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Nodal Burden and Oncologic Outcomes in Patients With Residual Isolated Tumor Cells After Neoadjuvant Chemotherapy (ypN0i+): The OPBC-05/ICARO Study

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ABSTRACT

PURPOSE The nodal burden of patients with residual isolated tumor cells (ITCs) in the sentinel lymph nodes (SLNs) after neoadjuvant chemotherapy (NAC) (ypN0i+) is unknown, and axillary management is not standardized. We investigated rates of additional positive lymph nodes (LNs) at axillary lymph node dissection (ALND) and oncologic outcomes in patients with ypN0i+ treated with and without ALND.

METHODS The Oncoplastic Breast Consortium-05/ICARO cohort study (ClinicalTrials.gov identifier: NCT06464341) retrospectively analyzed data from patients with stage I to III breast cancer with ITCs in SLNs after NAC from 62 centers in 18 countries. The primary end point was the 3-year rate of any axillary recurrence. The rate of any invasive recurrence was the secondary end point.

RESULTS In total, 583 patients were included, of whom 182 (31%) had completion ALND and 401 (69%) did not. The median age was 48 years. Most patients (74%) were clinically node-positive at diagnosis and 41% had hormone receptor–positive/human epidermal growth factor receptor 2–negative tumors. The mean number of SLNs with ITCs was 1.2. Patients treated with ALND were more likely to present with cN2/3 disease (17% *v* 7%, $P < .001$), have ITCs detected on frozen section (62% *v* 8%, $P < .001$), have lymphovascular invasion (38% *v* 24%, $P < .001$), and receive adjuvant chest wall (89% *v* 78%, $P = .024$) and nodal radiation (82% *v* 75%, $P = .038$). Additional positive nodes were found at ALND in 30% of patients, but only 5% had macrometastases. The 3-year rates of any axillary and any invasive recurrence were 2% (95% CI, 0.95 to 3.6) and 11% (95% CI, 8 to 14), respectively, with no statistical difference by type of axillary surgery.

CONCLUSION The nodal burden in patients with ypN0(i+) was low, and axillary recurrence after ALND omission was rare in patients selected for this approach. These results do not support routine ALND in all patients with ypN0(i+).

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

In the upfront surgery setting, volume of disease in the sentinel lymph nodes (SLNs) is an important predictor of the likelihood of additional non-SLN metastases at axillary lymph node dissection (ALND).[1-5] In the setting of neoadjuvant chemotherapy (NAC), patients with positive SLNs have higher residual nodal burden than patients with a positive SLN treated with upfront surgery, irrespective of the size of the nodal metastasis and tumor subtype.[6-9] Therefore, ALND is the current standard of care for residual micrometastatic and macrometastatic disease after NAC.[10-12]

CONTEXT

Key Objective

To investigate the role of axillary lymph node dissection (ALND) in patients with residual isolated tumor cells (ITCs) in the sentinel lymph nodes (SLNs) after neoadjuvant chemotherapy.

Knowledge Generated

In this cohort study of 583 patients with residual ITCs in the SLNs, additional positive lymph nodes were found at ALND in 30% of patients but contained macrometastases in only 5%. Axillary recurrence was rare in patients selected for omission of ALND.

Relevance (*K.D. Miller*)

These results are similar to those in patients undergoing primary surgery and clearly indicate that ITCs should not affect the management of the axilla. ALND should be limited to patients with locally advanced disease with gross nodal involvement.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

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Residual isolated tumor cells (ITCs) after NAC are found in approximately 1.5% of all patients undergoing NAC.[13] The likelihood of finding additional positive lymph nodes (LNs) at ALND and the optimal management of the axilla in these patients are currently unclear.[6,13-19] Despite lack of consensus on the oncologic safety of omitting ALND among this group, patterns of care studies suggest increasing adoption of this approach.[10,19] Given the lack of forthcoming prospective studies, this study assimilated real-world data from a large international cohort with the aim of determining the likelihood of non-SLN involvement in patients with ITCs in the SLNs and assessed clinical outcomes by use of ALND.

METHODS

Study Population

The Oncoplastic Breast Consortium (OPBC)-05/ICARO cohort study (ClinicalTrials.gov identifier: NCT06464341) retrospectively analyzed institutional databases from 62 cancer centers located in 18 countries (the majority of centers are within the OPBC network). Institutional review board approval was obtained for each site in the United States, with informed consent waived due to use of deidentified data. At sites outside of the United States, informed consent was sought according to ethical approval that was study-/database-specific or based on general consent, according to site-specific and national standards. A data use agreement was executed between Memorial Sloan Kettering Cancer Center (MSKCC) and the other North American institutions, and between MSKCC and the University Hospital of Basel, Switzerland, which served as the coordinating center to collect data from all OPBC sites. The study followed the Strengthening the Report of Observational Studies in Epidemiology guidelines for reporting observational studies.[20] The principal investigator at each site was responsible for data collection, curacy, and transfer, whereas data cleaning and analysis were conducted at MSKCC.

