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Original Article

# Risk factors for relapse of resectable pathologic N2 non small lung cancer and prediction model for time-to-progression

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ARTICLE INFO

*Article history:*
Received 27 April 2015
Accepted 14 September 2016
Available online 21 March 2017

*Keywords:*
N2 non-small-cell lung cancer
Relapse
Recurrence
Time to progress
Risk factor

ABSTRACT

*Background:* Pathologic N2 non-small-cell lung cancer (NSCLC) was demonstrated with poor survival among literature. In this study, we retrospectively reviewed patients with pathologic N2 NSCLC and received anatomic resection (i.e. lobectomy) for further relapse risk factor analysis. The aim of this study is to identify the clinicopathologic factors related to relapse among resectable N2 NSCLC patients and to help clinicians in developing individualized follow up program and treatment plan.

*Method:* From January 2005 to July 2012, 90 diagnosed pathologic N2 NSCLC patients were enrolled into this study. We retrospectively reviewed medical records, image studies, and pathology reports to collect the patient clinico-pathologic factors.

*Result:* We identified that patients with visceral pleural invasion ($p = 0.001$) and skip metastases along mediastinal lymph node ($p = 0.01$) had a significant relationship to distant and disseminated metastases. Patients who had 2 or more risk factors for relapse demonstrated poor disease free survival than those who had less than 2 risk factors ($p = 0.02$). The number of involved metastatic area were significantly influential to the period of time-to-progression. The duration of time-to-progression was correlated with square of number of involved metastatic areas. (Pearson correlation coefficient = −0.29; $p = 0.036$).

*Conclusion:* Relapse risk factors of resectable pathologic N2 NSCLC patient after anatomic resection were visceral pleural invasion, skip mediastinal lymph node involvement, and the receipt of neoadjuvant therapy. The duration of time-to-progression was correlated with square of number of involved metastatic areas.

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Peer review under responsibility of Chang Gung University.
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http://dx.doi.org/10.1016/j.bj.2017.01.005

## At a glance commentary

### *Scientific background on the subject*

Non small cell lung cancer patient with N2 mediastinal lymph node involvement as higher relapse risk. In case of disease relapse, the disease severity of these patients were IIIb or IV according to TNM stage. However, there was huge survival difference between individuals. Some patients would stable with disease for a period of time and some were not. We tried further analyze the relationship between relapse involved sites and time to progression survival.

### *What this study adds to the field*

Our result confirmed the involved relapse sites were corrected to time to progression survival. For patients with more extensive disease status, best supportive care may be considered instead of aggressive treatment because of short time to progression period.

Pathologic N2 non-small-cell lung cancer (NSCLC) was shown with poor survival rates among literature. The reported 5-year survival rate varied from 19.2 to 30% [1–7]. In this patient population, there are many subgroups that also showed similar survival curves [8]. Therefore, many studies had tried to further analyze these NSCLC patients in order to stratify the patient population and individualize treatment planning. These studies showed that the patients with the following clinical scenarios have especially poor disease prognosis: (1) tumor cell involved multiple mediastinal lymph node stations, (2) sub-carinal lymph node involvement, and (3) presence of extra-capsular extension [2,9–11]. Otherwise, patients with skip mediastinal lymph node were correlated to better survival [11–13]. However, the actual effect of these risk factors to disease prognosis remains unknown. In our study, we retrospectively reviewed patients with pathologic N2 NSCLC who received anatomic resection (i.e. lobectomy) for further relapse risk factor analysis. The aim of study is to identify the clinic-pathologic factors that are related to relapse among resectable N2 NSCLC and to help clinicians in developing individual follow up program and treatment plan.

## Materials and methods

### *Patients and follow up program*

From January 2005 to July 2012, 108 pathologic N2 NSCLC patients were enrolled into this study. Eighteen patients who did not receive anatomic resection were excluded from analysis. We retrospectively reviewed medical records, image studies, and pathology reports of these patients to collect their clinico-pathologic factors. Patient's pre-operative workups were reviewed thoroughly, which included chest computed tomography (CT), proton emission tomography (PET or PET-CT), brain CT, and spirometry. All the remaining patients in this study were those who received anatomic resection (i.e. lobectomy) and had confirmed pathologic N2 disease without distant metastases. After surgery, patients with well general status were given adjuvant cisplatin-base chemotherapy. All patients underwent regular surveillance in the outpatient department after complete treatment. The imaging tool that utilized for surveillance was chest CT. If the patients were suspected about the cancer relapse, further PET-CT or bone scan would be done. If a patient's lesion was easily accessible, biopsy would be performed. Disease relapse was confirmed with positive image finding or biopsy proven. Disease-free survival was defined as the period between diagnostic date to the date of confirmed relapse. Overall survival was the period from diagnostic date to patient death.

