Original Article

Prognostic factors in non-small cell lung cancer patients who received neoadjuvant therapy and curative resection

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Background: Lung cancer is the leading cause of cancer deaths in the world, and more and more treatment modalities have been introduced in order to improve patients' survival. For patients with advanced non-small cell lung cancer (NSCLC), survival prognosis is poor and multimodality neoadjuvant therapies are given to improve patients' survival. However, the possibility of occult metastases may lead to discrepancy between clinical and pathologic staging and underestimation of the disease severity. This discrepancy could be the reason for poor survival prediction reported by previous studies which conducted their analysis from the point of view of clinical stage. The aim of this study was to analyze the relationship between clinico-pathologic factors and survival from the pathologic point of view and to try to identify survival prognostic factors.

Methods: From January 2005 to June 2011, 88 patients received neoadjuvant therapy because of initial locally advanced disease, followed by anatomic resection and mediastinal lymph node (LN) dissection. All their clinico-pathologic data were collected from a retrospective review of the medical records and subjected to further analysis.

Results: We found that total metastatic LN ratio (P=0.01) and tumor size (P=0.02) were predictive factors for disease free survival (DFS). We used these two prognostic factors to stratify all patients into four groups. Group 4 (tumor size ≤5, total metastatic LN ratio ≤0.065) had the best DFS curve, while the DFS curve progressively deteriorated across group 3 (tumor size ≤5, total metastatic LN ratio >0.065), group 2 (tumor size >5, total metastatic LN ratio ≤0.065) and group 1 (tumor size >5, total metastatic LN ratio >0.065). However, no definitive prognostic factor could be identified in this study.

Conclusions: In conclusion, tumor size greater than 5 cm and total metastatic LN ratio greater than 0.065 could predict the DFS of patients with advanced NSCLC after multimodality therapies followed by surgical resection. Tumor size plays a more important role than total metastatic LN ratio in DFS. Moreover, patients identified with these factors need active post-operation surveillance and additional aggressive adjuvant therapies.

Keywords: Neoadjuvant therapy; lung cancer; prognostic factor

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Introduction

Lung cancer is the leading cause of cancer deaths in the world, and more and more treatment modalities have been introduced in order to improve patients' survival. Most patients with advanced non-small cell lung cancer (NSCLC), suffer disease relapse within three years and less than 10% of patients remain alive after a 5-year interval despite surgery (1,2). Because of poor survival, chemotherapy, radiotherapy and target therapy have been utilized in managing advanced NSCLC (3-6). From the literature review, neoadjuvant chemotherapy followed by surgical resection has been considered useful in select patients with advanced NSCLC, but the postoperative 5-year survival rates of these patients has ranged from 10% to 36% (1,7,8). In previous studies, the prognosis of patients with advanced NSCLC after neoadjuvant therapy has been based on the change in maximal standard uptake value (SUV_{max}) on fluorodeoxyglucose positron emission tomography (FDG-PET) scan, tumor size regression, lymph node (LN) status and clinical stage (9-12). However, these factors are usually evaluated preoperatively by radiologic imaging tools. Although chest tomography (CT) and FDG-PET scan provide more detailed information about disease severity, more and more studies have revealed significant differences between clinical and pathological stage (13-19). In patients who have received neoadjuvant therapy, occult metastases and alterations to the tumor microenvironment by chemotherapy may interfere with the FDG uptake and lead to a false negative result. This, in turn, would lead to discrepancy between clinical and pathologic stage and underestimation of the disease severity. The discrepancy would be the reason for poor survival prediction that has been reported by previous studies which conducted their analysis from the point of view of clinical stage (20-22). Therefore, the aim of this study was to analyze the relationship between clinico-pathologic factors and survival from the pathologic point of view and to try to identify survival prognostic factors.

Methods

Patients

From January 2005 to June 2011, a total of 609 patients received operations at Chang Gung Memorial Hospital. After exclusion, only 88 patients who had received neoadjuvant therapy because of initial locally advanced disease, and had subsequently undergone anatomic resection and mediastinal LN dissection were included in the study. Exclusion criteria included not receiving neoadjuvant therapy (442 patients), wedge resection due to poor pulmonary reserve (43 patients), small cell lung cancer (11 patients) and positive resection margin or TNM stage greater than IIIA (25 patients). All the clinico-pathologic data of the 88 included subjects were collected from a retrospective review of the medical records. The study was approved by the ethics committee of Chang Gung Memorial Hospital, under the Institutional Review Board number 103-5631B.