Patients with clinical T1-4 N0-3 breast cancer at diagnosis treated with NAC between March 2008 and May 2022 who were found to have ITCs only (clusters of tumor cells ≤0.2 mm or a cluster of <200 cells in a single cross-sectional image) at frozen section (FS) or on final paraffin sections determined by sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), or the marking axillary lymph nodes with radioactive iodine seeds (MARI) procedure were selected. The study was inclusive of both high-volume centers and small breast units in the private, public, and academic settings. Downstaging to clinically N0 was required for patients who presented with palpable nodal disease. Patients with inflammatory breast cancer, stage IV disease at presentation, who had ALND as a primary procedure, and who received neoadjuvant endocrine therapy were excluded. Those with micrometastases or macrometastases in any SLNs at FS or final pathology were ineligible. We excluded One Step Nucleic Acid Amplification technology due to the absence of standardization.

Surgical Technique

The SLNB procedure included removal of all LNs that were either blue (isosulfan blue dye, methylene blue) or radioactive (technetium Tc 99m). Palpably abnormal nodes were considered SLNs. For cN0 patients at presentation, single tracer was allowed, whereas for cN+ patients, 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 marker before NAC. Details of the surgical procedures specific to each site are provided in the Data Supplement (online only).

Pathology Assessment

Details regarding pathology assessment of the SLNs (FS, quantification of the volume of disease, and use of

immunohistochemical staining) specific to each institutions are provided in the Data Supplement.

Systemic and Radiation Therapy

NAC regimens, adjuvant systemic therapy, and regional nodal irradiation (RNI) were administered in accordance with national guidelines. Radiation dose, schedule, and treatment fields specific to each center are provided in the Data Supplement.

End Points

The primary end point was the 3-year rate of axillary recurrence (isolated or combined with local and distant recurrence within 30 days). Secondary end points included the 3-year rate of isolated axillary recurrence and the 3-year rate of any invasive recurrence, be this locoregional or distant. The proportion of additional positive LNs at ALND was also assessed.

Statistical Analysis

Clinicopathological 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 rate of additional positive LNs at ALND was compared between cN0 and cN+ patients at presentation using a chi-square test. Cumulative incidence of axillary recurrence and any invasive recurrence (locoregional or distant) was assessed using a competing risk analysis (Data Supplement). Follow-up data were obtained from the date of surgery. Three-year cumulative incidence rates were compared between patients treated with and without ALND using Gray's test. A $P < .05$ was considered statistically significant. Statistical analysis was performed using R 4.3.2 (R Core Development Team, Vienna, Austria).

RESULTS

Patient and Treatment Characteristics

Data were collected from a total of 694 patients, with 111 excluded due to failure to meet inclusion criteria (Fig 1). The study population included 583 patients with residual ITCs detected on SLNB, TAD, or MARI, among whom 31.2% (n = 182) were treated with ALND and 68.8% (n = 401) without. The baseline characteristics of the cohort, stratified by surgical group, are listed in Table 1. The median age was 48 (IQR, 41-57) years, and most patients had clinical (c) T2 tumors (57%) and were clinically node-positive (cN+) at presentation (74%). Fewer than half of tumors (41%) were hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–), 38% were HER2-positive, and the remainder (21%) triple-negative. More than three quarters (77%) of patients received adjuvant RNI. Patients treated with ALND were more likely to present with cN2/3 disease (17% *v* 7%, $P < .001$), have ITCs detected on FS (62% *v* 8%, $P < .001$), have lymphovascular invasion (38% *v* 24%, $P < .001$), and receive chest wall irradiation (89% *v* 78%, $P = .024$) and RNI (82% *v* 74%, $P = .038$). Conversely, this group was less likely to have a lobular phenotype (4.3% *v* 11%, $P = .021$).

Axillary Staging Characteristics

Among clinically node-positive patients, axillary staging was performed with SLNB, TAD, and the MARI technique in 58%, 34%, and 8% of patients, respectively. Patients who underwent TAD and MARI were less likely to undergo ALND compared with patients who underwent SLNB (26% *v* 42%, $P < .001$). Significantly fewer SLNs were removed in the ALND group compared with the non-ALND group (mean number of nodes 2.8 *v* 3.5, respectively; $P < .001$). However, the mean number of SLNs with ITCs was the same in both surgical groups (n = 1.2; Table 1). The practice of ALND did not change over the study period when comparing patients treated before and after 2019 ($P > .9$).

