Impact of non-sequential lymphatic spread on breast cancer prognosis

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Introduction

Skip metastasis, defined as lymphatic spread that bypasses anatomically contiguous lymph nodes, is frequently observed in breast cancer. Previous studies have reported that skip metastasis occurs in approximately 2.6% of invasive breast cancer cases[1]. Lymphatic dissemination typically follows a sequential pattern, with axillary level I nodes being the most common initial site, followed by levels II, III, and occasionally other nodal basins[2]. However, the precise patterns and underlying mechanisms of lymphatic spread remain unclear and warrant further investigation.

Methods and Materials

Retrospective observational cohort study
Site: Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Inclusion criteria
- ☐ Aged ≥ 18 years old
- ☐ Unilateral, invasive breast cancer, diagnosed between October 2013 to December 2023
- ☐ Underwent axillary lymph node dissection

Exclusion criteria
- ☐ De novo stage IV

Non-sequential nodal classification
- ☐ lymph node negative (LN-): no lymph node metastasis
- ☐ lymph node sequentially positive (LNs+) : metastases following a typical anatomic sequence, from proximal to distal
- ☐ lymph node non-sequentially positive (LNns+): involvement of distal nodes without proximal node involvement

Survival outcomes:
- ☐ Disease-free survival (DFS)
- ☐ Recurrence-free survival (RFS)
- ☐ Overall survival (OS)

Conclusions

- ☐ Non-sequential lymphatic metastasis may indicate more aggressive biological behavior than either the absence or sequential spread of nodal involvement.
- ☐ These patients may benefit from more potent treatments and closer surveillance during follow-up.

Results

	Level I-II	Rotter's	Level III	N (%)
LN-	N	N	N	1833 (64.6)
LNs+	P	N	N	803 (28.3)
	P	P	N	31 (1.1)
	P	P	P	24 (0.6)
LNns+	N	N	P	10 (0.4)
	N	P	N	14 (0.5)
	N	P	P	4 (0.1)
	P	N	P	119 (28.3)

Table 1. Details of non-sequential nodal classification

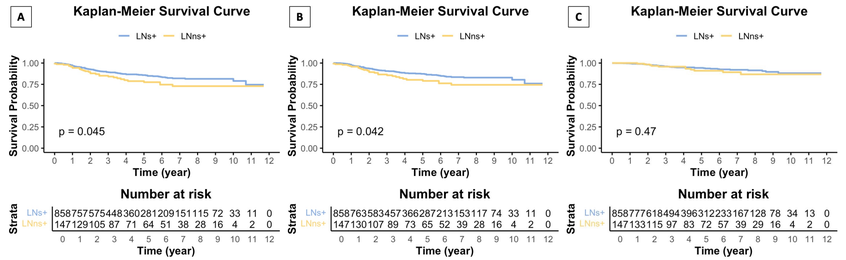


Figure 1. Kaplan-Meier Estimates of Survival for Patients With pN+ Breast Cancer by the nodal disseminating order for Disease-free Survival(A), Relapse-free Survival(B), Overall Survival(C).

Characteristic	LN- N = 1,837	LNs+ N = 861	LNns+ N = 149	P value
Age				0.003
≤50	568 (31.0%)	308 (35.9%)	61 (41.5%)	
>50	1,265 (69.0%)	550 (64.1%)	86 (58.5%)	
Pathological stage				<0.001
0	347 (19.7%)	0 (0.0%)	0 (0.0%)	
1	736 (41.7%)	1 (0.1%)	0 (0.0%)	
2	672 (38.1%)	497 (58.7%)	13 (9.0%)	
3	10 (0.6%)	348 (41.1%)	131 (91.0%)	
Unknown	68	12	3	
HR status				<0.001
HR-	429 (24.3%)	147 (17.5%)	21 (14.4%)	
HR+	1,340 (75.7%)	695 (82.5%)	125 (85.6%)	
Unknown	64	16	1	
HER2 status				0.013
HER2-	1,285 (72.3%)	655 (77.5%)	112 (76.7%)	
HER2+	493 (27.7%)	190 (22.5%)	34 (23.3%)	
Unknown	55	13	1	
Molecular subtype				<0.001
HR+HER2-	1,036 (58.9%)	566 (67.2%)	100 (68.5%)	
HR+HER2+	301 (17.1%)	129 (15.3%)	25 (17.1%)	
HR-HER2+	186 (10.6%)	60 (7.1%)	9 (6.2%)	
HR-HER2-	237 (13.5%)	87 (10.3%)	12 (8.2%)	
Unknown	73	16	1	

Table 2. Significant differences in clinical characteristics among study groups.

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References

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