Neoadjuvant therapy and pre-operation restaging

All patients initially presented as locally advanced disease based on complete image survey, with the clinical stage varying from IIIA to IV, before neoadjuvant therapy. Different types of neoadjuvant therapy were given according to patients' status. The majority of patients (53%, 63.64%) received 4 to 6 courses of cisplatin based chemotherapy, depending on their general condition. Twenty-four patients (27.27%) received systemic chemotherapy and radiotherapy for local disease control because of mediastinum and chest wall invasion. Six patients (6.82%) received 3-month tyrosine kinase inhibitor therapy because of intolerance to cisplatin-based chemotherapy and tumor genetic survey positive for epidermal growth factor receptor (EGFR) mutation. A total of 5 patients (5.69%) refused cisplatin-based chemotherapy. One of them (1.14%) received radiotherapy only due to absence of EGFR mutation. A total of 4 patients (4.55%) received 3-month tyrosine kinase inhibitor therapy because of positive EGFR mutation result. After completion of neoadjuvant therapy, treatment response was re-evaluated by imaging tool, including chest CT, FDG-PET scan, and brain CT or magnetic resonance image (MRI). A revised clinical stage was given according to image evaluation result. The possible distant metastases were complete excluded by image evaluation.Only patients who presented as resectable disease from image survey, i.e., less than stage IIIA, received further anatomic resection and mediastinal LN dissection (*Figure 1*).

Operation

Patients who presented as resectable disease after neoadjuvant therapy underwent anatomic resection with mediastinal LN dissection 3 to 4 weeks after completion of neoadjuvant therapy. All procedures were performed via open

