1, 2013, and May 31, 2023, who were found to have residual micrometastases (metastasis measuring >0·2 mm or >200 cells, not exceeding 2·0 mm in size) on frozen section or on final paraffin sections as determined by sentinel lymph node biopsy, targeted axillary dissection (sentinel lymph node biopsy with single or dual-tracer mapping plus image-guided localisation of the initially biopsy-proven and clipped node), or the marking axillary lymph nodes with radioactive iodine seeds (MARI) procedure were eligible for inclusion. The primary endpoint was the 5-year rate of any axillary recurrence (isolated or combined with local or distant recurrence) stratified by type of axillary surgery. Given the median follow-up, here we report 3-year rates and exploratory 5-year estimates. This study was registered with ClinicalTrials.gov, NCT06529302.

Findings 1585 female patients with ypN1mi disease were analysed, of whom 804 (50·7%) underwent ALND and 781 (49·3%) did not. Of 1585 women, 238 (15·0%) self-identified as Asian, 65 (4·1%) as Black, 200 (12·6%) as Hispanic, 968 (61·1%) as White, and 114 (7·2%) as unknown race and ethnicity. 925 (58·4%) of 1585 women had cT2 tumours, 1054 (66·5%) were node positive, and 1267 (79·9%) received nodal radiotherapy. The median follow-up was 3·1 years (IQR 1·8–5·2). The 3-year rate of any axillary recurrence (isolated or combined with local or distant recurrence) for the entire cohort was 2·0% (95% CI 1·3–2·9), with no statistical difference identified by extent of axillary surgery. However, patients with triple-negative disease who did not receive ALND had significantly higher rates of any axillary recurrence than women treated with ALND (8·7% [95% CI 4·4–15·0] *vs* 2·4% [95% CI 0·7–6·5], p=0·018). On multivariable analysis, triple-negative breast cancer (hazard ratio 3·83 [95% CI 1·72–8·52]) and omission of nodal radiotherapy (2·62 [1·19–5·73]) but not omission of ALND (0·86 [0·37–2·00]) were independently associated with an increased risk of any axillary recurrence.

Interpretation Overall, these results do not support ALND for all patients with ypN1mi on sentinel lymph node biopsy treated with nodal radiotherapy; however, tumour biology should be taken into account when considering ALND omission.

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Introduction

For patients with breast cancer who undergo surgery as the first step in their treatment, randomised clinical trials have demonstrated no benefit of axillary lymph node dissection (ALND) in patients with micrometastases and macrometastases in one or two sentinel lymph nodes.[1–3]

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Research in context

Evidence before this study

We searched PubMed from database inception to March 30, 2025, for studies published in English on oncological outcomes after omission of axillary lymph node dissection (ALND) in patients with residual nodal disease after neoadjuvant chemotherapy. 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 compared with less extensive axillary surgery, but the studies 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 neoadjuvant chemotherapy, 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 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 centres 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 triple-negative breast cancer 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 triple-negative breast cancer, 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 ypN1mi disease treated with nodal radiotherapy, but it underscores the importance of tumour biology when considering de-escalation of axillary surgery in the post-neoadjuvant chemotherapy setting. Future research should focus on the impact of ALND omission after neoadjuvant chemotherapy based on tumour biology.

In the neoadjuvant chemotherapy setting, omission of ALND in patients with nodal complete pathological response or residual isolated tumour cells after neoadjuvant chemotherapy does not affect oncological outcomes,[4–9] but whether this is the case for patients with residual micrometastases and macrometastases is unknown.

Several studies have demonstrated that the residual nodal burden in patients with positive sentinel lymph nodes after neoadjuvant chemotherapy is higher than in the upfront surgery setting, with additional positive lymph nodes 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 the paucity of oncological outcome data from randomised trials, several real-world studies have shown that ALND is increasingly being omitted in favour of regional nodal irradiation, particularly in patients with ypN1mi disease.[14–16] We conducted a multicentre, retrospective cohort study to assess oncological outcomes in patients with breast cancer and ypN1mi disease treated with and without completion ALND, focusing on the differences between tumour subtypes.

Methods

Study design and participants

OPBC-07/microNAC was a retrospective cohort study of data collected from the institutional databases of 84 cancer centres in 30 countries (the majority of centres are included in the Oncoplastic Breast Consortium [OPBC] network; appendix pp 1–84, 98–101).

Patients aged 18 years or older with clinical T1–4, N0–3 breast cancer at diagnosis, who were treated with neoadjuvant chemotherapy between Jan 1, 2013, and May 31, 2023, had micrometastases (metastasis measuring >0·2 mm or >200 cells, not exceeding 2·0 mm in size) on frozen section or final paraffin sections as determined by sentinel lymph node biopsy, targeted axillary dissection, or the marking axillary lymph nodes with radioactive iodine seeds (MARI) procedure were eligible for inclusion. Downstaging to clinical N0 after neoadjuvant chemotherapy was required for patients who presented with palpable disease. The concomitant presence of isolated tumour cells in other sentinel lymph nodes 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 tumour cells only or macrometastases in any sentinel lymph nodes at frozen section or final pathology were ineligible.

