

A Multicenter Retrospective Analysis on Lymph Node Metastasis in Clinically Node-Negative (cN0) Patients with Small-Sized Breast Cancer

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Purpose: Sentinel lymph node biopsy (SLNB) is the standard for early breast cancer, but its necessity in small tumors with clinically node-negative (cN0) status remains debated. This study evaluated the incidence of lymph node metastasis in cN0 patients to explore the feasibility of omitting axillary surgery.

Methods: A cohort of 579 women with unilateral small breast cancer and cN0 were enrolled from three hospitals in Jiangsu Province (March 2023–June 2024). Clinical nodal status was determined by ultrasonography, while pathology and immunohistochemistry assessed tumor size, node status, and molecular subtypes. Chi-square tests and logistic regression were used for analysis.

Results: Lymph node metastasis was detected in 79 patients (13.64%). Tumors ≤ 20 mm and Ki-67 $\leq 14\%$ showed significantly lower metastasis rates ($P < 0.0001$ and $P = 0.013$, respectively). Even in cN0 patients with both favorable factors, 6.15% still had nodal involvement. Logistic regression identified tumor size (T2) as an independent predictor of metastasis.

Conclusion: Small breast cancer with cN0 and low Ki-67 expression is associated with reduced but non-negligible nodal metastasis. These findings support caution in omitting axillary surgery and highlight the need for individualized risk stratification rather than universal omission.

Keywords: breast cancer, axillary surgery, lymph node metastasis, molecular subtypes

Introduction

The development of axillary surgery for breast cancer represents a patient-centered, evidence-based paradigm of treatment de-escalation. In the mid-20th century, Patey and Dyson first reported the modified radical mastectomy (MRM) for breast cancer, and for the following 40 years, MRM dominated the field of breast cancer surgery.¹ However, postoperative complications resulting from axillary lymph node dissection (ALND), such as upper limb edema, numbness, and functional impairment, have significantly affected patients' quality of life.²

In the early 1990s, a seminal shift occurred in the surgical management of the axilla. Krag et al pioneered the use of radioactive isotope tracing, while Giuliano et al employed isosulfan blue dye for sentinel lymph node biopsy (SLNB), marking the first major step in axillary surgery de-escalation.³ The application of SLNB is one of the milestone advancements in breast surgery in recent decades, allowing approximately 70% of breast cancer patients to avoid ALND while achieving comparable therapeutic outcomes.⁴

Subsequent exploration of axillary surgery continued. The American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) trial, first reported in 2010, suggested that patients with T1 or T2 breast cancer, clinically node-negative (cN0), and one or two positive sentinel lymph nodes who underwent breast-conserving therapy (BCT), radiation, and adjuvant systemic therapy could safely omit further ALND.^{5,6} The SOUND (Sentinel Node vs Observation After Axillary Ultra-Sound) trial further shed light on the surgical management of axillary lymph nodes.⁷

Its results indicated that, in breast cancer patients with tumors ≤ 20 mm and cN0 status, omission of axillary surgery was noninferior to SLNB.⁸

Before the SOUND trial, the American Society of Clinical Oncology's Choosing Wisely campaign had already recommended that patients aged 70 years or older with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer could omit SLNB when the adjuvant treatment plan was clearly defined.⁹ This approach underscores a continued trend toward less invasive procedures, aligning with the evolving paradigm of personalized and minimally invasive cancer care.

Although the proportion of patients aged 70 years or older with ER-positive and HER2-negative tumors is relatively low, these findings remain clinically meaningful. Building on evidence from prospective studies, we conducted a multicenter retrospective analysis of early-stage invasive breast cancer patients with cN0, treated at the First Affiliated Hospital of Nanjing Medical University, the First People's Hospital of Lianyungang City, and the Affiliated Huai'an Hospital of Xuzhou Medical University, Jiangsu Province, between March 2023 and June 2024. Our aim was to explore the relationship between lymph node metastasis, primary tumor size, and molecular subtypes, in order to identify patients who might be suitable candidates for omission of axillary surgery.

