Prognostic Value of Intraoperative Pleural Lavage Cytology as an Independent Prognostic Factor in Non-Small Cell Lung Cancer: A Retrospective Study

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Abstract

Background

The aim of this study is to demonstrate that intraoperative PLC has a role in predicting clinical outcomes in NSCLC patients.

Methods

Intraoperative PLC was performed in NSCLC patients who had no pleural effusion before the operation. PLC was performed three times for each patient. PLC1 was performed after the thoracotomy; PLC2 was performed immediately after complete operation; and PLC3 was performed after complete operation and washed the pleural cavity with 5,000 ml of normal saline solution. Clinical records of 178 patients in Ramathibodi Hospital from 2012 to 2016 were retrospectively reviewed and analysed for the relevance of intraoperative PLC and clinical outcomes.

Results

178 patients were included in this study; 67 patients were male (37.6%). Metastatic tumour from primary lung cancer occurred in 56 patients (31.4%). Positive intraoperative PLC was significantly associated with higher metastatic rate ($p < 0.05$). Survival rate in the positive intraoperative PLC group was significantly worse than that in the negative PLC group ($p < 0.05$).

Conclusions

This study shows positive intraoperative PLC was statistically significant for increasing metastatic rate and decreasing survival rate in NSCLC patients. Intraoperative PLC could provide important information for the prediction of disease progression and treatment planning.

Background

Lung cancer is the third most common cancer in Thailand[1-3]. Amongst them, NSCLC is the most common type, contributing 80-85 %. The current diagnosis and staging system for NSCLC is based on the TNM system, which is defined by using tumour size, lymph node metastasis, and distant metastasis. The TNM staging system is efficiently used for determining disease prognosis and treatment options. The overall five-year survival rate for NSCLC is 24%. However, the survival rate depends on several factors, especially the stages of disease. For patients with stage 1A disease, the overall five-year survival rate is more than 90%, whereas it is less than 10% for stage 4 patients. A different stage leads to a different treatment. In the early stage NSCLC, upfront surgery is the treatment of choice while chemoradiation is preferred in metastatic patients. In NSCLC, pleural effusion, especially malignant pleural effusion, demonstrates an advanced stage of NSCLC.

Pleural effusion with hemorrhagic or serosanguinous appearance is more likely to be malignant. In biochemical analysis, malignant pleural effusion is usually exudate. The simplest method to diagnose malignant pleural effusion is the presence of malignant cells from pleural fluid cytology. Another method is to demonstrate tumour cells in the pleural tissues which can be obtained from pleural biopsy. According to the TNM staging system for NSCLC, patients with malignant effusion are categorised as M1a or stage 4 disease [4]. However, pleural effusion

is only present in 7-23% of lung cancer patients and malignant pleural effusion is found in only 20% of patients with an advanced stage of disease [5, 6]. Several studies show that cancer cells can be detected in the thoracic cavity from pleural lavage, even in the absence of pleural effusion [7, 8].

IPL is the procedure done by using physiologic saline solution irrigate in the thoracic cavity over the lung surface. In our study, we performed 3 IPLs for each patient and sent specimens for cytologic analysis. Interestingly, IPL cytology has been reported to be associated with clinical outcomes in many studies [9-12]. Nevertheless, IPL cytology is not included in current methods for diagnosis and prognosis prediction [13]. We demonstrated here to determine whether intraoperative PLC can reveal micro metastasis and assess the prognostic significance in clinical outcomes.

Patients And Methods

Patients

This retrospective study was approved by the Ethics Committee of the Institute (MURA2017/695; ID 10-60-19) and compliance with Helsinki declaration. The need of informed consent was waived by ethical committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand. No identifying information was recorded by research team. We included all patients with NSCLC who underwent lung surgery and intraoperative pleural lavage in Ramathibodi Hospital from January 2012 to December 2016. Patients who had preoperative pleural effusion and patients whose data had been lost were excluded from this study. The final study sample consisted of 178 patients.

Procedure

We performed intraoperative PLC three times for each patient. The 1st PLC (PLC 1) was performed after the thoracotomy. The 2nd PLC (PLC 2) was performed after complete the operation and the 3rd PLC (PLC 3) was performed after complete the operation and carefully washed the pleural cavity with 5,000 ml of normal saline solution. 500 ml of pleural lavage fluid for each specimen was collected and sent for cytologic examination. The cytologic report of malignant cells or atypical cells was considered to be positive. The cytologic result came back within 2 weeks after the operations. PLC technique and surgical procedure were standardised in all patients and a single-surgeon surgeries were performed throughout the study. Pathological staging was performed by using the International Staging System for lung cancer[13].

