Original Article

Frequency and predictive factors of nodal micro-metastasis (NMM) in resectable non-small cell lung cancer

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Background: The frequency of lymph nodal micrometastasis (NMM) in resectable non-small cell lung cancer (NSCLC) is frequently underestimated when relying solely on standard hematoxylin and eosin staining during pathological examination.

Methods: This is a retrospective cross-sectional diagnostic research. Medical records of resectable pN0 NSCLC patients who underwent curative resection in Maharaj Nakorn Chiang Mai Hospital between January 2006 to December 2017 were retrospectively reviewed. Immunohistochemistry (IHC) staining using cytokeratin AE1/AE3, p53 and BerEP4 markers was employed to detect NMM. Primary objective of this study was to determine frequency of NMM in pN0 resectable NSCLC.

Results: This study included 98 patients with pN0 NSCLC, of which 47 were male and 51 were female. NMM was detected in 21 of 98 patients (21.43%). Lymph node station 10 and 7 were the most common site of micrometastasis among patients with N1 and N2 micrometastasis, respectively. Cytokeratin AE1/AE3 was the most sensitive antibody in detecting micrometastasis in lymph nodes, identifying 25 out of 27 positive lymph nodes. Tumor size greater than 4 cm was a statistically significant predictive factor for NMM with risk ratio 6.69 [95% confidence interval (CI): 2.38–18.85, P<0.001].

Conclusions: NMM was identified in 21.43% of pN0 resectable NSCLC patients and tumor size greater than 4 cm is predictive factor for NMM.

Keywords: Resectable non-small cell lung cancer (resectable NSCLC); nodal micrometastasis (NMM); occult micrometastasis; immunohistochemistry

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Introduction

Lung cancer is the leading cause of cancer mortality worldwide. Only 18% of all lung cancer patients can live more than 5 years after diagnosis and fall to 6% if left untreated (1). In the United States, lung cancer was diagnosed in 234,030 cases and an estimated 154,050 deaths were attributed to this disease (2). In 2020, According to GLOBOCAN database, lung cancer is the second most common cancer diagnosed in Thai-male patients (12.4%) and the fifth most common in Thai-female patients (8.5%). Lung cancer also ranked as the second most common cause of cancer death in Thailand, accounting for 16.3% of all cancer deaths (3). Despite complete surgical resection, there are differences in recurrent rates and survival between stages. The 5-year survival rates for stage I and stage III resectable non-small cell lung cancer (NSCLC) are 70% and 38%, respectively (4).

Surgical treatment is considered the most effective option for a cure in patients with resectable NSCLC. The prognosis of these patients is influenced by several factors, including the pathological lymph node staging, with 5-year survival rates of 56%, 38%, 22%, and 6% in pN0, pN1, pN2, and pN3, respectively (5). Despite complete oncologic resection, tumor recurrence is still observed in 30% of stage I and more than 60% of stage IIb patients (6). The presence of occult micrometastasis in mediastinal lymph nodes is associated with a higher recurrence rate and lower survival after complete surgical resection (7,8). However, the standard method of detecting lymph node metastasis, hematoxylin and eosin (H&E) staining, is not always accurate enough to detect isolated or small clusters of tumor cells in dissected lymph nodes (9). Immunohistochemical (IHC) staining is used as a supplemental tool to detect single tumor cells or small clusters of tumor cells that may be missed during standard pathological examination. Several markers, such as AE1/AE3, BerEP4, and DO-1, have been used in IHC staining to detect metastatic cells in lymph nodes (10-12). However, the value of IHC staining in detecting nodal micrometastasis (NMM) is still controversial and requires further investigation. The objective of this study is to evaluate the frequency of NMM and nodal upstaging in special IHC staining compared to standard H&E staining of mediastinal lymph nodes in pN0 resectable NSCLC patients and to determine the predictive factors of NMM. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1240/rc).