### *Definition of local and distal metastases*

Local metastases were defined as disease relapse at surgical stump or ipsilateral thorax. All other form of metastatic lesions were classified as distant metastases. In addition, we further divided the whole body into six areas, which includes nervous system, thorax cavity, mediastinum, abdomen, musculoskeletal system, and other soft tissue. We calculated the involved metastatic area from image survey (CT and PET-CT). Response evaluation criteria in solid tumor (RECIST) was utilized to differentiate patient disease status [14]. Time-to-progression was defined from the date of confirmed relapse to the date of confirmed progressive disease status by image finding according to RECIST criteria. This study was proved by Institutional Board Review of Chang Gung Memorial Hospital and the IRB number is 99-1586B.

### *Statistics*

All collected clinico-pathologic factors were further analysis by univariate analysis. Categorical variables were compared with 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 to further identify the clinico-pathologic factors in relation to disease-free and overall survival. A $p$-value of less than or equal to 0.05 was considered statistically significant. Reported confidence intervals (CI) are assumed to have a coverage probability of 95%. All the statistical analyses were performed using SAS, version 9 (SAS Institute, NC, USA).

## Results

Ninety N2 NSCLC patients who underwent anatomic resection (i.e. lobectomy) were included into analysis. The averaged patient age was 59.8 years and the female population was mildly predominant (48 patients, 53.3%). Majority (76 patients, 84.4%) of these patents did not received pre-operative neo-adjuvant therapy. From 2005 to 2009, surgical intervention was performed by open thoracotomy. In 2010, the operating procedure was switched from open thoracotomy to video-assisted thoracoscopic surgery (VATS). The most common cell type was adenocarcinoma (72 patients, 80%) and the tumor differentiation status was moderately differentiated (48

patients, 54.6%) The T-stage among patients ranged from T0 to T3. One patient received pre-operative neoadjuvant chemotherapy prior operation was found with no residual tumor within the resected specimen and classified as T0. In addition, three patients were classified with T3 lesions and all of them had tumor sizes of greater 7 cm in diameter. The total lymph node number removed was 19.8 ± 11.7 and number of metastatic lymph node was 4.2 ± 3.6. The median follow up duration was 1044 days. All patients' characteristics are shown in Table 1.

We categorized the disease relapse were into three subgroups, which includes local, distant, or disseminated (i.e. relapse involved both local and distant areas). The percentage of local, distant, and disseminated disease relapse was 18.8%, 27.5%, and 35%, respectively. We found that the types of relapse did not influence the overall patient survival rate [Fig. 1]. For patients with local relapse, no significant prognostic factor was identified. We identified that patients with visceral pleural invasion ($p = 0.001$) and skip metastases along mediastinal lymph node ($p = 0.01$) were significantly linked to distant metastases [Table 2]. In addition, patients with visceral pleural invasion ($p = 0.003$), skip metastases along mediastinal lymph node ($p = 0.004$), and neoadjuvant chemotherapy ($p = 0.02$) were shown to have higher risks for disseminated recurrence [Table 3].

We further stratify patients into two groups with three risk factors that included pre-operative neoadjuvant therapy, visceral pleural invasion, and skip mediastinal lymph node. Patients with two or more risk factors have worsened disease free survival time.

It was determined that the patients with two or more risk factors for relapse had poor disease free survival [$p = 0.02$, Fig. 2A] but not overall survival [Fig. 2B]. The clinical status of patients with confirmed relapse was further analyzed with RECIST. Numbers of involved metastatic areas were also calculated from computed tomography and image survey. We identified that the number of involved metastatic areas were significantly influential to the period of time-to-progression. The duration of time-to-progression was correlated with square of number of metastatic areas [Pearson correlation coefficient = −0.29; $p = 0.036$; Fig. 3].

