Korean J Thorac Cardiovasc Surg 2014;47:13-19 □ Clinical Research □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2014.47.1.13

The Prognosis According to Patterns of Mediastinal Lymph Node Metastasis in Pathologic Stage IIIA/N2 Non-Small Cell Lung Cancer

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Background: The aim of this study is to evaluate prognostic factors for survival in pathologic stage IIIA/N2 non-small-cell lung cancer (NSCLC), to identify the prognostic significance of the metastatic patterns of mediastinal lymph nodes (MLNs) relating to survival and to recurrence and metastasis. ***Methods:*** A total of 129 patients who underwent radical resection for pathologic stage IIIA-N2 NSCLC from July 1998 to April 2011 were retrospectively reviewed. The end points of this study were rates of loco-regional recurrence and distant metastasis, and survival. ***Results:*** The overall 5-year survival rate was 47.4%. A univariate analysis showed that age, pathologic T stage, and adjuvant chemotherapy were significant prognostic factors, while in multivariate analysis, pathologic T stage and adjuvant chemotherapy were significant prognostic factors. The metastasis rate was higher in patients with multi-station N2 involvement and with more than 3 positive MLNs. Further, non-regional MLN metastasis was associated with a higher loco-regional recurrence rate. ***Conclusion:*** Pathologic T stage and adjuvant chemotherapy were independent prognostic factors for long-term survival in pathologic stage IIIA/N2 NSCLC. The recurrence and the metastasis rate were affected by the metastatic patterns of MLNs. These results may be helpful for planning post-operative therapeutic strategies and predicting outcomes.

Key words: 1. Carcinoma, non-small cell, lung
2. Mediastinal lymph nodes
3. Neoplasm metastasis
4. Lung surgery

INTRODUCTION

In pathologic stage IIIA/N2 non-small-cell lung cancer (NSCLC), the reported 5-year survival rate ranges from 25% to 50% and many prognostic factors have been reported [1,2]. In the classification of mediastinal lymph node (MLN) metastasis as IIIA/N2, various subgroups may be recognized [3]. Previous studies have reported that the prognosis may be affected by these subgroups. According to the National Comprehensive Cancer Network (NCCN) guidelines, completely resected NSCLC refers to negative highest mediastinal lymph node metastasis [4]. According to the recommendations of the American College of Chest Physicians (ACCP) for patients with pathologic stage IIIA/N2 disease after resection, adjuvant chemotherapy is recommended in patients who have good performance status, and adjuvant radia-

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Received: July 1, 2013, Revised: August 31, 2013, Accepted: September 17, 2013
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tion therapy should be considered after chemotherapy to reduce local recurrence [5]. In the our study, the incidences of local recurrence and distant metastasis were investigated in patients diagnosed with postoperative pathologic stage IIIA/N2 NSCLC, and factors affecting the overall survival based on the presence of MLN metastases were examined. In addition, the appropriate treatment modality for patients with a highest MLN metastasis was assessed.

