

Interpectoral Lymph Node Dissection Can Be Spared in pN0/N1 Invasive Breast Cancer Undergoing Modified Radical Mastectomy: Single-Institution Experience from Mainland China

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Purpose: Interpectoral lymph nodes (IPNs) are one of the lymphatic drainage pathways in breast cancer. However, the clinical significance of IPN dissection is controversial, and there is no international consensus regarding the management of IPN for resectable breast cancer. Our study aims to identify the independent predictors of IPN metastasis in invasive breast cancer (IBC) and provide some evidence for rational decision-making.

Methods: Data from 214 IBC patients who were treated with modified radical mastectomy (MRM) plus IPN dissection or biopsy in Ningbo Medical Center Lihuili Hospital were retrospectively reviewed. Univariate analysis and multivariate logistic regression analysis were used to analyse the correlations between IPN occurrence or metastasis and clinico-pathological characteristics.

Results: The occurrence rate of IPN in overall population was 75.2%. Univariate analysis showed that tumour size, involvement of axillary lymph nodes (ALNs), histological grading, Ki67 index and molecular subtype were associated with the occurrence of IPN. However, involvement of ALN was the only independent predictor by multivariate logistic regression analysis. In 161 patients whose IPNs were detected, 46 (28.6%) patients had one or more metastatic IPNs. Univariate analysis showed that tumour size, involvement of ALN, oestrogen receptor status and molecular subtype were associated with IPN metastasis. However, involvement of ALN was the only predictor by multivariate logistic regression analysis. In total, 0%, 5.0%, 26.1% and 84.2% of pN0, pN1, pN2, and pN3 patients had metastatic IPNs, respectively.

Conclusion: The relatively low rate of IPN metastasis in patients with pN0/N1 breast cancer suggests that IPN dissection can be safely spared in patients with low tumour burden in axillary lymph nodes (pN0/N1), when MRM even breast conservation surgery is performed.

Keywords: breast cancer, interpectoral lymph node, axillary lymph node, metastasis

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Introduction

Interpectoral lymph nodes (IPNs) were first reported by Grossman in 1896.¹ Three years later, Rotter described these nodes in half of 33 surgical specimens from patients with breast carcinoma.² Anatomically, IPNs are located between the pectoralis major and minor muscles in the interpectoral fascia and do not belong to axillary lymph nodes (ALNs) and may further drain into the central or subclavicular node groups representing a possible “skip pathway” for tumour cells to metastasize from the breast to level III



nodes while bypassing levels I or II.^{3,4} Numerous studies have showed that sentinel lymph node biopsy (SLNB), instead of axillary lymph node dissection (ALND), has better cosmetic results⁵ and is associated with less arm and shoulder complications.^{6–8} However, in mainland China, ALND is still an essential surgical procedure for certain patients in whom cancer cells have spread heavily to axillary lymph nodes (ALNs) or who are unwilling to undergo SLN due to excessive anxiety.

The management of IPN has historically been controversial. Some surgeons held the view that IPN should be routinely dissected for breast cancer patients regardless of ALN status because as high as 4% of patients had IPN metastasis even in patients who had no metastatic ALNs,⁹ and IPNs have also been identified as a site of recurrence.⁴ However, other surgeons had moderate views that IPN dissection was only necessary for patients with locally advanced disease (large tumour or positive ALNs).¹⁰ Limited to rare high-quality studies of evidence-based medicine, the authoritative guideline of the National Comprehensive Cancer Network (NCCN) had no definite recommendation on the management of IPN for breast cancer patients. Whether IPN dissection or biopsy was performed often depended on the experience of the surgeons.