## Discussion

Visceral pleural invasion stages were defined as the following: (1) VP0 is lack of pleural invasion beyond the elastic layer, (2) VP1 is the invasion beyond the elastic layer, (3) VP2 is the invasion to the surface of the visceral pleura, and (4) VP3 is invasion of the parietal pleura [15]. It was reported among literature that the survival was shown to be significantly worse for VPI defined as (P1 or P2) compared to P0 [16–19]. In our study, only VP1 and VP2 were identified among our study population. However, we identified that patients with visceral pleural invasions not only have greater risks of distant metastases but also poor disease-free survival ($p = 0.02$, data not shown) as well. The result from our study is similar to those reported by previous literature. Visceral pleural invasion can adversely affect disease free survival because visceral pleural invasion could be linked to the possibility of distant or disseminated metastases.

For resectable pathologic N2 NSCLC patient, mediastinal lymph node involvement status can also influence the patient's survival. From literature review, patients had poor disease prognosis if following clinical scenarios were present: tumor cell involved multiple mediastinal lymph node stations, sub-carinal lymph node involvement, and presence of extra-capsular extension [2,9–11]. However, the role of skip mediastinal lymph node involvement still remains controversial. Some studies showed better survival rates [11–13].

**Table 1 Descriptive statistics (anatomic resection, n = 90).**

| Variables | N (%) | Variables | N (%) |
|---|---|---|---|
| Age (mean ± SD) | 59.8 ± 11.4 | No. of LN (total) | 19.8 ± 11.7 |
| Gender–male | 42 (46.7) | N2 station status | |
| Neoadjuvant chemotherapy – Yes | 14 (15.6) | Single | 64 (71.1) |
| VATS/OPEN category | | Multiple | 26 (28.9) |
| OPEN | 56 (62.2) | Type of skip lesion | |
| VATS | 34 (37.8) | Skip lesion | 40 (44.4) |
| Mediastinoscopy | 0 (0.0) | Non skip lesion | 50 (55.6) |
| Differentiated grade | | T Staging | |
| G1 | 19 (21.6) | T0 | 1 (1.1) |
| G2 | 48 (54.6) | T1a | 9 (10.0) |
| G3 | 17 (19.3) | T1b | 11 (12.2) |
| G4 | 4 (4.6) | T2a | 50 (55.6) |
| Cell type | | T2b | 16 (17.8) |
| Adenocarcinoma | 72 (80.0) | T3 | 3 (3.3) |
| Non adenocarcinoma | 18 (20.0) | Relapse site | |
| Visceral pleural invasion – Yes | 59 (65.6) | Local | 15 (18.8) |
| Angiolymphatic invasion – Yes | 56 (62.9) | Distant | 22 (27.5) |
| Perineural invasion – Yes | 6 (6.7) | Disseminated | 28 (35.0) |
| Metastatic ratio | 0.25 ± 0.18 | Median follow up period (days) | 1044 |
| Yes for highest LN | 49 (54.4) | Tumor size | 3.6 ± 1.8 |
| Extracapsular extension – Yes | 35 (38.9) | | |
| No. of LN (metastasis) | 4.2 ± 3.6 | | |
| No. of LN (non-metastasis) | 15.6 ± 10.5 | | |