Oestrogen receptor-positive and progesterone receptor-positive disease was defined as expression of 1% or higher. Human epidermal growth factor receptor 2 (HER2) status was classified by immunohistochemistry and fluorescence in situ hybridisation analysis (FISH). HER2-negative tumours were defined as those with an immunohistochemistry score of 0 or 1+ or 2+ with negative FISH results. HER2-positive tumours were defined as tumours with an immunohistochemistry score of 3+ or positive FISH.

Institutional review board approval was obtained for each site in the USA, with informed consent waived due

to use of de-identified data. The University Hospital of Basel (Basel, Switzerland) acted as a coordinating centre for the non-US sites and as the central ethics committee. The study received approval from the Ethics Committee of Northwestern and Central Switzerland (ID 2024-00186), and from the local, regional, or national institutional review boards of participating centres, whenever required by regulations. A data use agreement was established between Memorial Sloan Kettering Cancer Center (MSKCC) and the other institutions in North America, and between MSKCC and the University Hospital of Basel, which served as the OPBC coordinating centre. The study followed STROBE guidelines.[17] Data cleaning for the OPBC sites was initiated at the OPBC coordinating centre and completed at MSKCC. For all other sites, data cleaning was conducted at MSKCC where the statistical analysis was carried out. The study protocol is available in the appendix (pp 103–13). This study was registered with ClinicalTrials.gov, NCT06529302.

Procedures

The sentinel lymph node biopsy procedure included removal of all lymph nodes that were either blue (isosulfan blue dye, patent blue, or methylene blue), green (indocyanine green), radioactive (technetium-99m), or palpably abnormal. For patients with cN0 disease at presentation, single tracer was allowed, while for patients with cN+ disease, use of dual-tracer mapping was mandatory. Targeted axillary dissection consisted of sentinel lymph node biopsy with single or dual-tracer mapping plus image-guided localisation of the initially biopsy-proven and clipped node. The MARI procedure consisted of selective removal of the pathologically proven metastatic lymph node, which was marked with an iodine seed before neoadjuvant chemotherapy. Details of the surgical procedures, pathology assessment, and radiotherapy specific to each site are provided in the appendix (pp 1–84, 85–86).

Neoadjuvant chemotherapy regimens, adjuvant systemic therapy, and regional nodal irradiation were administered as per 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 were the rates of locoregional recurrence, and any invasive recurrence (defined as locoregional or distant), and the proportion of additional positive lymph nodes (stratified by tumour subtype) among patients who underwent ALND. We initially planned to analyse the rate of isolated axillary recurrence as a second primary endpoint and to conduct a multivariable analysis to assess factors associated with isolated axillary recurrence. However, due to the low number of events (n=7), this was not possible, and the rate of isolated recurrence was analysed as a post-hoc secondary endpoint; this decision had no impact on the remainder of the statistical analysis. Additionally, it was initially planned to report 5-year rates, but considering the median follow-up, 3-year rates as post-hoc secondary endpoints 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. Clinicopathological and demographic characteristics were compared between surgical groups using the Wilcoxon rank sum test or Student's *t*-test for continuous variables, and the χ^2 or Fisher's exact test for categorical variables. The mean number of sentinel lymph nodes was calculated excluding patients who underwent the MARI technique. The rate of additional positive lymph nodes at completion ALND was compared between tumour subtypes using the χ^2 test. An exploratory correlation analysis was conducted between the number of sentinel lymph nodes with micrometastases and the number of additional positive lymph nodes 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 87). 3-year cumulative incidence was compared between patients treated with and without completion ALND in the overall cohort and within tumour subtypes, using Gray's test. The assumption of proportionality was made through preliminary visual inspection of the cumulative incidence curves. Sensitivity analysis for this

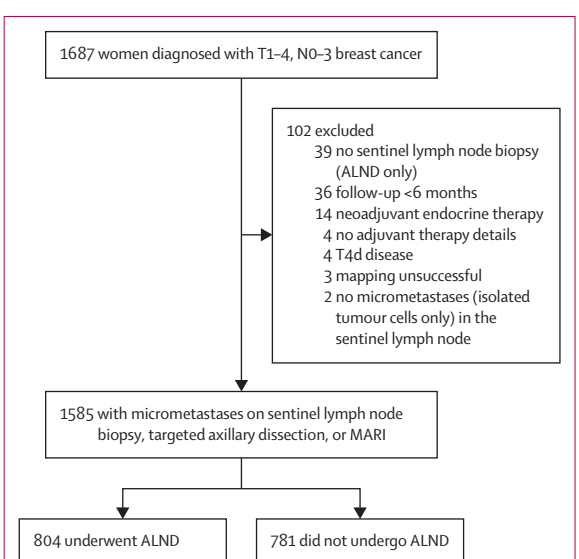

Figure 1: **Study profile**
ALND=axillary lymph node dissection. MARI=marking axillary lymph nodes with radioactive iodine seeds.

