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ORIGINAL RESEARCH

Risk of Residual Axillary Lymph Node Macrometastasis in Early Breast Cancer PATIENTS with One Positive Macrometastasis Sentinel Lymph Node

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Objective: To investigate the risk factors for residual axillary lymph node macro-metastasis in early-stage breast cancer patients with a single macrometastasis sentinel lymph node (SLN).

Methods: We retrospectively analyzed the clinical data of 119 breast cancer patients diagnosed between January 2018 and September 2023, each with one positive SLN stained with methylene blue, who subsequently underwent axillary lymph node dissection. The patients were divided into two groups based on the total number of SLNs identified: fewer than three and more than three. Fisher's exact test was used for statistical analysis between groups.

Results: Among the 119 patients evaluated, 30 patients had a total of 2 sentinel lymph nodes, with 15 testing positive for residual axillary lymph nodes, yielding a positivity rate of 50.0%. Another 30 patients had 3 sentinel lymph nodes, with a positivity rate of 33.3%. An additional 32 patients each had 4 sentinel lymph nodes, with a positivity rate of 3.13%. Finally, 27 patients had 5 sentinel lymph nodes, with a 0% positivity rate. The positivity rate of axillary lymph nodes was significantly higher in the group with ≤ 3 sentinel lymph nodes (less SLN group) compared to the group with > 4 sentinel lymph nodes (more SLN group). Binary logistic regression analysis confirmed that the number of SLNs was the only significant predictor of residual lymph node macrometastasis.

Conclusion: The number of sentinel lymph nodes (SLNs) is a key factor influencing the risk of residual axillary lymph node macrometastasis in early-stage breast cancer patients with one positive SLN. Identifying a higher number of SLNs (≥4) significantly lowers the risk of residual metastasis, supporting the use of thorough SLN mapping in these cases to improve patient outcomes.

Keywords: breast cancer, axillary lymph node dissection, sentinel lymph node, macrometastasis

Introduction

Breast cancer is one of the most common malignant tumors affecting women worldwide.[1] The rapid progression of breast tumors poses a significant threat to health and quality of life globally.[2] Surgical resection remains the primary treatment approach for early breast cancer.[3] This surgical treatment generally involves removal of the primary tumor and management of axillary lymph nodes (ALN). The primary tumor can be addressed through total mastectomy, breast-conserving surgery, or breast reconstruction. For ALN management, options include axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). ALN metastasis is a key indicator for breast cancer prognosis, and SLNB reliably detects ALN metastasis.[4,5]

ALND is the gold standard for patients with positive sentinel lymph nodes. However, in many cases, no additional positive lymph nodes are found, suggesting that ALND might be avoidable without affecting survival.[6] The ACOSOG Z0011 trial,[7] a pivotal randomized study, investigated the outcomes of breast-conserving surgery in patients with early-stage breast cancer who had 1 or 2 positive sentinel lymph nodes (SLNs). The trial found that there was no significant

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difference in overall survival or local recurrence rates between patients who underwent axillary lymph node dissection (ALND) and those who did not, suggesting that ALND may not be necessary for select patients with limited SLN involvement. Given that all patients in our study underwent total mastectomy, the omission of ALND is not yet standard practice in this population. Therefore, ALND was performed in our study to ensure accurate nodal staging and assess the risk of residual metastasis. Although current guidelines, such as those derived from the Z0011 trial, recommend the omission of ALND in selected patients with limited SLN involvement, these recommendations were based on cohorts undergoing breast-conserving surgery and do not directly apply to mastectomy patients. In China, where total mastectomy is still the predominant surgical choice, the omission of ALND in this subgroup remains controversial and has not been uniformly implemented in clinical practice. Accordingly, the use of ALND in our cohort reflects prevailing institutional protocols intended to ensure comprehensive staging and oncologic safety. However, recent literature and updated guidelines suggest that the Z0011 recommendations may also be applicable to certain patients undergoing total mastectomy, particularly for those with a limited number of positive SLNs. In these cases, the omission of ALND might be considered, as the risk of residual axillary metastasis is relatively low, aligning with the findings of the Z0011 trial.[8] Despite this, variations in clinical practice still exist, and the decision to omit ALND must be individualized based on factors such as the total number of SLNs and the specific characteristics of the patient.

