Pathologic Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes

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ABSTRACT

PURPOSE Axillary soft tissue (AXT) involvement with tumor cells extending beyond the positive lymph node (LN+) and extracapsular extension (ECE) has been overlooked in breast pathology specimen analysis.

MATERIALS AND METHODS We analyzed 2,162 LN+ patients, dividing them into four groups on the basis of axillary pathology: (1) LN+ only, (2) LN+ and ECE only, (3) LN+ and AXT without ECE, and (4) LN+ with both AXT and ECE. The primary end points were 10-year locoregional failure (LRF), the 10-year axillary failure, and 10-year distant metastasis rates. Multivariable Cox models, accounting for clinical factors, were fitted using the entire cohort, and subgroups analyses were conducted.

RESULTS The median follow-up was 9.4 years. The 10-year distant metastasis incidence was 42% for LN + AXT + ECE, 23% for both LN + AXT and LN + ECE only, and 13% for LN+ only. The 10-year axillary failure rates were 4.5% for LN + AXT + ECE, 4.6% for LN + AXT, 0.8% for LN + ECE only, and 1.6% for LN+ only. The 10-year LRF rates were 14% for LN + AXT + ECE, 10% for LN + AXT, 5.7% for LN + ECE only, and 6.2% for LN+ only. Multivariable analysis revealed that AXT was significantly associated with distant metastasis (hazard ratio [HR], 1.6; $P < .001$), locoregional failure (HR, 2.3; $P < .001$), and axillary failure (HR, 3.3; $P = .003$). Subgroup analyses showed that regional LN radiation (RLNR) improved locoregional tumor outcomes with AXT, ECE, or both (HR, 0.5; $P = .03$). Delivering ≤50 Gy to the axilla in the presence of AXT/ECE increased axillary failure (HR, 3.0; $P = .04$). Moreover, when delivering RLNR, axillary LN dissection could be de-escalated to sentinel node biopsy even in the presence of features such as AXT or ECE without significantly increasing any failure outcome: (HR, 1.0; $P = .92$) for LRF, (HR, 1.1; $P = .94$) axillary failure, and (HR, 0.4; $P = .01$) distant metastasis.

CONCLUSION Routine reporting of axillary tissue involvement, beyond LNs and ECE, is crucial in predicting breast cancer outcomes. Ruling out the presence of AXT is imperative before any form of axillary de-escalation, especially RLNR omission.

ACCOMPANYING CONTENT

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INTRODUCTION

Breast cancer remains a major global health concern, with lymph node (LN) involvement as a critical prognostic factor influencing locoregional and systemic therapies.[1-3] Studies suggested that LN involvement in breast cancer prognosis and treatment guidance considers the number of LNs involved and the extent of tumor burden within the LNs.[4] The involvement spectrum spans from isolated tumor cells (ITCs) and micrometastasis to macrometastases.

Extracapsular extension (ECE) was first described in 1976 by Fisher et al.[5] However, multiple single-institution studies have reported discordant results regarding ECE's impact on breast cancer outcomes.[5-14] Some indicated that ECE signifies an unfavorable prognosis only for patients with fewer than three axillary LN involved[11] while others revealed that ECE indicates worse locoregional failure (LRF) necessitating regional LN radiation (RLNR).[6] Moreover, some research has suggested that ECE leads to worse disease-free survival but not LRF and demands aggressive systemic therapies rather than RLNR[14] while others

CONTEXT

Key Objective

The current focus of axillary specimen pathology analysis is the tumor burden within the lymph node (LN) and extracapsular extension (ECE). No evidence defines the importance of tumor involvement within the axillary soft tissue (AXT) beyond the LN and ECE in predicting tumor outcomes and guiding treatment strategies.

Knowledge Generated

In this cohort study, including 2,162 patients, we show that AXT involvement predicts worse tumor outcomes.

Relevance *(K.D. Miller)*

Breast cancer can involve the axilla in several ways, including isolated LN involvement, LN involvement with direct ECE, or direct involvement of axillary tissue. All impact prognoses should be reported consistently, especially as we continue to tailor local therapy to individual patient risk.*

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

reported that ECE is not associated with any outcome.[7,15,16] Most studies were limited by small sample sizes and patients treated before the advent of modern and targeted oncologic therapeutics.[6,11-14,17]

Unlike head and neck cancers where ECE plays an important role in staging and adjuvant treatment recommendations,[18] ECE's role in breast cancer remains vague. Additionally, the American College of Pathologist guideline issued in 2020 describes the classification of ITC, micrometastasis, and macrometastasis and recommending ECE reporting as a binary factor (present or not).[19,20] A recent national survey of 300 pathologists reveals the need for refined pathology reporting for axillary contents.[20]

An overlooked factor in breast pathology specimen analysis is axillary soft tissue (AXT) involvement with tumor cells extending beyond the LN and ECE. During a sentinel biopsy (SLNB) or complete axillary dissection (ALND), the primary focus is the tumor burden within the LN and ECE.[4,20] However, no established evidence defines routine AXT reporting or its significance beyond involved LNs and ECE in prognosis and treatment recommendations. This study aims to elucidate the prognostic role of AXT with and without ECE and categorize distinct types of AXT to assess their impact on various tumor outcomes in different clinical contexts.

MATERIALS AND METHODS

After receiving Institutional Review Board approval, we conducted a retrospective review of 6,374 patients with breast cancer with invasive tumors who received treatment at our institution from 2000 to 2020. Patients with primary breast cancers, positive LNs (LN+), and without a history of prior or contralateral/simultaneous breast cancers were included. Detailed inclusion/exclusion criteria are available in the flow diagram (Fig 1). Patient demographics, tumor pathology data, chemotherapy, surgery, and radiation details were collected and stored in a prospectively maintained REDCap database (Vanderbilt University). Following inclusion criteria, 2,162 patients were included in the study analysis and were divided into four groups according to the axillary pathology: (1) patients with LN+ only, (2) LN+ and ECE only, (3) LN+ and AXT with no ECE, and (4) LN+ and both AXT and ECE.

Pathology Methodology

Pathology methodology is available in the Data Supplement (online only). Figure 2 depicts examples of different axillary contents.

End Points

The primary end points were to assess the 10-year LRF incidence defined as surgically/biopsy proven recurrence in the breast/chest wall or ipsilateral axilla, the 10-year axillary failure incidence defined as recurrence only in the axilla, and 10-year distant metastasis incidence rates across the four groups. For each end point, multivariable model accounting for various clinical factors was fitted using the entire cohort. Additionally, we conducted the following subgroups analyses:

1. Patients with one to three LN+ have been the focus of many axillary de-escalation clinical trials.[21-23] Moreover, previous data indicated that ECE matters only with ≤four LN+[11] while others did not show any importance of ECE in one to three LN+ patients.[15,17] Therefore, we conducted a subgroup analysis for all patients across the different study groups with one to three LN+ to explore the impact of ECE and AXT in this subgroup.
2. Among patients with AXT, we examined the impact of different AXT types on LRF, axillary failure, and distant metastasis incidence rates.

