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A multi-center retrospective analysis of ultrasound-guided fine needle aspiration biopsy for detecting additional positive axillary node metastasis in early breast cancer

Youjia Li^{1,6}, Mengru Dong^{2,6}, Shengyu Liao^{3,6}, Yu Jiang⁴, Yingjie Niu⁴, Yiqin Huang⁴, Wei Fu⁴, Debo Chen^{4,5}✉ & Zhipeng Hong^{4,5}✉

This study evaluates the effectiveness of ultrasound-guided fine needle aspiration biopsy (US-FNAB) in assessing additional positive axillary lymph node (ALN) metastasis following sentinel lymph node biopsy (SLNB) in clinically ALN-negative or N1 cases, aiming to refine patient management. A multi-center, retrospective analysis included 7617 patients with cT1-2 and cN0-1, who underwent US-FNAB for ALN and proceeding to SLNB or axillary lymph node dissection (ALND). Metastatic patterns were assessed, particularly focusing on correlations with positive FNAB results and additional ALN metastasis found during ALND, with statistical significance evaluated. Of those undergoing SLNB, 97.5% exhibited macrometastasis. In the SLNB-only group, 2.4% had 3 and more than 3 positive lymph node, compared to 19.2% in the SLNB & ALND group ($P < 0.01$). Among ALND patients, 63.3% had positive nodes, significantly higher in those with positive FNAB (91.9% vs. 22.8%, $P < 0.001$). Additionally, 40.9% were found to have additional positive ALNs in patients who underwent ALND following positive SLNB, with rates significantly higher in those with positive FNAB (60.3% vs. 35.4%, $P < 0.001$). LVI positivity, pT2-3, SLNR $> 50\%$ and positive FNAB were independent predictors of additional ALN metastasis in patients undergoing ALND after positive SLNB ($P < 0.05$). The proportion of additional positivity escalated with the number of positive SLNs. US-FNAB significantly improves the detection of additional ALN metastasis, guiding more effective strategy for ALN surgical decision-making. Our findings support the incorporation of US-FNAB into clinical practice to improve patient stratification and optimize treatment outcomes in early-stage breast cancer management.

Keywords Ultrasound-guided, Fine needle aspiration biopsy, Sentinel lymph node biopsy, Axillary lymph node dissection, Early breast cancer

For patients with breast cancer, it is often necessary to assess the staging of axillary lymph nodes (ALNs), as it serves as a strong prognostic indicator and decisive factor in formulating cancer treatment plans^{1,2}. Traditional axillary lymph node dissection (ALND) has been used for staging, but currently, the frequency and scope of sentinel lymph node biopsy (SLNB) have increased as an alternative for early-stage cancer patients^{3,4}. Notably, while SLNB can avoid unnecessary ALND in order to reduce complications associated with ALND, it is still an invasive procedure that may pose inconvenience for some patients who require two-stage surgeries⁵. Therefore,

¹Department of Ultrasound, Affiliated Quanzhou First Hospital of Fujian Medical University, Quanzhou 362000, Fujian Province, China. ²Standardization Training Office, Affiliated Quanzhou First Hospital of Fujian Medical University, Quanzhou 362000, Fujian Province, China. ³Department of Breast Surgery, Bazhong Central Hospital, Bazhong 636601, Sichuan Province, China. ⁴The School of Clinical Medicine, Fujian Medical University, Fujian, China. ⁵Department of Breast Surgery, Affiliated Quanzhou First Hospital of Fujian Medical University, Quanzhou 362000, Fujian Province, China. ⁶Youjia Li, Mengru Dong and Shengyu Liao contributed equally. ✉email: deboqz@163.com; debochensr@fjmu.edu.cn; hzp@fjmu.edu.cn

a technique that reliably assesses the likelihood of additional positive ALN retention after SLNB would have significant clinical benefits. Methods or minimally invasive surgeries used to determine ALN status would allow for SLNB to be performed if evidence confirms the absence of additional positive ALN metastasis. Conversely, patients who are found to have additional positive ALN metastases would proceed directly to ALND.

In terms of preoperative assessment for additional ALN positive metastasis, the sensitivity of physical examination is relatively low, ranging between 34–76%^{6,7}. In various studies, when combined with ultrasound-guided fine-needle aspiration biopsy (US-FNAB) of suspicious lymph nodes, ultrasound (US) examination of ALNs shows higher diagnostic accuracy^{8,9}. The sensitivity and specificity of US in assessing ALN metastasis are reported to be between 36 and 92% and 69–100%, respectively^{10,11}. Building upon this, the further inclusion of US-FNAB may increase specificity to between 93–100%^{8,12,13}.

However, most previous studies on US-FNAB involved small-scale, single-center patient populations, and the specific likelihood of additional ALN positive metastasis post-SLNB remains unclear. Thus, a multicenter study involving a larger patient population is required. The aim of our study is to evaluate the effectiveness of US-FNAB in assessing the incidence of additional ALN positive metastasis following SLNB in clinically ALN-negative or palpable ALN cases, in order to enhance clinical screening for patients who should exclusively undergo SLNB or require ALND.