Significant differences exist between Eastern and Western countries in SLN management. In Eastern countries, SLNs are typically marked with a single dye (usually methylene blue) due to its availability, cost-effectiveness, and ease of use. Although the dual-marker technique (using isotope dye and blue dye) offers higher sensitivity, methylene blue remains a reliable tool for SLN identification in our clinical setting, particularly given the practical constraints of dual-marker availability.[9] The sensitivity and specificity of SLNB are significantly lower with a single dye than with double markers. Additionally, breast-conserving surgery rate is lower in Eastern countries; whole breast resection remains the preferred option for most patients in China, whereas breast-conserving and reconstructive surgeries are more common in Western countries.[10] Moreover, in the ACOSOG Z0011 trial, 40% of positive SLNs were identified as micrometastases, which are often detected incidentally, limiting the clinical application of SLN micrometastasis. It should be noted that these figures are based on a Western cohort, and our study focuses on a predominantly Eastern cohort of early-stage breast cancer patients.

Selecting low-risk patients who can safely avoid ALND while maintaining an acceptable recurrence risk is a pressing issue in clinical practice in China. Therefore, this study aims to explore the high-risk factors for SLN-positive macrometastasis in residual ALNs following total mastectomy with single methylene blue dye in a predominantly Eastern cohort. The objectives are to determine the prevalence of residual macrometastasis in ALNs when fewer SLNs are identified and to assess whether the number of SLNs can predict the likelihood of additional metastases. By identifying these risk factors, this research seeks to refine prognostic assessments and surgical approaches in early breast cancer management, potentially reducing unnecessary ALNDs and associated morbidities in suitable cases.

Materials and Methods

Subjects

Patients with early breast cancer who underwent tumor surgery with sentinel lymph node biopsy (SLNB) at the First Affiliated Hospital of Bengbu Medical College, Anhui Province, between January 2018 and September 2023 were included in this study. Inclusion criteria: (1) Diagnosed with invasive breast cancer by core needle biopsy, or confirmed as invasive breast cancer by excision biopsy in special cases; (as core needle biopsy is generally the recommended method for initial diagnosis, excision biopsy is only used in specific circumstances for initial diagnosis). (2) Clinically early-stage breast cancer, with a tumor size no greater than 5 cm in long diameter; clinically negative axillary lymph nodes, or clinically positive axillary lymph nodes were defined as lymph nodes that appeared suspicious based on clinical examination or imaging (eg, ultrasound, MRI) but were confirmed to be negative for malignancy by fine-needle aspiration biopsy (FNA), core needle biopsy (CNB), or excision biopsy. Excision biopsy was performed in cases where needle biopsy results were inconclusive or when a more definitive pathological assessment was needed.; patients with distant metastasis were excluded. (3) No preoperative chemotherapy or radiotherapy was administered to any enrolled patients. Patients with HER2-enriched or triple-negative breast cancer (TNBC) were included only if they were clinically node-negative and did not meet standard indications for neoadjuvant therapy

according to institutional protocols. This decision was made to avoid potential biases introduced by the systemic therapy, as neoadjuvant treatment can influence tumor and lymph node status, potentially affecting the outcomes. All patients were diagnosed with early-stage disease (tumor ≤ 5 cm) and underwent total mastectomy as primary treatment without any evidence of distant metastasis. Therefore, HER2-positive and TNBC patients were managed with upfront surgery only when neoadjuvant therapy was not clinically indicated. By excluding patients who received neoadjuvant chemotherapy, we aimed to provide a clearer understanding of the relationship between SLN count and residual axillary lymph node metastasis without the confounding effects of preoperative therapy. Any patient who had received neoadjuvant chemotherapy was excluded from the study). (4) only one positive SLN with macrometastasis (defined as metastasis larger than 2 mm in size) was identified during or after surgery. (5) ALND was performed along with whole breast resection following SLNB. Exclusion criteria: (1) Patients with bilateral breast cancer were excluded due to the potential complexity in axillary lymphatic drainage patterns, which could affect the accuracy of SLN identification and count. Bilateral disease may also require a different surgical approach for lymph node management, potentially confounding the analysis of SLN count and residual axillary metastasis risk. To ensure homogeneity in the study population and maintain the reliability of our findings, only patients with unilateral breast cancer were included.; (2) Patients who were pregnant or lactating. These patients were excluded due to the potential risks associated with methylene blue dye, which is contraindicated during pregnancy and lactation. Additionally, the altered lymphatic flow during pregnancy may affect the accuracy of SLN mapping, potentially introducing bias in the results.

