Prognostic Factors in Resectable Pathological N2 Disease of Non-small Cell Lung Cancer

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Background: N2-positive non-small cell lung cancer (NSCLC) exhibits extremely low survival rates. The role of surgery in operable locally advanced N2 NSCLC remains controversial. In this study, we tried to analyze the role of surgery in resectable N2 NSCLC and the relationship between survival and clinico-pathologic factors from a pathologic point of view.

Methods: 108 resectable pathologic N2-positive NSCLC patients, diagnosed from January 2005 to July 2012, were enrolled in this study. We retrospectively reviewed the medical records, image studies, and pathology reports to collect the clinico-pathologic factors in these patients.

Results: Those who received lobectomy ($p = 0.002$) and had a metastatic lymph node ratio less than 0.4 ($p = 0.01$) had a better overall survival rate. In addition, our study also showed that perineural invasion may play a significant role in disease-free survival ($p = 0.01$)

Conclusions: Metastatic lymph node ratio greater than 0.4 and non-anatomic resection were poor prognostic factors for disease-free survival. Anatomic resection for selected N2 patients may play a crucial role in the overall survival rate. Perineural invasion showed an adverse impact on disease-free survival, but further investigation is warranted.

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Key words: N2-positive lung cancer, non-small cell lung cancer, prognostic factor

At a Glance Commentary

Scientific background of the subject

Poor survival rate was identified in pathologic N2 lymph node positive non-small cell lung cancer patients. We tried to identify the factors that may affect the prognosis.

What this study adds to the field

Patients with poor prognostic factors may need more individualized follow-up programs in order to evaluate the disease and enhance survival.

Non-small cell lung cancer (NSCLC) is a leading cause of death worldwide, as N2-positive NSCLC exhibits extremely low survival rates.[1] There are many subgroups in this population and show similar survival curves.[2] Literature review shows that most clinicians agree that NSCLC patients with N2 lymph node involvement are a heterogeneous group.[3,4] There had been many reports that tried to subclassify this population.[1,5,6] These studies showed that the disease prognosis was severe especially in the following clinical scenarios: Tumor cells involved multiple stations, subcarinal lymph node involvement, and presence of extracapsular extension. However, if patients with skip lesion can be identified, they would have better survival rates.[1,5,6] However, currently there is no conclusive consensus among the researches regarding these findings. In addition, the role of surgery for operable locally advanced N2 NSCLC remains controversial.[7-9] The third edition of the American College of Chest Physicians evidence-based

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clinical practice guidelines recommends that treatment plan for patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA) should be made with the input from a multidisciplinary team.[9] Ratto *et al.* reported good long-term survival and excellent local disease control. Surgery still plays an important role in the multimodality treatment of these patients.[8] The International Adjuvant Lung Cancer Trial Collaborative Group has reported the results of a large randomized trial showing a significant improvement of survival with cisplatin-based adjuvant chemotherapy in completely resected NSCLC.[10] In this study, we tried to analyze the role of surgery in resectable N2 NSCLC and the relationship between survival and the clinico-pathologic factors from a pathologic point of view.

METHODS

Patients

From January 2005 to July 2012, 108 resectable pathologic N2-positive NSCLC patients were enrolled in this study. The preoperative workup for the patients was reviewed thoroughly, which included chest computed tomography (CT), proton emission tomography (PET) or PET-CT, brain CT, and spirometery. Chest CT can be used to examine the anatomical relationship between lesions and vital organs, as well as to determine the possibility of curative resection. PET or PET-CT can be used to identify possible N3 and distant metastatic lesions. Brain CT can be used to rule out possible brain metastases. In addition, spirometery was utilized to evaluate patient's pulmonary reserve. All patients enrolled in this study were those with pathologic N2 disease without distant metastases. We retrospectively reviewed medical records in order to collect the clinico-pathologic factors of these patients. We did not obtain written or verbal informed consent from the patients. The data obtained from medical records was anonymized and de-identified prior to analysis. The study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital and the IRB number is 99-1586B.

Treatment strategy

During the study period, chest physicians and surgeons discussed the treatment plan for the patients with N2 disease in a combined conference. The treatment strategy is shown in Figure 1. If image survey demonstrated that curative resection (i.e. lobectomy) was possible, with adequate pulmonary reserve (forced expiratory volume in 1 s > 1.7 l), anatomic resection and mediastinal lymph node dissection were recommended. If image survey showed locally advanced disease, preoperative neoadjuvant therapy was be performed first, followed by repeat staging. If image survey revealed resectable, anatomic resection would be done for patients if they had adequate pulmonary reserve. For patients with poor pulmonary reserve, non-anatomic resection (i.e. wedge resection) and mediastinal lymph node sampling were done at the patient's request. All the patients received postoperative adjuvant therapy such as chemotherapy with or without radiation therapy.