Regarding IPNs, several questions have not been answered until now. First, previous studies did describe the lower rate of IPN metastasis in patients without positive ALNs, and the much higher rate in patients with positive ALNs; however, these studies did not specify the possibility of IPN metastasis based on the tumour burden in the ALNs, and they simply drew the conclusion that IPN dissection was necessary for all patients with positive ALNs. Second, surgeons were greatly interested in the IPNs from the 1960s to 1990s, after which less attention had been paid to this field; especially in the era of SLNB, the value of IPNs dissection for patients who had no positive SLNs or 1 to 3 positive SLNs was unknown, and more studies are needed. Third, as a developing country, China's mainstream population has the greatest number of breast cancer patients, and even in some underdeveloped areas, MRM is still the mainstream surgery; however, the study of IPNs in Chinese patients is still relatively deficient. Therefore, our study aimed to investigate the specific metastasis rates of IPN in Chinese breast cancer patients with different tumour burden in the axillas, to determine the predictors for IPN metastasis and to further provide some evidence for rational decision-making.

Materials and Methods

Patient Selection

The study obtained approval from the Institutional Ethics Committee of Ningbo Medical Center Lihuili Hospital (approval number KY2020PJ026). Informed consent was waived, because on the informed consent for surgery, there was a statement that data of patients could be used for clinical research and non-commercial in the future, and patients agreed. Data of patients were confidential, and the study protocol was conducted in accordance with the recommendations outlined in the Helsinki Declaration. Then, we collected and analysed the data of patients with IBC in our hospital between November 2014 and August 2018. MRM was performed on every patient, and IPNs were removed separately. Exclusion criteria included the following: (1) metastatic breast cancer; (2) locally advanced breast cancer treated with neoadjuvant therapy; (3) breast cancer with less than 15 ALNs removed; (4) incomplete clinicopathological information.

Data Collection

Clinical and pathological data were collected from medical records of the patients included in the study. The data included the following: patient age, laterality and location of the tumour, tumour size, histological grading, numbers of ALNs and IPNs removed, numbers of ALNs and IPNs involvement, oestrogen receptor (ER), progesterone Receptor (PR), human epidermal growth factor receptor-2 (HER2) and Ki-67 label index. ER and PR assays should be considered positive if immunostaining is seen in more than 1% tumour nuclei.¹¹ HER2 positivity was defined as either immunohistochemistry (IHC) 3+ or gene amplification by fluorescence in situ hybridization (FISH).¹² Adjuvant chemotherapy, radiotherapy, endocrine therapy and anti-HER2 therapy were administered in appropriate patients according to currently available clinical practice guideline.

Statistical Analysis

Chi-square or Fisher's exact tests were performed to assess associations between the rate of IPN occurrence or metastasis and categorical variables. Multivariate logistic regression analysis, including all variables from the univariate analysis that were associated with IPN occurrence or metastasis rate, was performed to test for factor independence. $P < 0.05$ was considered to indicate statistical significance, and statistical test was two-sided. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also

calculated. Analyses were performed using SPSS v. 20.0 Software (SPSS, Chicago, IL, <http://www.spss.com>).

Results

Patient Characteristics

Between November 2014 and August 2018, 1213 breast cancer patients received surgical treatment. According to the exclusion criteria, 214 eligible patients were included in our study. Figure 1 shows the flow chart of the study. All patients were female, and the median age was 51 years, ranging from 34 to 71. The percentages of pathological stage I/II/III were 19.6% (42/214), 33.6% (72/214), 46.7% (100/214), respectively. Details of clinicopathological characteristics and demographic features are shown in Table 1. IPN was detected in 161 patients, and the IPN occurrence rate was 75.2% (161/214). Among 161 patients, the average number of IPNs removed was 1.4,

ranging from 1 to 6. Of them, 103 patients had one IPN, 45 patients had two IPNs, 13 patients had three or more IPNs. The clinicopathological characteristics of 161 patients in whom IPN was detected are shown in Table 2.

Predictors for IPN Occurrence

Univariate analysis found that tumour size, histological grading, ALN involvement, Ki67 label index and molecular typing were associated with IPN occurrence; however, multivariate logistic regression analysis found that only ALN involvement was an independent predictive factor for IPN occurrence (Table 3).

