Survival of Non-Small Cell Lung Cancer Patients with Unexpected N2 after Complete Resection: Role of Aggressive Invasive Mediastinal Staging should be Considered

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ABSTRACT

Objective: Mediastinal lymph node (N2) metastasis is one of the poor prognostic factors in non-small cell lung cancer patients (NSCLC). However, the accuracy of mediastinal lymph node staging in real practice is uncertain and inadequate. Consequently, the aim of this study was to determine the survival of NSCLC patients with clinically non-suspicious mediastinal lymph node metastases who underwent complete resection but were pathologically confirmed as having N2 metastases (unexpected N2).

Materials and Methods: A retrospective review was performed of all pathology-proven N2 metastases NSCLC patients who underwent curative surgical resection from January 2007 to December 2016. A total of 158 patients were initially included in the study. After the exclusions (known N2, small cell carcinomas, neuroendocrine tumor), 125 unexpected N2 patients who underwent complete resection were analyzed. Survival analysis was determined using the Kaplan–Meier method and multivariate analysis was determined using the Cox regression method.

Results: The overall 2-year, 3-year, and 5-year survival rates were 40%, 24%, and 20% respectively. Complete resection was achieved in all patients. Invasive mediastinal staging (IMS) was performed in 47 patients (37.6%), by endobronchial ultrasonography (EBUS) in 46 (36.8%) patients (82.6% negative and 17.4% inadequate tissue) while only 1 patient underwent mediastinoscopy. The factors affecting the survival rate upon comparison were the histology type (p=0.019), differentiate characteristics (p=0.004), adjuvant therapy (p=0.011), and presence of distant metastasis by postoperative re-staging (p=0.003). The independent predictive factors for survival were chemo-radiation therapy (odds ratio 0.367, 95% confidence interval 0.176–0.766) and distant metastasis (odds ratio 2.280, 95% confidence interval 1.334–3.897). However, a small size, periphery lesion, T staging, and number of N2 lesions were not significant factors.

Conclusion: The survival rate of unexpected N2 patients was low despite complete resection being achieved in these patients. Adjuvant therapy seemed to improve survival for those with unexpected N2 metastasis as it is a systemic disease. However, not all patients received IMS, which was mostly done by EBUS and which had a high false negative, leading to underestimating the staging. Other modalities, such as cervical mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA) or open biopsy should be considered for the adequate e valuation of N2 metastasis, nonetheless further study is still needed.

Keywords: N2 disease, Unexpected N2, Non-small lung cancer (NSCLC), Invasive mediastinal staging (IMS), Stage 3A NSCLC (Siriraj Med J 2022; 74: 161-168)

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INTRODUCTION

The prognosis of non-small cell lung cancer (NSCLC) patients with mediastinal lymph node metastases (N2 disease) is usually poor.[1-3] N2 involvement is one of the important factors that determine the prognosis and treatment. Because N2 disease seems to indicate systemic spreading, systemic therapy, such as chemotherapy, radiation therapy, or combined chemo-radiation therapy, has better 5-year survival than surgery alone (38% vs 30%).[4] Despite the recommendation for mediastinal lymph node tissue confirmation when there is a high suspicion of N2 by imaging, such as enlarged lymph nodes seen by computed tomography (CT) or an increased uptake in the mediastinum by positron-emission tomography (PET)[5], the accuracy of the clinical staging still has a high false negative rate ranging from 25% to 40%[6]; therefore, some patients undergo surgery as the first course of treatment. Previous reports showed that unexpected N2 disease patients had a poor prognosis and a survival rate ranging from only 10%-35%.[7-10]

Consequently, the objective of this study is to determine survival rate in Thai population of the clinical N0 NSCLC patients who underwent complete pulmonary resection with systematic mediastinal lymph nodes dissection and who had unexpected N2 as a final pathological result.