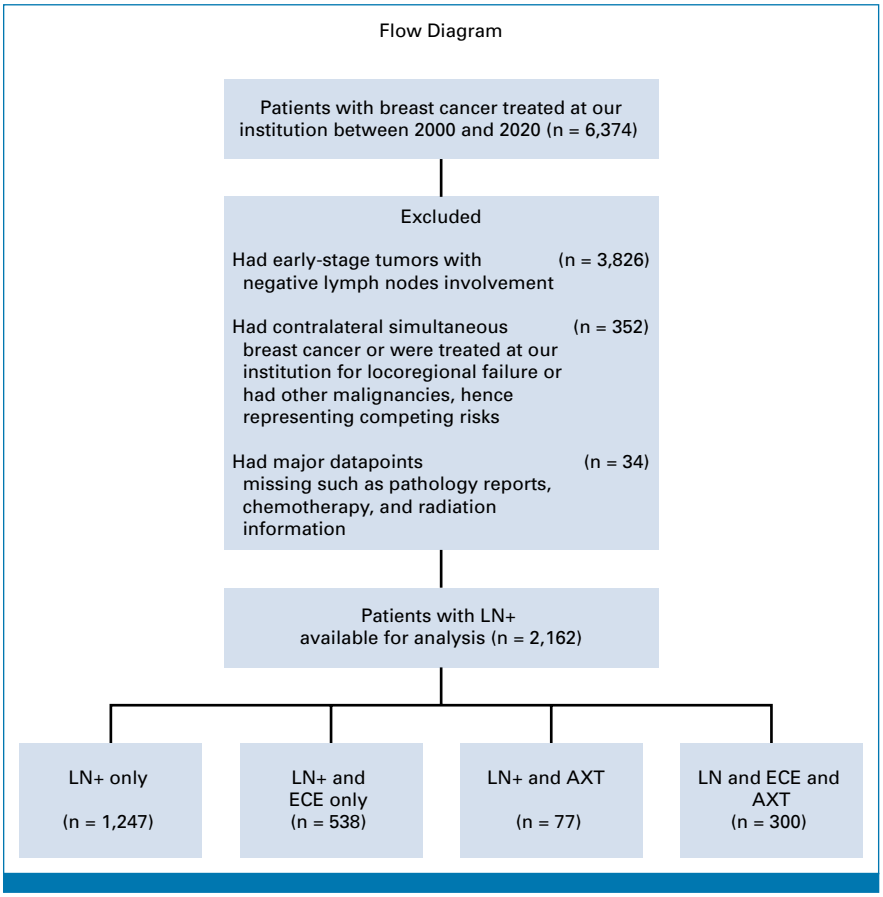

FIG 1. Flow diagram. AXT, axillary soft tissue; ECE, extracapsular extension; LN, lymph node; LN+, positive LN.

3. For patients with ECE or AXT or both, we assessed the impact of SLNB versus ALND and RLNR on outcomes in those patients. RLNR was defined in our database as treating the axillary, supraclavicular, and internal mammary nodes.
4. For patients with ECE or AXT or both and treated with RLNR, we evaluated the differences in total doses on tumor control end points. The current National Comprehensive Cancer Network guidelines endorses RLNR with a total dose ranging between 45 and 50.4 Gy in 25-28/fractions.[4] Therefore, we explored if delivering <50 Gy (namely, 45-46.8 Gy in 25-26/fractions) to the axilla was associated with higher risk of axillary failure.
5. Acknowledging the difference in tumor outcomes between patients who receive neoadjuvant chemotherapy and those receiving surgery up-front,[24] we explored the impact of AXT on tumor outcomes in neoadjuvant and non-neoadjuvant settings.

Statistical Analysis

Sample characteristics were described overall and by treatment group. The associations between potential risk factors and each of the study end points were assessed using Kaplan-Meier analysis and Cox proportional hazard regression. Potential confounders included in the multivariable models were prespecified on the basis of clinical judgment. To prevent overfitting, the number of covariate levels allowed in the MV model were restricted so that there were at least five outcome events per covariate level.[25] Models aiming to explore the impact of RLNR in high-risk patients excluded those who developed local recurrence or distant metastasis soon after surgery before receiving the planned adjuvant treatment. For instance, RLNR was delivered after the end point (n = 2 excluded in LRF models; n = 11 excluded for distant metastasis models). Hypothesis tests were two-sided, and the significance threshold was set to 0.05. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics

Among 2,162 patients, 1,247 had LN only, 538 had LN with ECE only, 77 had LN with AXT, and 300 had LN with AXT and ECE. The overall median follow-up was 9.4 years for the entire cohort (Q1-Q3, 5.5-14 years). Descriptively, patients in LN + ECE-only, LN + AXT, and LN + AXT + ECE groups had