Operation Method for SLNB

Methylene blue dye was used to mark and locate the sentinel lymph nodes during surgery. After disinfecting with iodophor, 1 mL of 1% methylene blue dye was injected subcutaneously above the tumor or in the nipple-areola area 15 minutes before surgery, and an additional 0.5 mL was injected peritumorally as a deep injection to enhance detection[11] (Figure 1). The skin and subcutaneous tissue were then incised, leaving skin flaps both above and below the incision. The first blue-stained lymph node was identified along the blue-stained lymphatic vessels (Figure 2); alternatively, the surgeon traced the blue-stained lymphatic vessels along the lateral edge of the pectoralis major muscle toward the axilla, ensuring thorough inspection of the posterior breast space to avoid missing any proximal blue-stained lymph nodes, thereby reducing the false-negative rate. The lymph nodes and surrounding lymph nodes in the axillary region where multiple blue-stained lymphatics converge were considered sentinel lymph nodes (including parasentinel lymph nodes). If other swollen lymph nodes, particularly firm ones, were found during surgery, they were also resected and sent for examination as sentinel lymph nodes. In accordance with standard SLNB principles, if additional axillary lymph nodes appeared enlarged, firm, or suspicious during intraoperative exploration-particularly in cases where dual-tracer methods were unavailable—these nodes were also considered part of the sentinel lymph node group and resected as such. These suspicious nodes were identified intraoperatively through visual and tactile assessment in conjunction with blue dye

Figure 1 After intradermal injection of methylene blue under the areola, the injection of methylene blue into the deep gland adjacent to the tumor is added.

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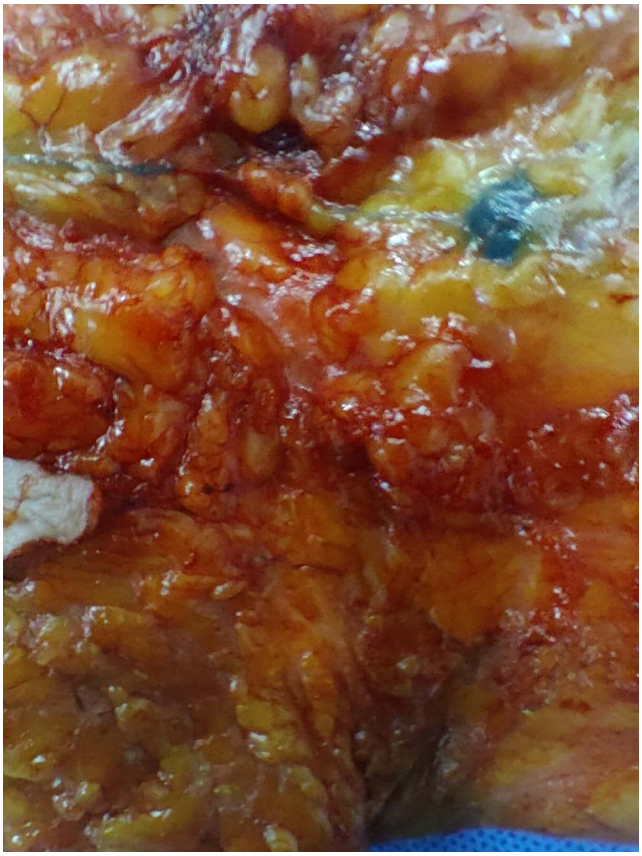

