Original Article

Efficacy of adjuvant chemotherapy for completely resected stage IB non-small cell lung cancer: a retrospective study

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Contributions: (I) Conception and design: MK Byun; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: HJ Park; (V) Data analysis and interpretation: HJ Park, MK Byun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Lung cancer is being increasingly detected in the early stages, highlighting the importance of lung cancer screening. However, there is no consensus on the post-operative management of stage IB non-small cell lung cancer (NSCLC). Therefore, this study aimed to identify the predictive factors for prognosis of stage IB NSCLC and determine the efficacy of adjuvant chemotherapy on recurrence and survival.

Methods: We enrolled 89 patients with stage IB NSCLC who underwent complete resection surgery at Gangnam Severance Hospital from Jan 2008 to Dec 2014. As per the National Comprehensive Cancer Network guidelines, patients were considered to be at high risk when they showed poorly differentiated tumors, lymphovascular invasion, tumor size >4 cm, and visceral pleural invasion (VPI).

Results: Among the 89 patients, 27 underwent adjuvant chemotherapy. Young patients or patients with squamous cell lung cancer received adjuvant chemotherapy frequently. Adjuvant chemotherapy was not a significant factor for disease-free survival and overall survival. Adjuvant chemotherapy did not show a significant protective effect for survival, even for high-risk patients. However, VPI was a significant risk factor for disease-free survival [hazard ratio (HR): 7.051; 95% confidence interval (CI): 1.570–31.659; P=0.011] and overall survival (HR: 8.289; 95% CI: 1.036–66.307; P=0.046), even after adjustment for various factors.

Conclusions: Adjuvant chemotherapy does not affect the prognosis of stage IB NSCLC, even in high-risk patients. Additionally, VPI is a strong prognostic factor of stage IB NSCLC.

Keywords: Lung cancer; early stage; adjuvant chemotherapy

Submitted Nov 23, 2017. Accepted for publication Mar 16, 2018.
doi: 10.21037/jtd.2018.03.184
View this article at: http://dx.doi.org/10.21037/jtd.2018.03.184

Introduction

Lung cancer is the most-common cause of loss of productivity and life, as it leads to premature cancer-related mortality (1-3). Furthermore, most cases of lung cancer are detected at an old age, resulting in poor prognosis (4). Early detection may allow treatment at early stages and improve the prognosis of lung cancer. Although some randomized clinical trials showed unsuccessful results of low-dose computed tomography for lung-cancer screening (5), recent studies have revealed that it can detect lung cancer early and thereby reduce mortality (6,7). Moreover, computer-aided detection systems have reduced the errors and false-negative rates, improved detection rate, and diagnosed lung cancer

more efficiently (8,9). Therefore, early detection of lung cancer can be frequently conducted, allowing management of early stage lung cancer. However, thus far, there is no consensus on the post-operative management of stage IB non-small cell lung cancer (NSCLC).

On the basis of the results of a previous meta-analysis (10), an international trial was conducted to determine the effects of adjuvant chemotherapy in lung cancer. The trial showed that cisplatin-based adjuvant chemotherapy improves survival of NSCLC in patients who underwent complete resection surgery (11). Following this trial, several studies have been conducted on stage IB NSCLC: some reported positive effects of adjuvant chemotherapy (12,13), whereas others reported negative effects (11,14,15). Strauss *et al.* showed that adjuvant chemotherapy had a positive effect on patients with stage IB tumors measuring >4 cm (16). In addition, the recent National Comprehensive Cancer Network (NCCN) guidelines stated that adjuvant chemotherapy can be used for patients with stage IB NSCLC having high-risk factors such as poorly differentiated tumor, vascular invasion, wedge resection, tumor size >4 cm, visceral pleural invasion, and incomplete lymph node (LN) sampling (17). However, the evidence to support this guideline is insufficient.

Therefore, this study aimed to identify the predictive factors for prognosis of stage IB NSCLC and to determine the efficacy of adjuvant chemotherapy on recurrence and survival in patients with stage IB NSCLC, especially in high-risk patients.

