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Association of Axillary Dissection With Systemic Therapy in Patients With Clinically Node-Positive Breast Cancer

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IMPORTANCE The role of axillary lymph node dissection (ALND) to determine nodal burden to inform systemic therapy recommendations in patients with clinically node (cN)–positive breast cancer (BC) is currently unknown.

OBJECTIVE To address the association of ALND with systemic therapy in cN-positive BC in the upfront surgery setting and after neoadjuvant chemotherapy (NACT).

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, observational, cohort study conducted from August 2018 to June 2022. This was a preplanned study within the phase 3 randomized clinical OPBC-03/TAXIS trial. Included were patients with confirmed cN-positive BC from 44 private, public, and academic breast centers in 6 European countries. After NACT, residual nodal disease was mandatory, and a minimum follow-up of 2 months was required.

EXPOSURES All patients underwent tailored axillary surgery (TAS) followed by ALND or axillary radiotherapy (ART) according to TAXIS randomization. TAS removed suspicious palpable and sentinel nodes, whereas imaging-guidance was optional. Systemic therapy recommendations were at the discretion of the local investigators.

RESULTS A total of 500 patients (median [IQR] age, 57 [48-69] years; 487 female [97.4%]) were included in the study. In the upfront surgery setting, 296 of 335 patients (88.4%) had hormone receptor (HR)–positive and Erb-B2 receptor tyrosine kinase 2 (*ERBB2*; formerly *HER2* or *HER2/neu*)–negative disease: 145 (49.0%) underwent ART, and 151 (51.0%) underwent ALND. The median (IQR) number of removed positive lymph nodes without ALND was 3 (1-4) nodes compared with 4 (2-9) nodes with ALND. There was no association of ALND with the proportion of patients undergoing adjuvant chemotherapy (81 of 145 [55.9%] vs 91 of 151 [60.3%]; adjusted odds ratio [aOR], 0.72; 95% CI, 0.19-2.67) and type of systemic therapy. Of 151 patients with NACT, 74 (51.0%) underwent ART, and 77 (49.0%) underwent ALND. The ratio of removed to positive nodes was a median (IQR) of 4 (3-7) nodes to 2 (1-3) nodes and 15 (12-19) nodes to 2 (1-5) nodes in the ART and ALND groups, respectively. There was no observed association of ALND with the proportion of patients undergoing postneoadjuvant systemic therapy (57 of 74 [77.0%] vs 55 of 77 [71.4%]; aOR, 0.86; 95% CI, 0.43-1.70), type of postneoadjuvant chemotherapy (eg, capecitabine: 10 of 74 [13.5%] vs 10 of 77 [13.0%]; trastuzumab emtansine–DM1: 9 of 74 [12.2%] vs 11 of 77 [14.3%]), or endocrine therapy (eg, aromatase inhibitors: 41 of 74 [55.4%] vs 36 of 77 [46.8%]; tamoxifen: 8 of 74 [10.8%] vs 6 of 77 [7.8%]).

CONCLUSION Results of this cohort study suggest that patients without ALND were significantly understaged. However, ALND did not inform systemic therapy recommendations.

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Standard axillary lymph node dissection (ALND) was replaced by the sentinel lymph node (SLN) procedure in most patients with node-negative breast cancer (BC).[1,2] In patients with clinically node-negative SLN-positive BC, several landmark trials showed noninferior survival and recurrence when ALND was omitted.[3-5] Limited knowledge of the exact number of positive nodes did not modify the likelihood to receive chemotherapy in these trials.[3,5] The staging role of ALND has been further diminished because chemotherapy is increasingly based on tumor biology, which currently applies to most patients with node-positive triple-negative (TN) or Erb-B2 receptor tyrosine kinase 2 (*ERBB2*; formerly *HER2* or *HER2/neu*)-positive BC.[6,7]