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	Overall (n=1585)	No ALND (n=781)	ALND (n=804)	p value*
Age, years	48 (41–58)	48 (40–59)	48 (41– 57)	0·89
Race or ethnicity				<0·0001
Asian	238 (15·0%)	96 (12·3%)	142 (17·6%)	..
Black	65 (4·1%)	23 (2·9%)	42 (5·2%)	..
Hispanic	200 (12·6%)	85 (10·9%)	115 (14·3%)	..
White	968 (61·1%)	502 (64·3%)	466 (58·0%)	..
Other or unknown	114 (7·2%)	75 (9·6%)	39 (4·9%)	..
Location				<0·0001
North America	557 (35·1%)	236 (30·2%)	321 (39·9%)	..
Other	1028 (64·9%)	545 (69·8%)	483 (60·1%)	..
Year of surgery				0·85
2013–16	308 (19·4%)	156 (20·0%)	152 (18·9%)	..
2017–19	428 (27·0%)	208 (26·6%)	220 (27·4%)	..
2020–23	849 (53·6%)	417 (53·4%)	432 (53·7%)	..
Clinical T stage at presentation				0·14
1	235 (14·8%)	114 (14·6%)	121 (15·0%)	..
2	925 (58·4%)	476 (60·9%)	449 (55·8%)	..
3	347 (21·9%)	155 (19·8%)	192 (23·9%)	..
4	76 (4·8%)	36 (4·6%)	40 (5·0%)	..
X	2 (0·1%)	0	2 (0·2%)	..
Clinical N stage at presentation				<0·0001
0	531 (33·5%)	309 (39·6%)	222 (27·6%)	..
1	889 (56·1%)	412 (52·7%)	477 (59·3%)	..
2	124 (7·8%)	38 (4·9%)	86 (10·7%)	..
3	41 (2·6%)	22 (2·8%)	19 (2·4%)	..
Tumour subtype				0·13
Hormone receptor-positive, HER2-negative	808 (51·0%)	402 (51·5%)	406 (50·5%)	..
Hormone receptor-positive, HER2-positive	344 (21·7%)	184 (23·6%)	160 (19·9%)	..
Hormone receptor-negative, HER2-positive	149 (9·4%)	68 (8·7%)	81 (10·1%)	..
Hormone receptor-negative, HER2-negative	284 (17·9%)	127 (16·3%)	157 (19·5%)	..
Tumour histology				0·48
Ductal	1434 (90·5%)	711 (91·0%)	723 (89·9%)	..
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%)	..
Tumour differentiation				0·57
Well	76 (4·8%)	37 (4·7%)	39 (4·9%)	..
Moderately	682 (43·0%)	343 (43·9%)	339 (42·2%)	..
Poorly	729 (45·8%)	346 (44·3%)	383 (47·6%)	..
Unknown	98 (6·2%)	55 (7·0%)	43 (5·3%)	..
Lymphovascular invasion	469 (29·6%)	218 (27·9%)	251 (31·0%)	0·21
Type of breast surgery				0·059
Breast-conserving surgery	763 (48·1%)	394 (50·4%)	369 (45·9%)	..
Mastectomy	820 (51·7%)	387 (49·6%)	433 (53·9%)	..
No breast surgery†	2 (0·1%)	0	2 (0·2%)	..
Breast pathological complete response (ypT0/is)	290 (18·3%)	140 (17·9%)	150 (18·7%)	0·49
Residual breast disease size, n/N (%)				0·57
<2 cm	815/1295 (62·9%)	401/641 (62·6%)	414/654 (63·3%)	..
2–5 cm	85/1295 (6·6%)	42/641 (6·6%)	43/654 (6·6%)	..
>5 cm	355/1295 (27·4%)	163/641 (25·4%)	192/654 (29·4%)	..
Unknown	40/1295 (3·1%)	35/641 (5·5%)	5/654 (0·8%)	..

(Table 1 continues on next page)