Methods

Study population

We analyzed 1,316 patients who underwent thoracic surgery at Gangnam Severance Hospital from Jan 2005 to Dec 2014. A total of 556 patients were diagnosed with lung cancer, of which 90 patients with stage IB NSCLC were enrolled. All the patients underwent one of the following definite complete resection surgeries: wedge resection, lobectomy, or pneumonectomy with systematic LN dissection. Exclusion criteria were as follows: serious comorbidity that could influence survival such as other cancers, synchronous lung cancer (two or more histologically distinct simultaneously detected malignancies), and small cell lung cancer (SCLC). After exclusion of one patient with synchronous lung cancer, 89 patients were finally recruited in this study. The requirement of patients' informed consent was waived owing to the retrospective nature of the study by the Institutional Review Board (IRB) of Gangnam Severance Hospital (number: 3-2016-0276).

Adjuvant chemotherapy

We defined adjuvant chemotherapy as post-operative chemotherapy involving the use of platinum-based agents; the therapy regimen was selected by respective clinicians. Most regimens included cisplatin (75 mg/m^2), carboplatin combined with vinorelbine (25 mg/m^2), or paclitaxel. Usually, 4 cycles of chemotherapy were performed using these regimens, and there was no definite indication of adjuvant therapy. Although the follow-up schedule varied, usually, chest computed tomography was performed every 3–6 months for the first 2 years, followed by once every 6–12 years. If recurrence was suspected, integrated positron emission tomography-computed tomography was performed.

Pathologic analysis

For histopathologic analysis, two pathology specialists reviewed all the samples of patients, independently. They had no knowledge of those patients' clinical outcomes. A decision was made on the basis of 2015 World Health Organization classification (18). If they have different opinions, they met, discussed, and reached a final diagnosis by consensus. Hematoxylin and eosin staining was performed for all samples, and additional staining was performed, when needed, according to the decisions of the pathology specialist. Lymphovascular invasion (LVI) was defined as the presence of tumor cells or emboli in the lymphatic or blood vessel lumen (19). Visceral pleural invasion (VPI) was defined as the presence of any distortion of the pleural elastic layer caused by malignant cells (20).

Definition of terms

As per the NCCN guidelines, high-risk patients were defined as those with poorly differentiated tumors, wedge resection, vascular invasion, tumor size >4 cm, VPI, and incomplete LN sampling. However, as only two patients underwent wedge resection and none underwent incomplete LN sampling, these two factors could not be included in this study. Therefore, after elimination of these factors, we defined high-risk patients as those with poorly differentiated tumors, vascular invasion, tumor size >4 cm, and VPI. Disease-free survival (DFS) was defined as the period between the date of resection surgery and the date of

recurrence, death, or the last date on which the patient was known to be alive. Overall survival (OS) was defined as the period between the surgery date and the death or the last date on which the patient was known to be alive.

Statistical analysis

The *t*-test and chi-square test were used to compare continuous variables and categorical variables between the two groups, respectively. All univariate and multivariate analyses for DFS and OS were performed using the Cox regression models. However, univariate analysis for survival curve was performed using the Kaplan-Meier method and the log-rank test. For the multivariate analysis, we used all the parameters included in this study as covariates, except the pathologic type of NSCLC (because the statistical value was immeasurable in univariate analysis) and predominant type (because of many missing values, as it was applicable only to the adenocarcinoma type). All P values <0.05 were considered statistically significant.

Results

Clinical characteristics of subjects

Among the 89 subjects, 27 underwent adjuvant chemotherapy. The adjuvant chemotherapy group had more elderly patients (>65 years) (40.7%) than the control group who did not undergo adjuvant chemotherapy (64.5%, P=0.037). The control group had more patients with squamous cell lung cancer (40.3%), whereas the adjuvant chemotherapy group more patients with adenocarcinoma lung cancer (74.1%, P=0.002). There was no significant difference in the sex, operation type, tumor size, predominant type, differentiation, VPI, LVI, and perineural invasion between the control and adjuvant chemotherapy groups (*Table 1*).

