Prognostic factors in resected pathological N1-stage II nonsmall cell lung cancer

**Chao-Yu Liu*,#,+, Jung-Jyh Hung*,#,+, Bing-Yen Wang¶,
Wen-Hu Hsu*,# and Yu-Chung Wu*,#**

ABSTRACT: Stage II nonsmall cell lung cancer (NSCLC) has been redefined in the seventh edition of tumour, node, metastasis (TNM) classification for lung cancer. Stages IIa and IIb both contain node-negative (N0) and node-positive (N1) subgroups. The aim of this study was to evaluate the prognostic factors for overall survival in patients with resected N1-stage II NSCLC.

Between January 1992 and December 2010, we retrospectively reviewed the clinicopathological characteristics of 163 N1-stage II (T1a-T2bN1M0) NSCLC in patients undergoing curative resection as primary treatment.

Median follow-up time was 37.2 months. The 1-, 3- and 5-yr overall survival rates were 85.3%, 62.1% and 43.5%, respectively. Tumour involvement of the hilar/interlobar nodal zone and poorly differentiated histological grade were significant predictors for worse overall survival using multivariate analysis (p=0.001 and p=0.015, respectively). There were trends toward worse overall survival in older patients and those with larger tumour size (p=0.063 and p=0.075, respectively).

In resected N1-stage II NSCLC, hilar/interlobar nodal involvement and poorly differentiated histological grade were significant predictors of worse overall survival. The differences in survival between these subgroups of patients may lead to the use of different adjuvant therapies or post-surgical follow-up strategies.

KEYWORDS: Hilar/interlobar nodal zone, histological grade, lymph nodes, stage II lung cancer

Lung cancer is the leading cause of cancer-related death worldwide. In Taiwan, it is also the most common cause of cancer-related death in females and the second most common cause of death in males [1]. Surgical resection is the treatment of choice for early-stage nonsmall cell lung cancer (NSCLC). Even with curative surgical resection the 5-yr overall survival rate is between 52% and 61% for stage IIa, and between 43% and 47% for stage IIb [2–4].

The prognostic factors in lung cancer have been widely investigated in order to properly identify high risk patients and provide for their effective treatment. The seventh edition of the tumour, node, metastasis (TNM) classification [5, 6], published in 2009, reclassified malignant pleural effusions and separate tumour nodules. Other changes included new size cut-off points and new subdivisions of the T1 (into T1a and T1b), T2 (into T2a and T2b), and M1 (into M1a and M1b) descriptors. However, the nodal descriptor remained unchanged.

Node-positive (N1) disease represents a heterogeneous group of NSCLC with varying survival rates [7]. In recent decades, many authors have suggested that within the subset of patients with pathological N1 disease, the prognosis may differ according to the number, level or type of lymph nodes involved [8–14]. Stage II NSCLC included a relatively smaller number of patients compared with those with stage I NSCLC. In the present study, we evaluated the prognostic factors in N1-stage II NSCLC with particular emphasis on the prognostic significance of the subgroups of N1 lymphadenopathy.

PATIENTS AND METHODS

Patient selection

The Institutional Review Board of Taipei Veterans General Hospital (Taipei, Taiwan) approved this study and granted a waiver of the informed consent process. From January 1992 to December 2010, a total of 210 consecutive patients who underwent pulmonary resection for pathologic N1-stage II NSCLC (T1a-2bN1M0) with curative intent at Taipei Veterans General Hospital were retrospectively reviewed. Adequate lymph node sampling ensures the accuracy of nodal status. LUDWIG et al. [15] suggested the number of lymph nodes sampled is somewhere between 11 and 16

to evaluate nodal status in lung cancer surgery. Therefore, we restricted our analysis to patients who underwent sampling of ≥12 regional lymph nodes during surgery to ensure the quality of nodal status evaluation. Patients with surgical mortality (n=6, 2.9%), defined as in-hospital death within 30 days after surgery, were excluded from our study. A total of 163 patients were included for analysis.

Pre-operative work-up

The pre-operative work-up included physical examination, serum biochemistry tests, flexible bronchoscopy, chest and upper abdominal computed tomography (CT), radionuclide bone scan, and CT or magnetic resonance imaging of the brain. In addition, positron emission tomography (PET)-CT scans were performed after 2007, if pre-operative tissue diagnosis was available. Mediastinoscopy was not routinely performed in pre-operative staging unless enlarged lymph nodes (with diameter >1.0 cm) were observed on CT and located on the contralateral side of the mediastinum from the cancer, or if the mediastinal lymph node uptake on fluorodeoxyglucose PET was >2.5 times the standard uptake values. Patients with suspected distant metastases were excluded from consideration for surgery. Once staged, a complete resection of all lung disease and lymph node sampling or radical dissection would be performed in all patients.