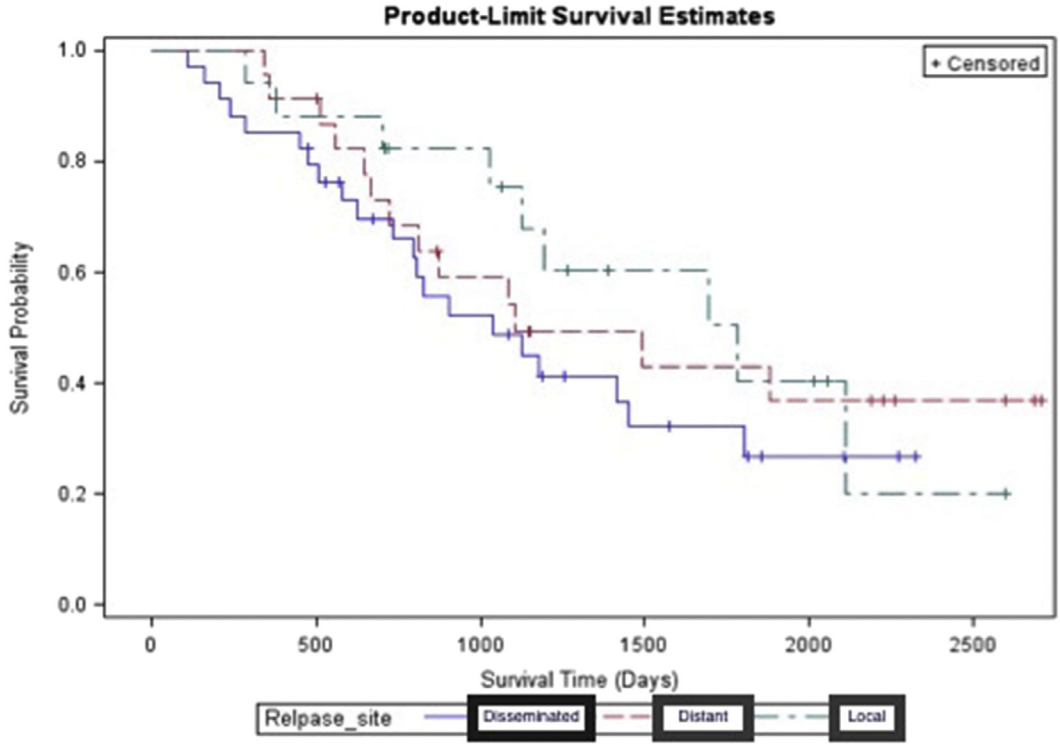


Fig. 1 Overall survival of different relapse pattern ($p = 0.43$).

**Table 2 Multiple logistic regression result for the outcome of distant relapse by stepwise model selection.**

| Variables | Estimate | Standard error | Chi-square | *p*-value |
|---|---|---|---|---|
| Visceral pleural invasion | −1.18 | 0.36 | 10.86 | 0.001 |
| Skip mediastinal lymph node involvement | −0.96 | 0.38 | 6.66 | 0.01 |

Reference group: Diagnosed pathologic N2 NSCLC patients without cancer relapse.

Other study had revealed that skip mediastinal lymph involvement did not affect survival [20,21]. In our study, we found that patients with skip mediastinal lymph node involvements may have risks for distant or disseminated metastases. This finding revealed that the lymph flows directly to the mediastinum without passage through the pulmonary hilum. This reported phenomenon can explain that the patient with skip mediastinal lymph node involvement is at high risk of tumor cell spread.

Patients who underwent neoadjuvant chemotherapy prior anatomic resection has poor survival impact. The initial disease presentations of these patients were more invasive and good tumor shrinkage was confirmed by image tools after neoadjuvant chemotherapy. Even though resected specimen, including resected pulmonary lobe and dissected mediastinal lymph nodes, were confirmed as N2 NSCLC by pathologist. However, current imaging tools cannot completely detect the possible micro-metastases prior resection and the possibility of metastases could not complete excluded. In addition, routine pathologic examination cannot exam a whole specimen thoroughly. These scenarios may be the reason that patients who underwent neoadjuvant chemotherapy and anatomic resection had more risks for disseminated metastases.

In our study, we further divided patients into two groups according to these three identified relapse risk factor. Patient who has less than two risk factors had better 5-year disease free survival compared to those with two or more risk factors ($p < 0.02$). This finding demonstrated that the patients with two

**Table 3 Multiple logistic regression result for the outcome of disseminated relapse by stepwise model selection.**

| Variables | Estimate | Standard error | Chi-square | *p*-value |
|---|---|---|---|---|
| Neoadjuvant chemotherapy | 1.21 | 0.50 | 5.69 | 0.02 |
| Visceral pleural invasion | 1.16 | 0.39 | 8.47 | 0.003 |
| Skip mediastinal lymph node involvement | 1.10 | 0.31 | 12.4 | 0.004 |

Reference group: Diagnosed pathologic N2 NSCLC patients without cancer relapse.