However, in patients with hormone receptor (HR)-positive *ERBB2*-negative BC, the indication for chemotherapy may still depend on the total number of positive nodes. Traditionally, most experts recommended chemotherapy in patients with luminal BC and 4 or more positive nodes.[7] More recently, genomic assays, such as the Oncotype DX Recurrence Score (Exact Sciences) or Mammaprint (Agendia), became available to refine chemotherapy indications in node-positive, HR-positive, *ERBB2*-negative BC.[8,9] Because patients with more than 3 positive nodes were ineligible for these trials, applicability of their results to patients who did not undergo ALND remains questionable. Similarly, the recent MONARCHE trial raised the question of whether the exact number of positive nodes is required to indicate the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, abemaciclib, after upfront surgery.[10] Finally, in the postneoadjuvant setting, response-driven therapy is increasingly used and may be influenced by surgical staging of the axilla.[11,12]

To our knowledge, the role of ALND to determine the nodal tumor burden to inform systemic therapy decisions in patients with clinically node (cN)-positive BC is not known. Oncoplastic Breast Consortium 03 (OPBC-03)/Tailored Axillary Surgery With or Without Axillary Lymph Node Dissection Followed by Radiotherapy in Patients With Clinically Node-positive Breast Cancer (TAXIS) is an ongoing, international, phase 3 surgical trial investigating noninferiority (with regard to disease-free survival [DFS], but with strong emphasis on quality of life) of axillary radiotherapy (ART) relative to ALND in the treatment of patients with cN-positive BC who undergo tailored axillary surgery (TAS).[13] Publication of the first prespecified substudy showed that patients in the ART arm were significantly understaged, with 70% of patients in the ALND arm having further nodal disease removed by ALND, of whom 37% had 4 or more additional positive nodes.[14] The present study was planned to gain relevant insight on the association of TAS with the use of adjuvant and postneoadjuvant systemic treatment, which, in turn, may be associated with the primary end point of the main trial. The aim of this analysis was to assess the role of ALND as a decision aid for systemic therapy in a contemporary cohort of patients with cN-positive BC in the upfront surgery and postneoadjuvant setting.

Key Points

Question Is the omission of axillary dissection in patients with clinically node-positive breast cancer associated with systemic therapy in the upfront surgery and postneoadjuvant setting?

Findings In this international cohort study embedded in a randomized clinical trial, a total of 500 patients had a high nodal tumor burden and were significantly understaged when axillary dissection was omitted. Nevertheless, this did not change adjuvant and postneoadjuvant systemic therapy.

Meaning Results of this cohort study suggest that axillary dissection did not inform systemic therapy recommendations in individuals with clinically node-positive breast cancer.

Methods

This study represents a prospective, observational, cohort study within the pragmatic, phase 3, international, multicenter, randomized clinical TAXIS trial.[13] The trial was approved by the local ethics committees and was performed in accordance with the requirements of the national regulatory authorities. Written informed consent was obtained from all patients. Included were patients with cN-positive BC, defined as nodal disease detected by palpation or imaging at the time of initial diagnosis and histologic or cytologic confirmation both in the primary tumor and lymph node metastasis. According to the pragmatic design, patients were included in the upfront surgery and neoadjuvant setting, while in the latter, confirmation of residual nodal disease at the time of surgery was mandatory. Patients with stage IV, cN3c, or cN2b BC; contralateral or other tumor malignancy within 3 years; and prior axillary surgery (except SLN biopsy) or prior axillary radiotherapy were excluded. Systemic therapy recommendations were at the discretion of the local investigators. All drugs used for adjuvant systemic anticancer treatment as chosen based on international and/or local guidelines were recorded. Follow-up was predefined in the study protocol.[13] The sample size of the main TAXIS trial was 1500 patients (750 per arm) and was based on the primary end point DFS. The patient population in the present study was a priori defined to include patients randomly assigned to treatment groups who were treated from August 2018 to June 2022 to address the association of staging information gleaned from ALND with adjuvant systemic therapy treatment decisions. The 2 groups of patients were as follows: (1) patients with cN-positive BC who underwent upfront surgery and (2) patients with cN-positive BC with persistent nodal involvement after neoadjuvant chemotherapy (NACT). Minimum follow-up after surgery was 2 months. Data extraction was performed after data cleaning on September 30, 2022. No participants were lost to follow-up until this analysis was performed. Participant race and ethnicity data were not gathered for this study as it was not planned in the study protocol. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[15]