	Overall (n=1585)	No ALND (n=781)	ALND (n=804)	p value*
(Continued from previous page)				
Neoadjuvant chemotherapy regimen for HER2-negative breast cancer, n/N (%)				<0·0001
Adriamycin and cyclophosphamide, followed by paclitaxel	790/1092 (72·3%)	356/529 (67·3%)	434/563 (77·1%)	..
Adriamycin and cyclophosphamide, followed by paclitaxel and carboplatin	83/1092 (7·6%)	44/529 (8·3%)	39/563 (6·9%)	..
Paclitaxel and carboplatin followed by adriamycin and cyclophosphamide in combination wtih pembrolizumab	77/1092 (7·1%)	37/529 (7·0%)	40/563 (7·1%)	..
Anthracycline-free regimen‡	39/1092 (3·6%)	15/529 (2·8%)	24/563 (4·3%)	..
Other	103/1092 (9·4%)	77/529 (14·6%)	26/563 (4·6%)	..
Neoadjuvant chemotherapy regimen for HER2-positive breast cancer, n/N (%)				0·99
Adriamycin and cyclophosphamide followed by paclitaxel and trastuzumab	21/493 (4·3%)	10/252 (4·0%)	11/241 (4·6%)	..
Adriamycin and cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab	107/493 (22·7%)	55/252 (21·8%)	52/241 (21·6%)	..
Docetaxel and carboplatin, in combination with trastuzumab	110/493 (22·3%)	55/252 (21·8%)	55/241 (22·8%)	..
Docetaxel and carboplatin, in combination with trastuzumab and pertuzumab	114/493 (23·1%)	60/252 (23·8%)	54/241 (22·4%)	..
Other	141/493 (29·6%)	72/252 (28·6%)	69/241 (28·6%)	..
Axillary staging technique in patients with clinically node-positive tumours, n/N (%)				0·0007
SLNB with dual-tracer mapping	659/1054 (62·5%)	285/472 (60·4%)	374/582 (64·3%)	..
Targeted axillary dissection	330/1054 (31·3%)	143/472 (30·3%)	187/582 (32·1%)	..
MARI	65/1054 (6·2%)	44/472 (9·3%)	21/582 (3·6%)	..
Number of sentinel lymph nodes removed§				0·024
Mean (range)	3·08 (0·00–20·00)	3·14 (0·00–12·00)	3·03 (0·00–20·00)	..
<3	640 (42·1%)	292 (39·6%)	348 (44·4%)	..
≥3	880 (57·9%)	445 (60·4%)	435 (55·7%)	..
Mean number of non-sentinel lymph nodes removed (range)	0·74 (0·00–11·00)	0·97 (0·00–11·00)	0·52 (0·00–9·00)	<0·0001
Number of sentinel lymph nodes with micrometastases				<0·0001
Mean (range)	1·17 (0·00–6·00)	1·13 (1·00–4·00)	1·22 (0·00–6·00)	..
1	1293 (85·2%)	654 (88·9%)	639 (82·0%)	..
2	192 (12·6%)	72 (9·8%)	120 (15·0%)	..
≥3	33 (2·2%)	10 (1·4%)	23 (2·9%)	..
Mean number of concomitant sentinel lymph nodes, targeted axillary dissection nodes, or MARI nodes with isolated tumour cells (range)	0·12 (0·00–9·00)	0·10 (0·00–4·00)	0·13 (0·00–9·00)	0·34
Mean number of lymph nodes removed (range)	10 (1–47)	4 (1–18)	16 (2–47)	<0·0001
Mean number of positive lymph nodes removed (range)	1·62 (1·00–17·00)	1·22 (1·00–6·00)	2·02 (1·00–17·00)	<0·0001
Micrometastases detected on frozen section	637 (40·2%)	135 (17·3%)	502 (62·4%)	<0·0001
Breast radiotherapy	745/763 (97·6%)	377/394 (95·7%)	368/369 (99·7%)	0·002
Chest wall radiotherapy	690/820 (84·1%)	311/387 (80·4%)	379/433 (87·5%)	0·004
Regional nodal irradiation	1267 (79·9%)	615 (78·7%)	652 (81·1%)	0·22
Adjuvant endocrine therapy	1104/1152 (95·8%)	562/586 (95·9%)	542/566 (95·8%)	0·68
Adjuvant abemaciclib	19/808 (2·4%)	9/402 (2·2%)	10/406 (2·5%)	0·83
Adjuvant anti-HER2 therapy	470/493 (95·3%)	242/252 (96·0%)	228/241 (94·6%)	0·45
Adjuvant capecitabine	188/1092 (17·2%)	77/529 (14·6%)	111/563 (19·7%)	0·02
Adjuvant olaparib	14 (0·9%)	7 (0·9%)	7 (0·9%)	0·99

Data are median (IQR) or n (%), unless otherwise stated. ALND=axillary lymph node dissection. HER2=human epidermal growth factor receptor 2. SLNB=sentinel lymph node biopsy. MARI=marking axillary lymph nodes with radioactive iodine seeds. *Values were calculated using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test or the χ^2 test of independence for categorical variables. †Occult carcinoma. ‡Included cyclophosphamide, methotrexate, fluorouracil, and docetaxel and cyclophosphamide. §65 patients who were treated with MARI were excluded.

Table 1: **Clinicopathological features of the study cohort, stratified by surgical group**

assumption is provided in the appendix (p 97). Exploratory 5-year cumulative incidence rates were also calculated. p values of less than 0·05 were considered to indicate a statistically significant difference. 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 to account for the clustering effect induced by each individual institution participating in the study. The 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 or ethnicity, clinical stage, tumour subtype, type of breast surgery, and receipt of regional nodal irradiation. We also performed two sensitivity analyses. The first, to take into account possible interinstitutional variability, was limited to patients treated in high-volume centres. The second, to take into account possible misclassification, was limited to patients who had one or fewer non-sentinel lymph nodes removed before ALND and ten or more lymph nodes removed at ALND. An exploratory subgroup analysis limited to patients with triple-negative breast cancer who received adjuvant capecitabine was also conducted. Statistical analysis was performed using R statistical software (version 4.4.2).