Methods

Study Populations and Oversight

Eligible patients were women diagnosed with invasive breast cancer and clinically node-negative axilla (cN0), with a maximum tumor diameter ranging from 1 to 50 mm (T1–T2), and no restrictions on surgical approach. Prior to surgery, all patients underwent ultrasound assessments of both the breast and axillary regions. Exclusion criteria included patients who had received neoadjuvant therapy, those with suspicious or indeterminate lymph nodes on preoperative ultrasonography, carcinoma in situ, extensive multifocality or multicentricity, bilateral breast cancer, a history of other malignancies, or immune-related diseases.

A total of 579 patients, aged 23–87 years (mean age: 52.67 years), were enrolled from the First Affiliated Hospital of Nanjing Medical University (434 cases), the First People's Hospital of Lianyungang City (93 cases), and the Affiliated Huai'an Hospital of Xuzhou Medical University (52 cases), all located in Jiangsu Province, China, between March 2023 and June 2024.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Ethics code: 2024-SR-404), the Ethics Committee of the First People's Hospital of Lianyungang City (Ethics code: KY-20220426003-01), and the Ethics Committee of the Affiliated Huai'an Hospital of Xuzhou Medical University (Ethics code: HEYLL2024055). The study complies with the Declaration of Helsinki.

According to the Chinese Anti-Cancer Association (CACA) Guidelines, 537 patients received chemotherapy, while 42 did not undergo or discontinued chemotherapy due to intolerance or low recurrence risk. Endocrine therapy was administered to 426 patients, including 174 treated with tamoxifen and 252 with aromatase inhibitors. Among 150 HER2-positive patients, 26 underwent dual anti-HER2 therapy (trastuzumab plus pertuzumab), 117 received trastuzumab monotherapy, and 7 did not undergo anti-HER2 therapy due to intolerance or low recurrence risk.

A total of 251 patients underwent radiotherapy, including 243 who received whole-breast irradiation (WBI), 5 who received both WBI and whole-axillary irradiation, and 7 who underwent whole-axillary irradiation alone. Radiotherapy was delivered using a Varian Clinac iX linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) with 6 MV X-rays. The whole breast received conventional fractionation with a total dose of 45.0–50.4 Gy in 25–28 fractions (1.8–2.0 Gy per fraction), five times per week. The same equipment was used for axillary irradiation, delivering a total dose of 50 Gy in 25 fractions (2.0 Gy per fraction).

Assessment Criteria of Clinical and Pathological Lymph Node

Clinical nodal status (cN) was assessed by ultrasonography (Philips EPIQ 7G ultrasound system, Philips Healthcare, Andover, MA, USA) and physical examination. Node-negative axillae were designated as cN0. According to the American Joint Committee on Cancer (AJCC) 8th edition criteria, the presence of any of the following ultrasound features was considered cN1: altered lymph node shape, cortical thickness >2.5 – 3.0 mm, loss of fatty hilum, irregular or bulging margins, or abnormal blood flow. If none of these features were present, the node was classified as cN0.

The definitive status of lymph node involvement was determined by pathological examination (pN). Lymph node metastasis was defined by histopathology; if tumor cells were identified on hematoxylin and eosin (H&E) staining or immunohistochemistry (IHC), the node was considered positive (pN1).

Assessment Criteria of T, ER, PR, Her-2 and Ki-67

In accordance with AJCC 8th edition criteria: T1a: >1 mm to ≤5 mm; T1b: >5 mm to ≤10 mm; T1c: >10 mm to ≤20 mm; T2: >20 mm to ≤50 mm. ER/PR positivity: nuclear staining in ≥1% of tumor cells by IHC. HER2 positivity: IHC score of 3+ or fluorescence in situ hybridization (FISH) amplification. Ki-67: evaluated by IHC, expressed as the percentage of positively stained tumor nuclei among at least 500 counted cells in representative high-power fields.

IHC was performed on 4-μm formalin-fixed paraffin-embedded (FFPE) sections using standard protocols. Antibodies included anti-ER (clone SP1), anti-PR (clone 1E2), anti-HER2 (clone 4B5), and anti-Ki-67 (clone MIB-1), all obtained from Roche Diagnostics. Staining was conducted using the Ventana BenchMark ULTRA automated system (Ventana Medical Systems, Tucson, AZ, USA). All slides were reviewed independently by two experienced breast pathologists, with discrepancies resolved by consensus.