Locoregional Treatment

The initially sampled and histologically or cytologically positive node was marked with a clip. TAS was defined by removal of SLNs (detection modality choice left up to surgeon; dual tracer not required) and palpable lymph node metastases; localization of the previously clipped biopsied node (which is a standard part of targeted axillary dissection) is not mandatory.[14] Importantly, in the experimental setting of TAS, palpation-guided removal of suspicious nodes is a key component, whereas palpable disease is usually a contraindication to the SLN procedure in today's clinical practice. Intraoperative exclusion criteria for surgical quality control included failure to remove (1) the clip, (2) at least 1 SLN, and (3) all suspicious palpable findings. Patients in the control group of the TAXIS trial underwent TAS followed by ALND after intraoperative randomization. When a patient was randomly assigned to the ALND group, the procedure was technically performed according to the standard of the treating surgeon in line with the pragmatic study design. However, the protocol required levels I and II to be cleared and a full level III dissection above and medial to the pectoralis minor muscle to be carried out only when there was gross nodal disease detected by palpation or imaging. In the other arm of the TAXIS trial, patients received ART. All patients underwent adjuvant whole-breast irradiation after breast-conserving surgery and chest wall irradiation after mastectomy. Although patients in the ALND group received regional nodal irradiation excluding the dissected axilla as a target volume, patients in the ART group received regional nodal irradiation including the axilla.

End Points

The primary end point for this substudy was patients undergoing adjuvant chemotherapy.[13] Secondary end points included patients undergoing postneoadjuvant systemic therapy, type of chemotherapy, and type of endocrine therapy. All of these end points were prespecified. Post hoc analyses included comparisons of differences in systemic therapies other than chemotherapy and endocrine therapy.

Statistical Analysis

Continuous end points were summarized using median and IQR, and the Hodges-Lehmann estimator with corresponding 95% CI was used to report differences between treatment arms. Categorical end points were summarized using frequency counts and percentages as well as differences in proportions between treatment arms with corresponding 95% CI. Due to the exploratory nature of this analysis, no hypothesis testing was performed. To assess the association of treatment arm with the administration of adjuvant systemic therapy and chemotherapy, unadjusted odds ratio (OR) as well as adjusted OR (aOR) with corresponding 95% CI for palpable vs nonpalpable disease, menopausal status, tumor subtype, tumor grade, age, year, and country were calculated using logistic regression models. All analyses were performed using R, version 4.2.1 (R Project for Statistical Computing).

Results

A total of 500 patients (median [IQR] age, 57 [48-69] years; 487 female [97.4%]; 13 male [2.6%]) were included at 44 breast centers from 6 European countries (**Table 1**). Overall, included subtypes were HR positive/*ERBB2* negative in 397 patients (79.4%), HR positive/*ERBB2* positive in 52 patients (10.4%), HR negative/*ERBB2* positive in 5 patients (1.0%), and HR negative/*ERBB2* negative in 35 patients (7.0%).

Of 335 patients (67.0%) who were treated in the upfront surgery setting, 296 (88.4%) had HR-positive/*ERBB2*-negative disease. Of these 296 patients, 145 (49.0%) underwent ART without ALND, and 151 (51.0%) underwent ALND after TAS. In the ART arm, the median (IQR) number of lymph nodes removed was 5 (4-8) nodes, of which 3 (1-4) nodes were positive. In the ALND arm, the median (IQR) number of lymph nodes was 19 (14-26) nodes, of which 4 (2-9) nodes were positive (**Table 2**). Four or more positive nodes were found in 49 of 145 patients (33.8%) in the ART arm and in 89 of 151 patients (58.9%) in the ALND arm. We observed no association of ALND with the proportion of patients with HR-positive/*ERBB2*-negative disease undergoing adjuvant chemotherapy (81 of 145 [55.9%] in the ART arm and 91 of 151 [60.3%] in the ALND arm; aOR, 0.72; 95% CI, 0.19-2.67) (**Table 3** and eTable in Supplement 1). Furthermore, we observed no differences in type of systemic therapy with the exception of tamoxifen, which was 30 of 151 (19.9%) with ALND vs 13 of 145 (9.0%) without ALND (**Table 4**).