Statistical analysis

Continuous data in this study were reported as mean with SD or median with IQR. The difference between mean or media was conducted using the independent t-test or the Mann-Whitney U-test. Categorical variables were presented and analysed by chi-squared test or Fisher's exact test. The survival and recurrent rate were analysed by Kaplan-Meier method. The differences between the survival curves were assessed by using the log-rank test. Statistical analysis was performed in STATA version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). P values of < 0.05 were considered statistical significance in all analyses.

Results

Patient characteristics

From 178 patients in total, 67 patients were male (37.6%). Intraoperative PLC was positive in 20 cases (11.23%). Patient baseline characteristics were not different between the recurrent/metastatic group and non-recurrent group. However, visceral pleural invasion, vascular invasion, lymphatic invasion and post-operative staging were higher in recurrent/metastatic group (Table 1). Similar results were reported when we analysed patient baseline characteristics in death and non-death groups (Table 2).

Pleural lavage cytology is associated with mortality

Patients with positive intraoperative PLC had a significantly higher recurrent/metastatic rate (80%) compared to those in the negative PLC group (25%) ($p < 0.001$; Fig.1). The prognosis of patients with positive intraoperative PLC was worse than that of patients with negative PLC, with 60% and 12% of mortality rate respectively ($p < 0.001$; Fig.2). The median follow-up time was 53 months. (IQR: 33-66 months) We also separately analysed the recurrent/metastatic rate and survival based on the results of PLC. The patient with either PLC 1, 2 or 3 positive was significantly associated with the increasing recurrent rate and the decreasing survival rate, compared to those in the negative PLC group ($p < 0.01$). Patients with PLC 1 positive had the worst prognosis (Fig.3). The association between PLC status and patient baseline characteristics and clinicopathological characteristics were shown in Table 3. Positive intraoperative pleural lavage cytology was significantly associated with visceral pleural invasion ($p=0.018$), lymphatic invasion ($p=0.043$), and pathological stage ($p=0.003$).

In our sub-group analysis, we analysed the association between intraoperative pleural lavage cytologic results and clinical outcomes for each pathological stage. We found that in pathological stage 1A and 1B, patients with positive PLC had significantly higher recurrent/metastatic rate compared to those with negative PLC ($p < 0.05$; Table 4). In addition, patients in pathological stage 1B with positive PLC had both higher recurrent rate and worse survival rate compared to patients with negative PLC ($p < 0.05$; Table 5) However, the recurrent/metastatic rate and survival rate were not significantly different between two patient groups in other pathological stages.

Discussion

Back in 1958, the first report about cytological examination for cancer cells in pleural cavities from pleural lavage at the time of thoracotomy was published [14]. Later, Kondo *et al* [15] and Okumura *et al* [16] analysed the clinical significance of intraoperative pleural lavage cytology and reported its prognostic value. Pleural lavage cytology has been proved to be associated with the degree of pleural extension, microscopic pleural dissemination, pathologic stage, and the presence of lymphatic or vascular invasion in these studies. In 2014, Hokka *et al* [17] published a report showing a prognostic value of pleural lavage cytology in NSCLC patients with stage 1 disease. In our study, we compiled a five-year collection of data in Ramathibodi Hospital with the aim to provide the information about the clinical significance of intraoperative PLC status in NSCLC patients. The yield of positive intraoperative PLC was 11.2%. This percentage is comparable with other previous studies [16, 18]. For primary outcomes, we compared the recurrent/metastatic and survival rate between positive and negative PLC groups. The results suggested that a positive PLC status is significantly associated with poor clinical outcomes: the increasing recurrent rate and the decreasing survival rate. Apart from the recurrent/metastatic and survival rate, PLC status is significantly associated with visceral pleural invasion, vascular invasion and lymphatic invasion. Patients with positive PLC also seemed to have a higher pathological staging. Moreover, from our sub-group analysis, NSCLC patients with pathological stage 1A and 1B, which current recommendation suggests

surveillance follow up without any adjuvant therapy [19], were found to have a statistically significant association between positive PLC status and their recurrent and survival rate. Since intraoperative pleural lavage is a non-invasive procedure and requires only simple equipment and a cytological examination, it can be easily added on to the usual operations. Besides, we recommend intraoperative pleural lavage cytologic status to be considered as one of the prognostic factors for further treatment planning and surveillance strategy, especially in NSCLC patients with pathological stage 1A and 1B.