Patients and methods

Patients

This retrospective study analyzed data from the Shanghai Jiao Tong University-Breast Cancer Database (SJTU-BCDB), a multicenter database. We identified consecutive patients diagnosed with clinical stage T1-2 N0-1M0 invasive breast cancer who were over 18 years old at the time of diagnosis and underwent ultrasound-guided fine-needle aspiration biopsy (US-FNAB) followed by surgical intervention between January 2009 and December 2023. Clinical nodal staging (cN0/cN1) was determined via physical examination and ultrasound, with cN1 defined by palpable or sonographically suspicious lymph nodes (cortical thickness > 3 mm, non-hilum blood flow, or irregular morphology). PET-CT was not routinely utilized in this cohort. The exclusion criteria included: (1) male patients; (2) diagnosis of carcinoma in situ without invasive disease; (3) synchronous bilateral breast cancer; and (4) history of prior or concurrent malignant diseases.

Comprehensive clinicopathological data were collected, which included age, menopausal status, type of surgical intervention, histopathology, tumor grade, pathologic tumor size, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER2) status, Ki-67 expression, total number of sentinel lymph nodes (SLNs) excised, and the number of positive SLNs. Patients were classified into two subgroups based on histological characteristics: invasive ductal carcinoma (IDC) and other histological types (HST). The Sentinel Lymph Node Ratio (SLNR) was defined as the number of positive SLNs divided by the total number of SLNs excised.

Ethical review

The study protocol received full approval from the Ethics Committee of Ruijin Hospital and was conducted in strict accordance with the ethical principles outlined in the 2013 revision of the Declaration of Helsinki. Given the retrospective nature of the investigation and the complete anonymization of all patient data, the Ethics Committee of Ruijin Hospital granted a waiver of informed consent requirement (Clinical Ethics Approval Number: [2020] 309).

Statistical analysis

Statistical analyses were performed using SPSS version 26 (SPSS, Inc., Chicago, IL, USA). Differences in the incidence of positive SLNs or additional ALNs between the negative and positive US-FNAB groups, as well as differences in clinical and pathological characteristics between the negative and positive ALN groups, were assessed using Chi-square or Fisher's exact tests. Univariable and multivariate logistic regression was performed to calculate adjusted odds ratios (ORs) for factors associated with additional ALN metastasis. A *p*-value of < 0.05 was considered statistically significant.

Results

Number of lymph nodes in SLNB surgery: SLNB only vs. SLNB & ALND

A total of 4,481 patients underwent SLNB surgery, among which 2,820 underwent SLNB only, and 1,661 completed ALND after SLNB. The median number of lymph nodes in the SLNB only group and the SLNB & ALND group was 4, with an interquartile range of 3 to 6 (Fig. 1A).

Lymph node metastasis during positive SLNB surgery

During the SLNB surgery, 97.5% of patients had macrometastasis. In the positive SLNB population, the proportions of patients with 1, 2, and ≥ 3 positive lymph nodes were 84.6%, 13.0% and 2.4%, respectively, in SLNB only group, while 55.5%, 25.3%, and 19.2%, respectively, in the SLNB & ALND group (Fig. 1B). In the SLNB & ALND group, compared to negative FNAB, positive FNAB showed a higher proportion of patients with ≥ 3 lymph node metastases (25.5% vs. 16.8%, *P* = 0.014), while no statistically significant difference was observed in the SLNB only group (4.1% vs. 2.0%, *P* = 0.381) (Fig. 1C-F).

Occurrence of positive lymph nodes during ALND surgery

Among all patients who underwent ALND, 63.3% had positive lymph nodes found during the procedure. The proportion of positive ALNs was higher in patients with positive FNAB compared to negative FNAB (91.9%