MATERIALS AND METHODS

Patients and staging

This study is a retrospective review of all the pathology-proven N2 metastases NSCLC patients included in the data registry of the Division of Cardio-Thoracic Surgery and in reports from the Department of Pathology, Siriraj Hospital, Bangkok, Thailand, between January 2007 and December 2016. Among all the patients aged 18 years old and older who received complete pulmonary resection with systematic mediastinal lymphadenectomy (n = 158), we excluded patients (n = 33) who had a diagnosis of N2 disease as either highly suspicious (14 patients whose CT shows enlarged N2 lymph node more than 1 cm in short axis) or confirmed from preoperative imaging (2 patients whose N2 uptake in PET-CT), small cell carcinoma (10 patients), and neuroendocrine tumor (7 patients). Following the exclusions, the remaining patients (n = 125) were proven to be NSCLC preoperatively or at the time of surgery, and had been clinically staged as N0 or N1 from an imaging study (CT or FDG-PET scan) and from invasive mediastinal staging if done. All of the included patients had not received neoadjuvant systemic chemotherapy nor radiation therapy before surgical resection. The Siriraj Ethic and Clinical Research Institutional Review Board approved this study as well as the electronic database used. The need for individual patient consent was waived due to the nature of the retrospective study design.

Staging was primarily performed by chest computed tomography (CT). Only a small number of patients received positron-emission tomography (PET-CT scan) due to the cost and availability. Invasive mediastinal staging, such as endobronchial ultrasound fine needle aspiration (EUS-FNA) or cervical mediastinoscopy, were performed in cases with a mediastinal lymph node larger than 1 cm in short axis as determined by the imaging and when all the results were negative for N2 disease. Nevertheless, there is no specific criteria in the institution for selecting patients to receive particular preoperative invasive mediastinal staging, the decision depends on experienced pulmonologists or surgeons.

Surgery was performed by both standard thoracotomy and video-assisted thoracoscopic surgery (VATS). Anatomical complete resection (R0 resection) was achieved by lobectomy, bi-lobectomy, or pneumonectomy. Systematic lymphadenectomy was performed in all patients and included lymph node stations 2R, 4R,[7-9] for the right-sided lesions, and stations[5-9] for the left-sided lesions. The pathological review was done using the standard technique for both the primary lung lesions and mediastinal lymph nodes.

All the patients received routine follow-up examination in the thoracic out-patient unit and were referred to an oncologist and radiotherapist for appropriate adjuvant chemotherapy or radiation therapy.

Statistical analysis

Data analysis was performed using SPSS statistical software (SPSS version 25, 2017, IBM Corporation). Categorial data are presented as the percentage and continuous variables are expressed as the mean. Continuous variables between groups were compared using the *t* test and discrete variables using Pearson's chi square test. Survival rates were calculated using the Kaplan–Meier method and log-rank test for adjusting for the differences between subgroups. Univariate analysis for the prognostic factors was performed using the log-rank test and multivariate analysis using multiple logistic regression analysis method. A *p*-value of less than 0.05 was defined as statistically significant.

RESULTS

In total, 125 patients were included in this study. Complete surgical lung resection and systematic mediastinal lymphadenectomy were achieved in every patient. As shown in Table 1, male and female in age group of 60 is

TABLE 1. Patients' characteristics (n = 125).

Gender	
Male	60 (48%)
Female	65 (52%)
Median age (years, range)	62 (31-82)
Clinical presentation	
Abnormal chest radiograph	66 (52.8%)
Chest discomfort	4 (3.2%)
Prolong cough	34 (27.2%)
Hemoptysis	16 (12.8%)
Dyspnea	3 (2.4%)
Weight loss	1 (0.8%)
Pneumonia	1 (0.8%)
Site of primary tumor	
Right upper lobe	32 (25.6%)
Right middle lobe	14 (11.2%)
Right lower lobe	30 (24%)
Left upper lobe	33 (26.4%)
Left lower lobe	16 (12.8%)
Invasive mediastinal staging (IMS)	47 (37.6%)
EBUS*(negative result)	38 (30.4%)
EBUS (inadequate tissue)	8 (6.4%)
Mediastinoscopic biopsy (negative result)	1 (0.8%)
Mean time to surgery (months)	1.29 (±0.875)
Extent of surgery	
Segmental resection	2 (1.6%)
Lobectomy	104 (83.2%)
Bilobectomy	11 (8.8%)
Pneumonectomy	8 (6.4%)
Adjuvant therapy	102 (81.6%)
Chemotherapy	45 (36%)
Radiation therapy	4 (3.2%)
Chemo-radiation therapy	53 (42.4%)
Distant metastases (restaging)	71 (56.8%)