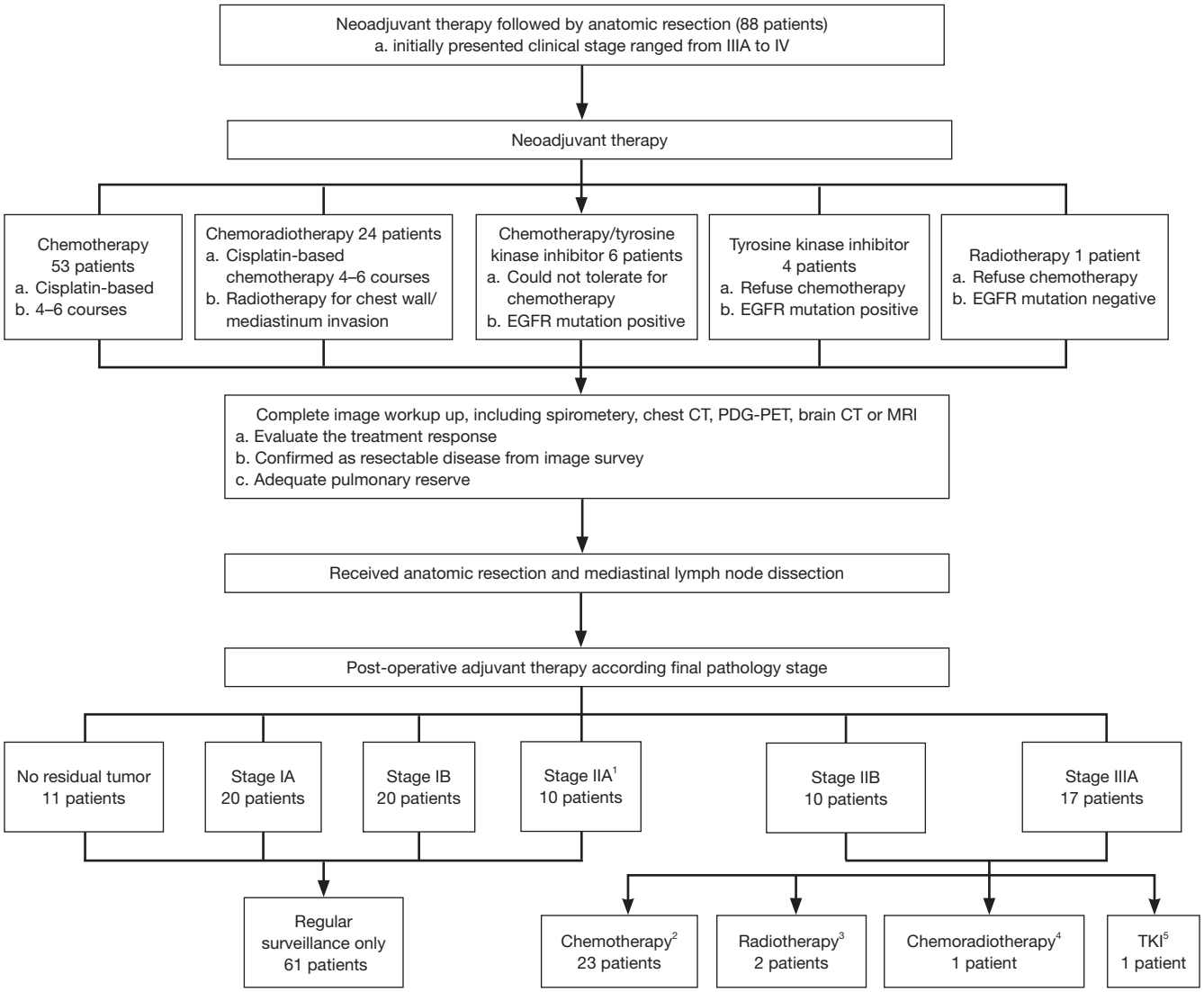

Figure 1 Management algorithm of patients who received neoadjuvant therapy followed by anatomic resection. [1], 10 patients recruited before year 2009 and presented as tumor 5–7 cm without mediastinal lymph node involvement, which classified them as stage IB in 6th edition AJCC stage, later reclassified as stage IIA in 7th edition AJCC stage. All of them were managed as stage IB without further adjuvant therapy; [2], 23 patients received cisplatin-based chemotherapy as post-operation adjuvant therapy; [3], on account of old age, 2 patients received radiotherapy only; [4], 1 patient received chemo-radiotherapy because resected specimen revealed chest wall invasion (negative resection margin); [5], 1 patient received tyrosine kinase inhibitor therapy because they refused chemotherapy. AJCC, American Joint Cancer Conference.

thoracotomy or video assisted thoracoscopic surgery (VATS).

The corresponding pulmonary vein, artery, and bronchus were individually identified and divided with the aid of suture ligation or endoscopic staples. Subsequently, complete mediastinal LN dissection was performed. All resected specimens were examined by pathologist and the pathologic stages were classified according to American Joint Cancer Conference (AJCC) staging.

Post-operative treatment and follow-up

Post-operative adjuvant therapies were given according to the National Comprehensive Cancer Network (NCCN) guideline recommendations and pathologic stage. For patients with no residual tumor, i.e., stage IA and stage IB, only a close surveillance program was performed. In this study, 10 patients classified as stage IIA were recruited

before 2009, and all presented with larger tumor size varying from 5 to 7 cm, but without mediastinal LN involvement. These patients were classified as stage IB in the 6th edition AJCC stage system and all were managed as stage IB without adjuvant therapy. Cisplatin-based chemotherapy was prescribed for patients if final pathologic stage was identified as stage II or higher.

Additional radiotherapy was given for adjuvant therapy if chest wall invasion was identified even with negative resection margin. However, if patients refused further adjuvant cisplatin-based chemotherapy, another alternative treatment, such as tyrosine kinase inhibitor or radiotherapy was given according to patients' status (*Figure 1*). Patients were required to return to the outpatient department every three months, at which point a chest plain film or chest computed tomography was produced.

Statistical analysis

All collected clinico-pathologic factors were evaluated by univariate analysis. Categorical variables were compared using chi-square tests, while continuous variables were compared using two sample *t*-tests.

Disease free survival (DFS) was defined as no evidence of relapse in the period from the date of the operation to the last follow up date or the confirmation date of disease relapse. Overall survival (OS) was defined as the period between the operation date and death of any cause. The survival status was calculated by the Kaplan-Meier method, and the differences were analyzed by means of the log-rank test. A cox proportional hazards model was used to examine the multiple variables that were thought to be potential prognostic variables for survival in univariate analysis. A P value less than 0.05 was considered statistically significant. All analyses were performed using SAS, version 9 (SAS Institute, NC, USA).