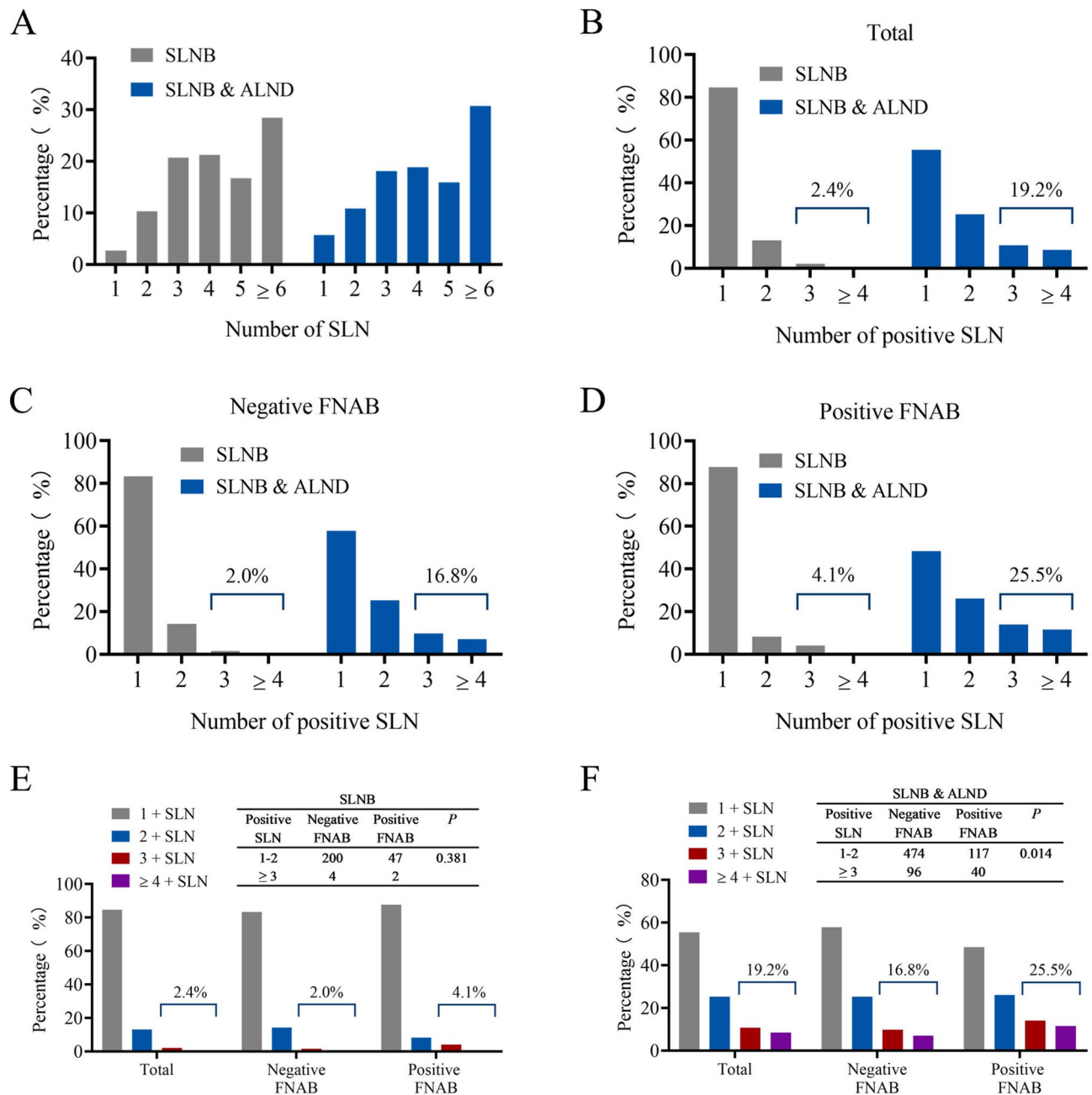


Fig. 1. Number and metastasis of lymph nodes in SLNB surgery. (A) The median number of lymph nodes in the SLNB only group and the SLNB & ALND group. (B) The proportions of patients with different number of positive SLNs in positive SLNB population. (C) The proportions of patients with different number of positive SLNs in negative FNAB group of positive SLNB population. (D) The proportions of patients with different number of positive SLNs in positive FNAB group of positive SLNB population. (E) The comparison of the proportion of patients with lymph node metastases between negative FNAB and positive FNAB group in SLNB only population. (F) The comparison of the proportion of patients with lymph node metastases between negative FNAB and positive FNAB group in SLNB & ALND population.

vs. 22.8%, $P < 0.001$) (Fig. 2A). Similar results were observed in the clinical cN0 (pos. vs. neg. FNAB: 90.0% vs. 18.7%, $P < 0.001$) and cN1 (pos. vs. neg. FNAB: 94.0% vs. 34.8%, $P < 0.001$) subgroups (Fig. 2B-C).

Occurrence of additional positive lymph nodes in patients undergoing ALND after SLNB

Of those who underwent ALND following negative SLNB, 6.3% were found to have additional positive ALNs. Compared to negative FNAB, a higher proportion of patients with positive FNAB were found to have additional positive ALNs (22.6% vs. 5.2%, $P < 0.001$) (Fig. 3A). Similar results were noted in the cN0 and cN1 subgroups,