Highlight box

Key findings

- Frequency of nodal micrometastasis (NMM) in resectable pN0 non-small cell lung cancer (NSCLC) is 21.43%.
- Tumor size greater than 4 cm is predictive factor of NMM.

What is known and what is new?

- Cytokeratin is the most sensitive antibody in NMM detection.
- A tumor exceeding 4 cm in size is indicative of the likelihood of NMM.

What is the implication, and what should change now?

- Currently, NMM is not included in the TNM staging system for lung cancer. The detection of micrometastasis using immunohistochemistry staining shows a high prevalence (21.43%). This finding may potentially establish a new standard for the pathological examination of nodal involvement in lung cancer, particularly if micrometastasis proves to significantly impact treatment outcomes and patient survival rates.

Methods

Population and data collection

This was a retrospective cross-sectional diagnostic research study conducted on 98 patients, consisting of 47 males and 51 females, who were diagnosed with pN0 resectable NSCLC and underwent curative-intent resection at Maharaj Nakorn Chiang Mai Hospital between January 2006 to December 2017. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the joint institutional research ethics committees of the Chiang Mai University (study code: SUR-2562-06766) and individual consent for this retrospective analysis was waived. All patients underwent preoperative staging by CT scan of the chest, which included the upper abdomen, and obtained tissue diagnosis by transbronchial/transthoracic biopsy as a standard protocol. PET/CT was optional due to it not being included in the reimbursement scheme. Preoperative cardiopulmonary evaluation, such as ECG, pulmonary function test, and stair climbing test, were routinely performed.

The computerized databased and medical records of pN0 NSCLC patients treated with curative-intent resection were reviewed. Patients who received preoperative radiation or chemotherapy, those lacking pathological slides of lymph nodes, and individuals with confirmed lymph node metastasis from the pathologic review were excluded from the study.

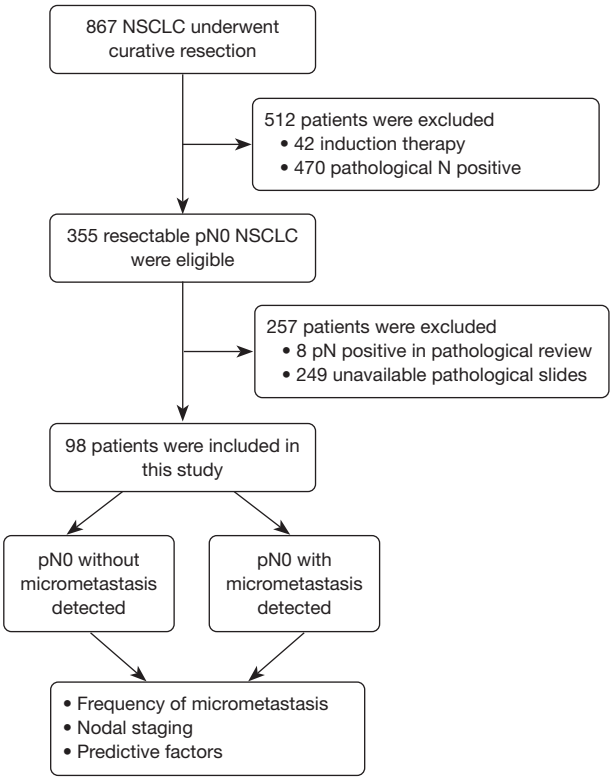

Figure 1 Study diagram. NSCLC, non-small cell lung cancer.

Information such as age, gender, co-morbidity, smoking status, tumor size, tumor location, pre-operative TNM-stage, post-operative TNM stage, total number of lymph node retrieved, histology of tumor, tumor differentiation, lymphatic invasion, vascular invasion, pleural invasion, perineural invasion, presence of tumor necrosis, presence of STAS, presence of NMM and number, EGFR mutation, ALK re-arrangement, extent of surgery and type of surgery were extracted from the medical records. The primary end point of this study was the frequency of NMM, and the secondary end points were the frequency of nodal upstaging and predictive factors of NMM. The surgical procedure was performed by a single surgical team under single-lung ventilation with double lumen endotracheal tube. The surgical procedure included wedge resection, segmentectomy, lobectomy, bilobectomy and pneumonectomy. Lymph node dissection of hilar, subcarinal, superior and inferior mediastinal zone was performed in all cases.