METHODS

A total of 129 cases involving patients who underwent radical resection for p-stage IIIA-N2 NSCLC from July 1998 to April 2011 at Chonnam National University Hospital under a single surgical team were retrospectively reviewed. For all of the patients, a resection greater than lobectomy, and a complete systemic lymph node dissection or sampling were performed. According to NCCN recommendations for R0 resections, adjuvant chemotherapy was administered. Additionally, for an R1 resection or according to the surgeon's opinion, adjuvant radiation therapy was added after considering the patient's general condition. To identify local recurrences and distant metastases after surgery, routine blood tests, bone scans, and chest computed tomography (CT) scans were performed every 6 months in the initial 5 years and repeated annually thereafter. Starting in 2004, positron emission tomography/CT was performed in the case of abnormal findings of other imaging studies or of the patient's need. The definition of local recurrence in lung cancer varies [6]. In the present study, we limited the definition of local recurrences only to the metastasis in the ipsilateral thorax, which also includes MLNs. Age, sex, stage-associated factors, histologic features, and adjuvant therapy were investigated. We considered chemotherapy, radiation therapy, and combined (chemoradiation) therapy to be the adjuvant therapies. The classification and the name of the lymph nodes were based on the TNM staging system of Mountain and Dresler [7]. The presence of the highest MLN metastasis, the number of positive N2 stations, the number of pathologically positive lymph nodes, the presence of skip N2 metastasis, and regional metastasis following surgery were analyzed separately. The highest MLN was defined as one of the resected MLNs located closest to the head; skip N2 metastasis was defined as an MLN metastasis without N1 nodal metastasis. Further, regional lymph node metastasis was defined as the involvement of lymph node levels 1 to 4 in the right upper lobe, levels 1 to 6 in the left upper lobe, and levels 7 to 9 in both lower lobes, based on the lymph node map published by the International Association for the Study of Lung Cancer (IASLC) [8]. The overall survival rate, local recurrence, and distant metastasis were investigated as the end point for evaluating the prognosis. The follow-up period lasted from the date of surgery to death or the last date of follow-up. The follow-up period was 0 to 157 months (mean, 40.4±31.3 months), with a median follow-up period of 32 months. To conduct frequency comparisons between the two groups, chi-square test and Fisher's exact test were used. An analysis of survival was carried out using the Kaplan-Meier method. A univariate analysis was performed using the log-rank test, and a multivariate analysis was carried out using Cox's proportional hazards model. A p-value of <0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of the patients are shown in Table 1. The mean age of the patients was 62.1 years (range, 35 to 83 years), and 88 of the patients (68%) were male. The distribution of MLN metastasis is presented in Table 2. Two hospital deaths (1.6%) occurred; pneumonia was the cause of death in both cases. The overall survival rates for the patients were as follows: 1 year, 80.6%; 3 years, 57.0%; and 5 years, 47.4%. During the follow-up period, 36 patients had a local recurrence, a distant metastasis was identified in 64 cases, and both recurrence and metastasis occurred in 14 cases. The most common local recurrence site was the MLNs in 18 cases, the ipsilateral lung in 15 cases, and the bronchial stump in 6 cases. The brain was the most common site of distant metastasis (26 cases), followed by the contralateral lung (15 cases), and bone (11 cases). A univariate survival analysis was performed (Tables 1, 2). Sex, location of tumor, the presence or absence of pneumonectomy, and histological differentiation or classification did not differ significantly between the groups. The 5-year survival rate was 51.1% for pa-

Table 1. Patient demographics and comparison of survival according to clinical characteristics

Variable	No. of patients	Median survival time (mo)	5-year survival (%)	p-value
Gender				0.803
Male	88	58	49.0	
Female	41	44	42.9	
Age (yr)				0.034
<70	109	61	51.1	
≥70	20	25	18.9	
Tumor site				0.407
Left	44	41	44.8	
Right	85	58	48.6	
Operation type				0.589
Pneumonectomy	22	NR	54.5	
Non-pneumonectomy	107	47	45.2	
Histology				
ADC/others	68/61	69/32	53.9/40.9	0.181
SQC/others	36/93	29/58	49.9/39.9	0.254
Differentiation				0.274
Well-differentiated	42	NR	55.1	
Others	62	64	55.1	
T stage				0.012
T1	31	NR	65.7	
T2-3	98	32	41.5	
Adjuvant therapy				0.004
Chemotherapy	69	NR	62.3	
Others	55	29	34.6	