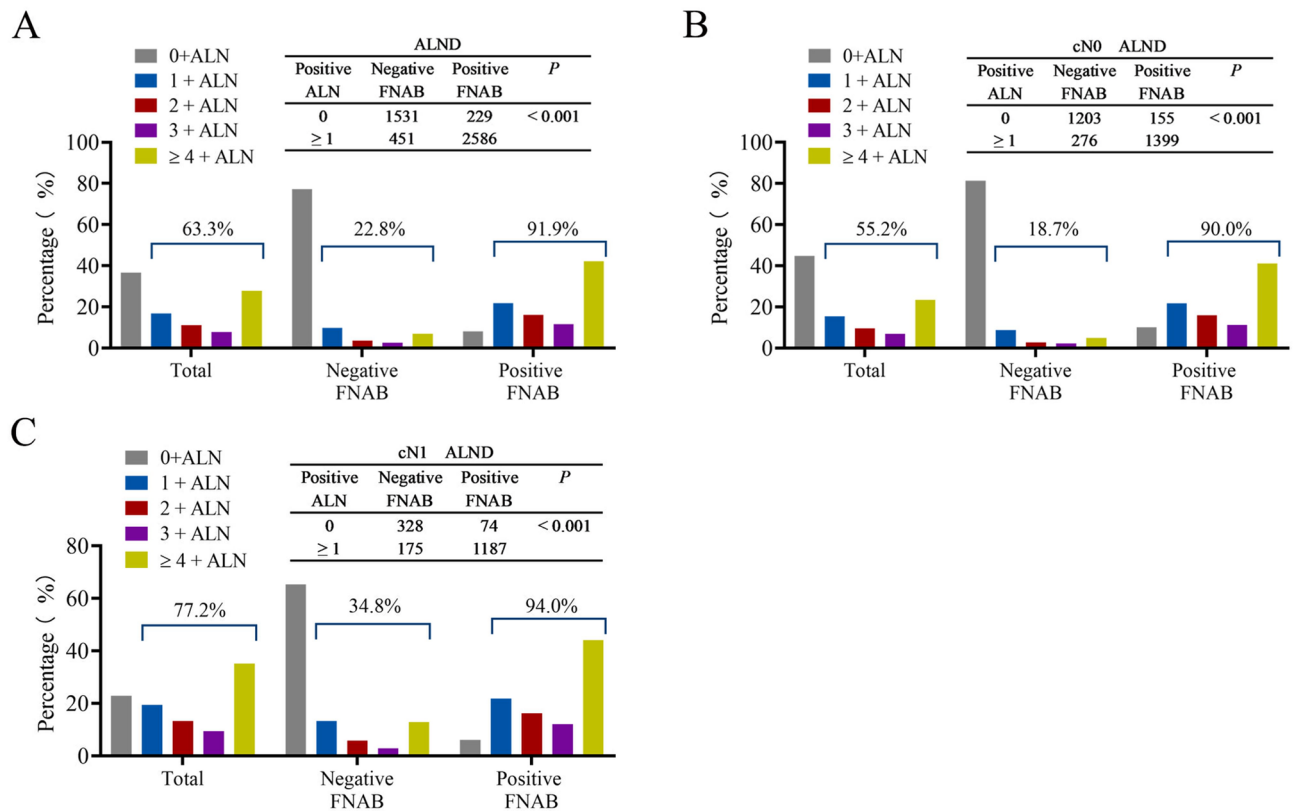


Fig. 2. Percentage of positive lymph nodes during ALND surgery. **(A)** The proportion of positive ALNs in patients with ALND. **(B)** The proportion of positive ALNs in cN0 patients with ALND. **(C)** The proportion of positive ALNs in cN1 patients with ALND.

with higher percentage of additional positive ALNs in positive FNAB group (cN0, pos. vs. neg. FNAB: 13.9% vs. 4.5%, $P = 0.006$; cN1, pos. vs. neg. FNAB: 42.1% vs. 8.0%, $P < 0.001$) (Fig. 3B–C).

Among patients who underwent ALND following positive SLNB, 40.9% were found to have additional positive ALNs. Compared to negative FNAB, positive FNAB group was observed to have higher proportion of additional positive ALNs (60.3% vs. 35.4%, $P < 0.001$) (Fig. 3D). Similar results were noticed in the cN0 and cN1 subgroups, displaying higher percentage of additional positive ALNs in positive FNAB group (cN0, pos. vs. neg. FNAB: 60.8% vs. 32.6%, $P < 0.001$; cN1, pos. vs. neg. FNAB: 59.2% vs. 41.9%, $P = 0.026$) (Fig. 3E–F). Further analysis indicated that LVI positivity (49.7%), pT2–3 (44.5%), SLNR > 50% (67.2%), and positive FNAB (60.2%) were associated with a higher rate of additional positive ALNs in ALND after positive SLNB ($P < 0.05$) (Table 1). Multivariable logistic regression analysis identified the following independent predictors of additional ALN metastasis: positive FNAB (OR = 2.78, 95% CI: 1.81–4.22, $P < 0.001$), SLNR > 50% (OR = 4.08, 95% CI: 2.73–6.10, $P < 0.001$), LVI positivity (OR = 1.82, 95% CI: 1.20–2.75, $P = 0.005$), and pT2–3 tumor size (OR = 1.56, 95% CI: 1.04–2.34, $P = 0.031$) (Table 1).

The relationship between at least one additional positive lymph node metastasis in ALND after SLNB and the number of positive SLN results

In the patient who underwent ALND with at least one additional positive lymph node, the proportion of patients with additional positive lymph nodes increased with the number of positive SLNs, particularly when there were 3 or ≥ 4 positive SLNs, where the proportions were 67.9% and 75.8%, respectively ($P < 0.001$) (Fig. 4A). Similar results were observed in the negative FNAB and positive FNAB subgroups. Notably, compared to negative FNAB subgroup, a higher proportion of additional positive ALNs was found in the positive FNAB subgroup, where the proportions for 2, 3, and ≥ 4 positive SLNs were 65.8%, 77.3%, and 90.9%, respectively ($P < 0.001$) (Fig. 4A).