A total of 151 of 500 patients (30.2%) underwent NACT, 13 had neoadjuvant endocrine treatment, and 1 had neoadjuvant double *ERBB2* blockade without chemotherapy. Of the 151 patients who received NACT with residual nodal disease, 74 (49.0%) underwent ART without ALND and 77 (51.0%) underwent ALND. In the ART arm, the median (IQR) number of lymph nodes removed was 4 (3-7) nodes, of which 2 (1-3) nodes were positive; in the ALND arm, the number was 15 (12-19) nodes, of which 2 (1-5) nodes were positive (Table 2). We observed no association of ALND in patients after neoadjuvant treatment with the proportion of patients undergoing postneoadjuvant systemic therapy (57 of 74 [77.0%] in the ART arm and 55 of 77 [71.4%] in the ALND arm; aOR, 0.86; 95% CI, 0.43-1.70) (Table 3 and eTable in Supplement 1). Furthermore, no differences in type of postneoadjuvant chemotherapy (eg, capecitabine: 10 of 74 [13.5%] vs 10 of 77 [13.0%]; trastuzumab emtansine–DM1: 9 of 74 [12.2%] vs 11 of 77 [14.3%]) or endocrine therapy (eg, aromatase inhibitors: 41 of 74 [55.4%] vs 36 of 77 [46.8%]; tamoxifen: 8 of 74 [10.8%] vs 6 of 77 [7.8%]) were observed (**Table 5**).

Discussion

To the authors' knowledge, this was the first study to prospectively assess the role of ALND to determine nodal tumor burden to inform systemic therapy in patients with cN-positive BC. The main finding was that use of ALND and associated detailed knowledge of the number of positive nodes did not sig-

Table 1. Clinicopathologic Characteristics of Study Cohort

Characteristic	Patients (N = 500)
Age, median (IQR), y	57 (48-69)
Sex, No. (%)	
Female	487 (97.4)
Male	13 (2.6)
Country, No. (%)	
Austria	29 (5.8)
Germany	31 (6.2)
Hungary	99 (19.8)
Italy	2 (0.4)
Lithuania	4 (0.8)
Switzerland	335 (67.0)
Menopausal status, No. (%)	
Postmenopausal	342 (68.4)
Premenopausal	157 (31.4)
Unknown	1 (0.2)
Histological findings, No. (%)	
Ductal	389 (77.8)
Lobular	60 (12.0)
Other	50 (10.0)
Unknown	1 (0.2)
Differentiation, No. (%)	
Well	32 (6.4)
Moderate	294 (58.8)
Poor	169 (33.8)
Unknown	5 (1.0)
Receptor status, No. (%)	
HR−/*ERBB2*−	35 (7.0)
HR−/*ERBB2*+	5 (1.0)
HR+/*ERBB2*−	397 (79.4)
HR+/*ERBB2*+	52 (10.4)
Unknown	11 (2.2)
Tumor size, median (IQR), mm	28 (20-40)
Unknown	17
Breast surgery, No. (%)	
Breast-conserving surgery	293 (58.6)
Mastectomy	207 (41.4)
Treatment arm, No. (%)	
Arm A: ALND	250 (50.0)
Arm B: no ALND	250 (50.0)
No. of LNs retrieved during TAS, median (IQR)	5 (3-8)
Unknown, No.	7
No. of additional LNs retrieved during ALND, median (IQR)	12 (9-17)
Unknown, No.	8
Type of clinical node positivity, No. (%)	
Nonpalpable, detected by imaging	242 (48.4)
Palpable	258 (51.6)

Abbreviations: ALND, axillary lymph node dissection; *ERBB2*−, Erb-B2 receptor tyrosine kinase 2 negative (formerly *HER2* or *HER2/neu*); *ERBB2*+, Erb-B2 receptor tyrosine kinase 2 positive; HR−, hormone receptor negative; HR+, hormone receptor positive; TAS, tailored axillary surgery.