Results

Patient characteristics

Eighty-eight patients with neoadjuvant therapy followed by anatomic resection were included in this study. The patient's characteristics are shown in *Table 1*. The median age of patients was 60.76 years (±10.65) and 46 patients (52.3%) were male. Among these patients, 53 patients (63.64%) received chemotherapy, 24 patients (27.27%) received chemo-radiotherapy, 6 patients (6.82%) received a combination of chemotherapy and tyrosine kinase inhibitor, 4 patients (4.55%) had target therapy, and 1 patient (1.14%) received radiotherapy. Seventy patients (79.6%) were found to be down stage from the image survey before operation. The cell types at final diagnosis showed 51 patients (57.9%) with adenocarcinoma, 29 patients (32.9%) with squamous cell carcinoma, 2 patients (2.3%) with adenosquamous carcinoma and 6 patients (6.8%) with other cell types.

Surgical outcomes and adjuvant therapy

Fifty-five patients (62.5%) underwent VATS. Pathological stage distribution was 20 patients (22.3%) with stage Ia, 20 patients (22.7%) with stage Ib, 10 patients (11.3%) with stage IIa, 10 patients (11.4%) with stage IIb, and 17 patients (19.3%) with stage IIIa. The mean tumor size was 2.87 (±1.79) cm and 11 patients (12.5%) were found with no viable residual tumor. Visceral pleural invasion, angiolymphatic invasion and perineural invasion were found in 34 patients (38.6%), 21 patients (23.9%) and 2 patients (2.3%) respectively. Forty-two patients (47.7%) were found to have tumor necrosis and 69 patients (78.4%) were found to have lymphocytic infiltration. The mean number of retrieved LNs was 16.13 (±10.49) and the mean number of metastastic LN was 0.79 (±1.87). Total metastatic LN ratio was 0.07 (±0.18), of which metastatic N1 LN ratio was 0.08 (±0.22) and metastatic N2 LN ratio was 0.04 (±0.14). Sixty-one patients (69.3%) received regular surveillance because of no residual tumor or stage I disease (*Figure 1*). Twenty-three patients (26.1%) received adjuvant cisplatin-based chemotherapy. Adjuvant chemo-radiation was given for 2 patients (2.3%). Additional radiotherapy was applied in 1 patient (1.1%), and tyrosine kinase was applied in 1 patient (1.1%).

Survival and prognostic factor analysis

The median follow-up period for all patients was 1,630 days. Five-year DFS and OS were 26.5% and 43.22%, respectively. The univariate and multivariate analysis of DFS in all patients are shown in *Tables 2* and *3*, respectively. In the univariate analysis, cell type (P=0.04) and total metastatic LN ratio (P=0.01) were found to have a significant impact on DFS. Tumor size showed a trend toward significance (P=0.09). In the multivariate analysis, we found that total metastatic LN ratio (P=0.01) and tumor size (P=0.02) were predictive factors for DFS. We found a tumor size of 5 cm and total metastatic LN ratio at 0.065 to be the threshold values with regard to DFS (*Figure 2A,B*) and further applied these two prognostic factors for