Nodal Burden in Patients Undergoing ALND

In the ALND group (n = 182), additional positive nodes were found in 55 (30%) patients, consisting of ITCs in 32 (18%), micrometastases in 13 (7%), and macrometastases in nine patients (5%; Fig 2A). Among the 32 patients with additional ITCs, the number of additional positive LNs was one in 18 (56%), two in seven (22%), three in five (16%), and ≥4 in two (6%) patients. Among the 13 patients with additional micrometastases, the number of additional positive LNs was one in three (23%), two in two (15%), three in four (31%), and ≥4 in four (31%) patients. Finally, among the nine patients with additional macrometastases, the number of additional positive LNs was one in five (56%), two in three (33%), and ≥4 in one (11%) patient. When stratified by clinical nodal stage at presentation, there was no statistically significant difference in the rate of positive nodes at ALND between patients who were cN0 and cN+ (27% *v* 31%, respectively, $P = .6$). The distribution of ITCs, micrometastases, and macrometastases in nonsentinel nodes was also similar among the two groups (Fig 2B). Among 57 patients with cN2/3 disease at presentation, 30 (53%) underwent an ALND. Additional positive LNs were found in 12 (40%) of 30 patients and consisted of additional ITCs in nine (30%), micrometastases in one (3%), and macrometastases in two patients (7%; Fig 2C).

Oncological Outcomes in Patients Treated With and Without ALND

The median follow-up for the entire cohort was 3.2 years (IQR, 1.8-4.9) and was comparable between the ALND (3.4 years, IQR, 1.9-5.6) and non-ALND (3.1 years, IQR, 1.8-4.8) groups. During the study period, there were five isolated axillary recurrences (two in the ALND group and three in the non-ALND group) and nine synchronous locoregional and distant recurrences (three in the ALND group, six in the non-ALND

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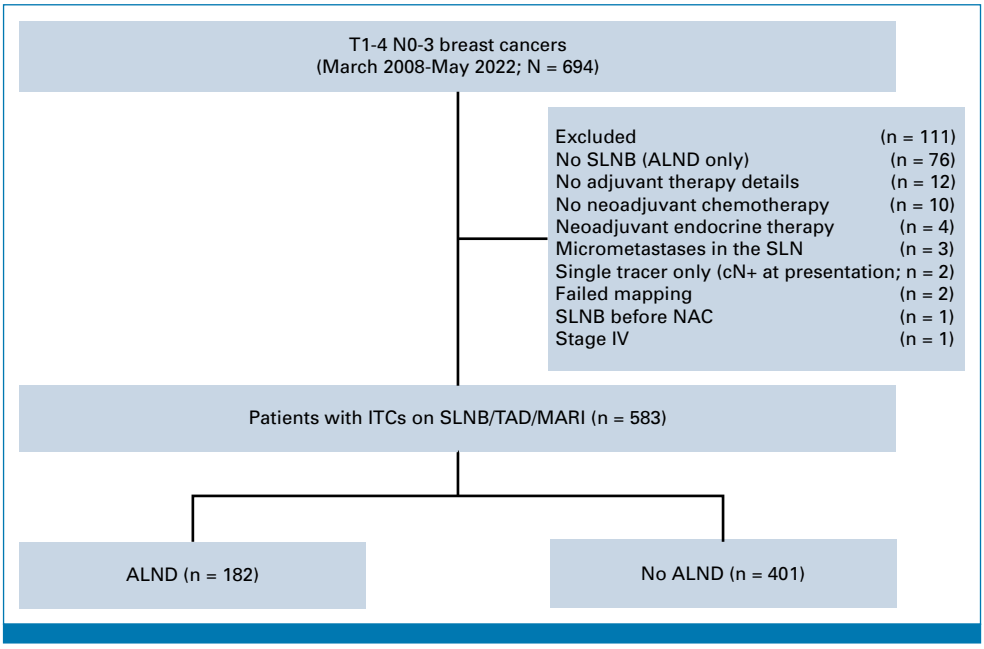

FIG 1. Flow diagram. ALND, axillary lymph node dissection; ITC, isolated tumor cell; MARI, marking axillary lymph nodes with radioactive iodine seeds; NAC, neoadjuvant chemotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

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group). 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, 0.95 to 3.6; Fig 3A), whereas the 3-year rate of isolated axillary recurrence was 0.58% (95% CI, 0.12 to 2.0; Fig 3B). Moreover, there were no statistically significant differences between patients treated with and without ALND for 3-year rates of any and isolated axillary recurrence (1.5% *v* 3.1%; $P = .8$ and 0.58% *v* 1.7%; $P = .7$), respectively (Figs 3C and 3D). The 3-year rate of any invasive (locoregional or distant) recurrence in the entire cohort was 11% (95% CI, 8 to 14; Fig 3E), with no significant difference in outcome between patients treated with and without ALND (8.1% *v* 12%, $P = .13$; Fig 3F). Exploratory 5-year results were as follows: the 5-year rate of any and isolated axillary recurrence was 4.4% (95% CI, 2.5 to 7.2) and 1.3% (95% CI, 0.47 to 2.9), respectively (with no significant differences between groups [ALND *v* no-ALND], 4.1% *v* 4.6%; $P = .8$ and 1.7% *v* 1.1%; $P = .7$, respectively), and the 5-year rate of any invasive recurrence was 18% (95% CI, 14 to 23; with no significant difference between groups [ALND *v* no-ALND], 16% *v* 19%; $P = .13$).