Figure 2 Methylene blue flows along blue lymphatic vessels to blue lymph nodes.

mapping, and their removal was performed as part of the SLNB procedure rather than as a separate excision biopsy (Figure 3). If the SLN tested positive, additional axillary dissection was performed. The specimen was fixed in 4% formaldehyde solution for routine pathological examination, followed by conventional paraffin embedding, continuous 4-μm sectioning, hematoxylin-eosin staining, and sealing. Two experienced pathologists then reviewed the slides to determine if there was tumor cell metastasis. If the frozen section was negative but subsequent paraffin-embedded pathology showed tumor metastasis in the sentinel lymph nodes, a secondary ALN dissection was performed.

Basic Information Collection

The clinicopathological information of breast cancer was categorized to include menopausal status, age, tumor location, tumor diameter, pathological grade, vascular invasion, estrogen receptor (ER) status, progesterone receptor (PR) expression, human epidermal growth factor receptor 2 (HER-2) expression, low and high Ki-67 expression levels, total number of SLNs, and the number of SLN with macrometastasis.

For cases with an ambiguous HER-2 status (++~+++), HER-2 expression was confirmed by fluorescence in situ hybridization (FISH). Molecular subtypes of breast cancer were classified based on ER, PR, HER-2 status, and Ki-67 expression according to the 2013 St. Gallen Consensus guidelines.

The SLN ratio was calculated as the number of positive lymph nodes divided by the total number of lymph nodes removed. Residual axillary lymph nodes (RALN) refer to all lymph nodes identified by axillary lymph node dissection, excluding those detected in SLNB. The total number of RALNs and the number of positive RALNs were also recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). For the analysis of multiple factors influencing outcomes, binary logistic regression was employed. Univariate comparisons were conducted using Fisher's exact test. Differences were considered statistically significant at a p-value less than 0.05.