Table 1 Patient's characteristics

Variables	Neoadjuvant therapy (n=88)
Age (mean ± SD)	60.76±10.65
Male, n (%)	46 (52.3)
Pre-operation neoadjuvant Tx, n (%)	
CCRT	24 (27.27)
Chemotherapy	53 (63.64)
Chemotherapy + target Tx	6 (6.82)
Radiotherapy	1 (1.14)
Target Tx	4 (4.55)
Down staging, n (%)	
No	18 (20.4)
Yes	70 (79.6)
Cell type, n (%)	
Adenocarcinoma	51 (57.9)
Squamous cell carcinoma	29 (32.9)
Adenosquamous carcinoma	2 (2.3)
Others	6 (6.8)
Grade, n (%)	
G1	24 (27.3)
G2	26 (29.6)
G3	19 (21.6)
G4	2 (2.3)
N/A	17 (19.3)
Visceral pleural invasion, n (%)	34 (38.6)
Angiolymphatic invasion, n (%)	21 (23.9)
Perineural invasion, n (%)	2 (2.3)
Tumor necrosis, n (%)	42 (47.7)
Lymphocytic infiltrates, n (%)	69 (78.4)
Tumor size (mean ± SD)	2.87±1.79
Mitosis	40 (45.5)
No. of LN (metastasis)	0.79±1.87
No. of LN (total)	16.13±10.49
Total LN ratio	0.07±0.18
Metastatic N1 ratio (mean ± SD)	0.08±0.22
Metastatic N2 ratio (mean ± SD)	0.04±0.14
VATS/thoracotomy, n (%)	55 (62.5)
Post-operation adjuvant Tx, n (%)	
Chemotherapy	23 (26.1)
CCRT	1 (1.1)
RT	2 (2.3)
Target Tx	1 (1.1)
None	61 (69.3)
Pathologic staging, n (%)	
IA	20 (22.3)
IB	20 (22.7)
IIA	10 (11.3)
IIB	10 (11.4)
IIIA	17 (19.3)
No residual tumor	11 (12.5)
Mean follow up period (days)	1,630
5-year disease free survival	26.5%
5-year overall survival	43.22%

Tx, therapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; LN, lymph node; VATS, video-assisted thoracoscopic surgery.

stratification. All patients were sub-grouped into four groups by these two factors (*Figure 2C*). Group 4 (tumor size ≤5, total metastatic LN ratio ≤0.065) had the best DFS curve, while the DFS curve progressively deteriorated through group 3 (tumor size ≤5, total metastatic LN ratio >0.065), group 2 (tumor size >5, total metastatic LN ratio ≤0.065) and group 1 (tumor size >5, total metastatic LN ratio >0.065). In addition, the more poor prognostic factors were identified, the higher risk of disease relapse were noted (*Figure 2D*).

The univariate and multivariate analyses of OS in all patients are shown in *Tables 4* and *5*, respectively. In the univariate analysis, operative method (P=0.02) was found to have significant impact on OS. Down staging (P=0.09), angiolymphatic invasion (P=0.07) and perineural invasion (P=0.09) were found to have a trend toward significance. In the multivariate analysis, we identified only perineural invasion (P=0.01) as a predictive factor for OS. Further investigation is warranted because only two patients were identified as having perineural invasion. In addition, no definite prognostic factor could be identified in this study.

Discussion

In this study, we tried to find predictive prognostic factors in patients with advanced NSCLC after neoadjuvant therapy followed by surgical resection. Our study included patients who initially presented in clinical stage varied from IIIA to IV before neoadjuvant treatment. Patients who presented as clinical stage IIIA showed similarity to those who presented with IIIB and IV because of the possibility

Table 2 Simple regression result of disease free survival (neoadjuvant group)

Variables	Parameter estimated	Standard error	Chi square	P value	Hazard ratio	95% CI
Age	–0.01	0.01	0.57	0.44	0.99	(0.97, 1.02)
Sex	–0.09	0.26	0.14	0.71	0.91	(0.55, 1.51)
Pre-operative clinical stage	0.12	0.10	1.51	0.22	1.13	(0.93, 1.38)
Type of neoadjuvant therapy	0.11	0.18	0.33	0.57	1.11	(0.78, 1.59)
Down staging	–0.15	0.14	1.67	0.28	0.86	(0.66, 1.13)
VATS/thoracotomy	0.42	0.27	2.33	0.13	1.52	(0.88, 2.59)
Cell type	–0.38	0.19	4.04	0.04	0.68	(0.46, 0.99)
Grade	–0.05	0.05	1.16	0.28	0.95	(0.86, 1.04)
Visceral pleural invasion	–0.08	0.08	0.92	0.34	0.92	(0.79, 1.09)
Angiolymphatic invasion	–0.01	0.05	0.07	0.78	0.99	(0.89, 1.09)
Perineural invasion	–0.03	0.06	0.31	0.58	0.97	(0.86, 1.09)
Tumor size	0.11	0.07	2.91	0.09	1.12	(0.98, 1.27)
Mitosis	0.10	0.26	0.14	0.70	1.11	(0.66, 1.84)
Tumor necrosis	–0.07	0.05	2.49	0.11	0.93	(0.84, 1.02)
Lymphocytic infiltrates	–0.08	0.05	2.29	0.13	0.93	(0.84, 1.02)
Metastatic N1 ratio	0.41	0.59	0.47	0.49	1.51	(0.47, 4.87)
Metastatic N2 ratio	1.55	0.79	3.82	0.05	4.72	(1.00, 22.34)
Total metastatic lymph node ratio	1.63	0.66	6.23	0.01	5.11	(1.42, 18.38)
Post-operation adjuvant therapy	–0.13	0.09	1.87	0.17	0.88	(0.74, 1.06)