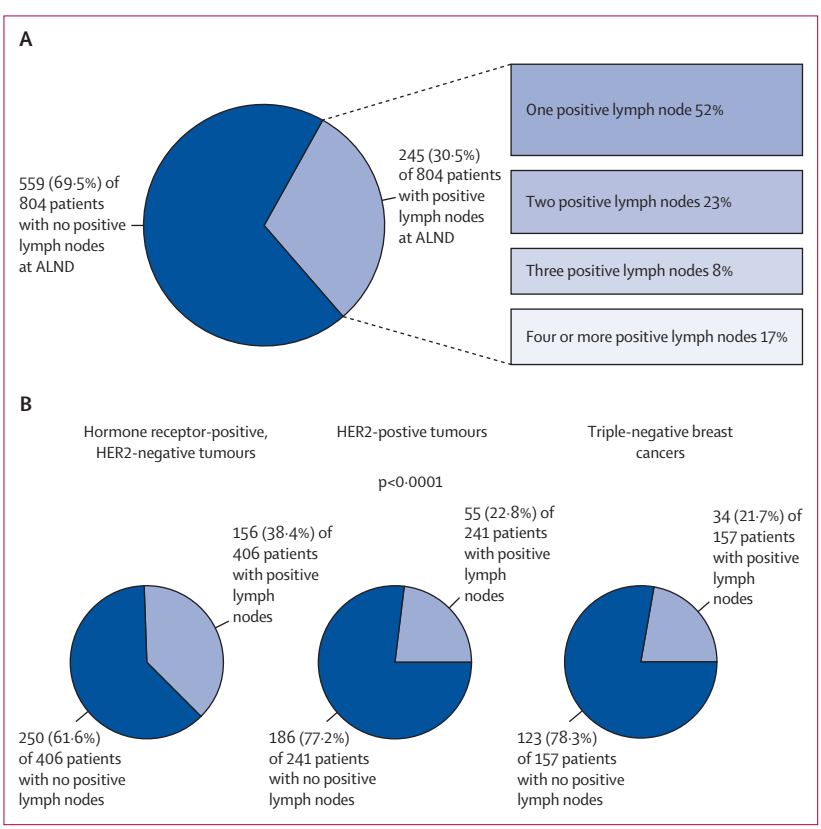

Figure 2: **Proportion of patients with additional positive lymph nodes at axillary lymph node dissection by ALND status (A; n=804) and stratified by tumour subtype (B)**
ALND=axillary lymph node dissection.

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

Results

1585 female patients with residual micrometastases detected on sentinel lymph node biopsy, targeted axillary dissection, or MARI were identified between Jan 1, 2013, and May 31, 2023,(figure 1). Of 1585 patients, 804 (50·7%) were treated with completion ALND and 781 (49·3%) were not. The median age of patients was 48 years (IQR 41–58; table 1). 925 (58·4%) of 1585 women had cT2 disease, 1054 (66·5%) were node positive, and 1267 (79·9%) received regional nodal irradiation. Of 1585 tumours, 808 (51·0%) were hormone receptor-positive, HER2-negative, 493 (31·1%) were HER2-positive, and 284 (17·9%) were triple-negative. Of 1585 women, 238 (15·0%) self-identified as Asian, 65 (4·1%) as Black, 200 (12·6%) as Hispanic, 968 (61·1%) as White, and 114 (7·2%) as unknown race and ethnicity. Patients treated with completion ALND were more likely to be non-White (299 [37·2%] of 804 women *vs* 204 [26·1%] of 781 women not treated with ALND; p<0·0001), present with cN+ disease (582 [72·4%] of 804 women *vs* 472 [60·4%] of 781 women; p<0·0001), have micrometastases detected intraoperatively on frozen section (502 [62·4%] of 804 women *vs* 135 [17·3%] of 781 women; p<0·0001), and have received breast radiotherapy (368 [99·7%] of 369 women *vs* 377 [95·7%] of 394 women; p=0·002) and chest wall irradiation (379 [87·5%] of 433 women *vs* 311 [80·4%] of 387 women; p=0·004), but not regional nodal irradiation (652 [81·1%] of 804 women *vs* 615 [78·7%] of 781 women; p=0·22).

Of the 804 patients who underwent ALND, additional positive nodes were identified in 245 (30·5%) patients, consisting of isolated tumour cells in 20 (8·2%) patients, micrometastases in 123 (50·2%) patients, and macrometastases in 102 (41·6%) patients. The number of additional positive lymph nodes is shown in figure 2A. The likelihood of identifying additional positive lymph nodes at ALND varied by tumour subtype (figure 2B). There was a positive correlation between the number of sentinel lymph nodes with micrometastases and the number of additional positive lymph nodes identified at ALND (Pearson's correlation 0·16; p<0·0001).