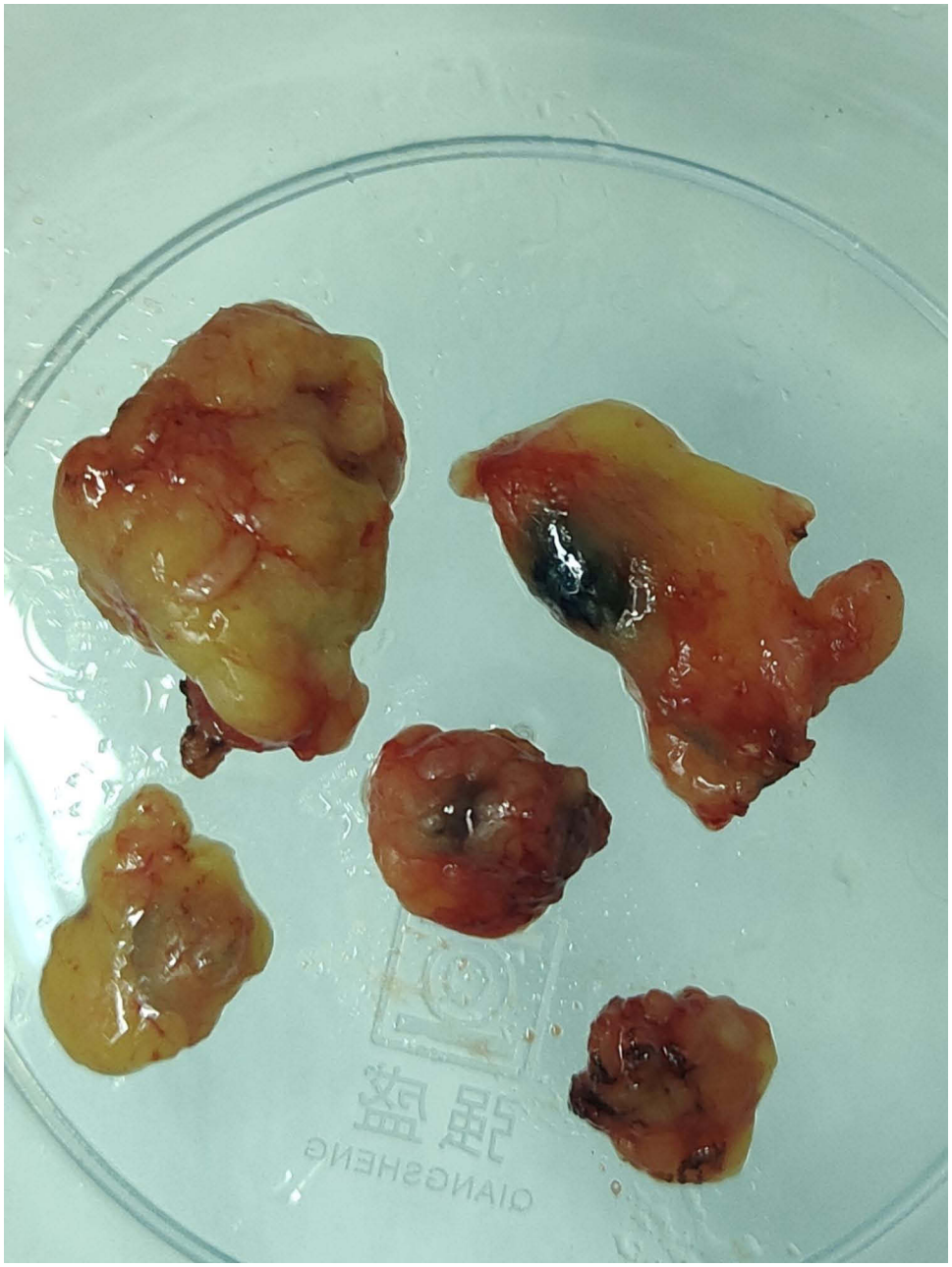

Figure 3 Blue stained lymph nodes and surrounding swollen lymph nodes (5 nodes).

Results

Clinical Characteristics of Patients

A total of 119 cases were included in our study with a median patient age of 48 years. In this cohort of breast cancer patients with positive SLNs (Table 1), 26 patients exhibited positive RALNs. No significant differences in RALN positivity rates were observed based on menopausal status, tumor size, or tumor location ($p > 0.05$). Similarly, histological grade, vascular invasion, and receptor status (ER, PR, HER-2) did not significantly impact RALN outcomes. A key finding, however, was the association between the number of SLNs examined and RALN positivity: patients with 2–3 SLNs had a significantly higher positivity rate compared to those with ≥4 SLNs ($p < 0.001$). This suggests that increasing the number of SLNs examined could reduce unnecessary axillary lymph node dissections.

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Table 1 Clinical and Pathological Characteristics of Patients and Their Correlation with Positive Distribution of Axillary Lymph Nodes

Characteristics	Total Cases	NSLN Positive	NSLN Negative	p value
Menstrual status				0.404
Premenopausal	73	18 (24.7%)	55 (75.3%)	
Postmenopausal	46	8 (17.4%)	38 (82.6%)	
Tumor size (cm)				0.302
≤2.0	76	15 (19.7%)	61 (80.3%)	
>2.0	43	11 (25.6%)	32 (74.4%)	
Position				0.168
Outer upper	58	10 (17.2%)	48 (82.8%)	
Other part	61	16 (26.2%)	45 (73.8%)	
Histological grade				0.103
I~II	83	15 (18.1%)	68 (81.9%)	
III	36	11 (30.6%)	25 (69.4%)	
Vascular invasion				0.131
Yes	20	2 (10.0%)	18 (90.0%)	
No	99	24 (24.2%)	75 (75.8%)	
ER status				0.212
Positive	72	18 (25.0%)	54 (75.0%)	
Negative	47	8 (17.0%)	39 (83.0%)	
PR status				0.417
Positive	73	16 (21.9%)	57 (78.1%)	
Negative	46	10 (21.7%)	36 (78.3%)	
HER-2 status				0.571
Positive	14	2 (14.3%)	12 (85.7%)	
Negative	105	24 (22.9%)	81 (77.1%)	
Ki67 status				0.506
Low (≤ 20%)	71	16 (22.5%)	55 (77.5%)	
High (>20%)	48	10 (20.8%)	38 (79.2%)	
Molecular type				0.291
Luminal A	48	10 (20.8%)	38 (79.2%)	
Luminal B	34	11 (32.3%)	23 (67.6%)	
HER-2 positive	14	2(14.3%)	12 (85.7%)	
Triple negative	23	3(13.0%)	20 (87.0%)	
Total SLN				<0.001
2~3	60	25 (41.7%)	35 (58.3%)	
≥4	59	1 (1.7%)	58 (98.3%)	
Tumor type				0.211
Infiltrating ductal carcinoma	107	25 (23.4%)	82 (76.6%)	
Others	12	1(8.3%)	11 (91.7%)	