DISCUSSION

Patients with a positive SLN after NAC have a higher axillary nodal burden than patients with a positive SLN in the upfront surgery setting.[6,7,9] Moreover, NAC patients were not included in earlier trials evaluating omission of ALND (with or without RNI) for patients with limited nodal disease on SLNB.[21-23] Axillary management in the setting of residual ITCs is largely non–evidence-based, and reliant upon clinical opinion and physician discretion. Uncertainty relates not just to the unknown nonsentinel nodal burden but also to the biological significance of ITCs after axillary downstaging in response to NAC.

In this cohort of 583 patients with ITCs detected on SLNB, TAD, or MARI, additional positive non-SLNs were found in 30% of the 182 ALND patients, with no statistically significant difference by clinical nodal status at presentation. Importantly, more than half of the patients with additional nodal disease involved ITCs only, with macrometastases and micrometastases found in only 5% and 7% of patients, respectively. The present results confirm previous findings from both the SN-FNAC and ACOSOG Z1071 trials evaluating feasibility of SLNB after NAC for biopsy-proven nodal disease, which reported that four (57%) of seven and four (36%) of 11 patients with ITCs had additional positive nodes at ALND, respectively. Similarly, Moo et al[6] found that one (17%) of six patients with ITCs had additional positive LNs at ALND.

We observed that completion ALND was omitted in more than two thirds of patients with no significant change in surgical practice over the study period. This accords with previous studies reporting ALND omission in a significant proportion of patients with low-volume residual disease after NAC. In a study from the American Cancer Society/American College of Surgeons National Cancer Database, Wong et al[24] found that among 12,965 women treated with NAC between 2012 and 2015, 37% of patients with residual ITCs and 24% of patients with micrometastases did not undergo completion ALND. Our study is the first to support the safety of ALND omission in patients with residual ITCs; indeed, there appears to be no oncologic detriment, with no

TABLE 1. Clinicopathological Features of the Study Cohort, Stratified by Surgical Group

Feature	Overall (n = 583)	No ALND (n = 401)	ALND (n = 182)	*P*[a]
Age, years (IQR)	48 (41-57)	49 (40-57)	49 (43-58)	.11
Race/ethnicity, No. (%)				.5
Asian	64 (11)	40 (10)	24 (13)	
Black	27 (4.6)	22 (5.5)	5 (2.7)	
Hispanic	31 (5.3)	23 (5.7)	8 (4.4)	
White	447 (77)	306 (76)	141 (77)	
Other/unknown	14 (2.4)	10 (2.5)	4 (2.2)	
Clinical T stage at presentation, No. (%)				.15
1	95 (16)	68 (17)	27 (15)	
2	332 (57)	219 (55)	113 (62)	
3	136 (23)	102 (25)	34 (19)	
4	19 (3.3)	12 (3.0)	7 (3.8)	
X	1 (0.2)	0 (0)	1 (0.5)	
Clinical N stage at presentation, No. (%)				**<.001**
0	150 (26)	120 (30)	30 (16)	
1	376 (64)	254 (63)	122 (67)	
2	44 (7.5)	21 (5.2)	23 (13)	
3	13 (2.2)	6 (1.5)	7 (3.8)	
Tumor subtype, No. (%)				.6
HR+/HER2−	240 (41)	161 (40)	79 (43)	
HR+/HER2+	161 (28)	109 (27)	52 (29)	
HR−/HER2+	60 (10)	41 (10)	19 (10)	
HR−/HER2−	122 (21)	90 (22)	32 (18)	
Histology, No. (%)				**.021**
Ductal	516 (89)	350 (87)	166 (91)	
Lobular or mixed	53 (9.1)	44 (11)	9 (4.3)	
Other	14 (2.4)	7 (1.7)	7 (3.8)	
Tumor differentiation, No. (%)				.13
Well	34 (6.4)	29 (7.8)	5 (3.1)	
Moderately	210 (39)	146 (39)	64 (40)	
Poorly	290 (54)	199 (53)	91 (57)	
Unknown	49	27	22	
LVI, No. (%)				**<.001**
Present	167 (29)	97 (24)	70 (38)	
Type of breast surgery, No. (%)				.13
BCS	267 (46)	192 (48)	75 (41)	
Mastectomy	316 (54)	209 (52)	107 (59)	
Breast pCR (ypT0/is), No. (%)				.8
Yes	162 (28)	110 (27)	52 (29)	
NAC regimen HER2− (n = 362), No. (%)				.8
AC-T	287 (79)	197 (78)	90 (81)	
AC-T + Carbo	24 (6.6)	15 (6)	9 (8.1)	
AC-T + Carbo + pembrolizumab	10 (2.8)	7 (2.8)	3 (2.7)	
Anthracycline-free regimen[b]	10 (2.8)	8 (3.2)	2 (1.8)	
Other	31 (8.6)	24 (9.6)	7 (6.3)	
NAC regimen HER2+ (n = 221), No. (%)				.068
AC-TH	50 (22.5)	31 (20.7)	19 (27)	
AC-THP	65 (29)	43 (29)	22 (31)	
TCH	4 (1.8)	2 (1.3)	2 (2.8)	