Predictors for IPN Metastasis

Among all 214 patients, 46 patients had one or more metastatic IPNs, and the IPN metastasis rate was 21.5% (46/214). In 161 patients in whom IPN had been detected,

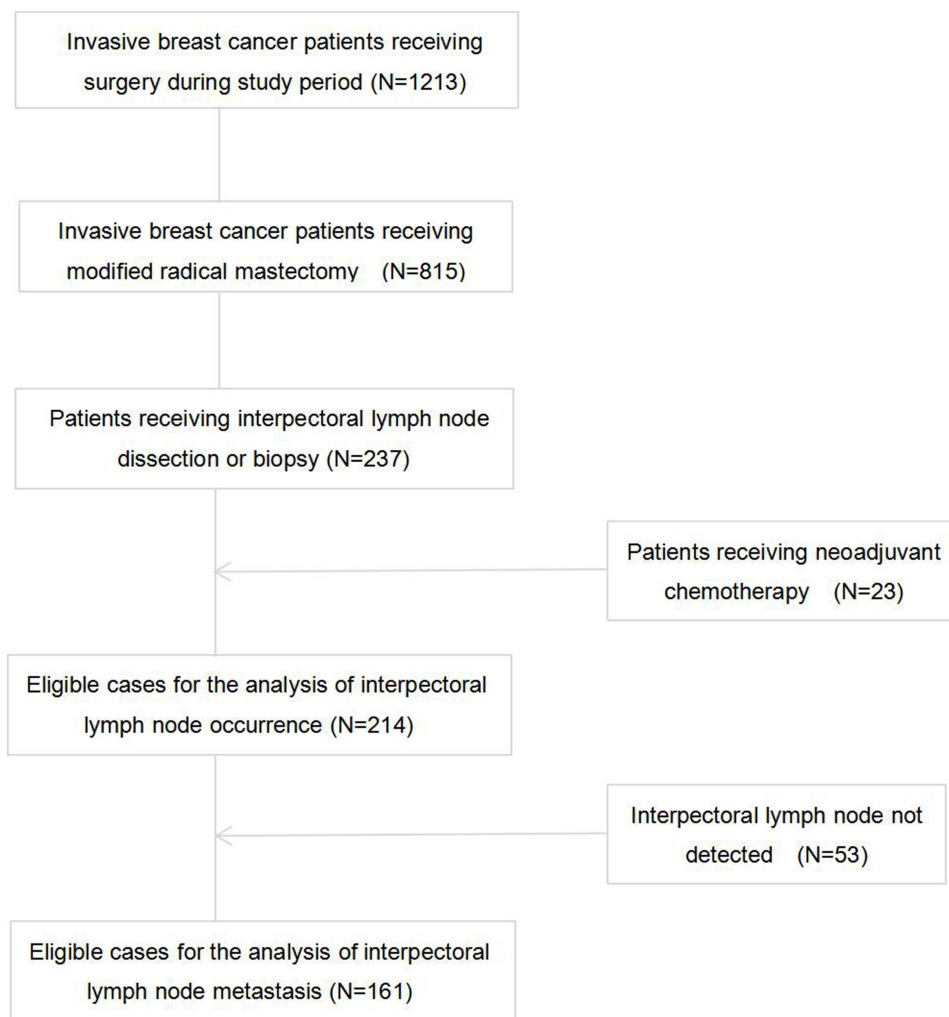


Figure 1 Flow chart of the study.

Table 1 Clinicopathologic Features of Patients Undergoing Modified Radical Mastectomy (N=214)

Variables	Number	%
Age (years)		
≤ 50	103	48.1
> 50	111	51.7
Tumor side		
Left	126	58.9
Right	88	41.1
Tumor location		
Upper Outer Quadrant	98	45.8
Lower Outer Quadrant	37	17.3
Upper Inner Quadrant	41	19.2
Lower Inner Quadrant	38	17.7
Histologic grade (MRB)		
G1	6	2.8
G2	107	50.0
G3	101	47.2
Tumor stage		
T1	81	37.9
T2	115	53.7
T3	18	8.4
Lymph node involvement		
N0	59	27.6
N1	66	30.8
N2	53	24.8
N3	36	16.8
AJCC stage		
I	42	19.6
II	72	33.7
III	100	46.7
ER status		
Positive	114	53.3
Negative	100	46.7
PR status		
Positive	97	45.3
Negative	117	54.7
HER2 status		
Positive	57	26.6
Negative	157	73.4
Ki67		
Low (≤30%)	99	46.3
High (>30%)	115	53.7
Radiotherapy		
Yes	165	77.1
No	49	22.9

(Continued)

Table 1 (Continued).