Follow-up

All patients underwent regular follow-ups in the outpatient department. Disease relapse was confirmed with positive image findings or confirmed biopsy. Chest CT was used as the diagnostic tool for imaging. If disease relapse was suspected, further PET-CT or bone scan was arranged. If the lesion was easily accessible, biopsy was used in confirming the suspect lesion. Disease-free survival was defined as the period between the date of diagnosis and the date of relapse, confirmed by techniques such as positive image finding or biopsy. Overall survival was defined as the period from the date of diagnosis to the date on which the patient died. Local relapse was defined as disease relapse at surgical stump or ipsilateral thorax. Metastatic lesions which were located out of ipsilateral thorax were considered distant metastases.

Statistical analysis

All the collected clinico-pathologic factors were first analyzed with univariate analysis. Categorical variables were compared using Chi-square or Fisher's exact tests. Survival data were analyzed using the Kaplan–Meier method. The Cox regression model (semi-parametric model) was utilized for further identification of clinico-pathologic factors, in order to clarify the effect on disease-free and overall survival.

A $p < 0.05$ was considered statistically significant. The reported confidence intervals (CI) are assumed to have a coverage probability of 95%. All the analyses were performed using SAS, version 9 (SAS Institute, Cary, NC, USA).

RESULTS

All the patient characteristics are shown in Table 1. Mean age was 60.2 years and majority of them were males (56 patients, 51.9%). Majority (94 patients, 87%) of the patents did not receive preoperative neoadjuvant therapy. Surgical intervention was performed by the way of open thoracotomy during 2005–2009. The operation procedure was later shifted from open to video-assisted thoracoscopic surgery (VATS) beginning from 2010. Most patients (90 patients, 83.3%) received anatomic resection (i.e. lobectomy). The most common cell type was adenocarcinoma (83 patients, 76.9%), and the differentiation status of tumor cell was moderately differentiated (56 patients, 54.6%). The T-stage varied from T0 to T3 among the patients. One patient received preoperative neoadjuvant therapy prior to

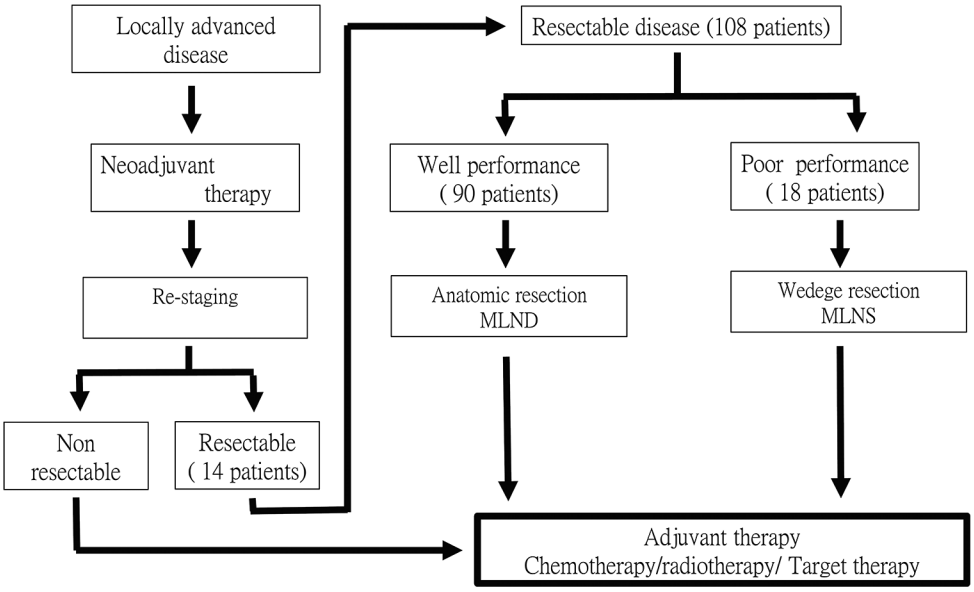

Figure 1: Treatment strategy.

operation, and the final pathologic examination showed no residual tumor within the resected specimen and classified it as T0. Six patients were classified as having T3 lesions. Three of them had tumor sizes larger than 7 cm in diameter. The other patients were diagnosed with partial chest wall invasion and received partial chest wall resection. The total number of lymph nodes and metastatic lymph nodes removed from the patients were 18.8 ± 11.9 and 4.1 ± 3.5, respectively. The median follow-up period was 869.5 days.