IHC staining

All pathologic slides of lymph node were reviewed by an experienced pathologist to confirm pN0. Formalin-fixed, paraffin-embedded tissue was sectioned at a thickness of 4 µm. The tissues were then stained with CK clone AE1/AE3 (1:200 dilution), Epithelial antigen clone BerEp4 (1:100 dilution), and p53 clone DO-7 (1:5,000 dilution) using a Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ, USA) according to the manufacturer's stated protocol. The quantification of immunoreactivity was assessed using ImageJ Fiji software, version1.2. The immunohistological slides were meticulously reviewed by an experience pathologist with expertise in the field. The pathologist maintained a blinded approach throughout the review process, ensuring they were unaware of any relevant clinical information about the patients.

Statistical analysis

Statistical analysis was performed using the STATA version 15.0. The sample size for this study was determined using a power analysis based on the results of a previous study conducted by Gu *et al.* (11). The analysis used an alpha level of 0.05 and a power of 0.8 to ensure adequate statistical power for detecting meaningful differences or associations in the current study. The continuous variables with normal distribution were analyzed by *t*-test and presented as a mean ± standard deviation. Non-normally distributed continuous variables were analyzed by the rank sum test and presented as median and interquartile range. Categorical variables were analyzed by the Exact McNemar's probability test and expressed as frequency and percentage. Risk regression analysis was used to determine predictive factors of NMM. A $P<0.05$ was considered significant. The missing parameter will be represented as "unknown" and incorporated into the data analysis using a complete case analysis approach.

Results

During the study period, a total of 867 patients diagnosed with NSCLC underwent curative resection. Among them, 470 patients were identified as pN positive, while 397 patients were classified as pN0. Out of the 397 pN0 patients, 42 individuals were excluded from the analysis due to receiving pre-operative treatment aimed at downstaging of the disease. Additionally, 249 patients had unavailable pathological slides, and during the slide review, 8 patients initially classified as pN0 were found to have lymph node metastasis (*Figure 1*). This study included 98 patients with NSCLC, of which 47 were male and 51 were female, with

Table 1 Basic characteristic

Characteristic	Values (N=98)
Age (years)	64.96±9.96
Gender	
Male	47 (47.96)
Female	51 (52.04)
Co-morbidity	
DM	13 (13.27)
Hypertension	39 (39.8)
Dyslipidemia	20 (20.41)
COPD	17 (17.35)
Other	12 (12.25)
Charlson index score	4.57±1.40
Smoking status	
Non-smoker	32 (32.65)
Active smoker	50 (51.02)
Pack-year	23.89±22.71
Passive smoker	12 (12.25)
Unknown	4 (4.08)
Tumor size, cm	
<3	40 (40.82)
3–5	34 (34.69)
5–7	10 (10.20)
>7	14 (14.29)
Mean ± SD	4.19±2.41
Pathologic stage	
Ia	36 (36.73)
Ib	17 (17.35)
IIa	13 (13.27)
IIb	14 (14.29)
IIIa	18 (18.37)

Data are presented as number (percentage) or mean ± standard deviation. DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

Table 2 Tumor characteristics

Characteristic	Values (N=98)
Histology	
Adenocarcinoma	73 (74.49)
Squamous cell carcinoma	21 (21.43)
Other NSCLC	4 (4.08)
Tumor differentiation	
Well differentiation	49 (50.00)
Moderately differentiation	25 (25.51)
Poorly differentiation	14 (14.29)
Unknown	10 (10.20)
Presence of lymphatic invasion	69 (70.41)
Presence of vascular invasion	34 (34.69)
Presence of perineural invasion	5 (5.10)
Presence of visceral pleural invasion	22 (22.45)
Presence of tumor necrosis	24 (24.49)
No. of LN retrieved (node/patient)	
N1	4.62±3.62
N2	13.18±8.87