Conclusion

The PLC status was positive in 11.23% of NSCLC patients who underwent lungresection surgery. The positive finding significantly associated with higher rates of visceral pleural invasion, vascular invasion, lymphatic invasion, and a higher pathological staging. More importantly, a positive PLC status was significantly associated with higher recurrent/metastatic rate and worse survival rate, particularly for patients with early-stage diseases.

Abbreviations

IPL: Intraoperative pleural lavage

IQR: Interquartile range

NSCLC: Non-small cell lung cancer

PLC: Pleural lavage cytology

SD: Standard deviation

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Faculty of Medicine Ramathibodi Hospital, Mahidol University and compliance with Helsinki declaration. (Certificate no. MURA2017/695; ID 10-60-19). The need of informed consent was waived by ethical committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand. Study protocol was in compliance with Helsinki declaration.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Author contribution

All authors (SE, PP and MN) have read and approved the manuscript. SE and MN conceptualized the study. SE conducted all of the data collection. SE and PP analysed the data. SE and MN wrote the first draft. SE and PP conducted reviewing and editing until the final version. MN was the supervisor of this study.

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Tables

Table 1. Patient baseline characteristic compare between non-recurrent and recurrent group.

Data	Total	Non-recurrent	Recurrent	p-value	Univariate		
	(n=178)	(n=122)	(n=56)		HR(95%CI)	p-value	
Gender							
Male	67(37.64)	42(34.43)	25(44.64)	0.191	1		
female	111(62.36)	80(65.57)	31(55.36)		0.676(0.39-1.14)	0.146	
Age(year), median(IQR)	65(59, 72)	65(61, 72)	63(56.5, 72.5)	0.279	0.990(0.96-1.02)	0.458	
BMI, mean±SD	24.13+3.81	24.25+3.53	23.87+4.39	0.536	0.981(0.91-1.05)	0.618	
DM, n(%)	32(17.98)	21(17.21)	11(19.64)	0.695	1.126(0.58-2.17)	0.724	
HT, n(%)	92(51.69)	67(54.92)	25(44.64)	0.203	0.701(0.41-1.18)	0.187	
DLP, n(%)	69(38.76)	18(32.14)	51(41.80)	0.219	0.673(0.38-1.18)	0.168	
Other, n(%)	68(38.20)	48(39.34)	20(35.71)	0.643			
History of lung disease, n(%)	34(19.10)	23(18.85)	11(19.64)	0.901	1.060(0.54-2.05)	0.862	
Never smoke, n(%)	127(71.35)	90(73.77)	37(66.07)	0.291	0.722(0.41-1.25)	0.25	
Current smoking, n(%)	15(8.43)	11(9.02)	4(7.14)	0.676	0.801(0.28-2.20)	0.671	
Incision, n(%) n=174							
Thoracotomy	100(57.47)	60(50.42)	40(72.73)	0.006	1		
VATS	74(42.53)	59(49.58)	15(27.27)		0.467(0.25-0.84)	0.012	
LOH(day), median(IQR)	6.50(5, 8)	6(5, 8)	7(6, 9)	0.173			
Vascular invasion, n(%) n=177							
Negative	138(77.97)	103(85.12)	35(62.50)	0	1		
Positive	39(22.03)	18(14.88)	21(37.50)		3.013(1.74-5.19)	0	
Visceral pleural invasion, n(%) n=177							
Negative	135(76.27)	102(84.30)	33(58.93)	0	1		
Positive	42(23.73)	19(15.70)	23(41.07)		2.958(1.73-5.05)	0	

Lymphatic invasion, n(%) n=176							
Negative	151(85.80)	114(95.00)	37(66.07)	0	1		
Positive	25(14.20)	6(5.00)	19(33.93)		5.446(3.10-9.56)	0	
Cytology-Specimen1, n(%)							
Negative	167(93.82)	122(100)	45(80.36)	0	1		
Positive	11(6.18)	0	11(19.64)		7.556(3.85-14.82)	0	
Cytology-Specimen2, n(%)							
Negative	165(92.70)	119(97.54)	46(82.14)	0	1		
Positive	13(7.30)	3(2.46)	10(17.86)		4.649(2.31-9.34)	0	
Cytology-Specimen3, n(%)							
Negative	167(93.82)	119(97.54)	48(85.71)	0.005	1		
Positive	11(6.18)	3(2.46)	8(14.29)		3.811(1.78-8.14)	0.001	
Cytology-Specimen all, n(%)							
Negative	158(88.76)	118(96.72)	40(71.43)	0	1		
positive	20(11.24)	4(3.28)	16(28.57)		5.545(3.05-10.07)	0	
Tumor size(cm), median(IQR)	2.6(1.8, 3.6)	2.3(1.7, 3.2)	3.5(2.5, 5.0)	0	1.243(1.09-1.41)	0.001	
Pathological Staging (post-op), n(%)							
1A	91(51.70)	79(65.29)	12(21.82)	0	1		
1B	42(23.86)	28(23.14)	14(25.45)		2.731(1.26-5.91)	0.011	
2A	16(9.09)	5(4.13)	11(20.00)		8.969(3.94-20.40)	0	
2B	12(6.82)	4(3.31)	8(14.55)		7.280(2.95-17.95)	0	
3A	12(6.82)	3(2.48)	9(16.36)		11.22(4.70-26.77)	0	
Death, n(%)	32(17.98)	3(2.46)	29(51.79)	0	10.365(6.05-17.75)	0	