VATS, video-assisted thoracoscopic surgery; CI, confidence interval.

Table 3 Multiple regression result of disease free survival (neoadjuvant group)

Variables	Parameter estimated	Standard error	Chi square	P value	Hazard ratio	95% CI
Cell type (adeno *vs.* others)	–0.41	0.28	2.21	0.13	0.66	(0.38, 1.14)
Total metastatic LN ratio	1.23	0.44	7.73	0.01	3.41	(1.44, 8.12)
Tumor size	0.69	0.29	5.89	0.02	2.01	(1.14, 3.52)

LN, lymph node; CI, confidence interval.

of occult metastases. The small occult metastases may be hidden in successive slice of computed tomography and may not appear in positron-emission tomography (23). The only difference between stage IIIA and other advance stage, including IIIB and IV, was microscopic and macroscopic metastasis, respectively. From NCCN guideline, surgical resection may be beneficial for these patients who presented with fore-mentioned scenarios that similar to those presented clinical stage IIIA (24). In addition, all patients who presented as resectable disease in tumor re-evaluation after neoadjuvant therapy were underwent anatomical resection and mediastinal LN dissection. Our study included all advanced NSCLC patients with similar presentation and those who may be beneficial from neoadjuvant therapy followed by surgical curative resection which was differ than other literatures. Our result revealed that pathological tumor size and total metastatic LN ratio are important prognostic factors with regard to DFS. In this study, we not only clarified that tumor size and metastatic LN ratio are correlated to DFS, but we also quantified these two factors, in particular, a tumor size greater than 5 cm and total metastatic LN ratio greater than 0.065, based on the pathological findings. Patients with tumor size ≤5 cm and total metastatic LN ratio ≤0.065 had the most sustained DFS, compared to those with tumor size >5 cm and total metastatic LN ratio >0.065. Furthermore,