In the clinical cN0 subgroup, similar results were observed. When there were 3 and ≥ 4 positive SLNs, the proportions of additional positive ALNs were 66.0% and 76.7%, respectively ($P < 0.01$) (Fig. 4B). However, compared to negative FNAB, a higher proportion of additional positive ALNs was observed in positive FNAB subgroup, displaying when there were 2, 3 or ≥ 4 positive SLNs, there will be 68.6%, 80.0% and 92.8% percentage of additional positive ALN ($P < 0.001$) (Fig. 4B).

In the clinical cN1 subgroup, when there were 2, 3 and ≥ 4 positive SLNs, the proportion of additional positive ALNs was 52.1%, 67.8% and 73.7%, respectively ($P < 0.05$) (Fig. 4C). The same results were observed in the negative FNAB and positive FNAB subgroups. Remarkably, compared to negative FNAB subgroup, a higher proportion of additional positive ALNs was noticed in the positive FNAB population when there were ≥ 2 positive SLNs ($P < 0.001$) (Fig. 4C).

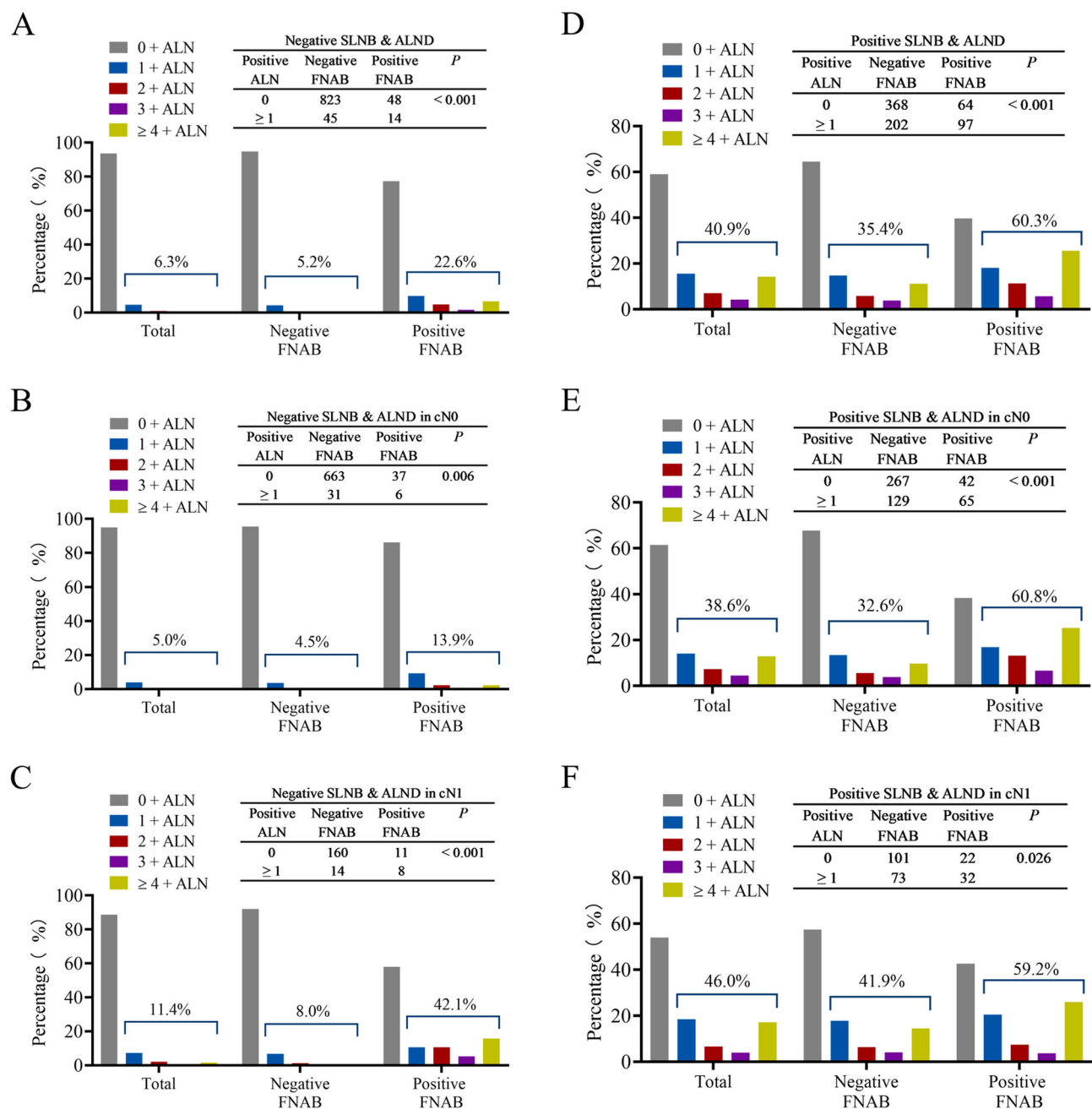


Fig. 3. Percentage of additional positive lymph nodes in patients undergoing ALND after SLNB. (A) The proportion of additional positive ALNs in patients undergoing ALND after negative SLNB. (B) The proportion of additional positive ALNs in cN0 patients undergoing ALND after negative SLNB. (C) The proportion of additional positive ALNs in cN1 patients undergoing ALND after negative SLNB. (D) The proportion of additional positive ALNs in patients undergoing ALND after positive SLNB. (E) The proportion of additional positive ALNs in cN0 patients undergoing ALND after positive SLNB. (F) The proportion of additional positive ALNs in cN1 patients undergoing ALND after positive SLNB.

