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Impact of adjuvant chemotherapy on prognosis of patients with stage IB non-small cell lung cancer with visceral pleural invasion

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Background

- The usefulness of adjuvant chemotherapy in patients with stage Ib NSCLC continues to be debated.

- Recently, even in Korea's national insurance standards, there is a movement not to allow adjuvant chemotherapy for stage Ib patients.

- However, adjuvant chemotherapy for stage Ib NSCLC patients should be evaluated according to the patient's risk factors.
  - Lung neuroendocrine tumors, vascular invasion, visceral pleural involvement, tumors > 4cm, wedge resection, unknown lymph node status (Nx), micropapillary type, lymphatic invasion

Aim

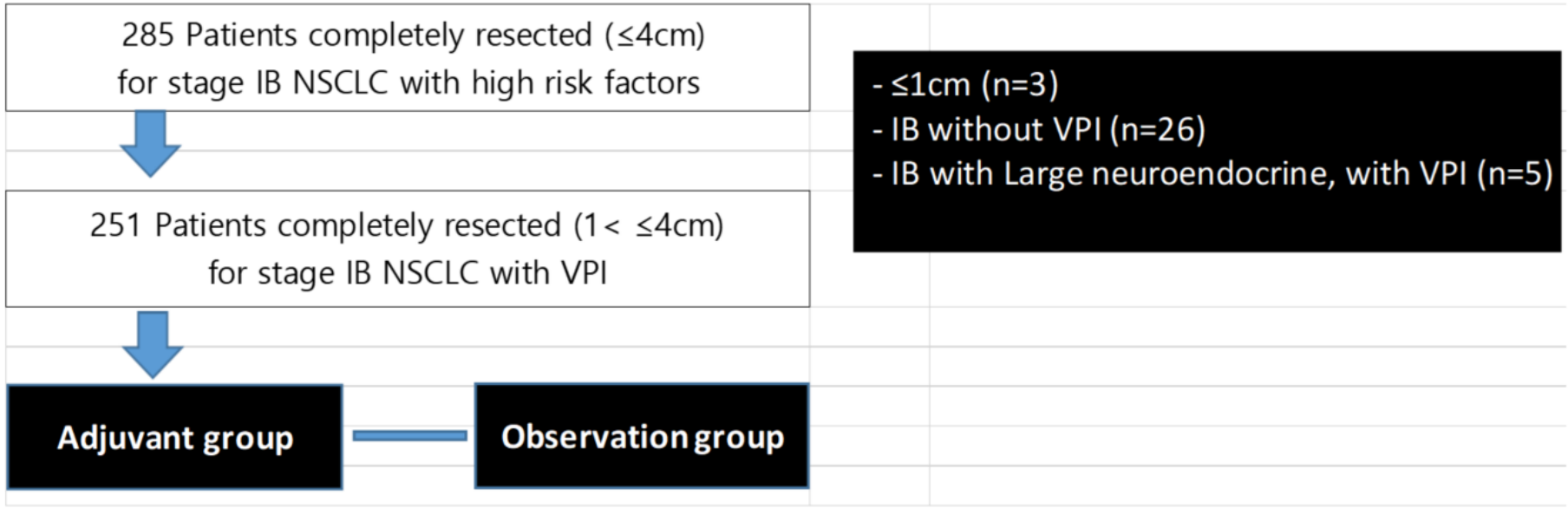
- In this regard, we previously evaluated the usefulness of adjuvant chemotherapy in patients less than 4 cm in diameter.
  - ***Korean J Intern Med. 2022 Jan;37(1):127-136. doi: 10.3904/kjim.2020.011.***
- At this time, we intend to further analyze only those patients with visceral pleural invasion (VPI).

This study aims to explore the prognostic significance of adjuvant chemotherapy (ACT) in stage IB (1 to <4cm) non–small cell lung cancer (NSCLC) with visceral pleural invasion (VPI).

Methods

Inclusion criteria	Exclusion criteria
1. Histologically proven primary NSCLC	1. Histologically proven primary NSCLC
(stage IB, TNM 8th edition)	- Tumor size 0< ≤ 1cm
- Tumor size 1< ≤ 4cm	2. IB with other risk factors, without VPI
- Pathologically negative LN (N0)	- Lung NE tumors, vascular invasion
2. Complete resection (R0 resection)	- Lymphatic invasion, Micro-papillary type
3. Age 18-85 years (44 to 83)	3. Lung NE tumors (VPI positive)
4. High risk factor	
- Visceral pleural involvement	
5. No patients received adjuvant radiotherapy	

Methods (Flowchart of the study population)



- The relationship between adjuvant chemotherapy and overall survival (OS) or recurrence-free survival (RFS) was analyzed using the Kaplan–Meier method and Cox proportional hazards model.