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TABLE 1. Clinicopathological Features of the Study Cohort, Stratified by Surgical Group (continued)

Feature	Overall (n = 583)	No ALND (n = 401)	ALND (n = 182)	*P*[a]
TCHP	67 (30)	54 (36)	13 (18)	
Other	35 (16)	20 (13)	15 (21)	
Axillary staging technique in cN+ (n = 433), No. (%)				**<.001**
SLNB with dual-tracer mapping	251 (58)	146 (52)	105 (69)	
TAD	147 (34)	104 (37)	43 (28)	
MARI	35 (8.1)	31 (11)	4 (2.6)	
SLNs removed, No. (mean, SD)[c]	3.3 (0, 16)	3.5 (1, 16)	2.8 (0, 10)	**<.001**
Non-SLNs removed, No. (mean, SD)	0.8 (1.52)	0.8 (1.46)	0.7 (1.64)	**.015**
SLNs with ITCs, No. (mean, SD)	1.2 (0, 6)	1.2 (0, 6)	1.2 (0, 6)	.6
Total lymph nodes removed, No. (mean, SD)	7 (1, 37)	4 (1, 16)	15 (4, 37)	**<.001**
ITCs detected on frozen section, No. (%)				**<.001**
Yes	139 (25)	31 (7.9)	108 (62)	
Not performed/unknown	20	11	9	
Breast RT (n = 267), No. (%)	262 (98)	187 (97)	75 (100)	.3
Chest wall RT (n = 316), No. (%)	259 (82)	164 (78)	95 (89)	**.024**
Nodal RT, No. (%)	447 (77)	298 (74)	149 (82)	**.038**
Adjuvant chemotherapy,[d] No. (%)	92 (16)	60 (15)	32 (18)	.4
Adjuvant endocrine therapy (n = 401), No. (%)	379 (95)	258 (96)	121 (92)	.2
Adjuvant anti-HER2 therapy (n = 221), No. (%)	211 (95)	142 (95)	69 (97)	.5

NOTE. Data are expressed as frequency (column percentage) for categorical variables, and median (IQR) or mean (SD) for continuous variables. Statistically significant values are indicated in bold.

Abbreviations: AC-T, doxorubicin hydrochloride (doxorubicin) and cyclophosphamide, followed by paclitaxel (taxol); AC-TH, doxorubicin hydrochloride and cyclophosphamide followed by paclitaxel or docetaxel and trastuzumab; AC-THP, doxorubicin hydrochloride and cyclophosphamide followed by paclitaxel or docetaxel, trastuzumab, and pertuzumab; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; Carbo, carboplatin; H, herceptin; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITC, isolated tumor cell; LVI, lymphovascular invasion; MARI, marking axillary lymph nodes with radioactive iodine seeds; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; RT, radiation therapy; SD, standard deviation; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TCH, docetaxel, carboplatin, and trastuzumab; TCHP, docetaxel or paclitaxel, carboplatin, trastuzumab, and pertuzumab.

[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]Includes cyclophosphamide, methotrexate, and fluorouracil; and taxotere and cyclophosphamide.

[c]MARI participants were excluded (n = 35).

[d]Capecitabine was the most common type of adjuvant chemotherapy (75%).

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significant differences in key end points of clinical outcome, between patients treated with and without ALND.

Clinicopathological factors, known before or during surgery, associated with performing an ALND included higher nodal stage at presentation (assessed by clinical examination and imaging) and detection of ITCs on FS.

As the evidence to support the feasibility and accuracy of SLNB in patients with cN2/3 is limited (the validation studies of SLNB after NAC only included a small proportion of patients with cN2 disease and did not include cN3 patients)[14,15,25,26] and as prospective data on the safety of ALND omission after downstaging with NAC in this population are lacking, this is to be expected. Until more data from prospective studies become available,[27] ALND remains the standard of care for patients presenting with locally advanced breast cancer.