Univariate analyses for DFS and OS

We tried to find any significant factors for survival using Cox-regression. Age, sex, operation type, size, pathologic type, predominant type, LVI, perineural invasion, and adjuvant chemotherapy was not significant predictive factor for DFS and OS. However, among all the factors analyzed, only VPI was a significant risk factor for DFS [hazard ratio (HR): 7.051; 95% confidence interval (CI): 1.570–31.659; P=0.011) and OS (HR: 8.289; 95% CI: 1.036–66.307; P=0.046) (*Table 2*).

Effect of adjuvant chemotherapy on DFS and OS according to the adjuvant chemotherapy

Kaplan-Meier survival analysis did not show any significant difference in DFS (P=0.662) and OS (P=0.866) between the two groups (*Figure 1*). We tried various combinations of factors to determine whether adjuvant chemotherapy is a significant predictor of survival. However, combinations of age, pathologic type, VPI, and etc., did not show any significant effect of adjuvant chemotherapy on DFS and OS (data are not shown).

Some patients were classified as high-risk patients (19.1% with poorly differentiated tumor, 27.0% with LVI, 28.1% with tumor size >4 cm, and 51.7% with VPI) as per the NCCN guideline definitions. However, even in these patients, adjuvant chemotherapy was not a significant factor for DFS and OS (*Table 3*).

Effect of VPI on DFS and OS according to the VPI

Kaplan-Meier survival analysis showed that VPI was a significant factor for DFS (P=0.003) and OS (P=0.017) (*Figure 1*). Multivariate analysis of VPI for survival showed that after adjustment for age, VPI was a significant risk factor for DFS (HR: 7.528; 95% CI: 1.664–34.059; P=0.009) and OS (HR: 8.748; 95% CI: 1.087–70.387; P=0.041). After adjustment for age and sex, VPI was still a significant risk factor for DFS and OS. However, after adjustment for other covariates including pathologic type, operation type, tumor size, LVI, perineural invasion, and adjuvant chemotherapy, VPI was a significant risk factor for DFS, but not for OS (*Table 4*).

Discussion

Although adjuvant chemotherapy is routinely performed for patients with stage II–III NSCLC, it has a negative effect on stage IA NSCLC due to its chemotoxicity and immunosuppressive effects (21). The effects of adjuvant chemotherapy on completely resected stage IB NSCLC are controversial: Some studies have shown beneficial effects of adjuvant chemotherapy (13,22,23), whereas others have shown non-significant effects on OS (12,16,24). Further, according to the NCCN guidelines, patients with completely resected stage IB NSCLC may not require adjuvant therapy, but high-risk patients may require chemotherapy. Moreover, in the literature, there are no absolute indications for adjuvant chemotherapy

Table 1 Clinical characteristics of enrolled subjects according to adjuvant chemotherapy

Characteristics	Control (n=62), n (%)	Adjuvant chemotherapy (n=27), n (%)	P value
Age >65 years	40 (64.5)	11 (40.7)	0.037
Sex (male)	50 (80.6)	17 (63.0)	0.075
Operation type			0.812
Wedge resection or lobectomy	59 (95.2)	26 (96.3)	
Pneumonectomy	3 (4.8)	1 (3.7)	
Size >4 cm	18 (29.0)	7 (25.9)	0.731
Pathologic type			0.002
Adenocarcinoma	35 (56.5)	20 (74.1)	
Squamous cell	25 (40.3)	2 (7.4)	
Adenosquamous cell	0 (0.0)	2 (7.4)	
Other*	2 (3.2)	3 (11.1)	
Predominant type[§]			0.129
Lepidic	2 (5.6)	0 (0.0)	
Acinar	23 (63.9)	9 (45.0)	
Papillary	4 (11.1)	8 (40.0)	
Micropapillary	4 (11.1)	2 (10.0)	
Solid	3 (8.3)	1 (5.0)	
Differentiation**			0.430
Well differentiation	5 (8.1)	1 (3.8)	
Moderate differentiation	47 (75.8)	18 (69.2)	
Poorly differentiation	10 (16.1)	7 (26.9)	
Visceral pleural invasion	31 (50.0)	15 (55.6)	0.630
Lymphovascular invasion	15 (24.2)	9 (33.3)	0.372
Perineural invasion	3 (4.8)	1 (3.7)	0.801