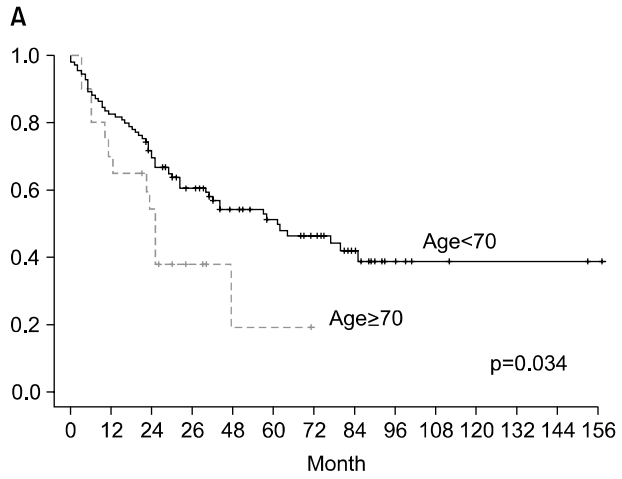
NR, not reported; ADC, adenocarcinoma; SQC, squamous cell carcinoma.

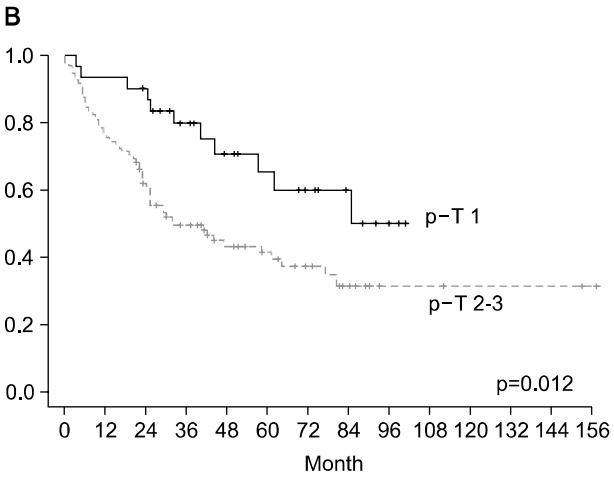
Table 2. LN status and survival according to LN invasion status

Variable	No. of patients	Median survival time (mo)	5-year survival (%)	p-value
Highest MLN status				0.877
Positive	52	44	45.8	
Negative	77	57	48.2	
N2 station no.				0.453
Single	74	61	50.9	
Multiple	55	44	42.9	
Involved N2 no.				0.642
<3	78	58	48.8	
≥3	51	44	45.5	
Distribution of MLN				0.474
Skip N2	45	47	43.4	
No-skip N2	84	57	49.5	
Regional N2 metastases				0.868
Regional	82	57	50.2	
Non-regional	38	41	44.4	
Clinical N factor				0.985
N0-1	74	42	43.4	
N2	53	61	51.9	

LN, lymph node; MLN, mediastinal lymph node.

tients aged <70 years and 18.9% for those aged >70 years (p=0.034) (Fig. 1A). With respect to the pathological T stage, since only a few patients (n=18) with T3 stage were included, we combined the patients with T2 stage and T3 stage into a single high risk group and analyzed them together. The 5-year survival rate in group T1 was 65.7% as compared to 41.5% in group T2-3 (p=0.012) (Fig. 1B). Sixty-nine patients were treated by chemotherapy, and 55 patients were treated by radiotherapy or combined therapy. Five patients were not treated with adjuvant therapy due to the patients' refusal or poor general condition. We analyzed these patients by dividing them into two groups: a group that was treated by only chemotherapy (n=69) and a group that underwent a treatment other than chemotherapy (n=55). The five-year survival rate among patients who received adjuvant chemotherapy after surgery was 62.3%; that for patients who received another treatment was 34.6% (p=0.004) (Fig. 1C). With respect to the patterns of MLN metastasis, in all cases, there was no significant difference in survival. However, among the patients with upper lobe cancer, the 5-year survival rate was significantly higher in patients with regional metastasis (53.9% vs. 27.3%, p=0.043) (Fig. 2). In a multivariate analysis, pathologic T stage and adjuvant chemotherapy were significant prognostic factors for survival (Table 3). The incidences of local recurrence and distant metastasis were different according to the pattern of lymph node metastasis (Table 4). Distant metastasis was more likely in cases involving multiple MLN stations (p=0.042) or three or more positive MLNs (p=0.016). Additionally, the non-regional lymph node metastasis group showed a higher frequency of local recurrence than the regional lymph node metastasis group (p=0.023). The highest MLN was identified in 52 patients and was targeted for additional analysis. Twenty-four patients were treated only with chemotherapy, and 17 patients were treated with combined therapy. In a comparison of the 5-year survival rate (67.7% vs. 47.2%, p=0.300), local recurrence