Data are presented as number (percentage) or mean ± standard deviation. NSCLC, non-small cell lung cancer; LN, lymph node.

a mean age of 65 years. Most patients had a history of smoking and only 32.65% of patients were non-smokers. More than half of the patients had early-stage NSCLC, with 36.73% at stage Ia and 17.35% at stage Ib. Three-fourths of the tumors were adenocarcinoma, while squamous cell carcinoma was found in 21.43% of patients. The total number of lymph nodes in the study was 1,745, including 453 N1 lymph nodes and 1,292 N2 lymph nodes, with a mean number of lymph nodes retrieved per patient of 17.8 nodes. Basic demographic data and tumor characteristics were presented in *Tables 1*,*2*.

The results of the study showed that NMM was detected in a small percentage of previously negative lymph nodes, with 1.11% of N1 nodes and 1.70% of N2 nodes testing positive for NMM. However, overall, 21.43% of patients had NMM to lymph nodes, regardless of the nodal location. Two patients had micrometastasis in both N1 and N2, while two patients only had N1 micrometastasis, and 17 patients only had N2 micrometastasis. Among N1 patients with NMM, lymph node station 10 was the most common site of micrometastasis with four micrometastasis detected. Micrometastasis to lymph node station 11 was found in only one node, and no micrometastasis was observed in lymph node station 12, 13 and 14. Moreover, we found that lymph node station 7 was the most common site of micrometastasis among patients with N2 micrometastasis. There were 15 NMM out of 19 patients

Table 3 Number of patient and % of pathological upstaging

Lymph node station	Conventional H&E stain		Special IHC staining		% of pathological upstaging
	LN negative	LN positive	LN negative	LN positive	
N1	98	0	93	4	4.01
N2	98	0	81	19	19.39
N1 + N2	98	0	78	21	21.43

H&E, hematoxylin and eosin; IHC, immunohistochemical; LN, lymph node.

Table 4 Lymph node micrometastasis by patients

Patient number	Lymph node station	AE1/AE3	p53	BerEp4
1	10	x	x	
	11			x
2	8	x	x	
3	9	x		
4	7	x	x	x
	7	x	x	x
5	7	x	x	x
	10	x		
6	10	x	x	x
7	7	x		
8	7	x	x	x
9	7	x	x	x
10	7	x		x
	10	x		x
11	7			x
	8	x	x	x
12	7	x		
13	8	x	x	
14	7	x	x	x
15	7	x	x	
16	4	x	x	
17	7	x	x	
18	8	x		
	9	x		
19	7	x	x	
20	7	x		
21	7	x		
Total		25	15	12

who had NMM in lymph node station 7. The details of the nodal upstaging and lymph node stations are presented in *Table 3*.

In this study, we utilized three different types of antibodies in order to improve the detection rate of micrometastasis compared to using just one or two types of antibodies. Our findings demonstrated that 21.43% of patients had NMM detected by all three antibodies. Cytokeratin AE1/AE3 proved to be the most sensitive antibody in detecting micrometastasis in lymph nodes, identifying 25 out of 27 positive lymph nodes (*Table 4*). In contrast, p53 and BerEp4 antibodies were only able to detect micrometastasis in 15 and 12 lymph nodes, respectively. Moreover, there was no micrometastasis demonstrated by p53 antibody alone.

In the univariable analysis, several factors were found to be associated with NMM, including tumor size greater than 4 cm, poorly differentiated tumor, and intra-tumoral blood vessel invasion. However, in the multivariable analysis, only tumor size greater than 4 cm remained a statistically significant predictive factor for NMM. The risk ratio was 6.69, with a 95% confidence interval of 2.38–18.85 and a P<0.001 (*Table 5*).