Variables	Number	%
Endocrine therapy		
Yes	121	56.5
No	93	43.5
Trastuzumab use		
Yes	50	23.4
No	164	76.6

Abbreviations: T, tumor; N, lymph-node; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

the IPN metastasis rate was 28.6% (46/161). In the 46 patients who had metastatic IPNs, 58 metastatic IPNs were detected, and the rates of one and two metastatic IPNs were 73.9% (34/46) and 26.1% (12/46), respectively.

Univariate analysis found that tumour size, ALN involvement, ER status and molecular typing were associated with IPN metastasis; however, multivariate logistic regression analysis found that only ALN involvement was an independent predictive factor for IPN metastasis (Table 4).

IPN Metastasis in Different Subgroups

According to pathological nodal staging, the rates of IPN metastasis were 0% (0/37), 5.0% (2/40), 26.1% (12/46) and 84.2% (32/38) in patients with axillary pN0, pN1, pN2, pN3, respectively. In axillary pN1 patients, 2 patients with one involved ALN had one metastatic IPN, and the remaining 44 patients, 10 with axillary pN2 and 22 with axillary pN3 had one metastatic IPN, 2 with axillary pN2 and 10 with axillary pN3 had two metastatic IPNs. When metastatic IPNs were added up to the metastatic axillary lymph nodes, the pathological nodal staging never changed in any of the patients.

Discussion

Previous studies have often focused on the occurrence and metastasis of IPN in nonmetastatic breast cancer. Anatomically, the number of IPNs varies from 0 to 4, and relative lymphatic drainage accounts for 0.7% of the entire breast.¹³ An early retrospective study showed that the detection rate of IPNs was as high as 73%,¹⁴ while the detection rate in Chinese breast cancer patients ranged from 9% to 46%. In the present study, IPNs were detected in 75.2% breast cancer patients. On one hand, since IPN could be detected in approximately 75% patients and the dissection or biopsy of IPN was easily done and did not cause extra harm to patients, IPN

Table 2 Clinicopathologic Features of Patients with Interpectoral Lymph Node Occurrence (N=161)

Variables	Number	%
Age (years)		
≤ 50	78	48.4
> 50	83	51.6
Tumor side		
Left	99	61.5
Right	62	38.5
Tumor location		
Upper Outer Quadrant	75	46.6
Lower Outer Quadrant	32	19.9
Upper Inner Quadrant	25	15.5
Lower Inner Quadrant	29	18.0
Histologic grade (MRB)		
G1	5	3.1
G2	88	54.7
G3	68	42.2
Tumor stage		
T1	61 (37.9)	37.9
T2	82 (50.9)	50.9
T3	18 (11.2)	11.2
Lymph node involvement		
N0	37	23.0
N1	40	24.8
N2	46	28.6
N3	38	23.6
AJCC stage		
I	32	19.9
II	41	25.4
III	88	54.7
ER status		
Positive	88	54.7
Negative	73	45.3
PR status		
Positive	72	44.7
Negative	89	55.3
HER2 status		
Positive	44	27.3
Negative	117	72.7
Ki67		
Low (≤30%)	85	52.8
High (>30%)	76	47.2
Radiotherapy		
Yes	130	80.7
No	31	19.3

(Continued)

Table 2 (Continued).

Variables	Number	%
Endocrine therapy		
Yes	92	57.1
No	69	42.9
Trastuzumab use		
Yes	43	26.7
No	118	73.3

Abbreviations: T, tumor; N, lymph-node; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

dissection or biopsy could be performed to patients with potential benefits. On the other hand, when the estimated rate of IPN metastasis is high, IPN dissection or biopsy should be performed routinely to decrease the potential recurrence at this site.