Discussion

Although SLNB is less invasive than ALND, it has some drawbacks, such as insufficient comprehensive assessment of ALNs for some patients and the inconvenience of requiring two-stage surgeries⁵. If the ALN metastatic status can be determined in advance, patients can directly undergo a one-stage axillary surgery, avoiding multiple procedures. Therefore, employing a more reliable and minimally invasive method to evaluate ALNs in cancer patients would provide more assist in accurate axillary surgery.

Our study shows that patients who underwent ALND after SLNB had a higher proportion of three or more SLN metastases compared to those who only underwent SLNB, particularly in the subgroup with positive FNAB. Simultaneously, the proportion of positive ALNs was higher in the positive FNAB subgroup across the entire

	Positive ALN		P	Univariable		Multivariable	
	0 (n = 432)	≥ 1 (n = 299)		OR (95% CI)	P	OR (95% CI)	P
Age, yr			0.224				
≤ 35, no. (%)	19(46.3)	22(53.7)					
36–64, no. (%)	346(60.1)	230(39.9)		0.57 (0.30–1.08)	0.087	0.61 (0.28–1.31)	0.206
≥ 65, no. (%)	67(58.8)	47(41.2)		0.61 (0.29–1.24)	0.171	0.62 (0.24–1.57)	0.309
Menopausal status, no. (%)			0.275				
Pre/peri-menopausal	212(57.1)	159(42.9)					
Post-menopausal	220(61.1)	140(38.9)		0.85 (0.63–1.14)	0.275	0.91 (0.60–1.37)	0.646
Clinical tumor size, no. (%)			0.789				
T1	182(59.7)	123(40.3)					
T2	250(58.7)	176(41.3)		1.04 (0.77–1.40)	0.789	1.09 (0.74–1.61)	0.650
Estrogen Receptor, no. (%)			0.225				
ER-	132(62.6)	79(37.4)					
ER+	300(57.7)	220(42.3)		1.22 (0.88–1.70)	0.23	1.93 (0.62–5.99)	0.256
Progesterone Receptor, no. (%)			0.183				
PR-	161(61.7)	100(38.3)					
PR+	271(57.7)	199(42.3)		1.23 (0.90–1.69)	0.183	0.67 (0.34–1.32)	0.245
HER2 status, no. (%)			0.904				
Negative	344(59.2)	237(40.8)					
Positive	88(58.7)	62(41.3)		1.02 (0.71–1.47)	0.904	0.89 (0.36–2.16)	0.79
Modified Bloom-Richardson score, no. (%)			0.069				
I	29(70.7)	12(29.3)					
II	269(56.3)	209(43.7)		1.88 (0.94–3.77)	0.076	1.72 (0.77–3.81)	0.190
III	134(63.2)	78(36.8)		1.41 (0.68–2.91)	0.358	1.08 (0.45–2.60)	0.86
Ki-67			0.325				
< 20%	142(61.7)	88(38.3)					
≥ 20%	290(57.9)	211(42.1)		1.13 (0.81–1.58)	0.482	1.58 (0.89–2.79)	0.116
Sub-type			0.485				
Luminal A	77(57.5)	57(42.5)					
Luminal B/HER2(-)	168(56.8)	128(43.2)		1.03 (0.68–1.56)	0.891	0.77 (0.41–1.12)	0.142
Luminal B/HER2(+)	56(58.9)	39(41.1)		0.94 (0.55–1.60)	0.823	0.58 (0.30–1.12)	0.103
HER2 enriched	32(58.2)	23(41.8)		0.97 (0.51–1.83)	0.928	0.58 (0.18–1.92)	0.366
TNBC	99(65.6)	52(34.4)		0.71 (0.44–1.15)	0.161	0.46 (0.22–1.24)	0.204
Tumor type, no. (%)			0.619				
Infiltrating ductal	158(60.3)	104(39.7)		1.08 (0.79–1.47)	0.62	0.83 (0.55–1.25)	0.372
other	274(58.4)	195(41.6)					
LVI, no. (%)			0.004				
No	335(62.3)	203(37.7)					
Yes	97(50.3)	96(49.7)		1.63 (1.17–2.28)	0.004	1.82 (1.20–2.75)	0.005
Pathological tumor size, no. (%)			0.009				
pT1	171(65.5)	90(34.5)					
pT2–3 ^a	261(55.5)	209(44.5)		1.52 (1.11–2.08)	0.009	1.56 (1.04–2.34)	0.031
SLNR, no. (%)			< 0.001				
≤ 50%	368(68.7)	168(31.3)					
Continued							