Data are presented as mean ± SD or percentage. *, other includes pleomorphic carcinoma, large cell carcinoma, mucoepidermoid carcinoma (n=2), and large cell neuroendocrine carcinoma; **, one datum is missing in the "Adjuvant chemotherapy" group; [§], predominant type was assessed only in adenocarcinoma lung cancer and pleomorphic carcinoma.

of completely resected stage IB NSCLC. With an aim to determine the effects of adjuvant chemotherapy on stage IB NSCLC, the present study showed that adjuvant chemotherapy does not have any significant benefits for stage IB NSCLC, even for high-risk patients.

The NCCN guidelines recommend that poorly differentiated tumors, LVI, wedge resection, tumor size >4 cm, VPI, and incomplete LN sampling are high-risk factors and can be considered when determining treatment with adjuvant chemotherapy. However, these factors have not proven to be independent factors in well-designed studies. Many clinicians decide to administer adjuvant chemotherapy on the basis of their experience and other recommendations for managing completely resected stage IB NSCLC. However, we found that these above factors are neither powerful for OS prognosis nor important for deciding whether to administer adjuvant chemotherapy. Therefore, adjuvant chemotherapy should be carefully considered for patients with completely resected stage IB NSCLC, and reliable detailed criteria should be established

Table 2 Univariate analyses for disease-free survival and overall survival

Variables	Disease-free survival			Overall survival		
	HR	95% CI	P value	HR	95% CI	P value
Age, years						
≤65	Reference	–	–	Reference	–	–
>65	1.449	0.485–4.333	0.507	1.357	0.324–5.684	0.676
Sex						
Female	Reference	–	–	Reference	–	–
Male	0.425	0.147–1.230	0.114	0.581	0.138–2.446	0.459
Operation type						
Wedge resection or lobectomy	Reference	–	–	Reference	–	–
Pneumonectomy	1.485	0.187–11.778	0.708	3.182	0.385–26.335	0.283
Size						
≤4 cm	Reference	–	–	Reference	–	–
>4 cm	2.406	0.831–6.964	0.105	1.631	0.387–6.868	0.505
Pathologic type						
Adenocarcinoma	Reference	–	–	Reference	–	–
Squamous cell	0.149	0.019–1.168	0.070	Unmeasurable		0.960
Adenosquamous cell	Unmeasurable		0.986	Unmeasurable		0.987
Etc.	2.615	0.313–21.837	0.375	7.724	0.638–93.559	0.108
Predominant type						
Lepidic/acinar/papillary	Reference	–	–	Reference	–	–
Micropapillary/solid	0.399	0.051–3.126	0.382	0.468	0.054–4.038	0.490
Visceral pleural invasion						
Absent	Reference	–	–	Reference	–	–
Present	7.051	1.570–31.659	0.011	8.289	1.036–66.307	0.046
Lymphovascular invasion						
Absent	Reference	–	–	Reference	–	–
Present	1.389	0.430–4.489	0.583	1.482	0.359–6.124	0.587
Perineural invasion						
Absent	Reference	–	–	Reference	–	–
Present	2.535	0.316–20.309	0.381	4.373	0.505–37.858	0.180
Adjuvant chemotherapy	0.749	0.204–2.750	0.663	1.130	0.273–4.684	0.866

Differentiation was unmeasurable (P=0.947–0.948). HR, hazard ratio; CI, confidence interval.

for selection of subjects.