For patients in whom IPN was detected, the rate of IPN metastasis was 28.6%, which was slightly higher than the 20.0% reported by Vrdoljak et al.⁹ The status of ALNs in the two study may explain the difference in IPN metastasis. In that study, nearly half of patients had negative ALNs, while in our study, only 23.0% (37/161) patients had negative ALNs. In our study, in the patients who had positive ALNs, the metastasis rate was 37.1% (46/124), which was consistent with 35 and 31.5% in previous studies.^{9,15} All these results indicate that a routine IPN dissection or biopsy needs to be performed because the surgical approach of this group is easy and the aesthetic result is not affected.

Our retrospective study showed that ALN involvement was not only an independent predictor for IPN occurrence, but also for IPN metastasis. In the study, the rates of IPN metastasis were 0 and 37.1% (46/161) in patients with or without positive ALNs, respectively. Although metastatic IPNs were also reported in patients who had negative ALNs,⁹ the proportion was small. Considering that the pedicle of the pectoral can produce damage at this level, which could also mean that the great pectoral muscle could develop partial atrophy, IPN dissection or biopsy is not recommended in patients with negative ALNs. Of course, SLNB is the preferred option for patients who are free from clinically ALN involvement. Since no metastasis is present in ALNs, including sentinel lymph nodes (SLNs), the rate of IPN metastasis is low enough that IPN dissection or biopsy can also be safely avoided.

Table 3 Univariate and Multivariate Analysis of Clinicopathological Factors Predicting IPN Occurrence (N=161)

Variables	Univariate (Chi Square/Fisher's Exact)			Logistic Regression, Multivariate		
	IPN Occurrence (Yes/No)		P	OR	95% CI	P
Age (years)						
≤ 50	78	25				
> 50	83	28	0.872	–	–	–
Tumor side						
Left	97	29				
Right	64	24	0.478	–	–	–
Tumor location						
Upper Outer Quadrant	70	28				
Others	91	25	0.236	–	–	–
Histologic grade (HMB)						
G1–G2	93	20				
G3	68	33	0.011	0.480	0.211–1.089	0.079
Tumor stage						
T1	61	20				
T2	82	33				
T3	18	0	0.032	0.957	0.452–2.026	0.908
Number of ALND						
≤ 20	108	41				
> 20	53	12	0.158	–	–	–
ALN involvement						
N0	37	22				
N1	40	26				
N2	48	5				
N3	36	0	<0.001	8.292	3.240–21.221	<0.001
ER status						
Positive	88	26				
Negative	73	27	0.478	–	–	–
PR status						
Positive	72	25				
Negative	89	28	0.756	–	–	–
HER2 status						
Positive	44	13				
Negative	117	40	0.689	–	–	–
Ki67 label index						
Low (≤30%)	85	14				
High (>30%)	76	39	0.001	0.482	0.220–1.056	0.076
Molecular typing						
Luminal A/B	90	27				
HER2 over-expression	33	5				
Triple negative	38	21	0.036	1.212	0.765–1.920	0.413

Abbreviations: T, tumor; N, lymph-node; ALN, axillary lymph node; ALND, axillary lymph node dissection; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 4 Univariate and Multivariate Analysis of Clinicopathological Factors Predicting IPN Metastasis (N=161)

Variables	Univariate (Chi Square/Fisher's Exact)			Logistic Regression, Multivariate		
	IPN Occurrence (Yes/No)		P	OR	95% CI	P
Age (years)						
≤ 50	20	58				
> 50	26	57	0.425	–	–	–
Tumor side						
Left	24	75				
Right	22	40	0.124	–	–	–
Tumor location						
Upper Outer Quadrant	24	51				
Others	22	64	0.368	–	–	–
Histologic grade (HMB)						
G1–G2	24	69				
G3	22	46	0.364	–	–	–
Tumor stage						
T1	10	51				
T2	30	52				
T3	6	12	0.027	1.271	0.758–2.131	0.364
Number of ALND						
≤ 20	27	77				
> 20	19	38	0.322	–	–	–
ALN involvement						
N0	0	37				
N1	2	38				
N2	12	34				
N3	32	6	<0.001	13.423	7.529–23.931	<0.001
ER status						
Positive	18	70				
Negative	28	45	0.012	2.608	0.520–13.709	0.244
PR status						
Positive	16	56				
Negative	30	59	0.109	–	–	–
HER2 status						
Positive	16	28				
Negative	30	87	0.180	–	–	–
Ki67 label index						
Low (≤30%)	24	61				
High (>30%)	22	54	0.920	–	–	–
Molecular typing						
Luminal A/B	18	72				
HER2 over-expression	14	19				
Triple negative	38	21	0.022	1.035	0.399–2.685	0.943