	Positive ALN		<i>P</i>	Univariable		Multivariable	
	0 (<i>n</i> = 432)	≥ 1 (<i>n</i> = 299)		OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
> 50%	64(32.8)	131(67.2)		4.48 (3.16–6.36)	< 0.001	4.08 (2.73–6.10)	< 0.001
US-guided FNAB			< 0.001				
Negative	368(64.6)	202(35.4)					
Positive	64(39.8)	97(60.2)		2.76 (1.93–3.96)	< 0.001	2.78 (1.81–4.22)	< 0.001

Table 1. Univariable and multivariable logistic regression analysis of factors associated with additional positive ALNs in ALND after positive SLNB. Abbreviations: ALN, axillary lymph node; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; yr, year; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer; LVI, lymphovascular invasion; SLNR, sentinel lymph node ratio; US, ultrasound; FNAB, fine needle aspiration biopsy; OR, odds ratio; CI, confidence interval.

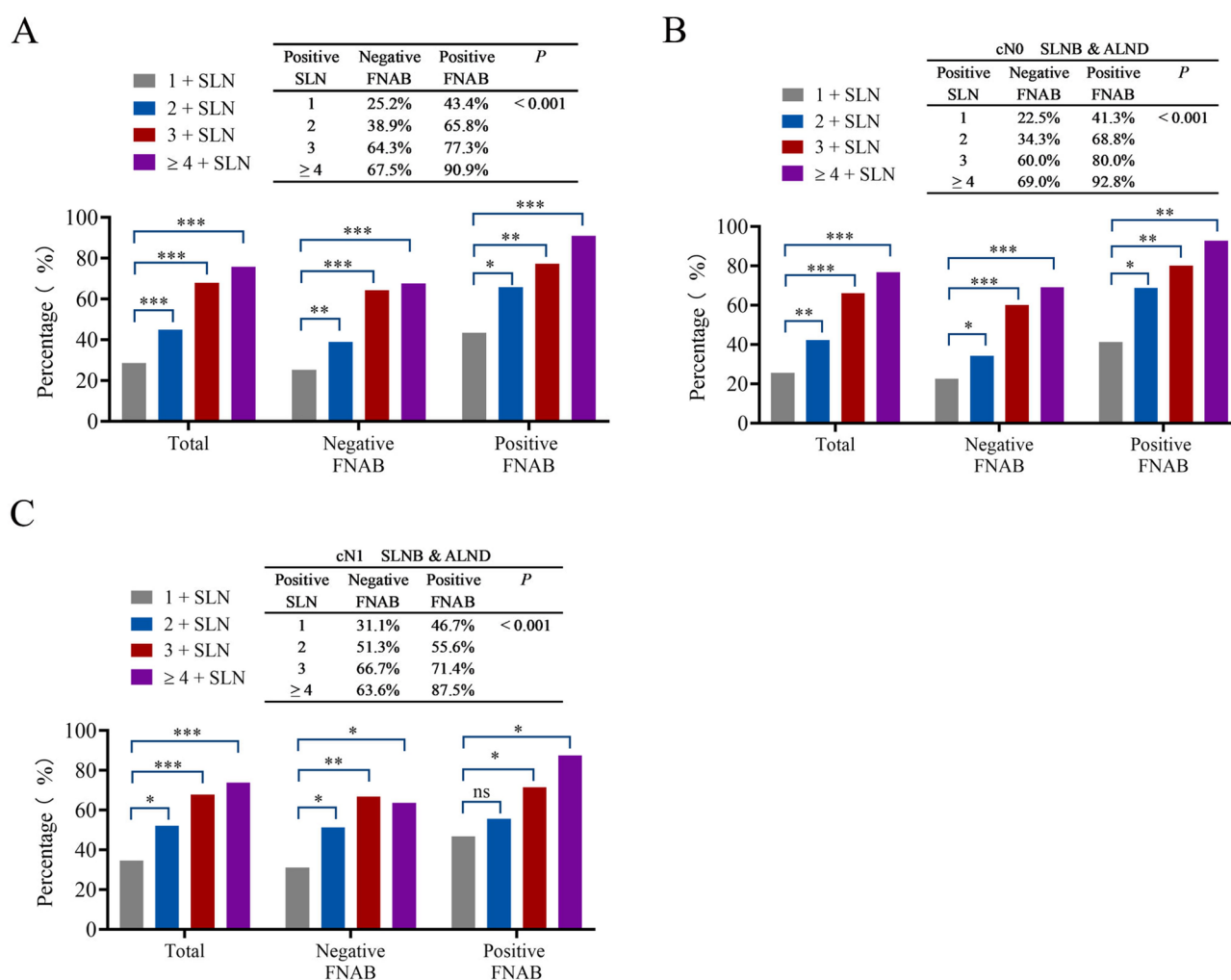


Fig. 4. The relationship between additional positive lymph node metastasis in ALND after SLNB and the number of positive SLN results when at least one additional positive lymph node in ALND. (A) Result in whole population. (B) Result in cN0 patients. (C) Result in cN1 patients.

population, including the cN0 and cN1 groups, indicating that the results of FNAB contribute to the assessment of ALN status.