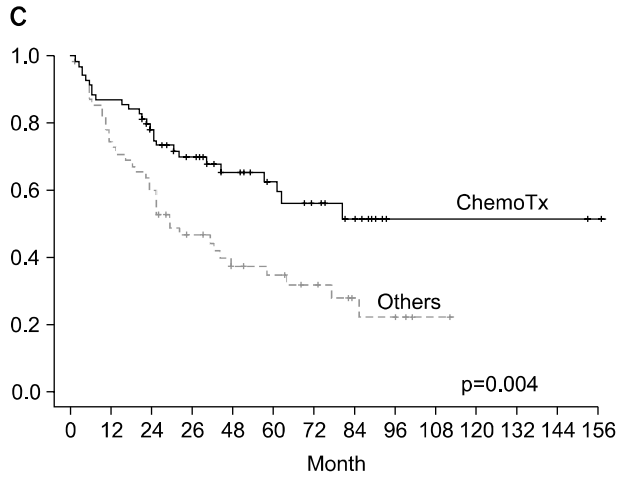


Fig. 1. Survival curve according to (A) age, (B) pathologic T stage, and (C) postoperative (adjuvant) therapy.

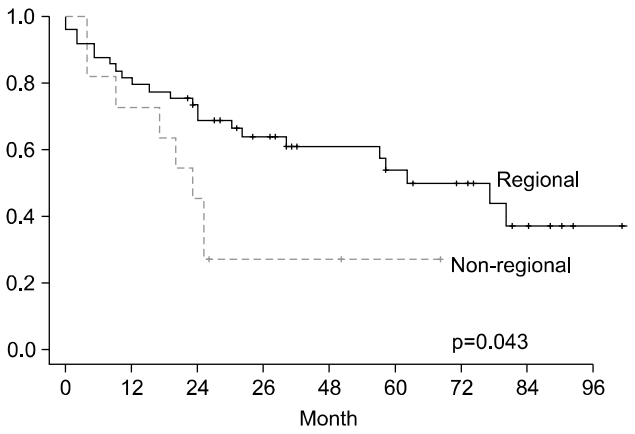


Fig. 2. Survival curve of patients with upper lobe cancer according to regional metastases.

rate (37.5% vs. 25.0%, p=0.408), and incidence of distant metastasis (58.3% vs. 50.0%, p=0.604) between patients who underwent adjuvant chemotherapy and patients who were treated with chemotherapy and radiation therapy, no significant difference was found (Fig. 3).

DISCUSSION

For patients with clinical IIIA/N2 stage NSCLC based on a radiological examination, bronchoscopy, or mediastinoscopic biopsy, concurrent chemoradiation therapy is recommended by the ACCP and NCCN [4,5]. For patients with pathologic stage IIIA/N2, adjuvant chemotherapy is recommended. Thereafter, radiation therapy to reduce local recurrence may be considered. These guidelines have been made subject to resection, and NCCN recommendations for complete resection

Table 3. Independent factors affecting survival using a Cox proportional hazard model

Variable	Hazard ratio	95% confidence interval	p-value
p-T stage (T1/T2-3)	0.492	0.255-0.948	0.034
Adjuvant therapy (ChemoTx/others)	0.513	0.308-0.854	0.010

Table 4. Recurrence and metastasis rate according to the sub-classifications of N2 metastasis