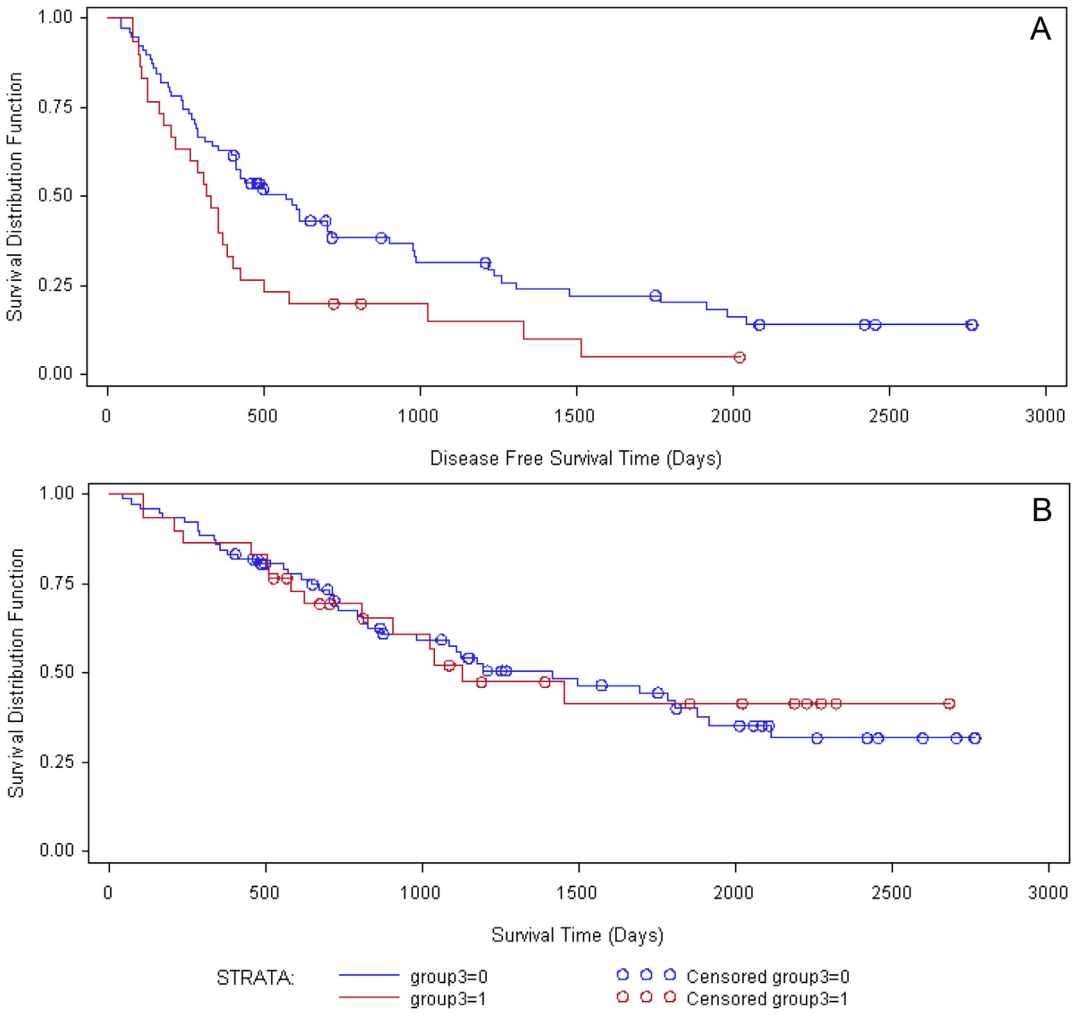


Fig. 2 (A) Patients with two or more prognostic factors were shown with decreased disease free survival ($p = 0.02$). (B) No overall survival difference between the two groups ($p = 0.87$).

or more relapse risk factors would have poor prognosis. Because all of the relapse factors were associated with distant metastases, Chest CT may not be a sufficient post-operation imaging tool for monitoring patients with these relapse risk factors. Whole body CT is recommended for patients with one risk factor, in order to identify distant relapse as earlier as possible.

There are a lot of studies that demonstrated the prognostic factors in order to identify high and low risk patients. By this additional information, clinical practitioners can prioritize adjuvant therapy for patients with poor prognostic factors, in order to improve disease-free and overall survival. However, there are no studies demonstrated the relationship between these risk factors and relapse pattern. In addition, we did not know that how long patient would survive after relapse. The TNM system could not provide predict power after patients were identified disease relapse. We have no idea about how long patient would be survived and all treatments were given according to physician experience. For patients with relapse, possible occult metastases could not complete exclude and all treated as those with distant metastases. Therefore, we try to analyze the relationship between disease severity and time to progression. We utilized image tools, including Chest CT and PET-CT for disease status evaluation. We divided body into six areas that included the nervous system, thorax cavity, mediastinum, abdomen, musculoskeletal system, and other soft tissue and calculated the number of involved area of metastatic lesions. Using the method, we analyzed the relationship between time-to-progression after relapse and disease severity. In this study, we found that the number of involved metastatic areas were significant influential to the period of time-to-progression. The duration of time-to-progression was correlated with square of number of metastatic areas. This information can provide clinical practitioners a quantitative model to predict patients' time-to-progression and individualize treatment planning.