In this study, the 5-year disease-free and overall survival rates were 16.7 and 40%, respectively [Figure 2]. The 19 clinico-pathologic factors that had been collected from medical records were further analyzed for their relationship with disease-free and overall survival rates. We found that the patients who received lobectomy ($p = 0.004$), those without perineural invasion ($p = 0.005$), and those with metastatic lymph node ratio lesser than 0.4 ($p = 0.01$) had better disease-free survival rates in univariate analysis. However, in the multivariate analysis [Table 2], only perineural invasion showed a significance in its adverse effect on disease-free survival rate (hazard ratio: 3.04, 95% confidence limits 1.27–7.28; p = 0.01) [Figure 3A]. We found that the patients who received lobectomy ($p < 0.001$), those without perineural invasion ($p = 0.009$), patients without mediastinal lymph node extracapsular extension ($p = 0.01$), and those with metastatic lymph node ratio lesser than 0.4 ($p = 0.01$) had better overall survival rates. By further multivariate analysis [Table 3], we identified that patients without perineural invasion (hazard ratio: 3.05, 95% confidence limits 1.25–7.46; $p = 0.01$) [Figure 3B], those who received lobectomy (hazard ratio: 0.24, 95% confidence limits 0.09–0.61; $p = 0.002$) [Figure 3C], and those with metastatic lymph node ratio less than 0.4 (hazard ratio: 2.18, 95% confidence limits 1.13–4.18; $p = 0.01$) [Figure 3d] had better overall survival.

DISCUSSION

The role of surgery in the treatment of operable locally advanced N2 NSCLC remains controversial.[7-9] The third edition of the American College of Chest Physicians evidence-based clinical practice guidelines recommend that treatment plan for patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA) should be made with the input from a multidisciplinary team.[9] Ratto *et al.* showed good long-term survival and excellent local disease control in their study. Surgery still plays an important role in the multimodality treatment of these patients.[8] In addition, the International Adjuvant Lung Cancer Trial Collaborative Group has recently reported the results of a large randomized trial showing a significant improvement of survival with cisplatin-based adjuvant chemotherapy in completely resected NSCLC.[10] Previous studies had reported that the 5-year survival rate of N2-positive NSCLC was around 19.2–30%.[3,6,11-16] In one large recent study, Koshy *et al*. showed that patients with clinical stage IIIA N2 NSCLC, who underwent neoadjuvant chemoradiation followed by lobectomy, were associated with an improved 5-year overall survival up to 33.5%.[17] In our study, the 5-year disease-free and overall survival rates were 16.7 and 40%, respectively. This result showed that our treatment outcome was non-inferior to previous studies. In patients who received anatomic resection and mediastinal lymph node dissection, the 5-year disease-free and overall survival rates were 20 and 48.2%, respectively. All patients who received non-anatomic resection and mediastinal lymph node sampling died within 5 years after surgery. Therefore, anatomic

Table 1: Patient characteristics

Variables	*N* (%)
Age (mean±SD)	60.2±11.5
Gender-male	56 (51.9)
Neoadjuvant Tx	14 (12.9)
Neoadjuvant modality	
None	94 (87.0)
CT	4 (3.7)
CT+RT	8 (7.4)
Target	2 (1.9)
VATS/open category	
Open	60 (55.6)
VATS	48 (44.4)
Category of operation	
Non anatomic resection	18 (16.7)
Anatomic resection	90 (83.3)
Differentiated grade	
G1	21 (20.6)
G2	56 (54.9)
G3	20 (19.6)
G4	5 (4.9)
N/A	6 (4.9)
Cell type	
Adenocarcinoma	83 (76.9)
Non adenocarcinoma	25 (23.1)
Visceral pleural invasion	68 (68.0)
Angiolymphatic invasion	61 (61.6)
Perineural invasion	7 (7.1)
No. of LN (metastasis)	4.1±3.5
No. of LN (non-metastasis)	14.8±10.6
No. of LN (total)	18.8±11.9
N2 station (metastasis)	
Single	64 (59.2)
Multiple	26 (24.1)
Others	18 (16.7)
Type of skip lesion	
Skip lesion	50 (46.3)
Non skip lesion	40 (37.0)
Others	18 (16.7)
Extracapsular extension	36 (37.5)
Tumor size staging	
T0	1 (0.9)
T1a	10 (9.3)
T1b	13 (12.0)
T2a	60 (55.7)
T2b	18 (16.7)
T3	6 (5.6)
Relapse site	
N	23 (23.7)
Local	17 (17.5)
Distant	23 (23.7)
Local+distant	34 (35.1)
N/A (missing)	11
Highest mediastinal LN involvement	55 (55.6)
Median follow up period (days)	869.5