*EBUS endobronchial ultrasonography.

not different for the lung cancer characteristics. The most common presentation was an abnormal chest radiography on annual check-up followings with prolong cough and hemoptysis. One-third of the patients received an invasive mediastinal staging procedure by endobronchial ultrasonography (EBUS), for which the results were all negative or there was inadequate tissue for evaluation, and only 1 patient received mediastinoscopy with lymph node biopsy. The mean time from diagnosis to surgery was less than 60 days. Lobectomy was performed most often, which was equally performed in the right upper lobe, right lower lobe, and left upper lobe. Among the study, almost patients received adjuvant therapy, comprising chemotherapy alone, radiation therapy alone, or combined chemo-radiation therapy.

For the tumor characteristics (Table 2), the most common T staging was still early (T2a). Adenocarcinoma was the predominant histologic subtype along with moderate differentiation. There was a rather high incidence of visceral pleural invasion and lymphovascular invasion. The most common site of mediastinal nodal metastasis for unexpected N2 disease was station 7 followed by stations 4R and 4L, while three quarters of patients had multiple N2 station metastases.

The overall 2-year, 3-year, and 5-year Kaplan–Meier survival rates were 40%, 24%, and 20%, respectively (Fig 1). For the pathological characteristics, the histologic subtype and differentiation had significant differences in their effect on the survival rates (Fig 2). The adenocarcinoma group had a better 5-year survival rate compared to the squamous cell carcinoma group (24% vs. 14%, p = 0.019), whereas good differentiation had a better 5-year survival rate than moderate and poor differentiation (45%, 24%, and 13%, p = 0.004). There was no significant difference among the T staging classes (p = 0.282, Fig 2). The presence of visceral pleural invasion of the tumor had a 5-year survival rate of 16% compared to the absence group, but this was not significantly different (p = 0.199, Fig 3). Lymphovascular invasion also showed no significant difference (p = 0.097, Fig 3), and the 5-year survival rate was 15% in the presence of lymphovascular invasion.

For unexpected N2 metastasis, the numbers of nodal stations were analyzed. Fig 4 shows the Kaplan–Meier 5-year survival for 39 patients with single nodal station metastasis compared to 86 patients with multiple nodal stations metastases (25% vs. 18% respectively), but the difference was not statistically significant (p = 0.103). In terms of the patient follow-ups, 23 patients declined the adjuvant therapy. Here, all the patients with or without adjuvant therapy were compared, and the best prognosis was found in the adjuvant chemo-radiation therapy

TABLE 2. Tumors' characteristics (n = 125).

Size of primary tumor (cm)	4.31 ± 1.921
Histology	
Adenocarcinoma	104 (83.2%)
Squamous cell carcinoma	16 (12.8%)
Other	5 (4%)
Differentiation	
Well	6 (4.8%)
Moderate	84 (67.2%)
Poor	27 (21.6%)
Not evaluated	8 (6.4%)
Visceral pleural invasion	87 (69.6%)
Lymphovascular invasion	94 (75.2%)
Adjacent structure invasion	16 (12.8%)
T staging (from pathology)	
T1a	5 (4%)
T1b	10 (8%)
T2a	69 (55.2%)
T2b	20 (16%)
T3	16 (12.8%)
T4	5 (4%)
N1 station involvement	
10R, 10L	45 (36%)
11R, 11L	71 (56.8%)
N2 station	
3	6 (4.8%)
4R,4L	55 (44%)
5	33 (26.4%)
6	3 (2.4%)
7	62 (49.6%)
8R,8L	2 (1.6%)
9R,9L	10 (8%)
Number of N2	
Single	39 (31.2%)
Multiple	86 (68.8%)