Table 2. Patient baseline characteristic compare between non-death and death group.

Data	Total	Non-death	Death	p-value	Univariate		
	(n=178)	(n=152)	(n=32)		HR(95%CI)	p-value	
Gender							
Male	67(37.64)	51(34.93)	16(50.00)	0.111	1		
female	111(62.36)	95(65.07)	16(50.00)		0.565(0.28-1.13)	0.107	
Age(year), median(IQR)	65(59, 72)	65(60, 72)	64.5(54, 73.5)	0.551	0.991(0.95-1.02)	0.622	
BMI, mean±SD	24.13+3.81	24.09+3.56	24.32+4.86	0.755	1.011(0.91-1.12)	0.823	
DM, n(%)	32(17.98)	28(19.18)	4(12.50)	0.373	0.698(0.24-1.99)	0.502	
HT, n(%)	92(51.69)	79(54.11)	13(40.63)	0.167	0.601(0.29-1.21)	0.158	
DLP, n(%)	69(38.76)	59(40.41)	10(31.25)	0.335	0.656(0.31-1.38)	0.27	
Other, n(%)	68(38.20)	52(35.62)	16(50.00)	0.129			
History of lung disease, n(%)	34(19.10)	30(20.55)	4(12.50)	0.294	0.674(0.23-1.92)	0.462	
Never smoke , n(%)	127(71.35)	106(72.60)	21(65.63)	0.429	0.716(0.34-1.48)	0.371	
Current smoking, n(%)	15(8.43)	12(8.33)	3(9.68)	0.732	1.145(0.34-3.77)	0.823	
Incision, n(%) n=174							
Thoracotomy	100(57.47)	79(54.86)	21(70.00)	0.127	1		
VATS	74(42.53)	65(45.14)	9(30.00)		0.682(0.31-1.49)	0.339	
LOH(day), median(IQR)	6.50(5, 8)	6(5, 8)	7.5(6, 9)	0.046			
Vascular invasion, n(%) n=177							
Negative	138(77.97)	120(82.76)	18(56.25)	0.001	1		
positive	39(22.03)	25(17.24)	14(43.75)		4.187(2.06-8.48)	0	
Visceral pleural invasion, n(%) n=177							
Negative	135(76.27)	118(81.38)	17(53.13)	0.001	1		
positive	42(23.73)	27(18.62)	15(46.88)		4.009(1.99-8.07)	0	
Lymphatic invasion, n(%)							

n=176							
Negative	151(85.80)	134(93.06)	17(53.13)	0	1		
positive	25(14.20)	10(6.94)	15(46.88)		8.572(4.25-17.27)	0	
Cytology-Specimen 1, n(%)							
Negative	167(93.82)	143(97.95)	24(75.00)	0	1		
positive	11(6.18)	3(2.05)	8(25.00)		6.897(3.08-15.43)	0	
Cytology-Specimen 2, n(%)							
Negative	165(92.70)	141(96.58)	24(75.00)	0	1		
Positive	13(7.30)	5(3.42)	8(25.00)		12.29(5.05-29.87)	0	
Cytology-Specimen 3, n(%)							
Negative	167(93.82)	141(96.58)	26(81.25)	0.005	1		
Positive	11(6.18)	5(3.42)	6(18.75)		9.219(3.51-24.21)	0	
Cytology-Specimen all, n(%)							
Negative	158(88.76)	138(94.52)	20(62.50)	0	1		
positive	20(11.24)	8(5.48)	12(37.50)		8.903(4.25-18.64)	0	
Tumor size(cm), median(IQR)	2.6(1.8, 3.6)	2.5(1.8, 3.5)	3.0(2.5, 5.0)	0.01	1.153(0.94-1.40)	0.152	
Pathological Staging(post-op), n(%)							
1A	91(51.70)	87(60.42)	4(12.50)	0	1		
1B	42(23.86)	36(25.00)	6(18.75)		3.415(0.96-12.11)	0.057	
2A	16(9.09)	7(4.86)	9(28.13)		15.576(4.79-50.61)	0	
2B	12(6.82)	7(4.86)	5(15.63)		15.67(4.11-59.79)	0	
3A	12(6.82)	5(3.47)	7(21.88)		28.14(8.10-97.81)	0	
Complication, n(%)							
AF, hepatitis, bronchopleural fistula	1	0	1				
PE	1	0	1				