As anticipated, only a minority of patients (25%) in this study were detected on FS, since the size of a nodal metastasis is directly proportional to its probability of being identified on FS, making detection of ITCs challenging.[28,29] Interestingly, those patients who underwent ALND were more likely to have ITCs detected on FS than those who did not (62% *v* 8%, respectively), suggesting that most surgeons are unlikely to perform second surgery for low-volume disease.

In patients with residual micrometastases and macrometastases on SLNB, omission of ALND was not associated with any differences in the use of postneoadjuvant systemic therapy.[30] In the setting of residual breast disease, the presence of ITCs is unlikely to alter subsequent systemic therapy decisions. However, in patients who achieve a breast pCR and have residual nodal ITCs, the presence of additional nodal disease removed by ALND may indeed prompt a recommendation change, particularly in HER2+ and triple-negative tumors. In this study, among patients with HER2+ tumors and triple negative breast cancer who had an ALND and achieved a breast pCR (n = 33), all those with additional positive non-SLNs (n = 9) had low-volume disease (in seven patients, the non-SLNs contained

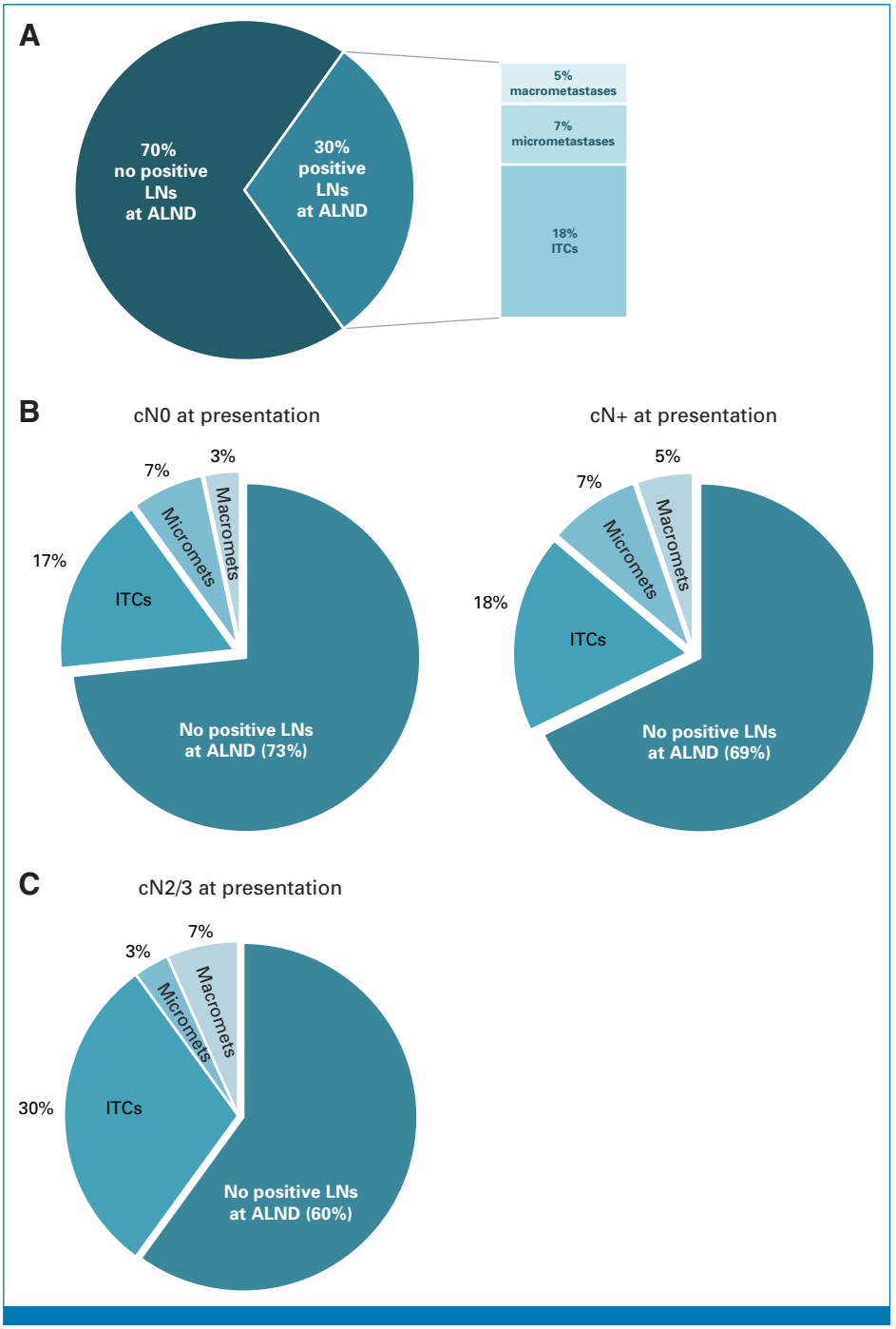

FIG 2. Proportion of patients with additional positive LNs at ALND by (A) all patients undergoing ALND (n = 182); (B) stratified by clinical nodal status at presentation (cN0 [n = 30] *v* cN+ [n = 152]); and (C) cN2/3 patients (n = 57). ALND, axillary lymph node dissection; LN, lymph node.