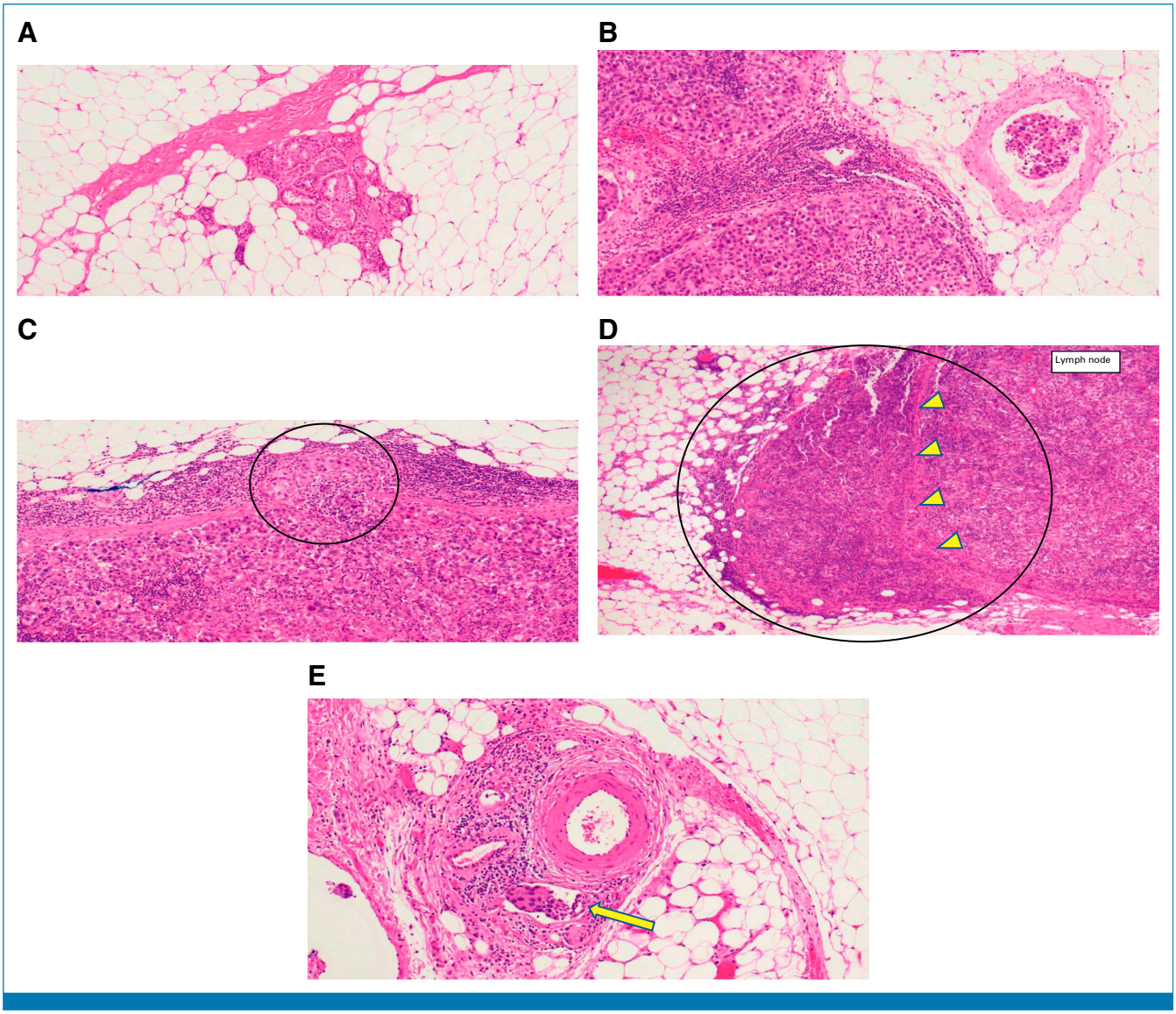

FIG 2. (A) Soft tissue tumor deposit, metastatic carcinoma in the axillary adipose soft tissue not associated with a lymph node. (B) Blood vessel invasion. Carcinoma in a blood vessel in the axillary soft tissue not associated with a lymph node. (C) Focal extranodal extension. Metastatic carcinoma cells in an axillary lymph node have focally invaded through the nodal capsule into adjacent adipose tissue, with associated chronic inflammation. (D) Extensive extranodal extension. Metastatic carcinoma in an axillary lymph node has invaded through nodal capsule (arrowheads) into adjacent adipose tissue along a broad front (circled area). (E) Tumor embolus in a lymphatic channel within axillary adipose tissue (arrow) not associated with a lymph node.

advanced tumor pathologic features compared with the LN-only group. The median size of breast tumors, the number of malignant LNs, presence of breast lymphovascular invasion (LVI), Pathologic T stage, and N stage were higher in those groups compared with the LN-only group (Table 1). Moreover, more patients in those three groups received a mastectomy, ALND, RLNR, and systemic therapy than LN-only patients (Table 1). The majority of the cohort (74%) were hormonal sensitive, 10% was triple negative, and 16% were human epidermal growth factor receptor 2 enriched. For patients with AXT with and without ECE (N = 377 in total), the types of AXT involvement were mainly in the form of lymphatic vessels (51%; Table 1).

Clinical Outcomes

The 10-year cumulative incidence of distant failure was the lowest in the LN-only group (13%) while the LN + ECE-only and LN + AXT groups had 23% rates. The LN + AXT + ECE had the highest 10-year distant failure incidence of 42% (Fig 3A). For locoregional failure, the presence of AXT yielded higher rates of locoregional failure where LN + AXT and LN + AXT + ECE had a 10-year incidence of 10% and 14%, respectively (Fig 3B). The LN + ECE-only and LN-only groups had lower 10-year locoregional failure rates (5.7% and 6.2%), respectively. The axillary failure 10-year outcomes (Fig 3C) had the highest incidence in AXT groups (4.6% for LN + AXT

TABLE 1. Demographics

Level	LN Only (n = 1,247)	LN and ECE (n = 538)	LN and AXT (n = 77)	LN and ECE and AXT (n = 300)	Overall (N = 2,162)
Age, years, median (Q1-Q3)	51 (44-61)	52 (46-61)	49 (45-56)	53 (45-62)	52 (45-61)
Breast surgery, No. (%)					
Lumpectomy	576 (46)	216 (40)	26 (34)	90 (30)	908 (42)
Mastectomy	671 (54)	322 (60)	51 (66)	210 (70)	1,254 (58)
Axillary surgery, No. (%)					
SLNB alone	611 (49)	89 (16.5)	15 (19.5)	14 (4.7)	729 (34)
ALND	636 (51)	449 (83.5)	62 (80.5)	286 (95)	1,433 (66)
RLNR,a No. (%)	548 (44)	400 (74)	62 (81)	258 (86)	1,268 (59)
RLNR dose, No. (%)					
≥50 Gy	364 (66)	294 (73.5)	43 (69)	210 (81)	911 (72)
<50 Gy (45-46.8 Gy in 25-26 fractions)	184 (34)	106 (26.5)	19 (31)	48 (19)	357 (28)
No. of LN removed, median (Q1-Q3)	7.0 (2.0-15)	14 (10-19)	14 (10-20)	16 (12-21)	12 (3.0-17)
No. of malignant LN, median (Q1-Q3)	1.0 (1.0-2.0)	2.0 (1.0-4.0)	3.0 (1.0-5.0)	6.0 (3.0-11)	2.0 (1.0-3.0)
HER2, No. (%)					
HER2-negative	1,008 (81)	466 (87)	60 (78)	248 (83)	1,782 (82)
HER2-positive	204 (16)	66 (12)	16 (21)	49 (16)	335 (16)
Unknown	35 (2.8)	6 (1.1)	1 (1.3)	3 (1.0)	45 (2.1)
ER status, No. (%)					
ER-negative	187 (15)	67 (13)	16 (21)	49 (16)	319 (15)
ER-positive	1,049 (84)	467 (87)	61 (79)	250 (83)	1,827 (85)
Unknown	11 (0.9)	4 (0.7)	0 (0.0)	1 (0.3)	16 (0.7)
PR status, No. (%)					
PR-negative	269 (22)	106 (20)	21 (27)	81 (27)	477 (22)
PR-positive	963 (77)	427 (79)	55 (71)	218 (73)	1,663 (77)
Unknown	15 (1.2)	5 (0.9)	1 (1.3)	1 (0.3)	22 (1.0)
Luminal subtypes,b No. (%)					
Luminal A	682 (55)	280 (52)	25 (32.5)	126 (42)	1,113 (51.5)
HER2 enriched	204 (16)	66 (12)	16 (21)	49 (16)	335 (15.5)
Luminal B	232 (19)	142 (26)	25 (32.5)	91 (30)	490 (23)
Triple negative	129 (10)	50 (9.3)	11 (14)	34 (11)	224 (10)
Breast tissue LVI-positive, No. (%)	465 (37)	243 (45)	56 (73)	195 (65)	959 (44)
Tumor grade, No. (%)					
Grade 1	124 (9.9)	51 (9.5)	1 (1.3)	3 (1.0)	179 (8.3)
Grade 2	637 (51)	255 (47)	29 (38)	135 (45)	1,056 (49)
Grade 3	473 (38)	229 (43)	46 (60)	160 (53)	908 (42)