air-leak	3	2	1	
stroke	1	1	0	
Recurrence, n(%)	56(31.46)	27(18.49)	29(90.63)	0

Table 3. Associations between pleural lavage cytology status and patient's clinicopathological characteristics.

Data	total	Cyto-Neg	Cyto-Pos	p-value
	(n=178)	(n=122)	(n=56)	
Gender				
Male	67(37.64)	59(37.34)	8(40.00)	0.817
female	111(62.36)	99(62.66)	12(60.00)	
Age(year), median(IQR)	65(59, 72)	65(59, 72)	66(57, 74.5)	0.646
BMI, mean $\pm$ SD	24.13 $\pm$ 3.81	23.97 $\pm$ 3.56	25.39 $\pm$ 5.36	0.26
DM, n(%)	32(17.98)	27(17.09)	5(25.00)	0.385
HT, n(%)	92(51.69)	80(50.63)	12(60.00)	0.43
DLP, n(%)	69(38.76)	61(38.61)	8(40.00)	0.904
Other, n(%)	68(38.20)	59(37.34)	9(45.00)	0.507
History of lung disease, n(%)	34(19.10)	31(19.62)	3(15.00)	0.769
Never smoke, n(%)	127(71.35)	109(68.99)	18(90.00)	0.065
Current smoking, n(%)	15(8.43)	15(9.62)	0	0.377
Incision, n(%) n=174				
Thoracotomy	100(57.47)	88(57.14)	12(60.00)	0.808
VATS	74(42.53)	66(42.86)	8(40.00)	
LOH(day), median(IQR)	6.50(5, 8)	7(5, 8)	6(5, 9)	0.899
Vascular invasion, n(%) n=177				
Negative	138(77.97)	125(79.62)	13(65.00)	0.137
Positive	39(22.03)	32(20.38)	7(35.00)	
Visceral pleura invasion, n(%) n=177				
Negative	135(76.27)	124(78.98)	11(55.00)	0.018
Positive	42(23.73)	33(21.02)	9(45.00)	
Lymphatic invasion, n(%) n=176				
Negative	151(85.80)	137(87.82)	14(70.00)	0.043
Positive	25(14.20)	19(12.18)	6(30.00)	
Pathological Staging(post-op), n(%)				
1A	91(51.70)	85(54.49)	6(30.00)	0.003
1B	42(23.86)	37(23.72)	5(25.00)	
2A	16(9.09)	16(10.26)	0	

2B	12(6.82)	7(4.49)	5(25.00)	
3A	12(6.82)	8(5.13)	4(20.00)	
Death, n(%)	32(17.98)	20(12.66)	12(60.00)	0
Recurrence, n(%)	56(31.46)	40(25.32)	16(80.00)	0

Table 4 Recurrent/metastatic in patients with pathological stage 1A and 1B comparing between positive and negative PLC result. The P value was determined using Fisher' exact test

Pathological stage	Total	Non-recurrent	Recurrent/metastasis	p-value
1A Cytology positive	6	3	3	0.28
Cytology negative	85	76	9	
1B Cytology positive	5	0	5	0.002
Cytology negative	37	28	9	

Table 5 Overall Survival in patients with pathological stage 1A and 1B comparing between positive and negative PLC result. The P value was determined using Fisher' exact test

Pathological stage	Total	Alive	Death	p-value
1A Cytology positive	6	5	1	0.242
Cytology negative	85	82	3	
1B Cytology positive	5	2	3	0.015
Cytology negative	37	34	3	

Figures

Figure 1

Kaplan-Meier plot of recurrent/metastatic rate in 178 patients with NSCLC and its association with the PLC result. The P value was determined using the log-rank test.

Figure 2

Kaplan-Meier plot of overall survival in 178 patients with NSCLC and its association with the PLC result. The P value was determined using the log-rank test.

Figure 3

Kaplan-Meier plot of recurrent/metastatic rate in 178 patients with NSCLC and its association with the PLC result divided by type of specimen. The P value was determined using the log-rank test.