Discussion

Lymph node metastasis is a significant factor affecting the prognosis of patients with resectable NSCLC. The survival and disease-free survival rates decrease rapidly in patients with lymph node metastasis. Nodal micrometastases are small clusters of tumor cells in lymph nodes measuring between 0.2–2 mm in maximum diameter (13). The current practice guideline for NSCLC management categorized NMM as pN1 or pN2 based on their location. However, it is unclear whether patients with NMM have the same prognosis as those with larger nodal metastasis. Currently, H&E staining is the standard method for detecting metastasis in lymph nodes. However, small clusters of

Table 5 Predictive factors of lymph node micro-metastasis

Characteristic	Univariable analysis			Multivariable analysis		
	RR	95% CI	P value	RR	95% CI	P value
Tumor size >4 cm	7.88	2.86–21.68	<0.001	6.69	2.38–18.85	<0.001
Tumor histology						
Adeno CA	1.00	Ref.	–			
Squamous cell CA	0.65	0.21–2.02	0.459			
Other NSCLC	1.14	0.20–6.58	0.883			
Tumor differentiation						
Well differentiation	1.00	Ref.	–			
Moderately differentiation	0.74	0.21–2.53	0.625	0.50	0.18–1.43	0.196
Poorly differentiation	3.06	1.35–6.97	0.008	0.99	0.54–1.84	0.990
Vascular invasion	2.69	1.22–5.93	0.014	1.30	0.69–2.43	0.416
Lymphatic invasion	7.16	1.01–50.81	0.049	3.42	0.50–23.29	0.209
Perineural invasion	0.96	0.16–5.78	0.961			
Presence of necrosis	1.19	0.51–2.76	0.683			
Pleural invasion	1.14	0.46–2.78	0.779			

RR, risk ratio; CI, confidential interval; CA, carcinoma; NSCLC, non-small cell lung cancer.

dysplastic cells can be easily missed among the massive amounts of lymphocytes and histiocytes in the lymph node, leading to false-negative diagnoses of nodal metastasis. IHC staining facilitates the detection of micrometastasis by pathologists. In this study, cytokeratin AE1/AE3, BerEp4, and p53 antibodies were used to detect NMM. The alteration of the p53 tumor suppressor gene is one of the common pathways for neoplasm development (14). In NSCLC, p53 mutation is present in about half of patients (15). Cytokeratin and BerEp4 are markers for epithelial cells expressed in all epithelial tumors, especially in NSCLC. However, they are not specific to malignant cells and are also present in normal epithelial cells. To confirm NMM, H&E slides of all positive IHC lymph nodes were reviewed to identify malignant features.

This study aimed to increase the detection rate of NMM by using three antibodies compared to using fewer antibodies for IHC staining. Previous studies by Marche*vsk*y, used only anti-cytokeratin AE1/AE3 alone, revealed 11 NMM from 463 lymph nodes (2.4%) or 5 nodal upstaging from 33 patients (15.2%) (16). A study from Poland used antibody to cytokeratin AE1/AE3 and BerEp4 in NMM detection. They found 14 instances of nodal upstaging among 148 patients (9.5%) (10). In our study, utilizing three types of antibodies, we detected 27 NMM among a total of 1745 pN0 lymph nodes (1.55%) or 21 instances of nodal upstaging in 98 patients (21.43%). When compared to the prior studies, it was observed that the detection of NMM showed no significant differences. However, a Japanese study by Gu *et al.* using two antibodies (anti-cytokeratin and p53) reported an even higher frequency of nodal upstaging at 44.9% (11). The used of three types of antibodies IHC staining could not ensure a higher rate of NMM detection in pN0 resectable NSCLC patients. Interestingly, the frequency of NMM was higher in patients from eastern regions than in those from western regions, possibly due to race, genetics, or environmental differences.