For the tumor characteristics (Table 2), the most common T staging was T2a (55.2%) with the median size of 4.31 cm. Adenocarcinoma was the predominant histologic subtype (83.2%) along with moderate differentiation (67.2%). There was a rather high incidence of visceral pleural invasion (69.6%) and lymphovascular invasion (75.2%). The most common site of mediastinal nodal metastasis for unexpected N2 disease was station 7 (49.6%) followed by stations 4R and 4L (44%), while 68.8% of patients had multiple N2 station metastases.

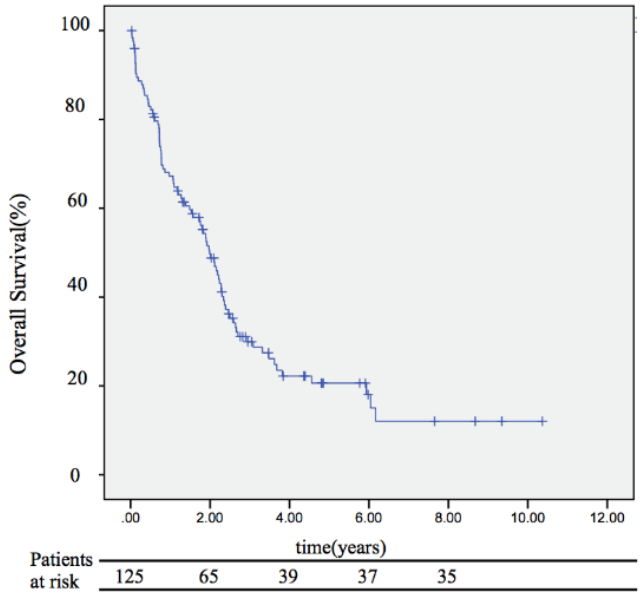


Fig 1. Overall 2-, 3-, and 5-year survival rates, which were 40%, 24%, and 20%, respectively.

group, which had a 5-year survival rate of 30%, while the 5-year survival rates of the radiation therapy alone group, chemotherapy alone group, and did not receive adjuvant therapy group were 25%, 15%, and 10%, and the difference was statistically significant (p = 0.011, Fig 4).

Post-treatment re-staging data were also collected and analyzed. The survival graph demonstrated the 5-year survival rate of patients with a presentation of distant metastasis in any organ was 10%; while for the group with no distant metastasis, it was 40%, and there was a highly significant difference in statistical terms as the *p*-value was 0.003 (Fig 4). The univariate analysis was insignificant. The multivariate analysis results in Table 3 depict that the independent predictive factors for survival were receiving adjuvant chemo-radiation therapy and a distant metastasis on re-staging.

DISCUSSION

Recently, Krantz and colleagues[11] did a study based on The Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD) participants in the United States (US) and reported that 34% of lung cancer patients staged by computed tomography and positron-emission tomography and first treated with anatomical resection underwent invasive mediastinal staging (IMS). Compatible with our study, which found that in all 125 "unexpected N2" disease patients, only 47 patients (37.6%) received IMS, which included 46 EBUS and only 1 who underwent