nificantly change systemic therapy in the upfront surgery and postneoadjuvant setting. All patients underwent TAS, which was shown to selectively remove positive nodes while remaining much less radical than standard ALND.[14] The vast majority of patients had luminal cancers. Because other subtypes were less commonly treated in the adjuvant setting and in the neoadjuvant setting, patients with these subtypes had a higher likelihood of being excluded due to nodal pathologic complete response (pCR). In fact, the present findings are of particular interest in patients with HR-positive/*ERBB2*-negative cN-positive BC, with 91 of 151 patients (60%) undergoing adjuvant chemotherapy when ALND is used, compared with 81 of 145 patients (56%) without ALND. The total number of 4 positive nodes removed in the ALND group reflects the traditional threshold for chemotherapy in luminal breast cancer, whereas only a median of 3 nodes were removed without ALND.[7] In fact, the proportion of patients with 4 or more positive lymph nodes was 89 of 151 (59%) and 49 of 145 (34%) with vs without ALND, respectively. This is substantially higher than in the American College of Surgeons Oncology Group Z0011 trial, where the corresponding numbers were 14% vs 1%.[3] Therefore, the present results suggest that even in a patient population with high nodal burden that is likely to be heavily understaged when ALND is omitted, the use of ALND to determine the exact number of positive nodes does not change systemic therapy. The only observed difference was the higher use of tamoxifen after ALND in ER-positive/*ERBB2*-negative BC. Because age and menopausal status were well balanced and the number of positive nodes was high with no difference between the groups, we could not determine why clinicians felt confident to use tamoxifen over an aromatase inhibitor in the ALND group. However, these associations will be reevaluated once the full TAXIS sample size is reached.

In recent years, gene expression profiles have been introduced to provide additional prognostic information in conjunction with nodal stage to inform systemic therapy recommendations in patients with luminal BC.[8,9] In the Clinical Trial Rx for Positive-Node, Endocrine-Responsive Breast Cancer (RxPONDER) trial, women with HR-positive, *ERBB2*-negative BC, 1 to 3 positive axillary lymph nodes, and an Oncotype DX Recurrence Score of 25 or lower were randomly assigned to endocrine therapy only or to chemotherapy plus endocrine therapy.[9] At 5 years, the invasive DFS rate among postmenopausal women was not different in the endocrine therapy-only group (91.9%) vs the chemoendocrine therapy group (91.3%). Based on these results, chemotherapy is not indicated in postmenopausal women selected accordingly. Importantly, in the RxPONDER trial, only 62% of patients were staged by ALND, and 37% underwent SLN biopsy alone with presumed nodal understaging. The second landmark trial that introduced molecular assays to refine chemotherapy indications in node-positive BC was the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial.[8] In the initial study design, all patients had to have lymph node–negative disease, but about halfway through, the protocol was revised to allow for the enrollment of women with up to 3 positive axillary nodes. Because both trials did not allow inclusion of patients with more than 3 positive nodes, to determine the total tumor load in the axilla and assess eligibility for these tests to inform systemic

Table 2. Number of Lymph Nodes Removed by Type of Surgery

No. of lymph nodes removed	Type of surgery		Difference (95% CI)[a]
	Arm A: ALND (n = 250)	Arm B: no ALND (n = 250)	
Overall, median (IQR)			
Total	18 (13-24)	5 (3-7)	12 (11-13)
Positive	4 (2-8)	2 (1-4)	1 (1-2)
Negative	12 (8-16)	2 (1-4)	9 (8-10)
Upfront surgery setting: HR+/*ERBB2*−, median (IQR)			
Total No.	151	145	NA
Total	19 (14-26)	5 (4-8)	14 (12-15)
Positive	4 (2-9)	3 (1-4)	2 (1-2)
Negative	12 (9-18)	2 (1-4)	10 (9-11)
Neoadjuvant chemotherapy,[b] median (IQR)			
Total No.	77	74	NA
Total	15 (12-19)	4 (3-7)	10 (9-12)
Positive	2 (1-5)	2 (1-3)	1 (0-1)
Negative	12 (7-15)	2 (1-4)	9 (7-11)

Abbreviations: ALND, axillary lymph node dissection; *ERBB2*−, Erb-B2 receptor tyrosine kinase 2 negative (formerly *HER2* or *HER2/neu*); HR+, hormone receptor positive; NA, not applicable.

[a] Hodges-Lehmann estimator.