Statistical Analysis

Clinical, pathological, and treatment data were collected from electronic medical records by two independent researchers using a standardized data collection form. Data were cross-verified to ensure accuracy and completeness.

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Associations between lymph node metastasis and clinicopathological characteristics were assessed using Chi-square (χ^2) tests. Significant factors were further analyzed in multivariate models using logistic regression. A two-sided P value <0.05 was considered statistically significant.

Results

Among the 579 enrolled patients, 248 underwent BCT and 331 underwent mastectomy. Pathological examination confirmed lymph node metastasis in 79 cases. The total number of metastatic lymph nodes ranged from 1 to 3: 66 cases (11.4%) had a single metastatic node, eight cases (1.38%) had two positive nodes, and five cases (0.86%) had three positive nodes. For the cN0 patients included in the analysis, the overall rate of lymph node metastasis was 13.64%. Patient characteristics are detailed in Table 1.

Table 1 Baseline Patient and Tumor Characteristics

Characteristic	cN0	pN0	pN1	P
Age at diagnosis				0.1757
<50	232	206	26	
≥50	347	294	53	
Tumor size				<0.0001
T1	362	330	32	
T2	217	170	47	
Grade				0.2252
I-II	310	273	37	
III	269	227	42	
ER status				0.0735
+	426	361	65	
-	153	139	14	

(Continued)

Table 1 (Continued).

Characteristic	cN0	pN0	pN1	P
PgR status				0.0992
+	375	317	58	
-	204	183	21	
Her-2				0.3352
+	150	126	24	
-	429	374	55	
Ki-67				0.0134
≤14%	79	75	4	
>14	500	425	75	
Type of Surgery				>0.9999
BCT	248	218	30	
Mastectomy	331	282	49	

Abbreviation: BCT, breast-conserving therapy.

From **Table 1**, a statistically significant difference was observed between T1 and T2 tumors ($P < 0.0001$). The rate of sentinel lymph node metastasis was 21.66% in patients with T2 tumors, compared with 8.84% in patients with T1 tumors.

We further conducted a detailed retrospective analysis by categorizing tumor sizes into T1a, T1b, T1c, and T2 for statistical analysis (**Table 2**). Due to the small number of T1a tumors, T1a and T1b were combined into the “less than 10 mm” category. Lymph node metastasis rates were then compared among three groups: <10 mm, 10–20 mm, and 20–50 mm. The results indicated that tumors smaller than 20 mm did not show a statistically significant difference in lymph node metastasis between the <10 mm and 10–20 mm groups ($P = 0.824$). However, a significant difference was observed when comparing tumors ≤20 mm (T1) with T2 tumors (>20 mm) ($P < 0.0001$), suggesting that larger tumors are more likely to metastasize to lymph nodes.

According to the CACA, a Ki-67 index ≤14% is classified as low expression, while >14% is considered high. There were 79 cases (13.64%) with low Ki-67 expression (**Table 3**). Despite the relatively low proportion, our data demonstrate a correlation between Ki-67 expression and lymph node metastasis in cN0 patients ($P = 0.013$). The rate of sentinel

Table 2 Subgroup Analysis of Tumor Size

Tumor Size (mm)	pN0	pN1	P
1-10	74	6	0.8237A
10-20	256	26	
20-50	170	47	<0.0001B

Notes: A, 1–10mm and 10–20mm group. B, 1–20mm and 20–50mm group.

Table 3 Subgroup Analysis of Subtype

Subtype	pN0	pN1	P
Luminal	290	49	>0.9999A
Her-2 +	53	8	0.2609B
TNBC	79	6	0.073C

Notes: A, Luminal and Her-2+group. B, Her-2 +and TNBC group. C, Luminal and TNBC group.

lymph node metastasis was 15% in patients with high Ki-67 expression, compared with 5.06% in patients with low Ki-67 expression, indicating that higher Ki-67 is associated with increased likelihood of lymph node metastasis.

We conducted a detailed analysis of various factors in cN0 breast cancer patients using both χ^2 and logistic regression analyses (Table 4), including age groups (<50 and \geq 50), ER status, PR status, Her-2 status, tumor grade, Ki-67, and molecular subtype. Due to the limited number of Grade I tumors (27 cases), Grade I and II were combined. Logistic regression results indicated that tumor size (T2) was an independent predictor of lymph node metastasis, while other factors did not reach statistical significance.