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TABLE 1. Demographics (continued)

Level	LN Only (n = 1,247)	LN and ECE (n = 538)	LN and AXT (n = 77)	LN and ECE and AXT (n = 300)	Overall (N = 2,162)
Unknown	13 (1.0)	3 (0.6)	1 (1.3)	2 (0.7)	19 (0.9)
Surgical (pathologic) T stage, No. (%)					
Missing	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Tis (Paget disease)	57 (4.6)	5 (0.9)	0 (0.0)	4 (1.3)	66 (3.1)
T1	736 (59)	237 (44)	41 (53)	94 (31)	1,108 (51)
T2	372 (30)	226 (42)	21 (27)	139 (46)	758 (35.1)
T3	72 (6)	61 (11)	12 (16)	54 (18)	199 (9.2)
T4	6 (0.5)	8 (1.5)	1 (1.3)	8 (2.7)	23 (1.1)
Tx (occult carcinoma)	3 (0.2)	1 (0.2)	2 (2.6)	1 (0.3)	7 (0.3)
Surgical (pathologic) N stage, No. (%)					
0+ (isolated tumor cells)	349 (28.0)	1 (0.2)	4 (5.2)	0 (0.0)	354 (16.4)
1	805 (64.6)	382 (71.0)	45 (58.4)	84 (28.0)	1,316 (60.9)
2	80 (6.4)	109 (20.3)	18 (23.4)	125 (41.7)	332 (15.4)
3	13 (1.0)	46 (8.6)	10 (13.0)	91 (30.3)	160 (7.4)
Clinical T stage (only available for patients receiving neoadjuvant chemotherapy, n = 481), No. (%)					
cT0/not able to evaluate	0 (0.0)	1 (0.8)	0 (0.0)	3 (2.9)	4 (0.8)
cT1	23 (10.6)	13 (9.8)	1 (5.0)	12 (11.4)	49 (10.3)
cT2	106 (48.6)	70 (52.6)	7 (35.0)	49 (46.7)	232 (48.7)
cT3	64 (29.4)	32 (24.1)	8 (40.0)	20 (19.0)	124 (26.1)
cT4	25 (11.5)	17 (12.8)	4 (20.0)	21 (20.0)	67 (14.1)
Missing	3 (0.01)	0 (0)	0 (0)	2 (0.01)	5 (0.01)
Clinical N stage (only for patients receiving neoadjuvant chemotherapy, n = 481), No. (%)					
cN0	54 (24.8)	24 (18.0)	3 (15.0)	21 (20.0)	102 (21.4)
cN1	141 (64.7)	94 (70.7)	17 (85.0)	65 (61.9)	317 (66.6)
cN2	15 (6.9)	10 (7.5)	0 (0.0)	11 (10.5)	36 (7.6)
cN3	8 (3.7)	5 (3.8)	0 (0.0)	8 (7.6)	21 (4.4)
Missing	3 (0.01)	0 (0)	0 (0)	2 (0.01)	5 (0.01)
Chemotherapy, No. (%)					
Adjuvant chemotherapy	672 (54)	317 (59)	50 (65)	167 (56)	1,206 (56)
Neoadjuvant + adjuvant	221 (18)	133 (25)	20 (26)	107 (36)	481 (22)
No chemotherapy	345 (28)	81 (15)	6 (7.8)	19 (6.3)	451 (21)
Patients refusing chemotherapy initially then receiving salvage chemotherapy	9 (0.7)	6 (1.1)	1 (1.3)	7 (2.3)	23 (1.1)
Pathologic tumor size, cm, median (Q1-Q3)	1.6 (1.0-2.5)	2.2 (1.5-3.2)	2.0 (1.3-2.8)	2.6 (1.8-4.5)	1.9 (1.2-3.0)

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TABLE 1. Demographics (continued)

Level	LN Only (n = 1,247)	LN and ECE (n = 538)	LN and AXT (n = 77)	LN and ECE and AXT (n = 300)	Overall (N = 2,162)
Type of axillary involvement, No. (%)					
Axillary lymphatic vessels	0	0	55 (71)	137 (46)	192 (51)
Axillary soft tissue metastasis	0	0	12 (16)	53 (18)	65 (17)
Axillary blood vessels	0	0	1 (1.3)	7 (2.3)	8 (2.1)
Axillary matted mass/nodes	0	0	0 (0.0)	14 (4.7)	14 (3.7)
Combination of any	0	0	7 (9.1)	83 (28)	90 (24)
Others (misc pathology forms)	0	0	2 (2.6)	6 (2.0)	8 (2.1)
Years from diagnosis to last follow-up, median (Q1-Q3)	10 (6.2-15)	8.8 (5.2-13)	9.3 (5.0-15)	7.4 (3.4-12)	9.4 (5.5-14)

Abbreviations: ALND, axillary LN dissection; AXT, axillary soft tissue; ECE, extracapsular extension; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; LVI, lymphovascular invasion; PR, progesterone receptor; RLNR, regional LN radiation; SLNB, sentinel LN biopsy.

[a]Patients who did not receive nodal radiation in LN+ group were whether patients with N0+ with isolated tumor cells (n = 349) or patients with N1mic or one positive LN and favorable biology. Patients in groups with ECE or AXT or both who did not receive RLNR were whether patients with one positive LN or those who completely refused any form of radiation.

[b]Luminal subtypes were defined as following: Luminal A: ER/PR+, HER2 negative, and tumor grade 1 or 2. Luminal B: ER/PR+, HER2 negative, and tumor grade 3. HER2-enriched tumors included both hormonal positive and hormonal negative but HER2-positive tumors.