Results (Baseline characteristics)

	Adjuvant group (n=122)	Control group (n=129)	P-value
Age			**<0.0001**
Mean±SD	63.18 ± 8.34	68.56 ± 9.00	
Median, IQR	64 (58, 69)	71 (63, 75)	
Sex			0.6723
Male	60 (49.18)	60 (46.51)	
Female	62 (50.82)	69 (53.49)	
Smoking Hx			0.8445
Ever-smoker	43 (35.25)	47 (36.43)	
Non-smoker	79 (64.75)	82 (63.57)	
Pulmonary function test			
FEV1/FVC	0.76 ± 0.12	0.77 ± 0.11	0.8002
FEV1/FVC <70%	30 (24.59)	24 (18.6)	0.2487
Histology			0.8209
Adenocarcinoma	108 (88.52)	113 (87.6)	
Non-adenocarcinoma	14 (11.48)	16 (12.4)	
Tumor diameter (1)			0.9334
Mean, SD	2.42 ± 0.73	2.39 ± 0.74	

	Adjuvant group (n=122)	Control group (n=129)	P-value
Tumor diameter (2)			0.8352
1< ≤2	40 (32.79)	39 (30.23)	
2< ≤3	55 (45.08)	63 (48.84)	
3< ≤4	27 (22.13)	27 (20.93)	
Mutation analysis			
EGFR mutation*			0.8138
L858R	26 (29.21)	21 (30.88)	
Del19	19 (21.35)	14 (20.59)	
Other	4 (4.49)	1 (1.47)	
ALK rearrangement[#]	8 (10.67)	9 (16.98)	0.2998
Adjuvant chemotherapy regimen			
Paclitaxel + platinum	75 (61.48)		
Vinorelbine + platinum	43 (35.25)		
Pemetrexed + platinum	4 (3.28)		
High-risk factors			
Micropapillary pattern	34(28.81)	33(24.81)	0.2055
Lymphovascular invasion	38 (31.15)	24 (18.6)	0.0213
Recurrence	24 (19.67)	34 (26.36)	0.2092
Mortality	6 (4.92)	19 (14.73)	0.0095

Results (Risk factors for recurrence-free survival of patients with IB NSCLC with visceral pleural invasion)

	Univariate analysis of RFS		Multivariate analysis of RFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.017 (0.987, 1.047)	0.2707		
Sex				
Male (vs. female)	1.258 (0.752, 2.106)	0.3821		
Smoking Hx				
Ever smoker (vs. never)	1.19 (0.7, 2.023)	0.5201		
Pulmonary function test				
FEV1/FVC <70% (vs. >70%)	0.852 (0.442, 1.643)	0.6334		
Histology				
Adenocarcinoma (vs. non-adeno)	0.741 (0.352, 1.564)	0.4321		
Tumor diameter				
1< ≤2	Reference			
2< ≤3	1.339 (0.718, 2.497)	0.3587		
3< ≤4	1.412 (0.681, 2.924)	0.3536		
Micropapillary pattern				
Yes (vs. no)	1.948 (1.15, 3.297)	0.0131	1.969 (1.159, 3.344)	0.0122
Lymphovascular invasion(LVI)				
Yes (vs. no)	2.064 (1.207, 3.527)	0.0081	2.207 (1.279, 3.81)	0.0045
Adjuvant chemotherapy				
Yes (vs. no)	0.687 (0.407, 1.158)	0.159	0.568 (0.334, 0.968)	0.0375

Results (Risk factors for overall survival of patients with IB NSCLC with visceral pleural invasion)

	Univariate analysis of OS		Multivariate analysis of OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.065 (1.013, 1.12)	**0.0131**	1.036 (0.988, 1.087)	0.1442
Sex				
Male (vs. female)	2.528 (1.091, 5.859)	**0.0305**	0.784 (0.206, 2.988)	0.7216
Smoking Hx				
Ever smoker (vs. never)	3.626 (1.602, 8.207)	**0.002**	5.143 (1.354, 19.535)	**0.0162**
Pulmonary function test				
FEV1/FVC <70% (vs. >70%)	1.218 (0.487, 3.051)	0.6733		
Histology				
Adenocarcinoma (vs. non-adeno)	0.478 (0.179, 1.273)	**0.1394**	1.501 (0.481, 4.689)	0.4846
Tumor diameter				
1< ≤2	Reference			
2< ≤3	1.895 (0.682, 5.26)	0.2201		
3< ≤4	1.772 (0.541, 5.807)	0.3446		
Micropapillary pattern				
Yes (vs. no)	0.673 (0.253, 1.795)	0.4292		
Lymphovascular invasion(LVI)				
Yes (vs. no)	4.625 (2.098, 10.198)	**0.0001**	6.126 (2.631, 14.264)	**<.0001**
Adjuvant chemotherapy				
Yes (vs. no)	0.318 (0.127, 0.797)	**0.0145**	0.23 (0.085, 0.618)	**0.0036**

Results

- Of the 251 patients, 122 (48.6%) underwent ACT after surgical resection and 129 (51.4%) were placed under observation.
- Multivariate Cox analysis indicated that ACT was independent factor for improving RFS (HR, 0.568, 95% CI, 0.334-0.968, P = 0.0375).
- The presence of lymphovascular invasion and micropapillary histologic pattern were associated with a higher risk of recurrence (HR, 2.207, 95% CI, 1.279-3.810, P = 0.0045; HR, 1.969; 95% CI, 1.159-3.344, P = 0.0122).
- On multivariable Cox analysis for OS, ACT was associated with significantly longer 5-year OS (HR, 0.230, 95% CI 0.085-0.618, P = 0.0036).
- However, different tumor sizes (1 to <2, 2 to <3 and 3 to <4 cm) were not an independent prognostic factors in IB NSCLC with VPI.

Conclusions

- Our study suggested that ACT might be an appropriate option for stage IB NSCLC patients (1 to <4cm) with VPI.