Variable	Recurrence	p-value	Metastasis	p-value
Highest MLN status		0.319		0.062
Positive (n=52)	17 (32.7)		31 (59.6)	
Negative (n=77)	19 (24.7)		33 (42.9)	
MLN station no.		0.147		0.042
Single (n=74)	17 (23.0)		31 (41.9)	
Multiple (n=55)	19 (34.5)		33 (60.0)	
Involved N2 no.		0.130		0.016
<3 (n=78)	18 (23.1)		32 (41.0)	
≥3 (n=51)	18 (35.3)		32 (62.7)	
Skip N2		0.292		0.219
Yes (n=45)	10 (22.2)		19 (42.2)	
No (n=84)	26 (31.0)		45 (53.6)	
Regional N2 metastases		0.023		0.432
Yes (n=82)	18 (22.0)		39 (47.6)	
No (n=38)	16 (42.1)		21 (55.3)	
c-N stage		0.992		0.642
N0-1 (n=74)	21 (28.4)		36 (48.6)	
N2 (n=53)	15 (28.3)		28 (52.8)	

Values are presented as number (%).
MLN, mediastinal lymph node.

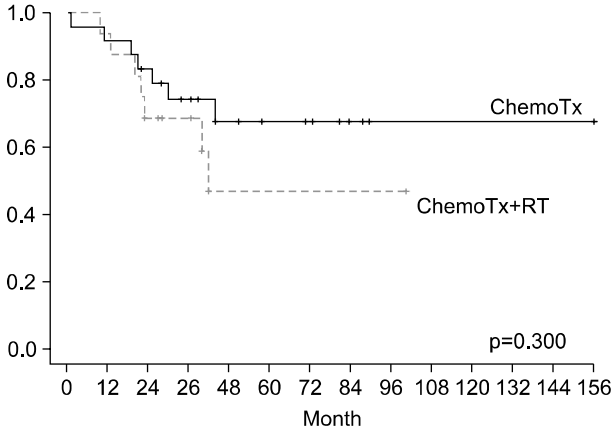


Fig. 3. Survival curve of patients with positive highest mediastinal lymph node according to (postoperative) adjuvant treatment (chemotherapy or combined therapy).

in the surgical treatment of NSCLC are associated with the following criteria: 1) negative resection margins, 2) systematic lymph node sampling or complete resection, 3) negative extracapsular invasion of lymph node, and 4) negative highest mediastinal lymph node. The appropriate treatment plan for patients with stage IIIA/N2NSCLC is controversial. The 5-year survival rate is reported to be 25% to 50%, and tumor location, histology, T stage, and distribution of metastatic lymph nodes have all been reported to be important prognostic factors [1-3]. In recent years, the size of the mediastinal lymph nodes (3 cm) has come to play an important role in determining whether surgery should be considered [9,10]. One of the reasons for such a variety of results of stage IIIA/N2 is that the MLNs may be present in various subgroups.

Many studies have investigated the pattern of MLN metastasis and reported prognostic factors as the number of MLN stations involved, the presence of a skip metastasis, and metastasis to the highest MLN. Misthos et al. [11] reported that among 302 patients with pathologic stage IIIA/N2 disease, 66% showed multiple stations of MLN metastases; in the multivariate analysis, the only factor associated with a good prognosis was the presence of one-station MLN metastasis. This was explained by the facts that the risk of non-regional or skip metastasis is relatively low in case of one-station involvement and there is little likelihood of systemic extension.

Skip metastasis has been reported in stage IIIA/N2 disease at a frequency of 17% to 41% [12]. Prenzel et al. [13] compared the 5-year survival rates between patients of the skip N2 group and those of the control group, and found a significantly better prognosis among those in the skip N2 group (41% vs. 14%, respectively). There are two distinct pathways of MLN metastasis (directly to the MLNs and through an N1 lymph node). Usually, a better prognosis of skip metastasis was explained by single pathway invasion [14].