Abbreviations: NSLN, Non-Sentinel Lymph Node; ER, Estrogen Receptor; PR, Progesterone Receptor; HER-2, Human Epidermal Growth Factor Receptor 2.

Binary Logistic Regression Analysis of the Factors Affecting the Positive Rate of RALN

Using remaining axillary node metastasis as the dependent variable, other clinicopathological factors were analyzed as independent variables in a binary logistic regression. The number of SLNs examined was the only factor significantly associated with RALN positivity (Table 2) ($P < 0.001$). Other clinicopathological factors, including tumor size, ER, PR, HER-2 status, showed no significant impact ($P>0.05$).

Correlation Analysis Between the Number of SLN and the Positive of RALN

A total of 119 breast cancer cases were identified with one positive SLN. Among them, cases with fewer SLNs exhibited a higher RALN positivity rate compared to those with a greater number of SLNs (Table 3). In cases with 5 or more SLNs, no RALNs were

Table 2 Binary Logistic Regression Analysis on the Impact of Residual Axillary Lymph Node Metastasis in Breast Cancer

Clinical Factors	B	Standard Error	Wald	Significance	Exp (B)
Age	−0.106	0.062	2.915	0.088	0.900
Menstrual status	−1.461	1.051	1.931	0.165	0.232
Tumor size	0.445	0.405	1.207	0.272	1.561
Vascular invasion	1.377	0.986	1.949	0.163	3.963
Histological grade	0.753	0.465	2.617	0.106	2.123
ER status	−0.410	0.800	0.263	0.608	1.507
PR status	0.152	0.657	0.053	0.810	0.859
HER-2 status	−0.450	1.176	0.146	0.702	0.638
Ki67 expression	−0.021	0.025	0.692	0.405	0.797
Total SLN	−1.526	0.376	16.502	<0.001	0.217

Abbreviations: SLN, Sentinel Lymph Node; ER, Estrogen Receptor; PR, Progesterone Receptor; HER-2, Human Epidermal Growth Factor Receptor 2.

Table 3 Analysis of the Relationship Between One Positive SLN Number and Positive Axillary Lymph Nodes in 119 Cases of Breast Cancer

Total SLN	Cases	Positive NSLN	*p* value
Less or equal 2	30	15 (50.0%)	
Equal 3	30	10 (33.3%)	
Equal 4	32	1 (3.13%)	
Equal 5	27	0 (0.00)	
Total	119	26 (21.8%)	< 0.001

Abbreviation: NSLN, Non-Sentinel Lymph Node.

positive, indicating a trend of zero RALN positivity (Figure 4). Specifically, in cases with fewer SLNs, a considerable proportion tested positive for residual RALNs. In contrast, those with more SLNs demonstrated a significantly lower RALN positivity rate during axillary dissection. Overall, the group with fewer SLNs had a markedly higher RALN positivity rate than the group with more SLNs. The difference between these two groups was statistically significant ($P < 0.001$).