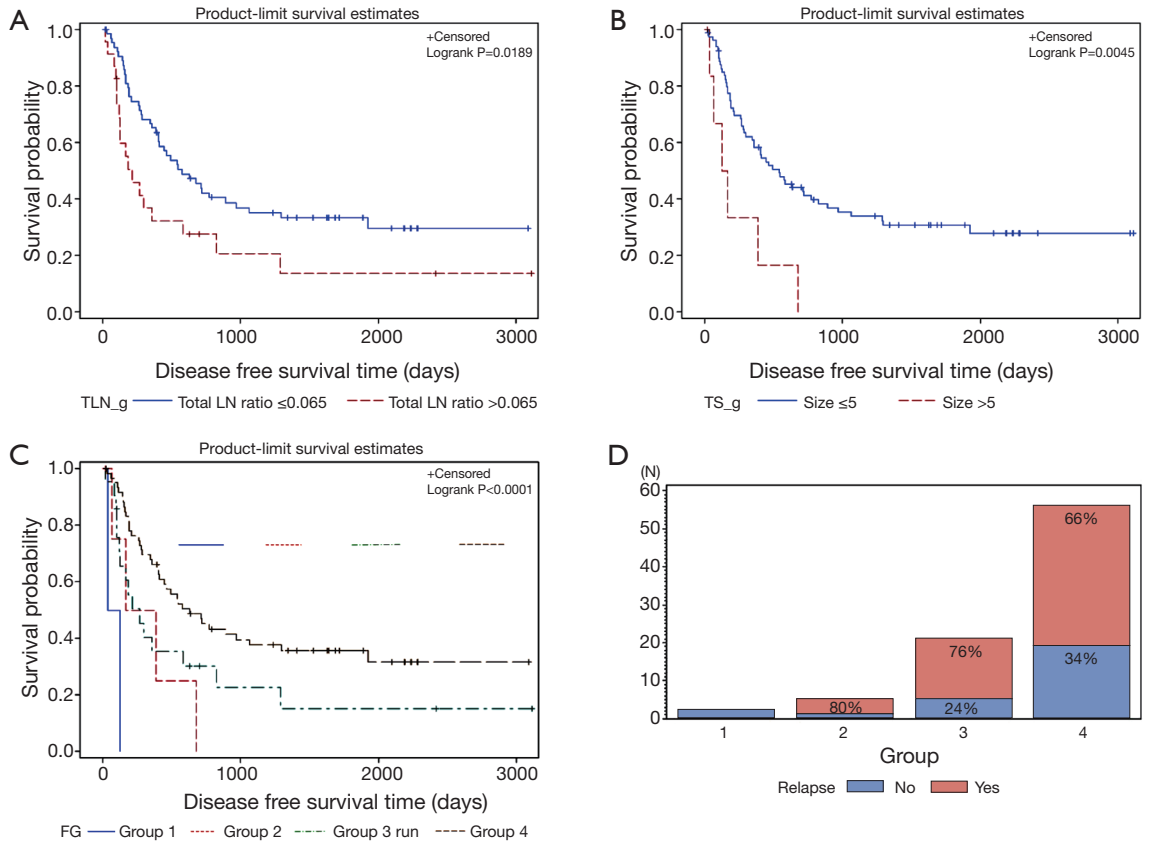

Figure 2 Disease free survival analysis of non-small cell lung cancer patients who received neoadjuvant therapy and curative resection. (A) Disease free survival between total metastatic lymph node ratio >0.065 and ≤0.065; (B) disease free survival between tumor size >5 and ≤5 cm; (C) stratified disease survival between subgroups (P<0.001). Group 1: tumor >5, metastatic LN ratio >0.065. Group 2: tumor >5, metastatic LN ratio ≤0.065. Group 3: tumor ≤5, metastatic LN ratio >0.065. Group 4: tumor ≤5, metastatic LN ratio ≤0.065; (D) relapse percentage in each group (P<0.001).

we found that tumor size plays a more important role than total metastatic LN ratio with regard to DFS. However, no definite prognostic factor was identified regarding OS except perineural invasion. From the literature review, the role of perineural invasion remains controversial (25,26). In our study, perineural invasion was identified as a prognostic factor regarding OS, but further investigation is warranted due to the limited number of cases.

For NSCLC patients who received neoadjuvant therapy, tumor down staging after evaluation by imaging tools was important for resectability evaluation. However, the discrepancy between clinical stage and pathologic stage was demonstrated with the agreement rate at around 35% (16,18). In addition, neoadjuvant therapy is thought to interfere with the interpretation of examination results (21). This leads not only to a lowered agreement rate between clinical and pathologic stage, but also less survival predicting power for DFS and OS (27). From the literature review, many prognostic factors have been identified for patients who have been treated with neoadjuvant therapy based on pathology findings. Metastatic LN ratio, number of residual metastatic LNs, smaller area of residual tumor (less than 400 mm^2) and negative pleural invasion, percentage of viable residual tumor cells, and low total macrophage number in the tumor have been correlated with survival in patients who have received neoadjuvant therapy and subsequent surgical resection (28-38). In this study, we identified tumor size larger than 5 cm and total metastatic lymph ratio less than 0.065 as correlated to DFS. This finding is similar to that of previous studies, but much easier for clinical application. We did not have to measure tumor volume, calculate viable tumor cell percentage, calculate the total macrophage

Table 4 Simple regression result of overall survival (neoadjuvant)