[b] Fourteen patients had other neoadjuvant therapy than chemotherapy.

Table 3. Proportion of Patients Undergoing Chemotherapy With or Without Axillary Lymph Node Dissection (ALND)

Group	Arm A: ALND	Arm B: No ALND	Difference (95% CI)[a]
Upfront surgery setting, No./total No. (%)			
All subtypes	101/169 (59.8)	92/166 (55.4)	4.3% (−6.8% to 16%)
HR+/*ERBB2*−	91/151 (60.3)	81/145 (55.9)	4.4% (−7.5% to 16%)
HR+/*ERBB2*− Premenopausal	36/47 (76.6)	28/37 (75.7)	0.9% (−18% to 20%)
HR+/*ERBB2*− Postmenopausal	55/104 (52.9)	53/108 (49.1)	3.8% (−11% to 18%)
Neoadjuvant chemotherapy,[b] No./total No. (%)			
All subtypes	24/77 (31.2)	20/74 (27.0)	4.1% (−12% to 20%)
HR+/*ERBB2*−	5/41 (12.2)	8/48 (16.7)	−4.5% (−21% to 12%)
HR+/*ERBB2*+	11/20 (55.0)	7/12 (58.3)	−3.3% (−42% to 35%)
HR−/*ERBB2*−	7/14 (50.0)	4/12 (33.3)	17% (−28% to 62%)
HR−/*ERBB2*+	0/1 (0)	1/1 (100)	−100% (−100% to 0%)
Premenopausal	11/27 (40.7)	10/34 (29.4)	11% (−16% to 39%)
Postmenopausal	13/50 (26.0)	10/40 (25.0)	1% (−18% to 20%)

Abbreviations: *ERBB2*−, Erb-B2 receptor tyrosine kinase 2 negative (formerly *HER2* or *HER2/neu*); *ERBB2*+, Erb-B2 receptor tyrosine kinase 2 positive; HR−, hormone receptor negative; HR+, hormone receptor positive.

[a] Difference in proportions.

[b] Fourteen patients had other neoadjuvant therapy than chemotherapy.

Table 4. Type of Adjuvant Systemic Therapy in Patients With Hormone Receptor–Positive and Erb-B2 Receptor Tyrosine Kinase 2 (*ERBB2*)[a]–Negative Subtype by Type of Surgery in the Upfront Surgery Setting

Type of therapy	No. (%)		Difference (95% CI)[b]
	Arm A: ALND (n = 151)	Arm B: no ALND (n = 145)	
Taxane-containing chemotherapy	80 (53.0)	72 (49.7)	3.3% (−8.7% to 15%)
Anthracycline-containing chemotherapy	78 (51.7)	64 (44.1)	7.5 (−4.5% to 20%)
Nontaxane/nonanthracycline-containing chemotherapy	88 (58.3)	76 (52.4)	5.9% (−6.1% to 18%)
Carboplatin/cisplatin	0 (0)	3 (2.1)	−2.1% (−5.1% to 0.92%)
Aromatase inhibitors	90 (59.6)	89 (61.4)	−1.8% (−14% to 10%)
GnRH analogs	17 (11.3)	10 (6.9)	4.4% (−2.8% to 12%)
Fulvestrant	1 (0.7)	2 (1.4)	−0.7 (−3.7% to 2.3%)
Tamoxifen	30 (19.9)	13 (9.0)	11% (2.3% to 19%)
CDK4/6 inhibitors	1 (0.7)	3 (2.1)	−1.4 (−4.7% to 1.9%)

Abbreviations: ALND, axillary lymph node dissection; CDK4/6, cyclin-dependent kinase 4/6; GnRH, gonadotropin-releasing hormone.

[a] Formerly *HER2* or *HER2/neu*.