Abbreviations: SD: Standard deviation; CT: Chemotherapy; RT: Radiotherapy; LN: Lymph node

Table 2: Cox regression modeling result for disease free survival

Variables	Parameter estimated	Standard error	Hazard ratio	*p*	95% confidence interval
T stage	0.21	0.16	1.23	0.19	(0.90, 1.68)
Angiolymphatic invasion	−0.16	0.25	0.84	0.51	(0.52, 1.38)
Perineural invasion	1.11	0.45	3.04	0.01	(1.27, 7.28)
Metastatic LN ratio >0.4	0.34	0.27	1.41	0.21	(0.82, 2.40)
LN excapsular extension	−0.16	0.19	0.85	0.38	(0.59, 1.22)
Category of operation	−0.72	0.41	0.48	0.08	(0.21, 1.09)
Post operation Tx	−0.16	0.31	0.85	0.59	(0.46, 1.56)

Abbreviation: LN: Lymph node

Table 3: Cox regression modeling result for overall survival

Variables	Parameter estimated	Standard error	Hazard ratio	*p*	95% confidence interval
T stage	0.19	0.19	1.05	0.30	(0.83, 1.76)
Angiolymphatic invasion	−0.08	0.31	0.93	0.80	(0.51, 1.69)
Perineural invasion	1.12	0.46	3.05	0.01	(1.25, 7.46)
MetastaticLN ratio >0.4	0.78	0.33	2.18	0.01	(1.13, 4.18)
LN excapsular extension	−0.38	0.32	0.68	0.24	(0.37, 1.29)
Category of operation	−1.41	0.47	0.24	0.002	(0.09, 0.61)
Post operation Tx	−0.58	0.38	0.56	0.13	(0.27, 1.19)

Abbreviation: LN: Lymph node

resection and post-operative adjuvant may be considered as a reasonable treatment plan cisplatin-based chemotherapy for resectable N2 NSCLC.

Analysis of treatment modalities showed anatomic resection as the major determinant factor. Anatomic resection exhibited a reduced hazard ratio in disease-free survival, but without statistical significance (hazard ratio: 0.48, 95% confidence limits 0.21–1.09; $p = 0.08$). However, anatomic resection exhibited a reduced hazard ratio in overall survival (hazard ratio: 0.24, 95% confidence limits 0.09–0.21; $p = 0.002$), which may be attributed to the protective effect of anatomic resection. This protective effect may be caused by the possibilities of occult metastases of N2 disease. This result implies that anatomic resection with mediastinal lymph node dissection can be used to remove as much tumor tissue as possible. Therefore, the lesser the remaining tumor tissue, the longer the patient would survive. In our study, only 14 patients underwent preoperative neoadjuvant therapy. Because of the limited number of cases, we could not account for the preoperative neoadjuvant's effect on disease-free and overall survival rates. In our study, the

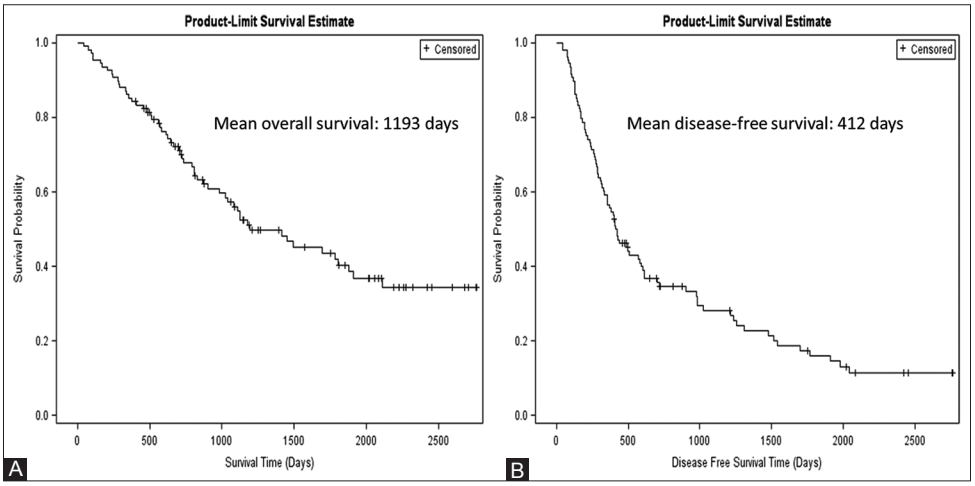

Figure 2: (A) Overall survival curve of all patients; (B) disease-free survival curve of all patients.