Our study showed that VPI is a strong predictive factor for DFS and OS. In the 1970s, Brewer *et al.* reported that patients with VPI had a significantly poor prognosis (25); consistent with their findings, many studies confirmed that VPI is an independent factor for poor prognosis of

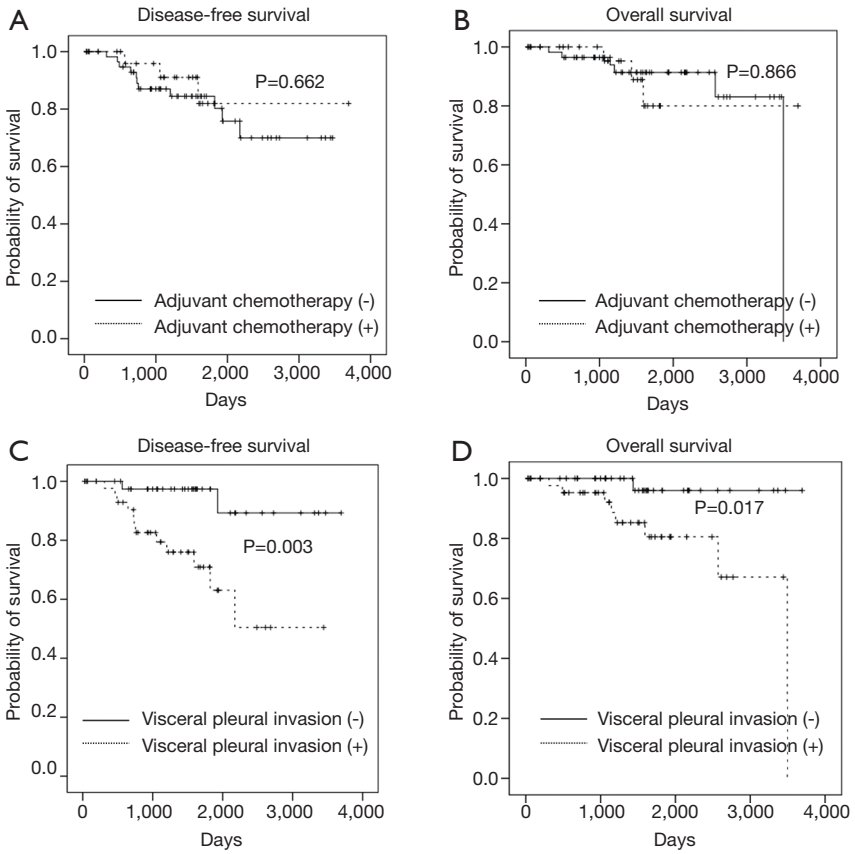

Figure 1 Disease-free survival and overall survival according to adjuvant chemotherapy (A,B) and visceral pleural invasion (C,D).

Table 3 Effects of adjuvant chemotherapy in high-risk patients

Conditions	Number (%)	Disease-free survival			Overall survival		
		HR	95% CI	P value	HR	95% CI	P value
Poorly differentiated tumors	17 (19.1)	0.617	0.056–6.854	0.695	0.596	0.054–6.613	0.674
Lymphovascular invasion	24 (27.0)	0.407	0.042–3.932	0.437	0.689	0.062–7.639	0.761
Tumors larger than 4 cm	25 (28.1)	0.514	0.060–4.405	0.544	0.631	0.063–6.323	0.695
Visceral pleural invasion	46 (51.7)	0.497	0.105–2.345	0.377	1.154	0.210–6.334	0.869

HR, hazard ratio; CI, confidence interval.

NSCLC (26,27). Furthermore, recent studies showed that VPI is an adverse prognostic factor for early stage NSCLC (28,29). This could be because tumors with VPI are likely to break through the visceral pleura and lead to pleural intraluminal metastasis. Our current results are consistent with those of the above-mentioned studies. However, in high-risk patients with VPI, adjuvant chemotherapy did not significantly affect the prognosis of NSCLC. Therefore, we believe that VPI is a significant risk factor for prognosis, but not a decisive factor for adjuvant chemotherapy.