Lymph node evaluation

N1 and N2 lymph nodes were defined according to the lymph node map published by the International Association for the Study of Lung Cancer (IASLC) in 2009 [16]. An N1 node was classified into "hilar/interlobar" and "peripheral" zones, according to the anatomical location. Hilar nodes (station 10) included nodes immediately adjacent to the mainstem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery. Interlobar node (stations 11) included nodes between the origins of the lobar bronchi.

The lymph node dissection or sampling was performed routinely, including nodes stations 2R, 4R, 7R and 10R on the right side and 5L, 6L, 7L and 10L on the left side. In lobectomy, station 11 (interlobar lymph nodes) were routinely sampled. The lymph nodes sampled by surgeons were labelled accordingly for pathological examination. However, stations 12, 13 and 14 were mainly examined by pathologists. The pathologists dissected the resected lung tissue along the major bronchus into lung parenchyma. If lymph nodes were found along the bronchial trees, they were labelled according to their anatomical location. The whole lung tissue was later sliced at 1-cm intervals. If lymph nodes were found, they were named as an "intrapulmonary lymph node".

The total number of lymph nodes removed during surgery was defined as the number of lymph nodes dissected or sampled by the surgeon during surgery (including those sent for frozen diagnosis) and intrapulmonary lymph nodes examined by pathologists; all lymph nodes were examined by pathologists. The nodes harvested from mediastinoscopy were also included in this study. Pathological staging was assessed after examination of the resected specimens and all resected lymph nodes were examined for metastatic carcinoma. Disease stages were based on the seventh edition TNM classification of NSCLC [17].

None of our patients had prior neo-adjuvant radiotherapy or chemotherapy. Adjuvant chemotherapy was given to patients after surgical resection unless the patient was unable to tolerate it. All patients were followed-up on a three-monthly basis at our outpatient department during the initial 2 yrs after resection and semi-annually thereafter. The outcome was defined as death attributable to either cancer or noncancer causes. The length of survival was defined as the interval in months between the date of surgical resection and the date of either death or the last follow-up.

Statistical analysis

The overall survival rate was calculated by the Kaplan–Meier method. Univariate and multivariate analyses were performed by means of Cox proportional hazards model using the SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). A stepwise regression procedure was used. Clinicopathological factors such as age, sex, tumour size, histological type (squamous cell or other histological types), histological grading (well-to-moderately differentiated *versus* poorly differentiated), presence of visceral pleural invasion (VPI), involved lymph node number (solitary *versus* multiple), involved lymph node ratio (defined as the number of positive lymph nodes divided by the number of total resected lymph nodes) and level of lymph node involved (hilar/interlobar zone *versus* peripheral zone) were included in the univariate analyses. Variables with a p-value <0.10 in univariate analysis were entered into multivariate analysis. A p-value <0.05 was considered statistically significant.

RESULTS

The median follow-up time for the 163 patients with surgically resected N1-stage II NSCLC was 37.2 months (mean 50.4 months, range 1.2–186.0 months). At the last follow-up session, 61 (37.4%) patients were alive and 102 (62.6%) patients died of either cancer or noncancer causes. The 1-, 3- and 5-yr overall survival rates were 85.3%, 62.1% and 43.5%, respectively (fig. 1). The demographic and clinicopathological characteristics of these patients are summarised in table 1.

The mean age of our cohort was 65 yrs and the male-to-female ratio was 2.40. A total of 85 (52.1%) patients had tumour within the right lung and 78 (47.9%) patients had tumour within the left lung. Surgical resection was mainly lobectomy (131 (80.4%) patients) for tumour removal, and only one patient had sublobar resection. The greatest dimension of each tumour was measured and recorded. 77 (47.2%) patients had a tumour size ≤3 cm and 86 (52.8%) patients had a tumour size >3 cm.

Adenocarcinoma was the main histological type within our cohort (90 (55.2%) patients). According to the pathology report, histological grading was divided into well-, moderately and poorly differentiated carcinoma. However, there were 45 (27.6%) patients with missing or histological grade "not described" in our cohort. Tumour with visceral pleural invasion was seen in 67 (41.1%) patients. However, there were 14 (8.6%) patients with "unknown status" regarding visceral pleural invasion. In the surgically dissected lymph nodes, a solitary metastatic lymph node was found in 88 (54.0%) patients. 75 (46.0%) patients were found to have ≥2 lymph nodes metastases. Lymph node ratio was defined as the ratio of involved lymph nodes to the total number of removed nodes.