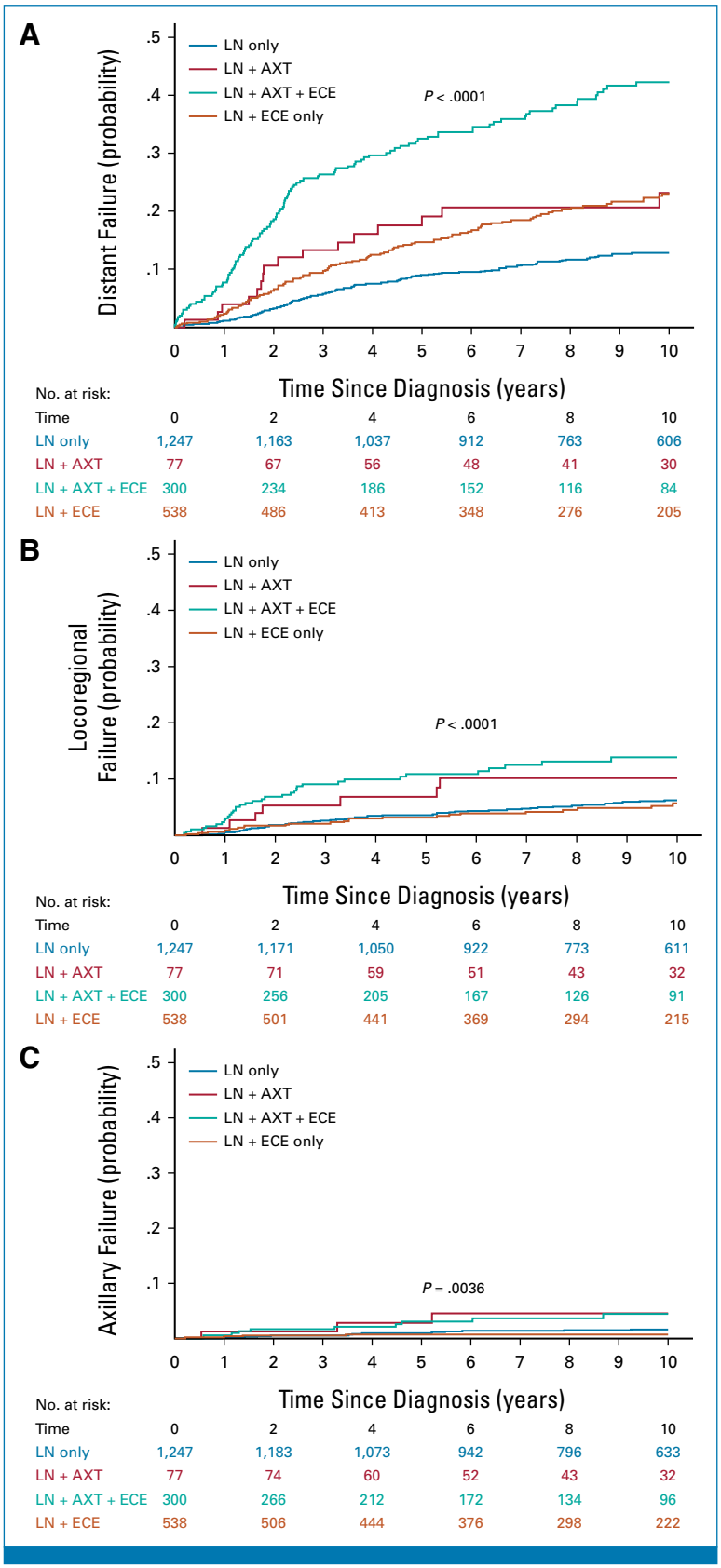

FIG 3. (A) 10-year cumulative incidence of distant failure across the four groups. (B) 10-year cumulative incidence of locoregional failure across the four groups. (C) 10-year cumulative incidence of axillary failure across the four groups. AXT, axillary soft tissue; ECE, extracapsular extension; LN, lymph node.

TABLE 2. Multivariable Analysis for Different Tumor Outcomes for the Entire Cohort

	Distant Failure		Locoregional Failure		Axillary Failure[a]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
ECE	1.60 (1.28 to 2.01)	<.001	0.91 (0.62 to 1.32)	.61	0.98 (0.47 to 2.05)	.96
AXT	**1.61 (1.28 to 2.04)**	**<.001**	**2.31 (1.52 to 3.52)**	**<.001**	**3.33 (1.51 to 7.36)**	**.003**
HER2 enriched *v* luminal A	1.24 (0.90 to 1.69)	.19	1.07 (0.64 to 1.78)	.81	—	—
Luminal B *v* luminal A	1.84 (1.44 to 2.36)	<.001	1.15 (0.73 to 1.82)	.55	—	—
Triple negative *v* luminal A	3.66 (2.76 to 4.86)	<.001	4.71 (3.13 to 7.11)	<.001	—	—
No. of malignant LN	1.05 (1.04 to 1.07)	<.001	1.005 (0.97 to 1.04)	.80	0.96 (0.87 to 1.05)	.36
Breast tissue LVI positive *v* no breast tissue LVI	1.15 (0.94 to 1.42)	.18	1.41 (1.00 to 1.98)	.049	1.76 (0.90 to 3.44)	.10
Tumor grade 2 or 3 *v* grade 1	1.81 (1.00 to 3.27)	.05	0.95 (0.47 to 1.94)	.89	—	—
Tumor size, cm	1.07 (1.03 to 1.11)	<.001	1.04 (0.97 to 1.13)	.27	—	—

NOTE. Bold indicates statistically significant association between the variable of interest and the outcome.
Abbreviations: AXT, axillary soft tissue; ECE, extracapsular extension; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LN, lymph node; LVI, lymphovascular invasion.
[a]For axillary failure outcomes, because of low No. of events and to avoid statistical overfitting/overestimation, full multivariable models containing all the risk factors could not be fit.

and 4.5% for LN + AXT + ECE) and lower incidence without AXT (0.8% for LN + ECE only and 1.6% for LN only).

On multivariable analysis (Table 2) controlling for biological subtypes, tumor grade, number of malignant LNs, breast LVI, and tumor size, we found that axillary soft tissue (AXT) involvement is significantly associated with distant failure (hazard ratio [HR], 1.6; $P < .001$), locoregional failure (HR, 2.3; $P < .001$) and axillary failure (HR, 3.3; $P = .003$). Conversely, ECE was only significantly associated with distant failure (HR, 1.6; $P < .001$) but not with locoregional failure (HR, 0.91; $P = .61$) nor axillary failure (HR, 0.98; $P = .96$).

Subgroup Analyses

Patients With Pathologic N1 Disease

For the subgroup of patients with only one to three malignant LNs, equivalent to pathologic N1 disease, the above findings regarding ECE and AXT remained the same. AXT was significantly associated with all tumor outcomes; (HR, 1.8; $P = .002$) for distant failure, (HR, 3.0; $P < .001$) locoregional failure, and (HR, 5.1; $P < .001$) axillary failure. ECE was not significantly associated with either locoregional failure (HR, 0.9; $P = .56$) or axillary failure (HR, 0.8; $P = .62$). Similar to the entire cohort analysis, patients with ECE had higher risks for distant failure with an HR of 1.3 and a near-significant *P* value (.08) (Table 3).

Impact of Different Types of Axillary Tissues Involvement

For patients with AXT with and without ECE (N = 377), we found that a combination of two or more forms of AXT is significantly associated with increase in distant failure (HR, 1.9; $P = .001$) (Data Supplement). There was no significant difference in locoregional, distant, and axillary failure between lymphatic vessels, blood vessels, matted masses, and soft tissue/fat metastasis (Data Supplement).

Impact of RLNR in the Setting of AXT or ECE or Both

For patients with AXT or ECE or both, we found that delivery of RLNR significantly improved locoregional control (HR, 0.5; $P = .03$). In contrast, there was no significant benefit for RLNR compared with the patients who did not receive it for distant failure (HR, 0.8; $P = .32$) and axillary failure (HR, 0.5; $P = .14$). In this subgroup, we also found no significant difference in locoregional failure (HR, 1.0; $P = .92$) and axillary failure (HR, 1.1; $P = .94$) between SLNB and ALND, respectively. However, interestingly, SLNB was significantly associated with better distant failure outcomes (HR, 0.4; $P = .01$) compared with ALND patients (Table 3).