ITCs, and in two patients they contained micrometastases). Another important question is whether omitting ALND would preclude eligibility for treatment with a cyclin-dependent kinase (CDK) 4/6 inhibitor on the basis of the total number of positive LNs.[31] Of the 80 patients with HR+/HER2− undergoing ALND, five (6%) of 80 had ypN2 disease, but only one patient would have not been eligible to receive a CDK 4/6 inhibitor on the basis of other high-risk features at presentation (tumor size or grade).

Overall, these results should reassure medical oncologists that ALND omission in this population would not negatively affect systemic therapy recommendations. Similar results were recently reported in a prospective study of ALND omission in node-positive patients, treated in both adjuvant and neoadjuvant settings, which found that omitting ALND was not associated with differences in systemic therapy recommendations.[30]

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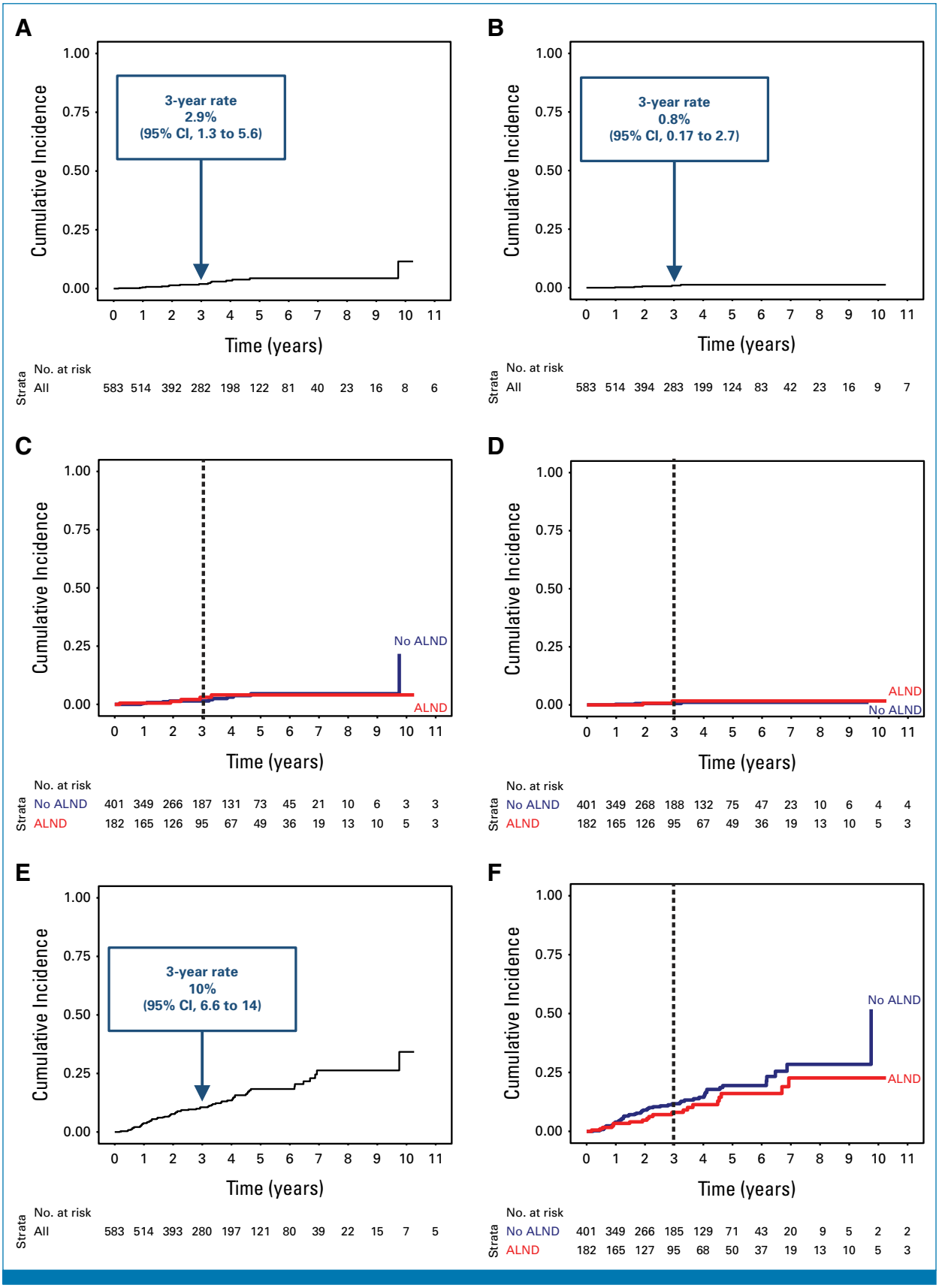