Out of the 27 NMM-detected lymph nodes, it was observed that anti-cytokeratin antibody alone had a remarkably high detection rate of 25 lymph nodes (92.6%), which was significantly higher than that of p53 and anti BerEp4 antibodies in this study (55.56% and 44.44%, respectively). Similar findings were reported by Gu *et al.*, where anti-cytokeratin alone detected 17 out of 22 NMM-positive patients (77.27%) (11). However, using anti-cytokeratin as a single antibody in NMM detection had a chance of false negative ranging from 8–23%. From

Table 4, it can be inferred that p53 antibody could detect 15 out of 27 NMM lymph nodes (55.56%) and it was found that all p53 antibody-positive lymph nodes had at least one other type of antibody-positive. Gu *et al.* stated that p53 staining can detected only 10 of 22 positive NMM (45.45%) (11). Moreover, p53 IHC staining was exclusively used in cases where the primary tumor was p53 positive, indicating that it was not an effective antibody for NMM detection. Although anti BerEp4 had a lower detection rate compared to other antibodies (45.45%), it had additional value in NMM detection when used in combination with anti-cytokeratin antibody. Therefore, it is recommended to use anti-cytokeratin antibody in combination with anti BerEp4 antibody for NMM detection in pN0 resectable NSCLC.

Regarding predictive factors for NMM, our study found that in univariable analysis, tumor size greater than 4 cm, poorly differentiated tumors, and intratumoral vascular invasion were associated with a higher rate of NMM. However, in multivariable analysis, only tumor size greater than 4 centimeters remained statistically significant for NMM (RR: 6.69, 95% CI: 2.38–18.85). A study from Replublic of Korea by Moon *et al.* reported that patients with elevated serum CEA levels, tumor invasive component size, visceral pleural invasion and lymphatic invasion had a higher chance of NMM (17). The issue of whether the size of the primary tumor is a factor that predicts NMM remains debated. Rena and colleague found that there was no difference in the frequency of NMM between T1 and T2 tumor (18). In our study, we found that tumor size more than 4 cm was a predictive factor for NMM. According to NCCN guideline, tumor size more than 4 cm is one of the risk factors for tumor recurrent and they recommend that these patients receive adjuvant chemotherapy (19). Our finding may explain why tumor size more than 4 cm had higher chance of recurrence.

Skip metastasis is a phenomenon in which lymphatic drainage bypasses the N1 lymph nodes and directly drains to mediastinal lymph nodes. Macroscopic skip metastasis has been reported to occur in 18–38% of cases (20-23), while the frequency of microscopic skip metastasis is even higher, ranging from 28–100% (24-26). In our study, we found that the frequency of skip NMM was 17 of 21 patient (80.95%). The presence of high frequency of skip NMM raises question about the value of sentinel lymph node biopsy in NSCLC, as presence of skip NMM suggests that there may be no true sentinel lymph node in these cases. We recommend systematic lymph node dissection in combination with IHC study to improve accuracy of staging in resectable NSCLC.

There are some limitations in this study. Firstly, the retrospective nature of the study introduced inherent limitations in term of data collection and potential bias. Secondly, there is a potential for bias due to the involvement of a single surgical team, which could result in patients being selected in a non-random manner, thereby introducing patient selection bias.

Conclusions

In conclusion, the addition of IHC staining to standard H&E staining improves the detection of NMM, with the combination of anti-cytokeratin and anti BerEp4 antibodies showing the highest detection rate. Our study also found that tumor size greater than 4 cm was a significant predictive factor for NMM. However, further investigation is needed to determine the true impact of NMM detection on recurrence and survival in resectable NSCLC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1240/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1240/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1240/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1240/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the joint institutional research ethics committees of the Chiang Mai University (study code: SUR-2562-06766) and individual consent for this retrospective analysis was waived.

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