[b] Difference in proportions.

therapy, ALND was revisited.[16] Although the main results of the RxPONDER trial were published rather recently, those of the MINDACT trial came out before this study started, and we did not observe any time trend during the study period (data

Table 5. Type of Postneoadjuvant Systemic Therapy by Type of Surgery

Type of therapy	No. (%)		Difference (95% CI)[a]
	Arm A: ALND (n = 77)[a]	Arm B: No ALND (n = 74)[a]	
Carboplatin/cisplatin	3 (3.9)	0 (0)	3.9% (−1.8% to 9.5%)
Capecitabine	10 (13.0)	10 (13.5)	−0.5% (−12% to 11%)
Trastuzumab	5 (6.5)	5 (6.8)	−0.3% (−8.5% to 7.9%)
Pertuzumab	1 (1.3)	1 (1.4)	−0.1% (−3.8% to 3.6%)
T-DM1	11 (14.3)	9 (12.2)	2.1% (−10% to 14%)
Checkpoint inhibitors	2 (2.6)	0 (0)	2.6% (−2.3% to 7.5%)
Aromatase inhibitors	36 (46.8)	41 (55.4)	−8.7% (−26% to 8.6%)
GnRH analogons	4 (5.2)	7 (9.5)	−4.3% (−14% to 5.4%)
Tamoxifen	6 (7.8)	8 (10.8)	−3.0% (−14% to 7.6%)
CDK4/6 inhibitors	3 (3.9)	4 (5.4)	−1.5% (−9.6% to 6.5%)
PARP inhibitors	0 (0)	1 (1.4)	−1.4% (−5.3% to 2.6%)

Abbreviations: ALND, axillary lymph node dissection; CDK4/6, cyclin-dependent kinase 4/6; GnRH, gonadotropin-releasing hormone; PARP, poly ADP ribose polymerase; T-DM1, trastuzumab emtansine–DM1.

[a] Difference in proportions.

not shown) or differences by menopausal status (Table 3). Therefore, the present results suggest that clinicians were not considering the total number of positive nodes as a major factor in the decision for use of chemotherapy, either directly or through use of molecular tests.

The present study cannot address the impact of the MONARCHE trial on use of ALND for staging purposes in patients with cN-positive BC because it was published toward the end of the study period.[10] Nodal stage was used for risk stratification, and patients with high-risk early-stage HR-positive disease were randomly assigned to receive endocrine therapy with the CDK4/6 inhibitor abemaciclib or endocrine therapy alone in the adjuvant setting. A significant improvement in invasive DFS could be demonstrated for high-risk patients defined as having either 4 or more positive nodes or 1 to 4 positive nodes with additional risk factors. Given the importance of the extent of nodal disease in MONARCHE, surgical management of the axilla has resurfaced as a question asked at multidisciplinary tumor boards. ALND is sometimes recommended by medical oncologists to assess eligibility for application of the trial protocol to individual patients in clinical practice.[16] In the present study, only 4 patients received CDK4/6 inhibitors, which may be explained by the initially conflicting results and the still hesitant adoption of the use of adjuvant CDK4/6 inhibition by the community, and the fact that the only positive trial, MONARCHE, was just recently published with short follow-up.[10,17]

The present study will be repeated once all 1500 patients have been randomly assigned to treatment groups in the TAXIS trial to investigate if future study findings may strengthen the role of ALND to determine the total number of positive nodes. However, morbidity is well documented to be increased after ALND compared with the SLN procedure.[18-21] Even though the SLN procedure was primarily introduced in clinical practice to stage the node-negative axilla with less harm for patients, several landmark trials established the safety of ALND omission in patients with cN-negative BC and positive SLN.[3-5,22-25] Ongoing trials such as the present OPBC-03/TAXIS and Alliance for Clinical Trials in Oncology A011202 aim at further de-escalating surgical treatment of the axilla by showing noninferiority of ART compared with ALND even in cN-positive BC.[13,26] Therefore, escalating axillary surgery for staging purposes seems counterintuitive, and we anticipate that surgeons are reluctant to go back and perform ALND for this reason, which is in line with the main findings of this study.