A cut-off point of 0.06 was obtained to equally separate our cohort into two groups for comparison. According to IASLC lymph node map, which categorised lymph nodes into ''zones'', cancer involvement of hilar/interlobar zone was seen in 61 (37.4%) patients and involvement of the peripheral zone was noted in 86 (52.8%) patients. 16 (9.8%) patients had both zones involved.

The factors associated with lung cancer prognosis were evaluated using univariate analysis. This analysis showed that age (as a continuous variable, p=0.001), cancer-involved lymph node ratio (p=0.044) and cancer involvement of hilar/interlobar lymph nodes (p=0.013) had a significant influence on overall survival (table 2). Survival was significantly better in younger patients, patients with lower cancer-involved lymph node ratios ($\leqslant 0.06$) and patients who had metastatic N1 lymph node involvement of other regions besides the hilar/interlobar zone. The hazard of death was greater in patients with a tumour size >3 cm (hazard ratio (HR) 1.440, 95% confidence interval (CI) 0.970–2.138; p=0.070), poorly-differentiated cell type (HR 1.589, 95% CI 0.968–2.609; p=0.067), and multiple cancer–involved N1 lymph nodes (HR 1.325, 95% CI 0.896–1.961; p=0.159). Although these factors did not reach statistical significance, the trend to predict survival was comparable with other reports from the literature. The variables with a p-value <0.10 were entered into multivariate analysis. Only histological grade (p=0.015) and tumour involvement of hilar/interlobar lymph nodes (p=0.001) were significant prognostic indicators on multivariate analysis (table 3). Older patients (p=0.063), large tumour size (p=0.075) and high involved lymph node ratio (p=0.199) showed a trend toward poorer overall survival.

DISCUSSION

Staging is important for predicting patient prognosis and selecting appropriate lung cancer treatment. The IASLC established an international staging committee to formulate a revision of the TNM classification of lung cancer that was published in the seventh edition of the Union International
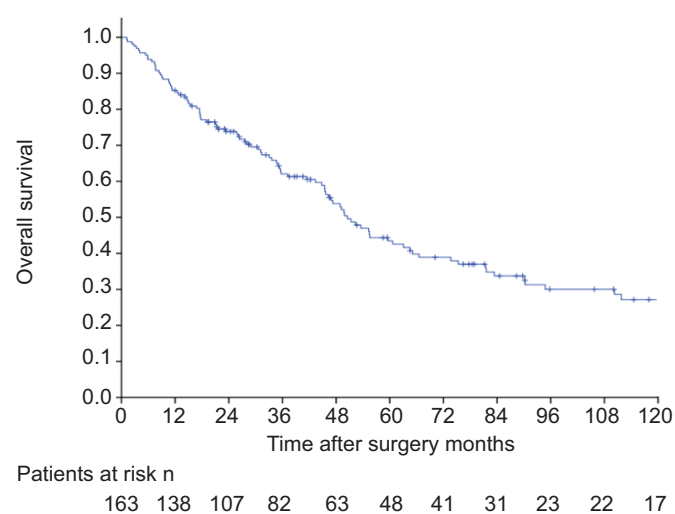
Contre le Cancer and American Joint Commission on Cancer (AJCC) cancer staging manuals in 2009 [5, 6]. The seventh edition of TNM classification of lung cancer provided a revision of the T descriptor, which divided T1 into T1a and T1b, and T2 into T2a and T2b according to new tumour size cut-off points [17]. Although the N descriptors remained unchanged in the new edition of TNM system, the IASLC staging committee developed a revised lymph node map that grouped lymph node stations into ''zones'', i.e. peripheral or hilar for N1, and upper or lower mediastinal, or aortopulmonary or subcarinal for N2 nodes [16].