There are still some limitations in this study. First, this is a retrospectively study with relative small population. Second, there were no available grading system for disease severity evaluation. Third, disease relapse and progress depend image evaluation while tissue prove is not feasible. However, we tried to analyze patients who were conformed as pathologic N2 disease in order to minimize the heterogeneity even though small population was recruited. In addition, we used imaging tools to quantify the disease severity and try to find the

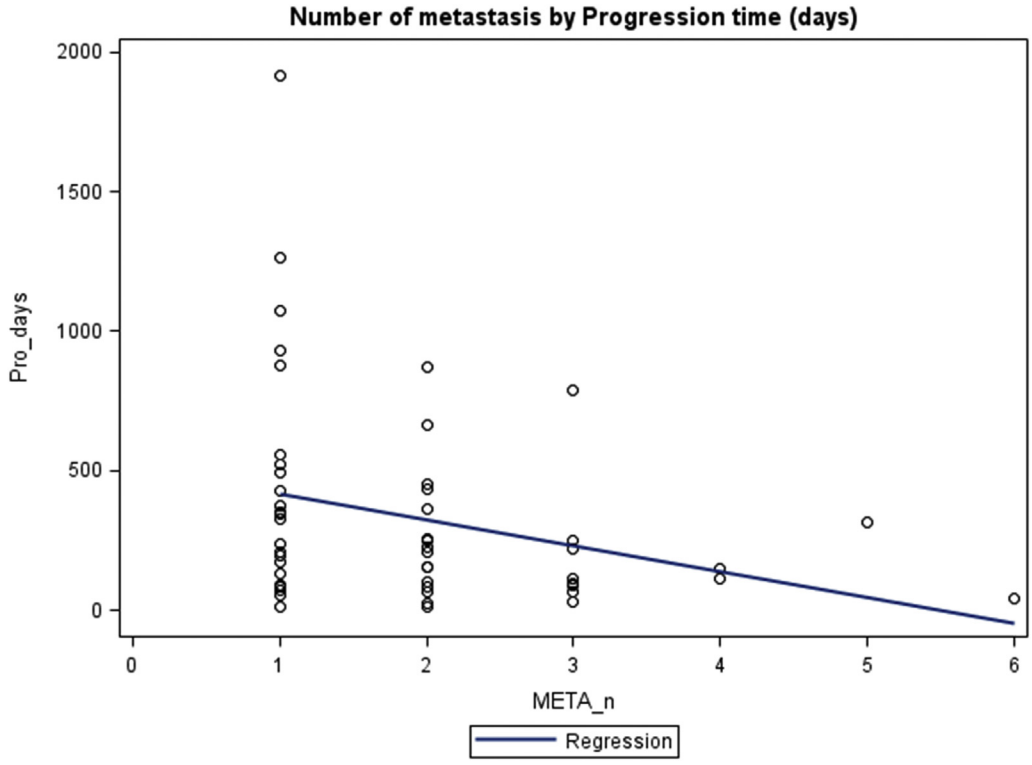


Fig. 3 Square of number of metastatic area has a significant relationship to time-to-progression; Pearson correlation coefficient = −0.29; $p = 0.036$.

relationship to time-to progression. Furthermore, we utilized RECIST criteria for disease evaluation that could be minimized observation bias. Even through limitations remain, our study still provided a thoroughly analysis from all aspects and obtained more information for individual treatment planning for patients with pathologic N2 non small cell lung cancer.

## Conclusion

Relapse risk factor of pathologic N2 NSCLC patient after anatomic resection were visceral pleural invasion, skip mediastinal lymph node involvement, and the receipt of neoadjuvant therapy. Whole body CT should be recommended for patients with these relapse risk factors. The duration of time-to-progression was correlated with square of number of involved metastatic areas.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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