Different Doses of RLNR and Tumor Outcomes

For patients with AXT or ECE or both and receiving RLNR, there was no significant difference between RLNR ≥50 and <50 Gy in terms of locoregional failure (HR, 1.1; $P = .7$) and distant failure (HR, 0.9; $P = .5$) (Table 3). Yet, delivering <50 Gy (45-46.8 Gy in 25-26 fractions) to the axilla was significantly associated with higher hazards of axillary failure (HR, 3.0; $P = .04$).

Outcomes in Neoadjuvant and Non-Neoadjuvant Settings

In non-neoadjuvant settings, AXT was significantly associated with distant failure (multivariable HR, 1.5; $P = .01$), locoregional failure (multivariable HR, 3.2; $P < .001$), and axillary failure (multivariable HR, 4.35; $P = .004$). Similarly, AXT

TABLE 3. Different Subgroups Multivariable Analysis Adjusted for Tumor Biology, Grade, LVI, No. of Malignant LN, and Pathologic Tumor Response

		Distant Failure		Locoregional Failure		Axillary Failure[a]	
Subgroup of Interest	Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
For all patients with 1-3 malignant LN	ECE	1.29 (0.97 to 1.73)	.08	0.88 (0.57 to 1.36)	.56	0.80 (0.33 to 1.93)	.62
	AXT	**1.83 (1.24 to 2.70)**	**.002**	**3.02 (1.80 to 5.07)**	**<.001**	**5.10 (2.04 to 12.7)**	**<.001**
For patients with high-risk features: Either ECE or AXT or both	RLNR *v* no nodal radiation	0.84 (0.61 to 1.18)	.32	**0.54 (0.31 to 0.94)**	**.03**	0.49 (0.18 to 1.28)[a]	.14[a]
	SLNB *v* ALND	0.44 (0.23 to 0.83)	.01	0.95 (0.40 to 2.28)	.92	1.06 (0.24 to 4.67)[a]	.94[a]
For patients with high-risk features ECE or AXT or both and receiving RLNR	SCV/RLNR total dose <50 *v* ≥50 Gy	0.88 (0.62 to 1.25)	.48	1.11 (0.59 to 2.10)	.74	**3.04 (1.07 to 8.68)[a]**	**.04[a]**
For patients receiving surgery up-front (non-neoadjuvant patients)	ECE	1.63 (1.21 to 2.19)	.001	0.57 (0.35 to 0.93)	.02	0.40 (0.14 to 1.14)	.09
	AXT	**1.51 (1.09 to 2.09)**	**.01**	**3.25 (1.89 to 5.58)**	**<.001**	**4.35 (1.61 to 11.8)**	**.004**
For patients receiving surgery up-front (non-neoadjuvant patients) with high-risk features: Either ECE or AXT or both	RLNR *v* no nodal radiation	0.81 (0.53 to 1.25)	.34	0.51 (0.25 to 1.07)[a]	.07	0.56 (0.13 to 2.37)[a]	.43[a]
	SLNB *v* ALND	0.61 (0.30 to 1.22)	.16	1.45 (0.58 to 3.62)[a]	.42[a]	1.98 (0.40 to 9.85)[a]	.40[a]
For patients receiving chemotherapy up-front (neoadjuvant cases)	ECE	1.28 (0.90 to 1.81)	.17	1.96 (1.04 to 3.72)	.04	3.09 (0.98 to 9.72)[a]	.05[a]
	AXT	**1.48 (1.05 to 2.10)**	**.03**	**1.45 (0.77 to 2.74)**	**.25**	**2.84 (1.03 to 7.85)[a]**	**.04[a]**
For neoadjuvant patients with high-risk features: Either ECE or AXT or both	RLNR *v* no nodal radiation	0.86 (0.49 to 1.50)	.59	0.43 (0.19 to 1.00)[a]	.05[a]	0.33 (0.09 to 1.26)[a]	.11[a]
	SLNB *v* ALND	0.23 (0.03 to 1.64)	.14	−0.00[b]	.04[b]	0.00[b]	.27[b]

NOTE. Pathologic response was included only for subgroups focusing on neoadjuvant patients. Full models for each outcome are available in the Data Supplement. Bold indicates statistically significant association between the variable of interest and the outcome.

Abbreviations: ALND, axillary LN dissection; AXT, axillary soft tissue; ECE, extracapsular extension; HR, hazard ratio; LN, lymph node; LVI, lymphovascular invasion; RLNR, regional LN radiation; SCV, supraclavicular ; SLNB, sentinel LN biopsy.

[a]For axillary failure and locoregional failure outcomes, because of low No. of events in some subgroups and to avoid statistical overfitting/overestimation, full multivariable models containing all the risk factors could not be fit. Full models with corresponding variables of interest are available in the Data Supplement.

[b]For patients receiving neoadjuvant chemotherapy and found to have AXT, ECE, or both during surgery, only 17 patients received SLNB and none (0 of 17) developed locoregional failure nor axillary failure. Likelihood ratio test *P* values are reported for the unadjusted HRs (0).

increased risks of distant failure (multivariable HR, 1.5; $P = .03$) and axillary failure (HR, 2.8; $P = .04$) for neoadjuvant patients. AXT increased hazards of locoregional failure for neoadjuvant patients but without statistical significance (multivariable HR, 1.45; $P = .25$) possibly due to low number of locoregional failure events in this setting. RLNR was associated with protective effects in patients with AXT in both neoadjuvant and non-neoadjuvant settings, with statistical significance level and number of events varying (Table 3).

DISCUSSION

In this study of 2,162 LN-positive patients with a median follow-up of 9.4 years, we demonstrate the importance of evaluating axillary tissue beyond the number of LN+, tumor extent within the LN, and presence of ECE. Current guidelines and staging systems do not emphasize AXT examination.[4,26] AXT involvement can result from direct LN extension with ECE (LN + ECE + AXT group, N = 300) or direct microscopic spread from the primary tumor without ECE (LN + AXT, N = 77). ECE presence in our cohort was associated with distant metastasis (HR, 1.6; $P < .001$) but not with locoregional failure (HR, 0.91; $P = .61$) or axillary failure (HR, 0.98; $P = .96$), consistent with some studies[8] but contrasting others.[5,7,13] The discrepancy can be attributed to differences in patient selection, end points definition, and cohort sizes[8-10,27] and that many studies defining the role of ECE[5,11,14] were published in presystemic targeted therapy (before the year 2000).