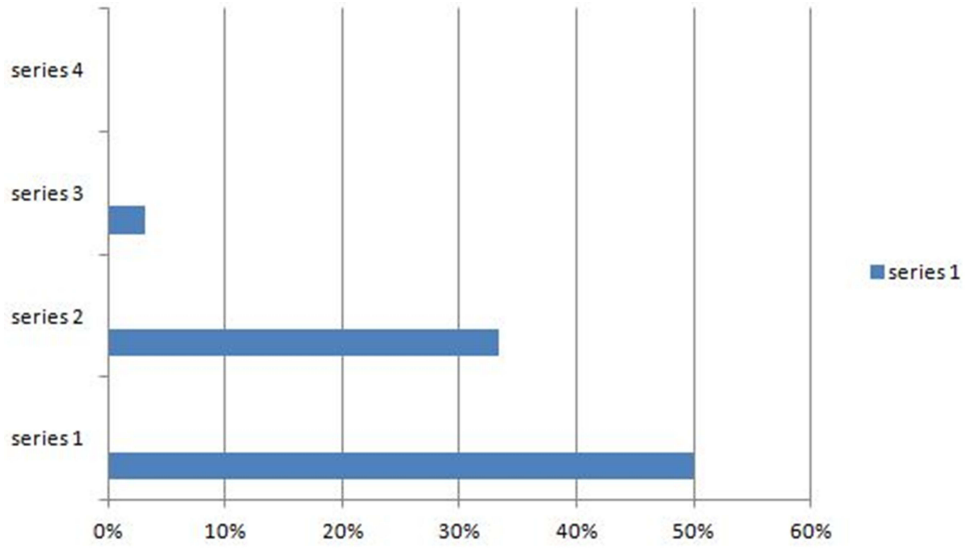

Figure 4 Correlation analysis between the number of SLN and the positive of RALN. Series 1: the number of SLN equal to 2 or fewer SLNs. Series 2: equal to 3 SLNs. Series 3: equal to 4 SLNs. Series 3: equal to 5 SLNs or more.

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Discussion

The question of whether selective ALND can be safely avoided in some SLN-positive patients has long been a clinical concern. A retrospective study found no statistically significant difference in local and regional recurrence rates between SLN positive patients who underwent ALND and those who did not, particularly among patients at low risk of recurrence.[12] In our study, 26 out of 119 cases of early breast cancer with one positive SLN had positive residual axillary nodes, resulting in a positivity rate of 21.8%, while 78.2% of cases showed no residual axillary node involvement. This finding is consistent with other research.[13] This indicates that while SLN is positive, not all patients exhibit RALN positivity, emphasizing the importance of identifying high-risk patients in clinical practice. In the field of prognostic biomarkers, the precise evaluation of whether SLN-positive patients need ALND remains a critical issue. Theoretically, ALND can be avoided for SLN-negative patients, reducing unnecessary surgery and improving quality of life. However, for SLN-positive patients, especially those with micro-metastasis, there is still debate about whether ALND should be avoided. In our study, binary logistic regression analysis showed that the number of SLNs was a significant risk factor for RALN positivity, independent of other clinico-pathological factors such as age, menopause, tumor size, location, molecular subtype, and particularly vascular invasion. This finding is important for clinical practice, especially when evaluating patients with fewer SLNs (eg, ≤3), as more caution may be needed regarding axillary dissection. An increased number of SLNs was associated with a lower RALN positivity rate, suggesting that SLN count can be used to develop more precise treatment strategies, While our results indicate that identifying at least four SLNs significantly reduces the risk of residual metastasis, we do not recommend a mandatory removal of five SLNs in all cases. Based on our findings, we recommend that thorough SLN mapping, with a focus on identifying at least four SLNs, should be prioritized in clinical practice. It is worth noting that our decision to perform ALND was based not on a rejection of international guidelines, but rather on the recognition that existing evidence—such as the ACOSOG Z0011 trial—does not directly address the needs of mastectomy patients. The Z0011 study specifically excluded patients undergoing mastectomy, and its conclusions cannot be extrapolated without reservation. In the absence of equivalent prospective data in mastectomy populations, and given the variability in the use of postmastectomy radiation therapy (PMRT), our institution continues to apply ALND in selected SLN-positive patients to ensure proper staging and treatment planning. This reflects a cautious and evidence-conscious approach within our local clinical context. This strategy may help to reduce unnecessary ALNDs and improve patient outcomes by minimizing overtreatment. Instead, thorough SLN mapping should be prioritized, utilizing dual-tracer techniques and meticulous intraoperative exploration to optimize SLN detection. Thereby avoiding overtreatment and reducing unnecessary ALND.[14,15] Apart from clinicopathological factors, differences in patient demographics and surgical approaches may influence axillary non-sentinel node metastasis. Factors such as age at onset, race, and environmental differences should be further explored in future studies to refine risk stratification strategies.