In the postneoadjuvant setting, patients with residual triple-negative disease showed improved oncologic outcomes when receiving capecitabine as did patients with residual *ERBB2*-positive disease when receiving trastuzumab emtansine-DM1.[11,12] In both trials, patients with tumor-positive lymph nodes were also eligible. Therefore, type of axillary surgery has the potential to influence response-driven chemotherapy in case of pCR in the breast and residual nodal disease that is missed by lesser surgical staging of the axilla. There are 2 reasons why this scenario is unlikely. First, the false-negative rate of TAS was shown to be as low as 2.6%.[14] Second, breast pCR is a strong predictor of nodal pCR. Data from an exploratory analysis within the Randomized Phase 3 Trial Comparing 2 Dose-Dense, Dose-Intensified Approaches (ETC and PM[Cb]) for Neoadjuvant Treatment of Patients With High-Risk Early Breast Cancer (GeparOcto) trial showed a breast pCR rate of 45.0%, of which 91.7% also showed axillary pCR.[27] This association was confirmed by a Korean trial as well as a Canadian series, showing axillary pCR in breast pCR in 86.6% and 83.0% of patients, respectively.[28,29] Because in the present study all included patients had confirmed residual disease in the nodes, the lack of differences in use of postneoadjuvant systemic therapy by type of axillary surgery was to be expected.

Limitations

This was a prospective observational cohort study embedded in a randomized clinical trial. Accordingly, although the 2 groups with or without ALND were well balanced for patient, tumor, and treatment characteristics as well as other known prognostic variables, residual confounding by unknown factors cannot be excluded. In addition, the present study was primarily designed to investigate the association of ALND use with proportion and type of systemic therapy; other aspects including, eg, density of dosing, were not addressed. Dose-dense adjuvant chemotherapy has been shown to improve DFS compared with standard interval chemotherapy in patients with node-positive early BC.[30] In patients who had 4 or more posi-

tive axillary lymph nodes, dose intensification has been shown to significantly improve event-free survival.[31] It would have been interesting to see if ALND had an impact on dose density.

Conclusions

Results of this cohort study suggest that omission of ALND was associated with understaging in patients with cN-positive BC with a high tumor burden in the axilla. However, missing knowledge of the exact number of positive nodes did not have a relevant impact on adjuvant and post-neoadjuvant systemic treatment decisions. Therefore, although ALND may be considered in individual patients being treated by a multidisciplinary team, results of the present study suggest that nodal burden as determined by TAS without ALND does not generally result in underuse of systemic therapy.

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Invited Commentary

Will Targeted Axillary Surgery Suffice for Adjuvant Treatment Decision-Making?

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Weber and colleagues[1] have published the results of a preplanned prospective observational cohort study of the first 500 randomized patients in the international, multicenter, phase 3 Tailored Axillary Surgery With or Without Axillary Lymph Node Dissection Followed by Radiotherapy in Patients With Clinically Node-Positive Breast Cancer (TAXIS) trial. This substudy was designed to address the association of staging information gleaned from axillary lymph node dissection (ALND) with adjuvant systemic therapy treatment decisions in 2 groups of patients with breast cancer: (1) patients with clinically node (cN)-positive breast cancer who undergo upfront surgery and (2) patients with cN-positive breast cancer and persistent nodal disease after neoadjuvant chemotherapy (NACT). For this study, the analytic cohort consisted of patients who underwent targeted axillary surgery (TAS), defined as removal of sentinel and palpable lymph nodes, from August 2018 through June 2022. The authors found that although omission of ALND in the patients who only received TAS plus axillary radiotherapy led to understaging of patients with cN-positive disease and significant axillary tumor burden, not knowing the exact number of positive nodes was not significantly associated with adjuvant treatment decisions in either recipients of NACT or upfront surgery, even if involved lymph nodes were, by implication, left behind.

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This study is limited by its observational design, absence of a prespecified power analysis to optimize sample size, and low numbers of patients with hormone receptor (HR)-negative/*ERBB2* (formerly *HER2* or *HER2/neu*)-positive disease. This study also did not require a standardized approach to TAS: neither dual tracer nor localization of the clipped node was required, and type of tracer was not specified, limiting quality control assessments. Although we recognize this flexibility may enable generalizability of study findings to clinical settings in which axillary localization is not possible, these limitations raise questions as to the reproducibility of TAS as an alternative to ALND and its concomitant outcomes across different surgeons, institutions, and countries. Also not addressed is whether TAS is noninferior to targeted axillary dissection (TAD, which includes sentinel lymph node biopsy and localized excision of the clipped node)[2] in disease staging and whether