The first lymph node map, developed by NARUKE [18] during the 1960s, was initially widely used in North America, Europe

TABLE 1	Characteristics of 163 patients of resected N1-stage II nonsmall cell lung cancer
Age yrs	67 (65.2±10.1)
Sex	
Male	115 (70.6)
Female	48 (29.4)
Tumour location	
Right lung	85 (52.1)
Left lung	78 (47.9)
Tumour size cm	
$\leqslant 2$	33 (20.2)
>2 to $\leqslant 3$	44 (27.0)
>3 to $\leqslant 5$	65 (39.9)
>5 to $\leqslant 7$	21 (12.9)
Pathological stage	
IIa	142 (87.1)
IIb	21 (12.9)
Extent of pulmonary resection	
Lobectomy or wedge resection	132 (81.6)
Bilobectomy or pneumonectomy	31 (18.4)
Histological type	
Squamous cell carcinoma	57 (35.0)
Adenocarcinoma	90 (55.2)
Others	16 (9.8)
Histological grade	
Well-to-moderately differentiated	81 (49.7)
Poorly differentiated	37 (22.7)
Unknown	45 (27.6)
Visceral pleural invasion	
Present	67 (41.1)
Absent	82 (50.3)
Unknown	14 (8.6)
Lymph nodes involved n	
Solitary	88 (54.0)
Multiple	75 (46.0)
Involved lymph node ratio	
$\leqslant 0.06$	84 (51.5)
>0.06	79 (48.5)
Zone of lymph node involved	
Hilar/interlobar	61 (37.4)
Peripheral	86 (52.8)
Both	16 (9.8)

Data are presented as median (mean±SD) or n (%).

FIGURE 1. The Kaplan–Meier survival curve of 163 N1-stage II nonsmall cell lung cancer patients after curative surgical resection.

Patients at risk n
163 138 107 82 63 48 41 31 23 22 17

TABLE 2	Univariate analyses for overall survival in patients with resected N1-stage II nonsmall cell lung cancer	
Variables	**HR (95% CI)**	**p-value**
Age yrs	1.036 (1.014–1.060)	0.001
Sex		0.857
Female	1	
Male	1.041 (0.673–1.611)	
Tumour size		0.070
⩽3 cm	1	
>3 cm (⩽7 cm)	1.440 (0.970–2.138)	
Pathological stage		0.249
IIa	1	
IIb	1.382 (0.797–2.394)	
Histology type		0.686
Squamous cell	1	
Nonsquamous cell	1.089 (0.721–1.645)	
Histological grade		0.067
Well-to-moderately differentiated	1	
Poorly differentiated	1.589 (0.968–2.609)	
Visceral pleural invasion		0.315
No	1	
Yes	1.251 (0.808–1.937)	
Lymph nodes involved n		0.159
Solitary	1	
Multiple	1.325	
Involved lymph node ratio		0.044
⩽0.06	1	
>0.06	1.499 (1.010–2.224)	
Hilar/interlobar lymph node involved		0.013
No	1	
Yes	1.651 (1.112–2.452)	

HR: hazard ratio.

TABLE 3	Multivariate analyses for overall survival in patients with resected N1-stage II nonsmall cell lung cancer	
Variables	**HR (95% CI)**	**p-value**
Age yrs	1.028 (0.998–1.058)	0.063
Tumour size		0.075
⩽3 cm	1	
>3 cm (⩽7 cm)	1.631 (0.953–2.793)	
Histological grade		0.015
Well-to-moderately differentiated	1	
Poorly differentiated	1.975 (1.142–3.414)	
Involved lymph node ratio		0.199
⩽0.06	1	
>0.06	1.404 (0.857–2.355)	
Hilar/interlobar lymph node involved		0.001
No	1	
Yes	2.595 (1.507–4.469)	

HR: hazard ratio.

and Japan. However, subsequent attempts to refine the anatomical descriptors of the Naruke map led to the development of maps by the American Thoracic Society (ATS) and the so-called Mountain–Dresler modification of the ATS map (MD-ATS). The revised lymph node map reconciled differences between the Japanese (Naruke) and MD-ATS maps and provided more specific anatomical definitions for each of the lymph node stations [16]. In the new version of TNM classification system, stage IIa and stage IIb both contain node-positive (stage IIa contains T1a-T2aN1 and stage IIb contains T2bN1) and node-negative (stage IIa contains T2bN0 and stage IIb contains T3N0) cases. In the present study, given the revised lymph node map and a new staging system, we examined the prognostic factors used to predict survival in the node-positive stage II NSCLC, with emphasis on the characteristics of N1 lymphadenopathy.