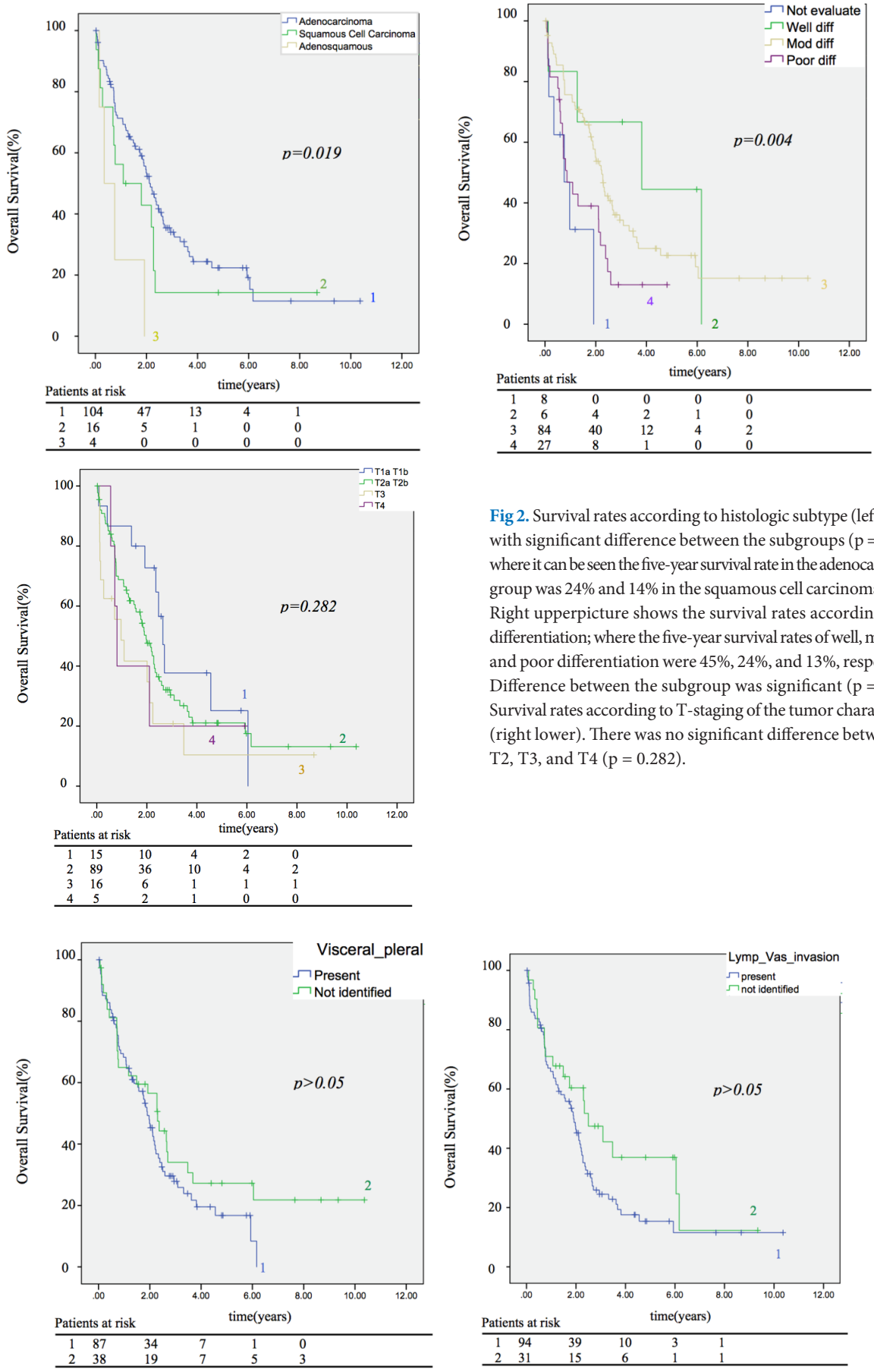