Adjuvant chemotherapy is frequently performed for young patients and patients with adenocarcinoma type rather than old patients and those with squamous cell type in this study. This might be because the toxicity of adjuvant chemotherapy is higher at an old age than at a young age. Furthermore, the relatively good prognosis of squamous cell lung

Table 4 Multivariate analyses of visceral pleural invasion for disease-free survival and overall survival

Other covariates	Disease-free survival			Overall survival		
	HR	95% CI	P value	HR	95% CI	P value
Age	7.528	1.664–34.059	0.009	8.748	1.087–70.387	0.041
Age, sex	8.527	1.861–39.058	0.006	8.801	1.098–70.568	0.041
Age, sex, pathologic type	7.569	1.589–36.054	0.011	6.392	0.789–51.780	0.082
Age, sex, pathologic type, operation type	10.218	1.798–58.062	0.009	5.613	0.676–46.605	0.110
Age, sex, pathologic type, operation type, size	14.244	2.452–82.755	0.003	5.328	0.637–44.575	0.123
Age, sex, pathologic type, operation type, size, lymphovascular invasion	14.508	2.573–81.796	0.002	5.456	0.562–52.924	0.143
Age, sex, pathologic type, operation type, size, lymphovascular invasion, perineural invasion	16.143	2.659–97.992	0.003	6.459	0.663–62.962	0.108
Age, sex, pathologic type, operation type, size, lymphovascular invasion, perineural invasion, adjuvant chemotherapy	16.270	2.603–101.695	0.003	6.845	0.631–74.269	0.114

HR, hazard ratio; CI, confidence interval.

cancer might deter clinicians from administering adjuvant chemotherapy (30). However, the present study reported that tumor size, differentiation, LVI, and VPI, which are defined as high-risk factors in the NCCN guidelines, need not be considered when making a decision about adjuvant chemotherapy. Although many researchers rely on their own experience and other recommendations with insufficient evidence to make a decision about adjuvant chemotherapy, it is important to note that our data are sourced from only one institute (with five pulmonologists); therefore, our results should be carefully considered and applied.

Despite our important findings, this study had a few limitations. First, it included a small number of patients and short period, which might have yielded suboptimal results. Especially, subgroup analysis cannot have powerful credit. Then, efficacy of adjuvant chemotherapy should be carefully assessed. Second, we included some patients who had recently undergone surgery. Such inclusion could result in confounding findings, with a high censor rate in statistical analysis. Third, only two patients in our cohort underwent wedge resection and none of the patients underwent incomplete LN sampling. Therefore, we could not determine whether these factors are high-risk factors that should be considered when making a decision about adjuvant chemotherapy. Fourth, physicians decided adjuvant chemotherapy; and this bias might lead insignificant results of adjuvant chemotherapy. Last, we did not determine the amount of VPI, quantitatively. Sub-group analysis between focal invasion and extensive invasion will be interesting.

In conclusion, this study suggested that adjuvant chemotherapy may not be significantly effective for the treatment of patients with stage IB NSCLC, even for high-risk patients. In addition, VPI is a strong prognostic factor for survival. Further long-term and multi-center prospective studies are required to confirm our findings.

Acknowledgements

This study was financially supported by Boryung Pharmaceuticals, Ltd.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (number: 3-2016-0276). The requirement of patients' informed consent was waived owing to the retrospective nature of the study.

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Cite this article as: Park HJ, Park HS, Cha YJ, Lee S, Jeung HC, Cho JY, Kim HJ, Byun MK. Efficacy of adjuvant chemotherapy for completely resected stage IB non-small cell lung cancer: a retrospective study. J Thorac Dis 2018;10(4):2279-2287. doi: 10.21037/jtd.2018.03.184