Abbreviations: T, tumor; N, lymph-node; ALN, axillary lymph node; ALND, axillary lymph node dissection; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Previous studies always considered patients with positive ALN as a whole, and then concluded that a routine IPN dissection or biopsy should be performed on breast cancer patients with positive ALNs. Different tumor burdens in ALN have different nodal stages and may have different probability of IPN metastasis. Our study is the first to specify the rate of IPN metastasis based on different tumour burdens in the ALNs. Indeed, in our study, we observed different rates of IPN metastasis in different nodal stages, with 0%, 5.0%, 26.1% and 84.2% in patients with axillary pN0, pN1, pN2, pN3, respectively.

In pN1 patients, the 5% IPN metastasis rate in our study was low enough that IPN dissection or biopsy should also be spared, which can be deduced from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial. In ALND group, 86.3% patients had one to three involved ALNs (pN1 patient), and the remaining 13.7% patients had four or more positive ALNs; after a median follow-up of 6.3 years, no recurrence was found at IPN site.^{16,17} In our study, as low as 5% metastatic IPNs were found, and metastatic IPN occurred in patients with a low tumour burden (one positive ALN), which seems to indicate that IPN dissection or biopsy could also be safely spared. Of course, the sample number of patients with pN1 disease in our study was small, and a large-scale study is needed to further test our result.

Our findings have important clinical significance for patients who undergo MRM. In the current study, there was no IPN metastasis when ALN was negative, and only 5% of patients had IPN metastasis when one to three ALNs were involved, which indicated that IPN dissection could be safely spared. Even for patients who undergo breast conserving surgery (BCS) and SLNB, our study also has potential significance. In the Z0011 trial, only 1.0% of patients had four or more involved ALNs in the SLNB group, and after a median follow-up of 6.5 years, there was no recurrence at the site of IPNs.^{16,17} Of course, if the IPNs were the SLN in certain patients, and these IPNs were not removed during the procedure of SLNB, we could not accurately assess the status of SLNs. Fortunately, there is little possibility for SLNs to serve as INPs. Estourgie et al³ found that only 2.2% cN0 patients with invasive breast cancer exhibited drainage toward INPs as SLNs, and the rates of INPs as SLNs were 2.6%, 2.1%, 1.1%, 2.7% and 2.3% in patients when the tumour was located in the upper outer, upper inner, lower outer, lower inner quadrants and the center, respectively. Therefore, we can conclude that IPN dissection can also be spared when the patients meet the inclusion criteria of the Z0011 trial: tumor \leq 5 cm, no palpable or swollen lymph node, no more than three involved SLNs

and receiving whole-breast irradiation. Of course, large-scale prospective studies are necessary for patients who meet the inclusion criteria and undergo BCS and SLNB to further verify our findings.

The limitations of this study should also be acknowledged. First, retrospective nature and small sample size may lead to bias in data selection and analysis. Second, in the study, the analysis of the predictors for IPN metastasis was based on the patients in whom IPN was successfully detected. However, IPNs were not detected in as many as 24.8% of patients, which may have influence on final analysis. If the IPNs were actually present but were ignored by either surgeons or pathologists, the rate of IPN metastasis in our study would not be accurate. Third, our analysis was based on the final pathology, and the status of ALN and the number of metastatic ALNs were not known intraoperatively. Thus, it seems to be somewhat difficult to make decisions whether to perform IPN dissection or biopsy. However, SLNB and intraoperative pathology can provide relatively accurate information on the status of SLNs.

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Disclosure

The authors declare no competing financial and non-financial interests in this work.

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