The median follow-up was 3·1 years (IQR 1·8–5·2). During follow-up there were seven (0·4%) isolated axillary recurrences in 1585 cases, 34 (2·1%) any axillary recurrences, and 251 (15·8%) 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 2·0% (95% CI 1·3–2·9; figure 3A), and the 3-year rate of isolated axillary

recurrence was 0·3% (0·1–0·7). A statistically significant difference was identified in the rate of any axillary recurrence across tumour subtypes (figure 3B). No significant differences were identified between patients treated with and without ALND for 3-year rates of any axillary recurrence (1·7% [95% CI 0·9–2·9] *vs* 2·3% [1·4–3·7]; p=0·92; figure 3C) or isolated axillary recurrence (0·1% [0·0–0·7] *vs* 0·5% [0·2–1·3]; p=0·67). In the entire cohort, the 3-year rate of locoregional recurrence (local, regional and locoregional) was 4·1% (95% CI 3·1–5·3) and the rate of any invasive recurrence (locoregional or distant) was 14% (12–16). No significant differences in outcome were identified between patients treated with and without ALND (4·1% [95% CI 2·7–5·8] *vs* 4·2% [2·8–5·9], p=0·55; 15% [13–18] *vs* 13% [11–16], p=0·60, respectively). 3-year rates of any invasive recurrence were statistically different across subtypes (appendix pp 89).

The 5-year rate of any recurrence was 2·7% (95% CI 1·8–3·8) and of isolated axillary recurrence was 0·49% (95% CI 0·19–1·1) with no significant differences identified between ALND and no ALND groups (3·1% [95% CI 1·7–5·1] *vs* 2·3% [1·4–3·7]; 0·5% [0·1–1·6] *vs* 0·5% [0·2–1·3], respectively). The 5-year rate of any invasive recurrence was 21% (95% CI 18–23), with no significant difference identified between ALND and no ALND groups (21% [95% CI 18–25] *vs* 20% [17–24]). Multiple sensitivity analyses and a propensity-matched analysis showed consistent results (appendix pp 90–95, 97).

On multivariable analysis, ALND was not independently associated with the risk of any axillary or any invasive recurrence, while the triple-negative subtype, omission of regional nodal irradiation, and more advanced clinical T category were independently associated with the risk of any axillary or any invasive recurrence (table 2). In the triple-negative breast cancer group, there were 92 any invasive recurrence events, of which 15 (16·3%) were axillary (three isolated, six combined axillary and supraclavicular, one locoregional, and five synchronous locoregional and distant). When comparing patients with triple-negative breast cancer treated with ALND (n=157) and without ALND (n=127), those without ALND had significantly higher rates of any axillary recurrence (8·7% [95% CI 4·4–15·0] *vs* 2·4% [0·7–6·5]; p=0·018; figure 3D) but no significant differences were identified in the rates of any invasive recurrence (35% [27–44] *vs* 32% [23–41]; p=0·86; appendix