HER2 and ER/PR receptor status are biomarkers that, as shown in some studies, are closely associated with axillary lymph node metastasis. We also compared SLN count with prognostic biomarkers such as HER2 and ER/PR receptor status. While HER2 positivity was associated with a lower risk of non-sentinel lymph node metastasis, the interaction between these biomarkers and SLN count requires further investigation. It is important to clarify that HER2-positive (14 cases) and TNBC (23 cases) patients constituted a relatively small proportion of the overall cohort. These patients were included only if they did not meet clinical indications for neoadjuvant therapy based on tumor size, nodal status, and institutional guidelines. Moreover, both subgroups exhibited relatively low residual axillary metastasis rates (14.3% and 13.0%, respectively), suggesting no significant bias in study outcomes due to the inclusion of these cases. These findings underscore the complexity of predicting axillary metastasis solely based on biomarker status. For example, HER2-positive patients typically exhibit a lower risk of non-sentinel lymph node metastasis, which aligns with our findings.[16] However, our results do not fully explain inconsistencies with other literature reports. Apart from molecular biomarkers, factors such as age at onset, race, and environmental differences may play significant roles in the progression of axillary non-sentinel node metastasis, which warrants further exploration in future studies.

Furthermore, our study emphasizes the close relationship between the number of SLNs and the risk of residual axillary metastasis. Recent studies have shown that tumors in lymph nodes can induce local immune tolerance, further promoting distant metastasis.[17] Therefore, in SLN-positive patients, especially those with fewer SLNs, ALND or radiotherapy should be considered to avoid missing positive lymph nodes, which can become sources of

local recurrence, distant metastasis, and dissemination of breast cancer.[18,19] It is well established that patients with early-stage breast cancer can avoid ALND if SLN is micro-metastasis.[20] A large clinical trial in England found that patients with HER2-positive disease had a lower risk of axillary non-sentinel node metastasis.[16]

Additionally, previous studies have demonstrated that an increase in the number of negative SLNs correlates with a reduction in the risk of residual axillary metastasis.[21,22] Although our study provides valuable clinical data on the association between SLN count and RALN positivity, the small sample size and the retrospective design of the study may introduce selection bias. This study's limitations include the relatively small sample size (119 patients) and its retrospective design, which may limit the generalizability of our findings. Additionally, the study was conducted at a single institution in China, which may not fully represent the global patient population. Larger multicenter prospective studies are necessary to validate these results and further refine clinical decision-making. Future multicenter, large-sample prospective studies are needed to validate our findings and further optimize treatment strategies for early-stage breast cancer patients.[23]

Conclusion

This study indicate that the number of sentinel lymph nodes (SLNs) is a key factor influencing the risk of residual axillary lymph node macrometastasis. Specifically, patients with fewer SLNs exhibited a significantly higher RALN positivity rate compared to those with a greater number of SLNs. When the SLN count is at least four, the risk of residual axillary metastasis is significantly reduced. While our findings do not mandate the removal of a specific number of SLNs, they emphasize the importance of thorough SLN mapping to improve risk assessment and potentially reduce unnecessary ALND. This finding supports reducing axillary dissection in low-risk patients, and further studies are needed to validate the effectiveness of this approach.

Abbreviations

ALN, axillary lymph nodes; ALND, ALN dissection; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; ER, estrogen receptor; PR, progesterone receptor; RALN, residual axillary lymph nodes.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval and Consent to Participate

All participants provided written informed consent. This study was approved by the Medical Ethics Committee of Bengbu Medical College (No. 2021161), and it adheres to the principles outlined in the Declaration of Helsinki.

Consent for Publication

All authors have consented to the publication of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest in this work.

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