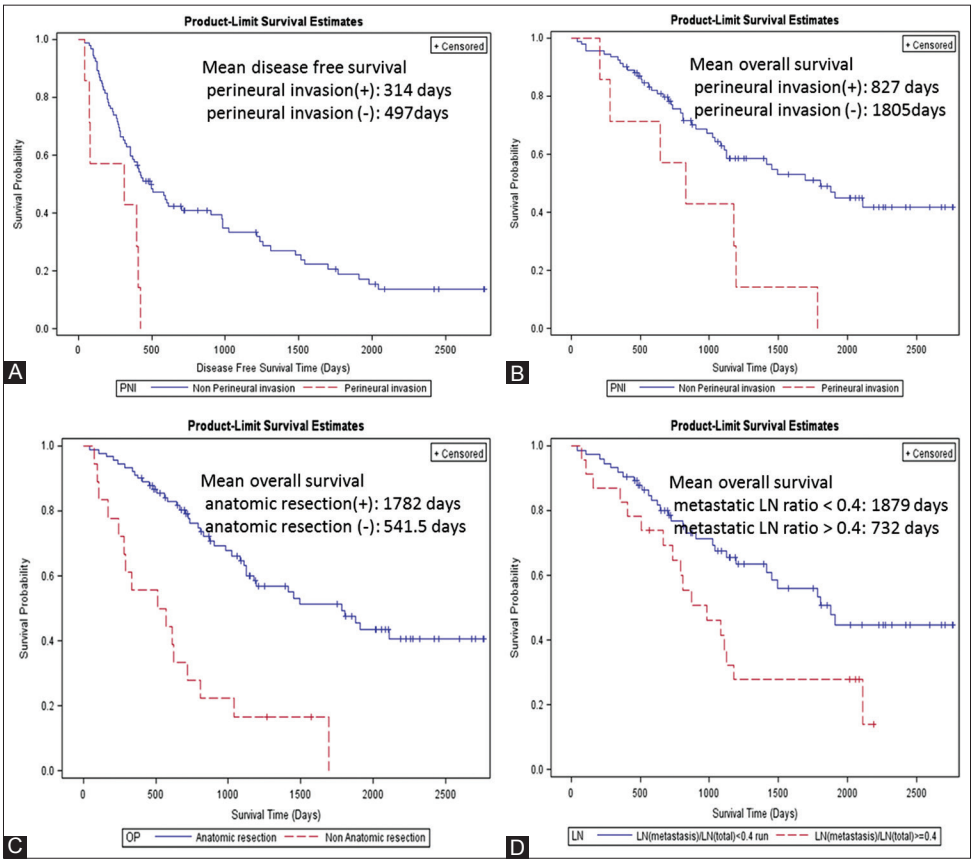

Figure 3: (A) Disease-free survival curve of patients with and without perineural invasion (hazard ratio: 3.04, 95% confidence limits 1.27–7.28; $p = 0.01$); (B) overall survival curve of patients with and without perineural invasion (hazard ratio: 3.05, 95% confidence limits 1.25–7.46; $p = 0.01$); (C) overall survival curve of patients who underwent anatomic resection and those who underwent non-anatomic resection (hazard ratio: 0.24, 95% confidence limits 0.09–0.61; $p = 0.002$); (D) overall survival curve of patients with metastatic lymph node ratio greater and less than 0.4 (hazard ratio: 2.18, 95% confidence limits 1.13–4.18; $p = 0.01$).

postoperative therapy also did not show any significant effect on the disease-free and overall survival rates. But postoperative therapies such as radiotherapy and chemotherapy may have protective effects on the overall survival rate (hazard ratio: 0.38; 95% confidence limits 0.27–1.19; $p = 0.13$). Miller *et al.* had demonstrated similar findings, where the 5-year survival rate was 23.7%.[18] Further investigations are still required to identify the relationship between treatment modality and survival rate. However, anatomic resection may play a crucial role on overall survival in patients with resectable N2 disease.