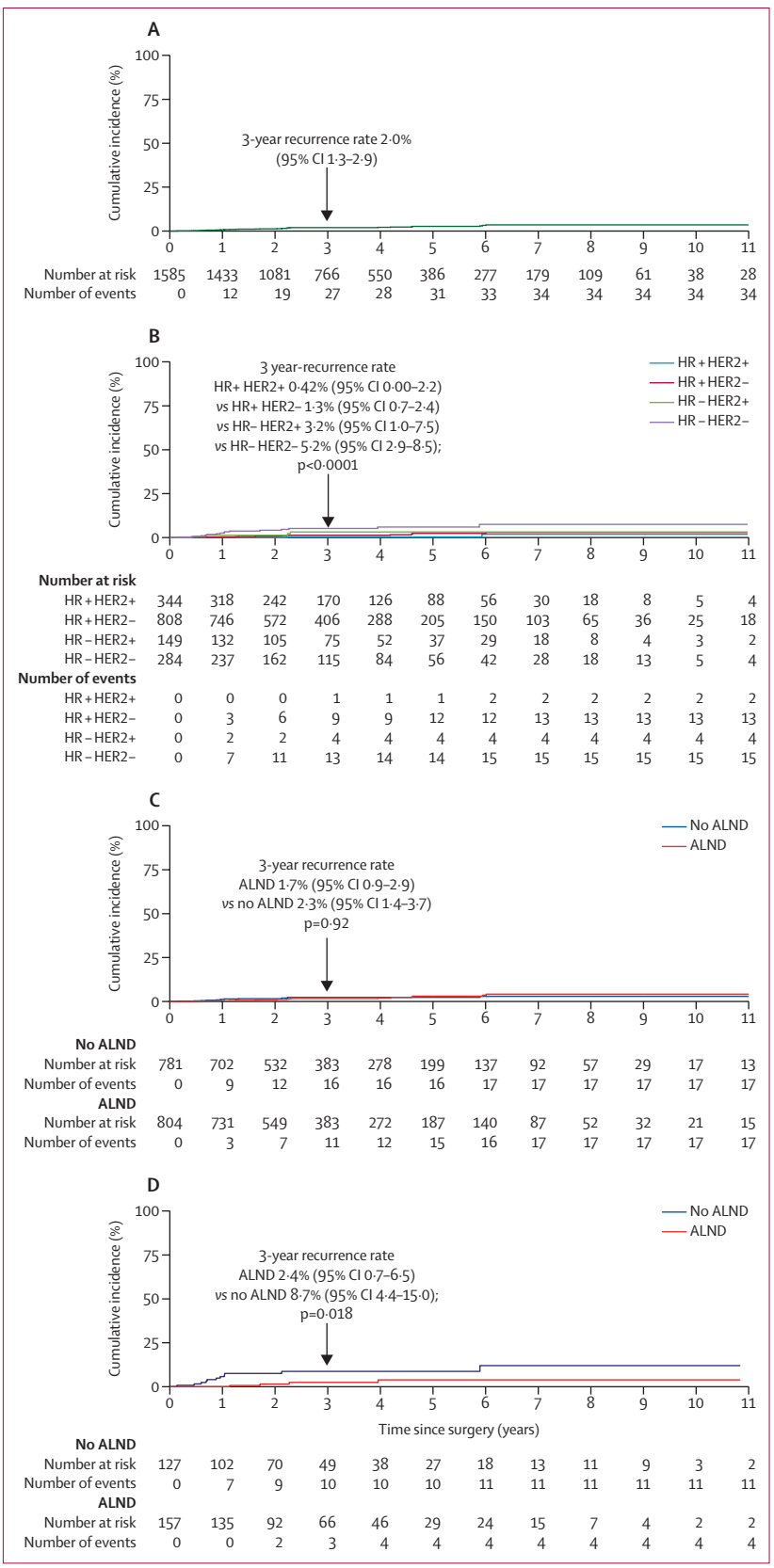

Figure 3: **Competing risk analysis of any axillary recurrence (overall cohort; A), any axillary recurrence (stratified by tumour subtype; B), any axillary recurrence (stratified by axillary surgery; C), and any axillary recurrence among triple-negative breast cancer patients (stratified by surgical group; D)**

HR+=hormone receptor-positive. HR-= hormone receptor-negative. HER2+=human epidermal growth factor receptor 2-positive. HER2–=human epidermal growth factor receptor 2-negative. ALND=axillary lymph node dissection.

	Any axillary recurrence		Any invasive recurrence	
	HR (95% CI)	p value	HR (95% CI)	p value
Age*	0·97 (0·94–1·00)	0·025	1·01 (1·00–1·02)	0·11
ALND				
No	1 (ref)	..	1 (ref)	..
Yes	0·86 (0·37– 2·00)	0·73	1·05 (0·78–1·41)	0·77
Breast surgery				
Breast-conserving surgery	1 (ref)	..	1 (ref)	..
Mastectomy	0·74 (0·36–1·50)	0·40	1·02 (0·77–1·35)	0·88
T stage at presentation				
x–1	1 (ref)		1 (ref)	
2	6·19 (0·83–46·10)	0·075	1·51 (1·04–2·19)	0·030
3–4	11·10 (1·13–108·00)	0·039	2·00 (1·32–3·03)	0·001
N stage at presentation				
0	1 (ref)	..	1 (ref)	..
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 (0·87–10·90)	0·08	1·22 (0·64–2·32)	0·54
Subtype				
HR+HER2–	1 (ref)	..	1 (ref)	..
HER2+	0·81 (0·39–1·68)	0·60	0·89 (0·66–1·20)	0·45
Triple-negative breast cancer	3·83 (1·72–8·52)	<0·0001	3·17 (2·30–4·35)	<0·0001
Regional nodal irradiation				
Yes				
No	2·62 (1·19–5·73)	0·016	1·61 (1·20–2·15)	0·002

ALND=axillary lymph node dissection. HER2=human epidermal growth factor receptor 2. HR=hormone receptor. *Per 1-year increase.

Table 2: **Multivariable analysis of the association between clinicopathological factors and the risk of any axillary recurrence and any invasive recurrence**

p 88). In an exploratory analysis limited to the 131 (46·1%) of 284 patients with triple-negative breast cancer who received adjuvant capecitabine, results were similar: the 3-year rate of axillary recurrence in this group was 4·1% (95% CI 1·5–8·8) and was significantly lower among those who underwent ALND than those who did not (0% [0–0] *vs* 10% [4–21]; p=0·017).

Discussion

This large multicentre cohort study provides evidence that ALND might not confer oncological benefit for most patients with residual micrometastases after neoadjuvant chemotherapy. Although current guidelines recommend completion ALND for all patients with residual micrometastases and macrometastases after neoadjuvant chemotherapy,[18,19] in the present study, ALND was omitted for almost half (781 [49·3%]) of 1585 patients. This is consistent with data from the National Cancer Database, which found that ALND was omitted for 40–69% of patients with ypN1mi disease treated between 2012 and 2021.[20] Similarly, of 242 patients with a positive sentinel lymph node after neoadjuvant chemotherapy treated in the ISPY2 trial between 2011–21, ALND was omitted in 144 (60%) patients.[16] In our study, clinicopathological factors associated with performing an ALND included higher nodal stage at presentation and detection of micrometastases on frozen section. Patients who underwent ALND also had fewer sentinel and non-sentinel lymph nodes removed, and had more sentinel lymph nodes with micrometastases than patients who did not undergo ALND; however, these differences were 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 might be justified. Additionally, in our study, compared with 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 USA, where the population is more ethnically diverse.