Historical evidence suggested that ECE is important only for patients with ≤four LN+[11] while others showed that ECE has no prognostic role in patients with one to three LN+ and that the numbers of LN+ matter more.[15,17] In our study, we demonstrate that after controlling for different risk factors including the number of LN+, AXT was significantly associated with distant metastasis (HR, 1.6; $P < .001$), locoregional failure (HR, 2.3; $P < .001$), and axillary failure (HR, 3.3; $P = .003$). Moreover, the 10-year incidence (Fig 3) of each tumor outcome was higher when AXT was positive compared with LN-only and LN + ECE-only groups. Although it could be contended that the group of LN + ECE + AXT is the highest risk group which intuitively yields worse tumor outcomes, we showed that the LN + AXT group without ECE also has a higher 10-year incidence of locoregional recurrence and axillary failure compared with LN + ECE-only and LN-only groups (10% *v* 5.7% *v* 6.2% for LRF and 4.6% *v* 0.8% *v* 1.6% for axillary failure), respectively. This clearly illustrates that even when the tumor burden in the LN is minimal without ECE, AXT remained a prognostic factor requiring aggressive local and systemic treatment. The majority of AXT forms (50%) were lymphatic vessels involved in the axilla. Our study did not identify a significant difference between soft tissue or fat metastasis, matted tumor masses in the axilla, and axillary lymphatic vessels involvement in tumor outcomes. However, a combination of two or more AXT forms was associated with worse distant failure only (HR, 1.9; $P = .001$) but not locoregional failure (HR, 1.3; $P = .3$) or axillary failure (HR, 1.3; $P = .6$) (Data Supplement).

In the subgroup analysis of patients with one to three LN+, it was observed that AXT still maintained a significant association with all tumor-related outcomes, despite the minimal number of malignant LNs involved (Table 3).

Interestingly, this subgroup with one to three LNs has been the focus of many treatment de-escalation trials.[21,22] However, the seminal trials such as AMAROS and Z011 confirming substituting ALND with SLNB + RLNR did not report/include patients with ECE. Reports from Memorial-Sloan-Kettering (MSK)[28,29] suggested that after applying Z011 criteria, the substitution of ALND by SLNB alone can be offered to patients with focal ECE (<2 mm), but patients with extensive ECE (>2 mm) may still require completion ALND. Others have found similar results[30-32] but using different cutoffs for ECE quantitation. This varied practice highlights the need for a universal and standardized methodology to quantify ECE and prognostic significance of its extent. Another MSK series applying Z011 criteria,[33] showed that extranodal tumor deposit beyond the LN (which mimics our AXT definition here) is associated with more LN+ similar to the demographics presented in Table 1. However, they had only 113 AXT patients without any subclassification of AXT forms, and the authors clearly stated that they did not aim to correlate AXT with tumor outcomes and did not control for RLNR.[33]

Our study shows the importance of expanding the focus beyond LN number/morphology and ECE. This is particularly important as the ongoing axillary de-escalation trials focus mainly on LN number/morphology with little to no mention of ECE and AXT. For instance, NSABP-B51 randomly assigns neoadjuvant patients who achieve complete nodal pathologic response to RLNR or no RLNR; the Alliance-A011202 randomly assigns those with positive sentinel node after neoadjuvant chemotherapy to ALND completion or SLNB + RLNR encompassing all axillary/supraclavicular levels; and MA.39 randomly assigns non-neoadjuvant patients with luminal A, oncotype score <18, and one to three positive sentinel node to RLNR or no RLNR. We showed that in non-neoadjuvant settings, AXT significantly increased the risk for all tumor outcomes (Table 3). AXT significantly increased the risks of distant and axillary failure for neoadjuvant cases as well. It was also associated with higher hazards of locoregional failure without achieving statistical significance possibly due to the low number of events in this subgroup. Therefore, ruling out the presence of AXT will inform and guide safe de-escalation of axillary treatment, whether in neoadjuvant or non-neoadjuvant settings.

Hence, we examined the impact of RLNR/no RLNR and SLNB/ALND in patients with AXT, ECE, or both (Table 3). For all these patients, RLNR was associated with lower hazards

of any type of failure, but statistical significance was only achieved for locoregional-failure outcomes (multivariable HR, 0.5; $P = .03$). Neither distant failure (HR, 0.8; $P = .32$) nor axillary failure (HR, 0.5; $P = .14$) reached statistical significance of these protective hazards rates. Stratifying patients with AXT, ECE, or both by neoadjuvant and non-neoadjuvant settings, we found that RLNR was associated with protective effects on all tumor outcomes in both settings, with statistical significance level and number of events varying (Table 3). Moreover, ALND did not significantly improve tumor outcomes compared with SLNB in any subgroup as long as RLNR was adjusted for in the analysis. This aligns with current strategies of substituting ALND by SLNB + RLNR and reinforces that AXT needs to be ruled out before deciding on RLNR omission.

Current RLNR guidelines are not clear regarding RLNR in settings of ECE, and practice patterns in settings of ECE vary by clinical experience or subjective judgment. In addition to advocating for a standardized assessment of AXT beyond ECE, our findings indicate that presence of any feature such as ECE or AXT, irrespective of tumor biology, LN count, or tumor burden, independently warrants administration of RLNR. Moreover, current National Comprehensive Cancer Network guidelines recommend RLNR doses ranging from 45 to 50 Gy. Our study suggests that RT doses <50 Gy significantly increased the risk of axillary failure by three folds (HR, 3.0; $P = .04$) but not for locoregional failure (HR, 1.1; $P = .7$) and distant failure (HR, 0.9; $P = .5$).

Our study has limitations. The retrospective nature hindered capturing the RLNR volumes delineation as radiation details were captured mainly from fields/prescriptions stored in treatment-recording software (MOSAIQ, Elekta AB, Stockholm, Sweden). RLNR was administered using conventional fractionation (45-50 Gy in 1.8-2 Gy/fraction). RLNR hypofractionation trials may yield different conclusions with different dose calculations. Moreover, not all the patients had genomic markers testing. Because of constraints associated with conducting a prospective randomized trial focusing mainly on AXT, the investigation of AXT and its prognostic impact relies on the large retrospective study design. Our time-to-event analyses, subgroup analyses and controlling for all potential confounders aimed to overcome the retrospective shortcomings. Finally, the locoregional failure and axillary failure incidence in the breast cancer population are known to be low 5%-10% and 1%, respectively.[34,35] Despite such low incidence, we showed the significant detrimental impact of AXT on those outcomes. However, not all subgroups had many events to detect statistical significance of the RLNR protective hazards. In theory, patients in the LN+ only group in our study who underwent SLNB only could have had AXT if ALND had been completed with more axillary tissue excised. This reinforces the role of RLNR when ALND is avoided and ruling out AXT before omitting RLNR.

Our findings have significant implications for breast pathology practices. Current American Pathologists protocols for reporting breast cancer do not require specifying (LVI) location (eg, whether it is present in the breast *v* AXT), distinguishing lymphatic channels from blood vessels, or quantifying the extent of LVI. Furthermore, per American Joint Committee on Cancer guidelines, invasive tumor nodules in the axillary fat without histologic evidence of associated LN tissue are considered LN metastases (pN). We suggest revisiting those guidelines with a unified approach regarding ECE characterization, quantitation of LVI in the breast (type of vessel: focal *v* extensive) and routine reporting of tumor deposits in the axillary soft tissue and their nature (lymph vessel, blood vessel, etc).