Variables	Parameter estimated	Standard error	Chi square	P value	Hazard ratio	95% CI
Age	0.007	0.01	0.24	0.62	1.01	(0.97, 1.04)
Sex	0.17	0.27	0.37	0.54	1.19	(0.69, 2.05)
Pre-operative clinical stage	0.08	0.10	0.61	0.43	1.09	(0.88, 1.33)
Type of neoadjuvant therapy	–0.13	0.20	0.43	0.51	0.88	(0.58, 1.30)
Down staging	–0.49	0.29	2.81	0.09	0.62	(0.35, 1.09)
VATS/thoracotomy	0.76	0.33	5.29	0.02	2.15	(1.12, 4.14)
Cell type	0.18	0.14	1.56	0.22	1.20	(0.90, 1.61)
Grade	0.01	0.05	0.08	0.77	1.01	(0.93, 1.11)
Visceral pleural invasion	–0.05	0.08	0.40	0.53	0.95	(0.81, 1.12)
Angiolymphatic invasion	–0.18	0.10	3.17	0.07	0.84	(0.68, 1.02)
Perineural invasion	–0.17	0.10	2.88	0.09	0.84	(0.69, 1.03)
Tumor size	–0.001	0.07	0.01	0.91	0.99	(0.87, 1.14)
Mitosis	0.13	0.28	0.21	0.64	1.14	(0.65, 1.98)
Tumor necrosis	–0.01	0.05	0.11	0.74	0.99	(0.90, 1.08)
Lymphocytic infiltrates	–0.02	0.05	0.18	0.67	0.98	(0.89, 1.08)
Metastatic N1 ratio	0.69	0.51	1.79	0.18	1.99	(0.73, 5.45)
Metastatic N2 ratio	0.28	0.82	0.12	0.73	1.32	(0.27, 6.58)
Total metastatic lymph node ratio	0.69	0.57	1.46	0.23	2.00	(0.65, 6.18)
Post-operation adjuvant therapy	0.02	0.11	0.03	0.87	1.02	(0.83, 1.25)

VATS, video-assisted thoracoscopic surgery; CI, confidence interval.

Table 5 Multiple regression result of overall survival (neoadjuvant)

Variables	Parameter estimated	Standard error	Chi square	P value	Hazard ratio	95% CI
Thoracotomy *vs.* VATS	0.67	0.34	3.77	0.05	1.96	(0.99, 3.89)
Angiolymphatic invasion	0.11	0.32	0.12	0.71	1.12	(0.59, 2.12)
Down staging	–0.47	0.33	2.03	0.16	0.62	(0.32, 1.19)
Perineural invasion	1.83	0.76	5.93	0.01	6.29	(1.32, 27.67)

VATS, video-assisted thoracoscopic surgery; CI, confidence interval.

number in the tumor area, or elaborate further elastin stain for visceral pleura invasion confirmation. All of these measurements may be vulnerable to bias between different pathologists. Our result was obtained through a quite simple measurement that minimized observational bias. In addition, factors correlating to disease invasion status, i.e., tumor size and metastatic LN were included that could be more precise in survival prediction. Our result could help clinicians set up individually tailored follow-up programs and treatment strategies for patients with advanced NSCLC after neoadjuvant therapies followed by surgical resection. More aggressive post-operation adjuvant and maintenance therapy should be considered when patients are identified with one or two of the prognostic factors, and individualized follow up programs should be planned if needed. However, further investigation is warranted to clarify the real survival impact mechanism.

There are some limitations to our study. First, this study was conducted as a retrospective review.

Second, the sample size of this study was too small to stratify patients into different subgroups resulting in unreliable parameter validation. Third, different types of neoadjuvant and post-operation adjuvant therapy were used for these patients and we could differentiate the effect on

survival in this study. However, because of the small sample size, further investigation should be conducted to validate the predictive values of tumor size and total metastatic LN ratio. Although limitations remain, out study was able to stratify patients treated with neoadjuvant therapy followed by surgical resection into different subgroups. Patients with tumor size greater than 5 cm and metastatic LN ratio greater than 0.065 revealed extremely poor DFS and aggressive adjuvant therapy should be considered.

Conclusions

In conclusion, tumor size greater than 5 cm and total metastatic LN ratio greater than 0.065 can predict the DFS of patients with advanced NSCLC after multimodality therapies followed by surgical resection. Tumor size plays a more important role than total metastatic LN ratio on DFS. Moreover, patients who are identified with these factors need aggressive post-operation surveillance and additional aggressive adjuvant therapies.

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Footnote

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

Ethical Statement: The study was approved by the ethics committee of Chang Gung Memorial Hospital, under the Institutional Review Board number 103-5631B.

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