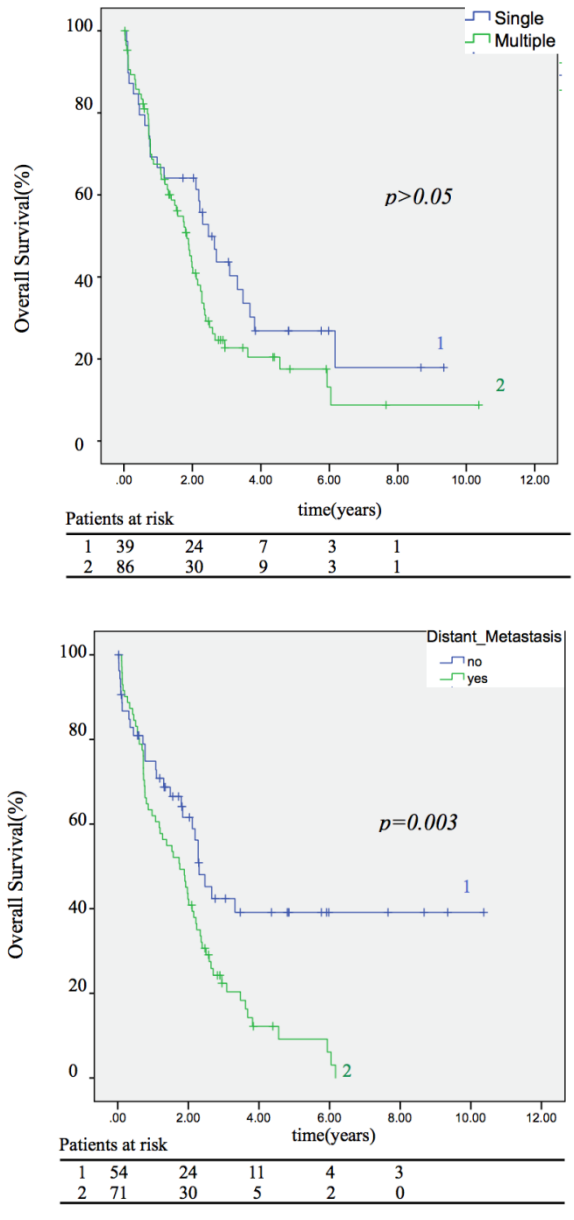