In conclusion, routine pathologic evaluation and reporting axillary tissue involvement, beyond LN quantification and ECE is crucial predicting breast cancer outcomes. Ruling out the presence of AXT is imperative before omitting any form of axillary treatment, especially regional nodal radiation.

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REFERENCES

1. Fisher B, Bauer M, Wickerham DL, et al: Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: An NSABP update. Cancer 52:1551-1557, 1983
2. Keshtgar MRS, Ell PJ: Clinical role of sentinel-lymph-node biopsy in breast cancer. Lancet Oncol 3:105-110, 2002
3. Naxerova K: Defining the role of lymph node metastasis in systemic breast cancer evolution. eBioMedicine 10.1016/j.ebiom.2020.102852
4. Gradishar WJ, Moran MS, Abraham J, et al: Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20:691-722, 2022
5. Fisher ER, Gregorio RM, Redmond C, et al: Pathologic findings from the national surgical adjuvant breast project. (Protocol no. 4). III. The significance of extranodal extension of axillary metastases. Am J Clin Pathol 65:439-444, 1976
6. Fisher BJ, Perera FE, Cooke AL, et al: Extracapsular axillary node extension in patients receiving adjuvant systemic therapy: An indication for radiotherapy? Int J Radiat Oncol Biol Phys 38:551-559, 1997
7. Hetelekidis S, Schnitt SJ, Silver B, et al: The significance of extracapsular extension of axillary lymph node metastases in early-stage breast cancer. Int J Radiat Oncol Biol Phys 46:31-34, 2000
8. Kanyılmaz G, Fındık S, Yavuz BB, et al: The significance of extent of extracapsular extension in patients with T1-2 and N1 breast cancer. Eur J Breast Health 14:218-224, 2018
9. Layse de Menezes Dantas M, Hugo da Silva Santos Y, Alcântara da Silva PH, et al: Prevalence of extracapsular extension in metastatic sentinel lymph nodes in breast cancer. Surg Oncol 38: 101594, 2021
10. Ma X, Yang X, Yang W, et al: Prognostic value of extranodal extension in axillary lymph node-positive breast cancer. Sci Rep 11:9534, 2021
11. Mambo NC, Gallager HS: Carcinoma of the breast: The prognostic significance of extranodal extension of axillary disease. Cancer 39:2280-2285, 1977
12. Neri A, Marrelli D, Roviello F, et al: Prognostic value of extracapsular extension of axillary lymph node metastases in T1 to T3 breast cancer. Ann Surg Oncol 12:246-253, 2005
13. Nottegar A, Veronese N, Senthil M, et al: Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis. Eur J Surg Oncol 42:919-925, 2016
14. Pierce LJ, Oberman HA, Strawderman MH, et al: Microscopic extracapsular extension in the axilla: Is this an indication for axillary radiotherapy? Int J Radiat Oncol Biol Phys 33:253-259, 1995
15. Gruber G, Bonetti M, Nasi ML, et al: Prognostic value of extracapsular tumor spread for locoregional control in premenopausal patients with node-positive breast cancer treated with classical cyclophosphamide, methotrexate, and fluorouracil: Long-term observations from International Breast Cancer Study Group Trial VI. J Clin Oncol 23:7089-7097, 2005
16. Fujii T, Yajima R, Yamaguchi S, et al: Extracapsular invasion of sentinel lymph nodes is not associated with disease recurrence in breast cancer. Int Surg 99:305-308, 2014
17. Drinka E, Allen P, McBride A, et al: Metastatic tumor volume and extranodal tumor extension: Clinical significance in patients with stage II breast cancer. Arch Pathol Lab Med 139:1288-1294, 2015
18. Caudell JJ, Gillison ML, Maghami E, et al: NCCN guidelines insights: Head and neck cancers, version 1.2022: Featured updates to the NCCN guidelines. J Natl Compr Cancer Netw 20:224-234, 2022
19. Fitzgibbons PL, Connolly JL, Bose S, et al: Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast. Version 4.4.0.0, 2020. https://documents.cap.org/protocols/cp-breast-invasive-resection-20-4400.pdf
20. Tang P, Moravek M, Oprea-Ilies G, et al: Extranodal extension, an international survey on its evaluation and reporting in breast cancer patients. Pathol Res Pract 237:154070, 2022
21. Giuliano AE, Ballman KV, McCall L, et al: Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (alliance) randomized clinical trial. JAMA 318:918-926, 2017
22. Bartels SAL, Donker M, Poncet C, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-Year results of the randomized controlled EORTC 10981-22023 AMAROS trial. J Clin Oncol 22:01565, 2022
23. Sávolt A, Musonda P, Mátrai Z, et al: Optimal treatment of the axilla after positive sentinel lymph node biopsy in early invasive breast cancer: Early results of the OTOASOR trial. Orv Hetil 154: 1934-1942, 2013
24. Xia L-Y, Hu Q-L, Zhang J, et al: Survival outcomes of neoadjuvant versus adjuvant chemotherapy in triple-negative breast cancer: A meta-analysis of 36,480 cases. World J Surg Oncol 18:129, 2020
25. Vittinghoff E, McCulloch CE: Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 165:710-718, 2007
26. Amin MB, Greene FL, Edge SB, et al: The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67:93-99, 2017
27. Nottegar A, Veronese N, Senthil M, et al: Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis. Eur J Surg Oncol 42:919-925, 2016
28. Gooch J, King TA, Eaton A, et al: The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1-T2 breast cancer. Ann Surg Oncol 21: 2897-2903, 2014
29. Barrio AV, Downs-Canner S, Edelweiss M, et al: Microscopic extracapsular extension in sentinel lymph nodes does not mandate axillary dissection in Z0011-eligible patients. Ann Surg Oncol 27: 1617-1624, 2020
30. Choi AH, Blount S, Perez MN, et al: Size of extranodal extension on sentinel lymph node dissection in the American College of Surgeons Oncology Group Z0011 trial era. JAMA Surg 150:1141-1148, 2015
31. Leonard C, Corkill M, Tompkin J, et al: Are axillary recurrence and overall survival affected by axillary extranodal tumor extension in breast cancer? Implications for radiation therapy. J Clin Oncol 13:47-53, 1995
32. Palamba HW, Rombouts MC, Ruers TJ, et al: Extranodal extension of axillary metastasis of invasive breast carcinoma as a possible predictor for the total number of positive lymph nodes. Eur J Surg Oncol 27:719-722, 2001
33. Mamtani A, Barrio AV, Goldman DA, et al: Extranodal tumor deposits in the axillary fat indicate the need for axillary dissection among T1-T2cN0 patients with positive sentinel nodes. Ann Surg Oncol 27:3585-3592, 2020
34. Konkin DE, Tyldesley S, Kennecke H, et al: Management and outcomes of isolated axillary node recurrence in breast cancer. Arch Surg 141:867-874, 2006
35. Siegel RL, Miller KD, Fuchs HE, et al: Cancer statistics, 2022. CA Cancer J Clin 72:7-33, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pathologic Exploration of the Axillary Soft Tissue Microenvironment and Its Impact on Axillary Management and Breast Cancer Outcomes

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