It should be noted that the definition of the highest MLNs has varied in previous reports. They have often been defined as the lymph nodes above the horizontal plane of the left brachiocephalic vein [7]; moreover, lymph node level 4 on the left side and lymph node level 1/2 on the right side may

be defined for them [15]. However, they are most commonly defined as one of the resected MLNs located closest to the head. In a study by Sakao et al. [16], patients without metastasis to the highest MLN had a 3-year survival rate of 52%, while those with metastasis to the highest MLN had a 3-year survival rate of 21% ($p < 0.001$). Involvement of the highest MLN is a poor prognostic factor, irrespective of the number of involved MLN stations, clinical N stage, or pathologic T stage. Nakagiri et al. [17] found significant differences in the survival rate according to various patterns of MLN metastasis, including pathologic T factor, clinical N factor, metastasis of the highest MLNs, and skip N2 metastasis. An additional analysis of the recurrence status revealed that there were significant differences among the disease-free survival rates according to the metastasis of the highest MLNs, skip N2 metastasis, and the number of metastatic node stations. Based on these results, they emphasized that the sub-classification of lymph node metastasis is required for predicting the prognosis in patients with pathologic stage IIIA/N2.

Contrary to the viewpoints presented in these studies, Lacasse et al. [18] asserted that the highest MLN involvement had no effect on prognosis, and the IASLC reported no significant difference in survival rates according to the subtypes of MLN metastasis [19]. Our study also did not show any significant difference in the overall survival rate, brought about by the pattern of MLN metastasis. In the multivariate analysis, pathologic T stage and adjuvant chemotherapy were shown to be significant prognostic factors for survival. The 5-year survival rate was significantly higher among those patients who received adjuvant chemotherapy (62.3%). However, there was no difference between the chemotherapy group and the chemotherapy plus radiation therapy group.

Patients with the involvement of multiple stations of MLNs and three or more positive lymph nodes had a significantly higher incidence of distant metastasis. Further, patients with non-regional lymph node metastases showed a higher incidence of local recurrence. Asamura et al. [20] observed different patterns of MLN metastasis according to the location of the primary tumor in the lungs (right upper lobe, levels 3 and 4; left upper lobe, level 5; both lower lobes, level 7), and similar results were obtained in our study. In general, patients with a non-regional metastasis had relatively poor outcomes. We assumed that patients with a non-regional metastasis had a higher recurrence rate; this was corroborated with the results of the present study.

There was no significant difference in the 5-year survival rate, local recurrence rate, or incidence of distant metastasis between the chemotherapy group and the chemotherapy plus radiation therapy group among patients with metastasis of the highest MLN. Thus, we carefully suggest that the use of radiation therapy to prevent recurrence in patients with the highest MLN metastasis be reconsidered. However, this result has a limitation in that we considered a smaller number of patients undergoing radiation therapy than other studies. Further prospective studies are required to confirm the above-mentioned result.

The present study has some limitations. Firstly, this was a retrospective analysis of medical records. Secondly, because of the relatively long study period, the homogeneity of the group decreased and the treatment paradigms of stage IIIA/N2 NSCLC may have changed. Additionally, we used a multivariate analysis and the overall survival rate of up to 70 years; however, the result does not reflect disease-specific and disease-free survival rates. Hence, a well-designed, prospective analysis is required.