The status of regional lymph nodes is a strong prognostic indicator and has a major impact on treatment decisions for patients with NSCLC [19]. Although the N descriptors in the

new edition of TNM system were not changed, several studies have reported that, within the N1 category, there are several prognostic modifiers. These include the number of lymph nodes involved (solitary versus multiple) [19–21], the ratio of lymph nodes involved [20, 21], the level of lymph nodes involved (hilar versus lobar) [7, 11, 12, 22, 23], and the pattern of lymph nodes involved (direct invasion versus separate metastases) [24, 25]. Several studies have highlighted that N1 disease represents a heterogeneous group of patients with different lymph node-related factors affecting prognosis. The identification of subgroups of patients with different outcomes could help to tailor post-operative management, such as aggressive chemotherapy or closer follow-up strategy.

The number of involved lymph nodes has been recognised as a significant predictor of survival in N1 NSCLC. JONNALAGADDA et al. [21] analysed the data from the Surveillance, Epidemiology, and End Results database, including 3,399 patients with N1 NSCLC. They concluded that the number of positive lymph nodes is an independent prognostic factor for survival in patients with N1 NSCLC. In our study, with a relatively smaller sample size, multiple lymph node involvement with tumour showed a trend toward poorer overall survival on univariate analysis (HR 1.325, 95% CI 0.896–1.961; p=0.159). However, the association between survival and number of tumour-involved lymph nodes is inherently confounded by the number of removed lymph nodes. Therefore, WISNIVESKY et al. [26] reported the prognostic impact of the lymph node ratio (LNR) on 1,682 patients aged >65 yrs diagnosed with pathological N1 NSCLC [26]. A median value of eight lymph nodes was resected in each patient within their cohort. They divided their patients into three groups according to the LNR: ⩽0.15, 0.15–0.5 and >0.5. Within the population studied, they found that the overall survival was significantly worse as the LNR increased. In our

series, a median number of 23 lymph nodes was resected, which was three times larger than the median number resected in the study by WISNIVESKY *et al.* [26]. We also found that patients with a LNR >0.06 had a significantly higher hazard risk of death (HR 1.499, 95% CI 1.010–2.224) than patients with a LNR ≤0.06 on univariate analysis (p=0.044). Our study echoed other previous studies in which LNR was found to be a prognostic factor for survival in patients with N1 NSCLC.

In addition to the number and ratio of lymph node involvement, the level of nodal involvement is a frequently investigated prognostic factor in N1 NSCLC, with a worse outcome for hilar station involvement compared with interlobar or more peripheral station metastases. SHIMADA *et al.* [22], with the use of the lymph node map developed by NARUKE *et al.* [27], concluded that patients with node 10 (hilar)-positive N1 disease have an unfavourable prognosis, as the disease behaves like N2 disease [22]. With the use of the IASLC lymph node map, we showed that patients with tumour involvement of the hilar/interlobar zone had a significantly higher hazard risk of death both on univariate analysis (HR 1.651, 95% CI 1.112–2.452; p=0.013) and multivariate analysis (HR 2.595, 95% CI 1.490–4.427; p=0.001). The 5-yr overall survival rates in patients with and without tumour involvement of hilar/interlobar nodal zone were 37.1% and 49.9%, respectively (p=0.012) (fig. 2). Our study showed that the tumour involvement of hilar/interlobar zone is an independent prognostic factor in N1-stage II NSCLC.

We also found that histological grade (cell differentiation) was a significant predictor for overall survival in N1-stage II NSCLC. Patients with poorly differentiated carcinoma had an increased hazard risk of death both on univariate analysis (HR 1.589; 95% CI 0.968–2.609; p=0.067) and multivariate analysis (HR 1.997; 95% CI 1.154–3.455; p=0.013). In the published literature, the impact of cell differentiation on survival was discussed primarily in patients with stage I NSCLC. HSU *et al.* [28] reported that in NSCLC patients with stage Ib (pT2N0M0), cell differentiation is a significant prognosticator for overall survival (p=0.0024). In a previous study, we also showed that cell differentiation was associated with overall survival in stage I NSCLC (p=0.04) [29]. However, cell differentiation has rarely been discussed in stage II NSCLC. We noted that patients with poorly differentiated carcinoma were associated with poorer overall survival after including other prognostic factors for mutual adjustment (p=0.015). However, larger sample sizes are needed to confirm this finding.

The influence of visceral pleural invasion (VPI) on stage II NSCLC remains unclear. VAN VELZEN *et al.* [11] reported that the presence of VPI unfavourably affected survival in T2N1M0 NSCLC patients (p=0.0093). However, in the study by RIQUET *et al.* [12], VPI did not correlate with overall survival in pathological N1 NSCLC patients (p=0.65). In our study, patients with VPI showed a trend toward a slightly higher hazard risk of death compared with their counterparts on univariate analysis; however, the result was not significant (HR 1.251, 95% CI 0.808–1.937; p=0.315).