The NSABP B-32 study showed that the probability of non sentinel ALN positivity in SLN negative patients is less than 10%. In SLN negative patients, ALND can be safely avoided, thereby successfully avoiding or reducing

complications caused by axillary lymph node dissection^{14,15}. For patients with positive SLNs, previous meta-analyses have found that 53% of patients have ALN metastasis outside the sentinel, while for patients with SLN micrometastasis, the probability of non SLN metastasis decreases to 20%¹⁶. In patients with isolated tumor cells in SLNs, the metastasis rate to non SLNs decreases to 12%^{16–18}. In our study, the proportion of positive ALNs post-negative SLNB was 6.3%, which consistent with the result of NSABP B-32. However, the patient with positive FNAB manifested higher possibility of non sentinel ALN positivity, even though the negative outcome of SLNB. About 40.9% of patients undergoing ALND following positive SLNB had additional positive ALNs, also showing rates significantly higher in those with positive FNAB. Consequently, a positive FNAB result provides a signal that more active intervention is required in the management of ALNs.

The proportion of additional positivity escalated with the number of positive SLNs, particularly in the cN0 population with positive FNAB, where the proportions of additional positive ALNs were 68.8%, 80.0%, and 92.8% for 2, 3, and ≥ 4 positive SLNs, respectively. The result suggests that in cN0 patients with positive FNAB, when there are two or more positive SLNs, ALND should be performed more actively. For cN0 patients with negative FNAB, ALND is recommended when there are three or more positive SLNs, consistent with the findings of the Z0011 study¹⁹. Houssami et al. (2007) similarly highlighted the role of preoperative US-FNAB in identifying patients with high nodal burden²⁰, advocating for its integration to streamline surgical planning. Our findings reinforce this approach, particularly in cN1 patients where FNAB positivity strongly predicts additional ALN metastases. In the cN1 population, when there are two or more positive SLNs, more than half of the proportion presenting additional positive ALNs, regardless of whether the FNAB result is positive or negative. Therefore, patients with cN1 should undergo ALND more proactively, especially when exiting two or more positive SLNs, or patients should recommend to undergo preoperative neoadjuvant chemotherapy. In summary, this once again highlights the strong guiding role of FNAB positive results in ALN management.

Several studies have reported that patients with negative FNAB cytology should undergo SLNB^{4,21–23}. Conversely, other studies suggest that the proportion of patients who can be exempt from SLNB ranges from 1–26%^{11,24}. Our study indicates that among cN0 patients with positive FNAB, the proportion of positive ALNs during ALND can be as high as 90.0%, compared to 18.7% in negative FNAB patients (Fig. 2B). More detail analyses in cN0 patients who underwent SLNB followed by ALND showing that the proportion of those with positive ALN metastasis in the positive FNAB group was 13.9% and 60.8% when SLNB result is negative and positive, respectively, while in the negative FNAB group, it was 4.5% and 32.6%, respectively. Similar results were observed in the cN1 population, where the proportion of patients with positive ALN metastasis after SLNB in the positive FNAB group was 42.1% and 59.2% when SLNB result is negative and positive, respectively. These results suggest that SLNB remains the best choice for FNAB negative patients, but patients with positive FNAB should be further evaluated with other indicators to identify those who may be eligible to exempt SLNB and proceed directly to ALND.

It has been reported that US-FNAB is more sensitive in detecting LN metastasis in patients with larger primary cancers, as lymph node metastasis tends to be higher in larger breast cancer cohorts²⁵. Our study demonstrates that FNAB positivity, SLNR $> 50\%$, LVI positivity, and larger tumor size (pT2–3) are independent predictors of additional ALN metastasis in patients undergoing ALND after positive SLNB. The multivariable analysis revealed that patients with positive FNAB had a 2.75-fold increased risk of additional ALN involvement, while SLNR $> 50\%$ was associated with the highest risk. These findings align with previous studies highlighting the role of SLNR and FNAB in axillary staging but further quantify their predictive value in a large multicenter cohort. The strong association between LVI positivity and additional ALN metastasis underscores the biological aggressiveness of tumors with LVI, which may facilitate nodal spread. Similarly, the correlation between pT2–3 tumors and residual ALN involvement supports the notion that larger tumors are more likely to harbor occult nodal disease. These factors collectively provide a robust framework for preoperative risk stratification, enabling clinicians to tailor surgical interventions more effectively.

In conclusion, US-FNAB is a useful tool for the preoperative assessment of axillary lymph nodes in breast cancer patients. It serves as a reliable method for evaluating axillary metastasis and is valuable in planning appropriate axillary management for patients with early breast cancer.

Data availability

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

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Author contributions

DB-C and ZP-H designed the study. YJ-L analyzed the data, wrote and revised the manuscript. MR-D and SY-L analyzed the data, organized photos and revised the manuscript. Y-J, YJ-N, YQ-H and W-F helped with the data analysis, visualization and manuscript modification. All authors have read and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to D.C. or Z.H.

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