In the present study, additional positive lymph nodes were found in 245 (30·5%) of 804 patients undergoing completion ALND. In the ongoing prospective ALLIANCE A011202 trial (NCT01901094), which randomly assigned patients with residual disease in the sentinel lymph nodes to completion ALND with regional nodal irradiation or regional nodal irradiation alone, the proportion of additional positive lymph nodes 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 hormone receptor-positive, HER2-negative tumours, which have higher rates of positive lymph nodes.[21]

In this cohort of patients, where 1267 (79·9%) of 1585 patients received regional nodal irradiation, we found no difference in the rates of any axillary or any invasive recurrence based on ALND use, with the exception of patients with triple-negative breast cancer who had significantly higher rates of axillary recurrence after ALND omission. On multivariable analysis, factors associated with an increased risk of any axillary recurrence included triple-negative breast cancer and omission of regional nodal irradiation, which were associated with an almost 3·8 times and a 2·6 times increase in risk, respectively. Despite the higher risk of any axillary recurrence observed in the triple-negative breast cancer 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 triple-negative breast cancer with residual nodal disease after neoadjuvant chemotherapy. This group of patients, who are likely to harbour micrometastatic disease beyond the regional lymph nodes, is at increased risk of early locoregional and distant recurrence,[22] and randomised trials have demonstrated a benefit of escalating adjuvant systemic therapy with capecitabine[23] and olaparib in *BRCA* carriers.[24] Although 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 (211 [75%] of 284) received regional nodal irradiation. From a mechanistic perspective, it is plausible that even in patients without additional positive lymph nodes left behind at the time of surgery, circulating tumour cells might 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 identified in 34 (21·7%) of patients with triple-negative breast cancer who underwent ALND, 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 have axillary recurrence, and since synchronous locoregional and distant recurrences represented a minority of cases, many of these patients were treated with curative intent. Additionally, only about a quarter of patients with triple-negative breast cancer received adjuvant immunotherapy, and despite statistical significance, caution should be taken when interpreting these findings, since the increased use of effective post-neoadjuvant systemic therapy might affect the association between ALND omission and the risk of axillary recurrence in the future. However, an exploratory subgroup analysis among patients with triple-negative breast cancer who received adjuvant capecitabine showed a benefit of ALND in reducing the risk of any axillary recurrence. Since patients treated with pembrolizumab were a small minority (77 [27%] of 284 patients) and had a short follow-up, we were 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 hormone receptor-positive, HER2-positive tumours who received adjuvant therapies for a considerable period of time after surgery. However, in contrast to triple-negative breast cancer, hormone receptor-positive, HER2-negative tumours recur over a longer period of time (10–15 years),[22] and therefore caution should be taken when interpreting these results, since 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 hormone receptor-positive, HER2-negative tumours tends to occur early,[1,3] and smaller studies in the neoadjuvant chemotherapy 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 triple-negative breast cancer with incomplete response to neoadjuvant chemotherapy. Prospective studies[12,27,28] are awaited to guide clinical management in these patients at high risk of recurrence.

Our study has several limitations that require consideration. First, 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 neoadjuvant chemotherapy changed. As a consequence, only a minority of the included patients with triple-negative breast cancer 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. Second, since 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 generalisable to all patients with ypN1mi disease. However, propensity-score-matched analysis, matching patients for all baseline differences, showed consistent results. Omission of ALND in favour of regional nodal irradiation in patients with ypN+ disease is being investigated in randomised trials that will be published in the future.[12,29] Our results are important to inform current surgical decisions, since there was a large group of patients with ypN1mi disease who likely do not benefit from ALND. Additionally, the ongoing randomised controlled trials are unlikely to answer subtype specific questions. Only 12·5% of patients enrolled in the ALLIANCE A011202 trial had triple-negative breast cancer,[12] and although the OPBC-03/TAXIS trial is currently accruing patients, only 7% were reported to have triple-negative breast cancer.[28] Third, despite our pooled analysis of data from 84 centres, sample size determination was based on the number of cases available at the participating sites. Fourth, the median follow-up was relatively short (3·1 years [IQR 1·8–5·2]). Although longer follow-up is planned, previous neoadjuvant chemotherapy 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 standardised pathological assessment and centralised 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 regional nodal irradiation, systemic therapy, dual-tracer mapping, targeted axillary dissection, or MARI techniques is unclear, and caution should be taken when extrapolating these findings to low-resource settings. Finally, due to the retrospective nature of the study, we were unable to collect lymphoedema 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 triple-negative breast cancer. Omission of regional nodal irradiation and triple-negative breast cancer biology were independently associated with an increased risk of axillary recurrence. Overall, these results provide evidence supporting de-escalation of axillary surgery in hormone receptor-positive, HER2-negative tumours, and in HER2-positive tumours with residual micrometastases. However, omission of ALND in patients with triple-negative breast cancer who do not achieve nodal complete pathological response seems 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.

Contributors

GM and WPW designed the study. All authors collected data. GM, VS, MG, and WPW were additionally responsible for clinical data management and quality assurance. GM, SM, MF, MM, and WPW oversaw the protocol. VS analysed 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. GM and WPW directly accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

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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 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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