FIG 3. Competing risk analysis for (A) any axillary recurrence (overall cohort); (B) isolated axillary recurrence (overall cohort); (C) any axillary recurrence (stratified by surgical group); (D) isolated axillary recurrence (stratified by surgical group); (E) any invasive recurrence (overall cohort); and (F) any invasive recurrence (stratified by surgical group). ALND, axillary lymph node dissection.

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It is important to note that the majority of patients (77% overall, 74% with no ALND) in this cohort received RNI. In four of the five patients who experienced an isolated axillary recurrence, nodal RT was omitted, suggesting that RNI contributed to the extremely low rate of axillary failure observed in this cohort. Because of the small number of events and the inability to account for the random variation present at the single-institution level, we were not able to assess the independent effect of RNI on nodal recurrence. However, recent results from a time-driven analysis of the NSABP-B51 trial, which randomly assigned node-positive patients who were found to be ypN0/i+ at surgery to RNI versus no RNI, found no benefit of RNI for either the primary end point of invasive recurrence-free survival or the secondary end points of locoregional-free survival or distant recurrence-free survival (overall survival data immature due to fewer recurrence events than expected).[32] Although the exact number of patients with ITCs included was not reported (ypN0 category included ITCs) and the median follow-up is short (59.5 months), these data suggest that locoregional therapy in patients with ypN0(i+) may be further de-escalated.

Although immunohistochemistry (IHC) is not routinely used in all centers for SLN examination post-NAC, it can increase detection of small tumor foci in SLNs. In the SN-FNAC trial, for example, all patients with ITCs (n = 6) were detected by IHC,[15] although the likelihood of detecting occult macrometastases by IHC is very low.[33] As the presence of residual ITCs does not appear to influence surgical and adjuvant treatment decisions for the great majority of patients, results of this study argue against routine use of IHC for analysis of SLNs after NAC.

To our knowledge, this is the first study to compare outcomes in patients with residual ITCs treated with and without ALND, and to evaluate the residual nodal burden in this patient population. Our study, however, has several limitations, mainly related to its retrospective design, the real-world origin of the data, and selection bias, as the decision to omit ALND was based on lower baseline risk as well as surgeon, and perhaps patient, choice. Although we demonstrated excellent oncologic outcomes, the selection bias limited direct comparisons between patients treated with and without ALND. However, to the authors' knowledge, high-level evidence to address this clinical question is not expected. Patients with residual ITCs only were excluded from the ALLIANCE A011202 trial, which evaluates omission of ALND in favor of RNI in patients with ypN+. Although patients with residual ITCs are eligible for the ongoing TAXIS trial, whereby ALND is omitted as part of tailored axillary surgery, only very few patients with ypN0(i+) have been included.[8,34] In the absence of level 1 evidence to guide routine clinical care, the present real-world study was performed to reduce surgical overtreatment. A second limitation of our study is that despite the pooled analysis from 62 centers, the determination of the sample size was pragmatic and based on the number of patients available at the participating sites. A post hoc power analysis showed that a 10-times larger sample size would have been necessary to achieve adequate power to detect the observed difference in cumulative incidence rates. A third limitation of our study is its relatively short median follow-up of 3.2 years. Although longer follow-up is planned, based on data from the upfront surgery setting, axillary recurrence is an early event, with most events occurring within 5 years.[21,35] It is therefore anticipated that these findings will be reaffirmed with more prolonged follow-up. Other limitations include lack of standardized pathological assessment and centralized review, and a low number of events, which precludes an adjustment for baseline characteristics and location-based differences.

In conclusion, the likelihood of finding additional positive LNs on completion ALND for residual ITCs in the SLN after NAC was lower than for patients with residual micrometastases and macrometastases, with additional macrometastases found in only 5% of patients. Rates of axillary and invasive recurrence were low in patients selected for ALND omission on the basis of lower clinical risk at baseline and increased use of nodal RT. Overall, these results do not support routine ALND in patients with residual ITCs after NAC, thereby questioning the routine use of IHC staining for SLN examination after NAC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nodal Burden and Oncologic Outcomes in Patients With Residual Isolated Tumor Cells After Neoadjuvant Chemotherapy (ypN0i+): The OPBC-05/ICARO Study

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