Discussion

With the development of comprehensive therapies, particularly the emergence of targeted therapy and immunotherapy,¹⁰ the overall survival of breast cancer patients has gradually improved in recent years.^{11,12} Consequently, in some countries, breast cancer is increasingly being managed within the chronic disease framework.¹³ Therefore, enhancing the postoperative quality of life for breast cancer patients is garnering more attention from clinical physicians. However, ALND in breast cancer can lead to a series of complications, notably affecting upper limb function on the operated side.¹⁴ Consequently, there is a growing body of research focused on the omission of axillary surgery in breast cancer management.

Numerous previous studies have reported a positive correlation between tumor size, Ki-67 expression, and lymph node metastasis.^{15–17} One study involving 693,686 patients found that the rate of lymph node metastasis in patients with tumors \leq 20 mm was 19.5%, while the rate for tumors 20–50 mm was 50.6%.¹⁷ Similarly, patients with low Ki-67

Table 4 Logistic Regression Analysis

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis				
<50	Ref.		Ref.	
\geq 50	[0.865–2.359]	0.162	[0.429–1.231]	0.235
Tumor size				
T1	Ref.		Ref.	
T2	[1.493–3.316]	<0.001	[1.505–4.339]	<0.01
Grade				
I–II	Ref.		Ref.	
III	[0.807–2.807]	0.283	[0.509–1.428]	0.545
ER status				
+	Ref.		Ref.	
–	[0.972–3.289]	0.062	[0.236–1.548]	0.311
PgR status				
+	Ref.		Ref.	
–	[0.885–2.527]	0.132	[0.328–1.683]	0.476
Her-2				
+	Ref.		Ref.	
-	[0.77–2.179]	0.34	[0.466–1.462]	0.51
Ki-67				
\leq 14%	Ref.		Ref.	
>14	[1.175–9.317]	0.021	[0.125–1.088]	0.071
Subtype				
TNBC	Ref.		Ref.	
Luminal	[0.202–1.553]	0.092	[0.644–4.954]	0.265
Her-2 +	[0.531–2.292]	0.792	[0.314–1.941]	0.595

Abbreviations: Ref, Reference value; CI, confidence intervals.

expression exhibited a lower rate of lymph node metastasis compared to those with high Ki-67 expression.^{18–20} Our study demonstrated that tumor size and Ki-67 expression were positively correlated with lymph node metastasis, consistent with existing research. However, in our cohort of patients with clinically negative axillary lymph nodes (cN0) and tumors ≤ 20 mm, the rate of lymph node metastasis was 8.84%, while the rate was 21.66% in patients with cN0 and T2 tumors. Moreover, the rate of lymph node metastasis in patients with low Ki-67 expression in our study was 5.06%, which was significantly lower compared to results from studies involving broader breast cancer populations (14.83–16%).²¹ Even among cN0 patients with both $T \leq 2$ cm and low Ki-67 expression, the rate of lymph node metastasis was 6.15%. The probability of lymph node metastasis for T1 or T2 tumors was significantly lower compared to existing studies involving the general population, and the same was true for Ki-67 expression.

Studies on the omission of ALND and SLNB have yielded preliminary positive results. The earliest ACOSOG Z0011 trial⁵ pioneered the omission of axillary surgery. Subsequent trials, including the SOUND trial,⁷ BOOG 2013–08 trial,^{22,23} and INSEMA (Intergroup Sentinel Mam) trial,²⁴ were all designed to evaluate the safety and efficacy of omitting SLNB in patients with cN0, small tumors undergoing BCT and radiotherapy. Primary results from the SOUND trial showed that omission of axillary surgery was noninferior to sentinel lymph-node biopsy in patients with small breast cancers up to 2 cm. This suggested that a subset of early breast cancer patients may omit SLNB. The BOOG 2013–08 trial, after a 5-year follow-up, found no difference in regional recurrence rates or recurrence-free survival between the SLNB group and no SLNB group in patients with cT1-2N0 tumors who underwent BCT and radiotherapy.^{22,23} According to the latest findings from the INSEMA study (published in March 2025), omission of surgical axillary staging was noninferior to SLNB after a median follow-up of 6 years, consistent with the results of the SOUND trial. Notably, the SOUND trial enrolled 1405 patients with tumors up to 2 cm, while INSEMA enrolled 5502 early-stage breast cancer patients with tumors up to 5 cm.²⁴ Our study suggests that for early-stage breast cancer patients with cN0, T1 tumors and low Ki-67 expression, regardless of grade, ER, PR, or Her-2 status, the rate of lymph node metastasis is low. However, even in this low-risk population, the rate of sentinel lymph node metastasis remains 8.84% in patients with cN0, $T \leq 20$ mm tumors, and 5.06% in patients with cN0 and low Ki-67 expression. Among cN0 patients with both $T \leq 2$ cm and low Ki-67 expression, the rate of lymph node metastasis is 6.15%. Moreover, in prospective trials, all eligible patients underwent BCT and radiotherapy, whereas in our study, less than half (42.83%) of patients underwent BCT (Table 5). In these patients, omitting SLNB could pose a risk of missed lymph node metastasis. Our findings provide valuable supplementary data to the aforementioned trials.