Lymph node metastases are present in most cases of stage II NSCLC. However, the impact of any non-nodal factor is less clear than in stage I disease. HOLMES [30] reported significant survival differences favouring squamous cell lung cancer in T1N1 and ICHINOSE *et al.* [31] showed similar results in T1-2N1 disease. However, neither MARTINI *et al.* [32] nor YANO *et al.* [8] found any significant histological benefit favouring squamous cell lung cancer over nonsquamous cell lung cancer. CHANSKY *et al.* [33] published a prognostic analysis of a cohort of 9,137 surgically managed stage I to stage IIIA NSCLC patients (the IASLC staging project). In their study, the squamous cell carcinoma may have a better prognosis than the nonbronchioloalveolar carcinoma type adenocarcinoma, particularly among male patients with early-stage disease. Our results from a population of T1a-2bN1 NSCLC showed no survival benefit in squamous cell carcinoma over nonsquamous cell carcinoma. In an adjusted analysis for sex, the survival prognosis remained similar in both groups. Therefore, our study failed to identify the cancer cell type to be a significant prognostic factor in surgically managed N1-stage II NSCLC patients. The results of CHANSKY *et al.* [33] and our study may reflect the fact that the prognostic impact of cell type, compared with nodal status, are less significant in N1 NSCLC.

Tumour size in stage II NSCLC does not appear to significantly affect overall survival. MARTINI *et al.* [32] found that tumour size <3 cm in diameter had a higher survival rate compared with those >5 cm. In our series of N1-stage II NSCLC, tumour size >3 cm but ≤7 cm had an increased hazard risk of death compared with those ≤3 cm in diameter (HR 1.631; p=0.075). Although our result did not reach statistical significance, it implied that the tumour size may have an impact on survival in N1-stage II NSCLC if a larger-sized population is studied.

Our study had several limitations. We performed a retrospective analysis over a long period of time. Data are lacking in some patients for certain variables, such as visceral pleural
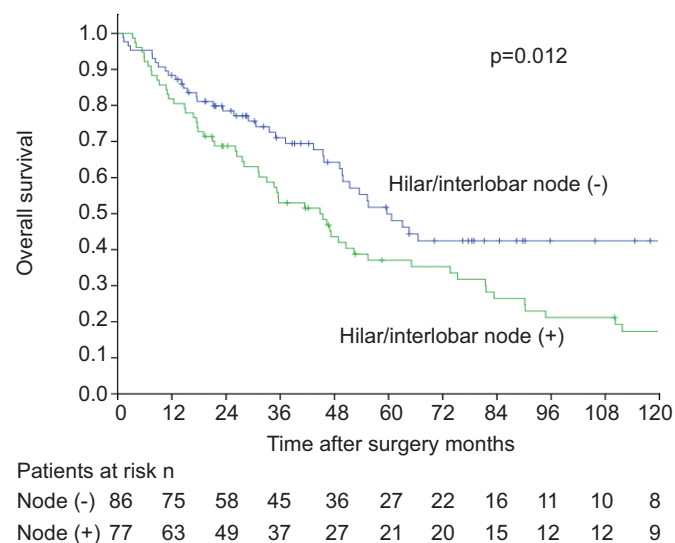

FIGURE 2. The Kaplan–Meier survival curves of 163 N1-stage II nonsmall cell lung cancer patients who had hilar/interlobar node positive and negative. Log rank p<0.001.

invasion and histological grade, which may have affected our results. Several different surgeons performed the pulmonary resections and not all patients received radical mediastinal lymph node dissection in our cohort. Additionally, resected N1 nodes were not examined and reported by the same group of pathologists. Therefore, the quantity and quality of lymph node dissection/sampling were not the same among all our patients, despite the cases we excluded from our study with <12 sampled lymph nodes. Lack of data regarding recurrence-free survival was another limitation of our study.

Conclusions

Stage II NSCLC comprises a heterogeneous group of node-positive and -negative tumours. Prognostic factor analysis confers a better evaluation of this subgroup of patient. In the present study of N1-stage II NSCLC, hilar/interlobar nodal involvement and poorly differentiated histological grade were significant predictors of worse overall survival. The differences in survival between these subgroups of patients may lead to the use of different adjuvant therapies or post-surgical follow-up strategies. Future clinical trials will have to consider the survival difference of these subgroups of patient and stratification will be necessary to test adjuvant therapies.

STATEMENT OF INTEREST

None declared.

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