We further analyzed the characteristic features of tumor cells among patients who underwent anatomic resection, in order to identify its effect on disease-free and overall survival rates. Previous studies had reported that several pathological factors were related to survival rate; these factors include visceral pleural invasion,[19-22] vascular invasion,[23] perineural invasion,[24-26] histologic grade,[27] and nuclear atypia.[28] Our multivariate analysis indicated that only perineural invasion had a significant effect on disease-free and overall survival rates among N2 NSCLC patients. Perineural invasion was defined as cancer cell spreading to the space surrounding a nerve and was confirmed by the pathologist. In literature reports, the reported incidence of perineural invasion was 3–29%.[24-26] In our study, the incidence was 7.1% and this result is similar to that reported in the study of Poncelet *et al*.[25] In addition, the majority (6/7, 85.7%) of patients with perineural invasion had tumor cells with moderate to poor differentiation. Because of the limited number of cases, further investigations are still required to identify its clinical significance and to understand the actual mechanism of perineural invasion that can lead to poor disease-free and overall survival rates.

The low survival of N2 disease can be attributed to mediastinal lymph node involvement. Previous reports mentioned that the survival of N2 disease is characterized by several subgroups with variable survival rates. Okada *et al*. showed patients with following mediastinal metastasis would have acceptable survival after radical resection, including those with upper nodes from upper lobe tumor, lower nodes from lower lobe tumor, or aortic nodes from left upper lobe tumor.[12] In addition, patients with skip metastases,[5,29] without extracapsular spread,[6] and with single station[1,16] involvement exhibited better survival rates. However, even with demonstration of these studies, there is still no consensus on the factors affecting the survival rates. The reason for the non-consensus is the complex nature of the lymphatic pathway to the mediastinum. Riquet *et al*. had reported that direct lymph channels into the mediastinum are more frequently observed in the upper lobes.[30]

Imai *et al*. utilized indocyanine injection for pulmonary lymphatic drainage survey in their study and showed that 21.4% of N2 NSCLC patients had direct lymphatic flow to the mediastinum (3/14).[31] In our study, mediastinal lymph node involvement factors were not related to disease-free survival. This may be related to the possible systemic tumor spread of N2 disease. However, the severity of mediastinal lymph node, i.e. metastatic lymph node ratio, still had a significant impact on the overall survival rate. Wang *et al*. showed that metastatic lymph node ratio greater than 0.18 is a poor prognostic factor among stage II–IIIa patients.[32] In our study, we found that N2 patients with metastatic lymph node ratio greater than 0.4 had poor overall survival. Generally, the more extensive is the tumor spread in the mediastinum lymph node, the more unoptimistic the prognosis would be. However, in our study, only stage IIIa with N2 disease patients were included. This may be the reason why our cut-off value of metastatic lymph node ratio was greater than that of the Wang's study.

There are some limitations in this study. (1) Due to its retrospective nature, the treatments were determined by the clinical decisions of the physicians caring for the patients under the principle of intent to treatment and following the guidelines set by the hospital. The patients were not randomized to each treatment group and selection bias might exist, which could influence the disease-free and overall survival rates. (2) Although all the patients in the present study were evaluated for their lesions by chest radiograph, CT, MRI, bone scintigraphy, or PET according to predetermined management protocols set by the hospital, the intervals between evaluations were not as accurate as those in a prospective trial, which may also affect the precision of disease-free and overall survival rates. (3) We included 18 patients who underwent wedge resection and mediastinal lymph node sampling because of poor pulmonary reserve. The poor general condition of these patients and the selected surgical procedure may lead to poor survival thereafter. However, patients who received anatomic resection in our study still showed non-inferior outcome to Koshy's result[17] (5-year overall survival: 48.2% vs. 33.5%). (4) The study population was small and epidermal growth factor receptor (EGFR) mutation data was lacking for further subgroup survival analysis. (5) There were only seven patients who were identified with perineural invasion, but the effects of prognosis need further investigation due to the small population. Even through limitations remain, our study still provided clinical information for management of pathologic N2 NSCLC patients.

Conclusions

Metastatic lymph node ratio greater than 0.4 and non-anatomic resection were poor prognostic factors for overall survival. Survival of N2 disease is influenced not only by tumor cell characteristics, but also by the mediastinal involvement status. Perineural invasion was found to be a poor prognostic factor for disease-free survival of N2 NSCLC, but needs further investigation due to the small study sample. Finally, anatomic resection for selected N2 patients may play a crucial role in improving overall survival.

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