In conclusion, pathologic T stage and adjuvant chemotherapy were independent prognostic factors for long-term survival in patients with pathologic stage IIIA/N2 NSCLC. There were no differences in the survival rate according to the patterns of MLN metastasis. Although adjuvant chemotherapy was a prognostic factor, there was no significant difference in the survival rate between the chemotherapy group and the chemotherapy plus radiation therapy group, even among patients with the highest MLN metastasis. The recurrence and the metastasis rate were affected by the metastatic patterns of the MLNs (non-regional metastasis for recurrence, and multi-station and positive MLNs ≥ 3 for metastasis). These results may be helpful in formulating postoperative therapeutic strategies and predicting their outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Inoue M, Sawabata N, Takeda S, Ohta M, Ohno Y, Maeda H. *Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe.* J Thorac Cardiovasc Surg 2004;127:1100-6.
2. Saito M, Kato H. *Prognostic factors in patients with pathological and N2 non-small cell lung cancer.* Ann Thorac Cardiovasc Surg 2008;14:1-2.
3. Kim DJ, Kim KD, Kim CY, Chung KY. *Nodal station as a prognostic factor in resected stage IIIA N2 non-small cell lung cancer.* Korean J Thorac Cardiovasc Surg 2003;36: 489-96.
4. National Comprehensive Cancer Network. *National Comprehensive Cancer Network (NCCN) guidelines* [Internet]. Fort Washington (PA): National Comprehensive Cancer Network; 2013 [cited 2013 Mar 1]. Available from: http://www.nccn.org/index.asp.
5. Alberts WM; American College of Chest Physicians. *Diagnosis and management of lung cancer executive summary: ACCP evidence-based clinical practice guidelines (2nd Edition).* Chest 2007;132(3 Suppl):1S-19S.
6. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, DeCamp MM. *Varying recurrence rates and risk factors associated with different definitions of local recurrence in patients with surgically resected, stage I nonsmall cell lung cancer.* Cancer 2010;116:2390-400.
7. Mountain CF, Dresler CM. *Regional lymph node classification for lung cancer staging.* Chest 1997;111:1718-23.
8. Rusch VW, Asamura H, Watanabe H, et al. *The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer.* J Thorac Oncol 2009;4:568-77.
9. Cerfolio RJ, Bryant AS. *Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer.* Ann Thorac Surg 2008;86:362-6.
10. Andre F, Grunenwald D, Pignon JP, et al. *Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications.* J Clin Oncol 2000;18:2981-9.
11. Misthos P, Sepsas E, Kokotsakis J, Skottis I, Lioulias A. *The significance of one-station N2 disease in the prognosis of patients with nonsmall-cell lung cancer.* Ann Thorac Surg 2008;86:1626-30.
12. Bonner JA, Garces YI, Sawyer TE, et al. *Frequency of noncontiguous lymph node involvement in patients with resectable nonsmall cell lung carcinoma.* Cancer 1999;86:1159-64.
13. Prenzel KL, Monig SP, Sinning JM, et al. *Role of skip metastasis to mediastinal lymph nodes in non-small cell lung cancer.* J Surg Oncol 2003;82:256-60.
14. Riquet M, Hidden G, Debesse B. *Direct lymphatic drainage of lung segments to the mediastinal nodes. An anatomic study on 260 adults.* J Thorac Cardiovasc Surg 1989;97: 623-32.
15. Zheng H, Hu XF, Jiang GN, et al. *Define relative incomplete resection by highest mediastinal lymph node metastasis for non-small cell lung cancers: rationale based on prognosis analysis.* Lung Cancer 2011;72:348-54.
16. Sakao Y, Miyamoto H, Yamazaki A, et al. *Prognostic significance of metastasis to the highest mediastinal lymph node in nonsmall cell lung cancer.* Ann Thorac Surg 2006;81: 292-7.
17. Nakagiri T, Sawabata N, Funaki S, et al. *Validation of pN2 sub-classifications in patients with pathological stage IIIA N2 non-small cell lung cancer.* Interact Cardiovasc Thorac Surg 2011;12:733-8.
18. Lacasse Y, Bucher HC, Wong E, et al. *"Incomplete resection" in non-small cell lung cancer: need for a new definition. Canadian Lung Oncology Group.* Ann Thorac Surg 1998;65:220-6.
19. Rusch VW, Crowley J, Giroux DJ, et al. *The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer.* J Thorac Oncol 2007;2: 603-12.
20. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. *Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis.* J Thorac Cardiovasc Surg 1999;117:1102-11.