While molecular subtypes were not associated with lymph node metastasis in our cohort, existing research indicates varying incidences of lymph node metastasis across different molecular subtypes of breast cancer. Luminal-type breast cancers exhibit a higher rate of lymph node metastasis compared to Her-2-positive and TNBC.¹⁶ Specifically, within the Luminal A subtype, the hazard ratio for the ratio of metastatic lymph nodes to tumor size (Np/T) is the highest, whereas it is lowest in the TNBC subtype.¹⁶ In our retrospective analysis, no correlation was observed between molecular subtypes and lymph node metastasis. This lack of association may be attributed to the limited sample size of early-stage patients with cN0 disease included in the study. Another possible explanation is that previous studies have focused on the

Table 5 Type of Surgery

Type of Surgery	Total	pN0	pN1
BCT			
SLNB	223	218	5
ALND	25	0	25
Mastectomy			
SLNB	285	282	3
ALND	46	0	46

Abbreviations: BCT, breast-conserving therapy; SLNB, Sentinel lymph node biopsy; ALND, axillary lymph node dissection.

entire population of breast cancer patients, whereas our study specifically conducted a subgroup analysis of patients with cN0 and small tumors. This finding further supplements the existing data.

In this study, the assessment of clinically node-negative status was conducted using ultrasound examination. Ultrasound is widely utilized in breast examinations due to its convenience, non-invasiveness, cost-effectiveness, and excellent reproducibility.²⁵ However, it has certain limitations in detecting lymph node involvement. The sensitivity of ultrasound can vary depending on equipment quality and the experience of the examining physicians, resulting in a sensitivity range of 24% to 94%.^{26,27} Nonetheless, current evidence supports ultrasonography as the preferred method for evaluating axillary lymph node status.²⁷⁻²⁹ In this study, all ultrasound assessments were performed by two qualified ultrasonologists, ensuring the reliability of the results. According to our statistical analysis, the lymph node metastasis rate among cN0 patients was 13.64%.

This study has several limitations. First, it is a retrospective analysis. Whether axillary surgery can be safely omitted in these low-risk patients who undergo mastectomy requires further prospective studies to establish conclusive evidence. Additionally, the patient cohort was derived exclusively from three hospitals over a period of just over one year, with two of these hospitals contributing relatively small sample sizes, which may limit the generalizability of our findings.

Conclusions

This study suggests that early breast cancer patients with tumors smaller than 20 mm, cN0, and low Ki-67 expression have a low risk of lymph node metastasis. However, the rate of sentinel lymph node metastasis remains 8.84% and 5.06% in these subgroups. These findings highlight the residual risk of lymph node involvement even in low-risk patients, indicating that individualized risk assessment is necessary when considering omission of axillary surgery.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics Statement

All participants provided written informed consent, and the protocols were approved at all clinical centers. (2024-SR-404, KY-20220426003-01, HEYLL2024055)

Acknowledgments

We thank all study subjects for their participation in this study.

Funding

This work was supported by the National Natural Science Foundation (82203119), Natural Science Foundation of Jiangsu Province (BK20220733), and Jiangsu Funding Program for Excellent Postdoctoral Talent (2022ZB715).

Disclosure

The authors declare that they have no competing interests.

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