Fig 2. Survival rates according to histologic subtype (left upper) with significant difference between the subgroups (p = 0.019), where it can be seen the five-year survival rate in the adenocarcinoma group was 24% and 14% in the squamous cell carcinoma group. Right upperpicture shows the survival rates according to cell differentiation; where the five-year survival rates of well, moderate and poor differentiation were 45%, 24%, and 13%, respectively. Difference between the subgroup was significant (p = 0.004). Survival rates according to T-staging of the tumor characteristic (right lower). There was no significant difference between T1, T2, T3, and T4 (p = 0.282).

Fig 3. Survival rate according to visceral plural invasion (left) and lymphovascular invasion (right). The 5-year survival rate of patients with pleural invasion was 16%, while it was 26% in the absence group, with no significant difference (p = 0.199). For the lymphovascular invasion, the presence group had a 5-year survival of 15%, while the absence group it was 38%; however, there was no significant difference (p = 0.097).



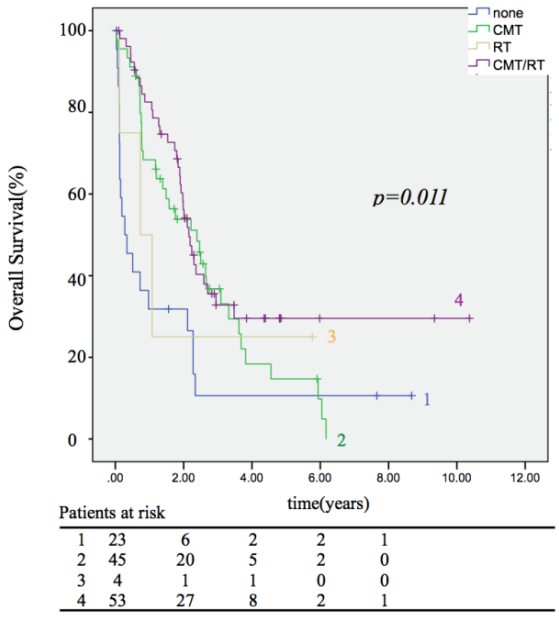


Fig 4. Survival rate according to number of N2 station metastasis (left upper); the 5-year survival rate of single station metastasis was 25% while the multiple station metastasis was 18%. However, there was no statistically significant difference (p = 0.103). Survival rate according to receiving adjuvant therapy (Right upper); the 5-year survival rate of patients who had received CMT/RT was 30%, while for radiation therapy alone, chemotherapy alone or had not received adjuvant therapy, the rates were 25%, 15%, and 10%, and the difference was statistically significant. The left lower figure showed survival rate according to post-treatment re-staging; the 5-year survival of patients with the presentation of distant metastasis in any organ was 10% while the group with no distant metastasis was 40%. The significant difference was high, p = 0.003.

TABLE 3. Multivariate analysis of the risk factors of mortality.

Variables	Number of patients	Adjusted OR (95%CI)	*p*-value
Adenocarcinoma	103	1.378 (0.655–2.902)	0.398
Poor differentiation	27	2.345 (0.734–7.489)	0.150
Visceral pleural invasion	81	0.838 (0.477–1.474)	0.541
Lymphovascular invasion	88	0.725 (0.421–1.247)	0.245
Multiple N2	82	1.429 (0.819–2.494)	0.209
Adjuvant therapy (CMT/RT)	52	0.367 (0.176–0.766)	0.008
Distant metastasis	66	2.280 (1.334–3.897)	0.003

Adjusted OR, adjusted odds ratio; CI, confidence interval.

mediastinoscopy; all the invasive study results were either negative for malignancy or had inadequate tissue for evaluation. Although our population was based on a clinical non-N2 group with pathological N2 disease confirmed by the final pathological report, the rate of patients who received IMS was not different. Whereas numerous population-based studies have shown low rates of lung cancer patients who have underwent IMS, ranging from 21%-27%,[12-18] our result showed higher rates of IMS.

The information suggests that preoperative non-invasive image staging only revealing a low suspicion of N2 metastasis is not adequate. For patients who had a preoperative PET/CT done, the information provided was also inadequate. Further prospective randomized trials on the role of PET/CT are needed. All the patients who received IMS staging, such as by EBUS, had many false negatives, leading to a dispute over inadequate tissue. This was similar to a previous study by Sawhney,[19] which showed a very low incidence of unexpected N2 disease by EBUS (3%) when only a CT scan was performed for preoperative staging, which, when compared to other modalities, such as mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA), or open biopsy of mediastinal lymph node, might play an important role in the preoperative staging consensus with previous studies. Further, Bendzsak et al,[20] showed 85% of patients used IMS, which concorded with the guidelines,[6,21-23] Call et al,[24] concluded that VAMLA is a feasible and highly accurate technique, with a rate of unexpected N2–3 of 18%.

Compared to previous reports[3,4,25], we considered the different results about which adenocarcinoma cell type and cell differentiation were factors impacting the survival rate in the comparisons; however, not T staging (T2), visceral pleural invasion, and lymphovascular invasion, which had insignificant differences in the survival rates in comparison, even though we found this coincident with the N2 metastasis (71.2%, 69.6%, and 75.2%). The number of N2 stations and associated N1 did not show a statistical relation with unexpected N2, although the coincidence of multiple N2 stations was rather high (68.8%). Mediastinal lymph node station 7 was the most common position for finding unexpected N2 (49.6%), which was compatible with Eckardt and colleagues[26], who reported subcarinal lymph node metastases were common in NSCLC regardless of the primary location and should be considered an IMS modality or routinely dissected during operation.

The present study reported an overall 5-year survival of only 20% for patients with unexpected N2 disease despite complete pulmonary resection and systematic mediastinal lymphadenectomy being achieved, which correlated with previous studies that reported 5-year survival rates varying from 10%–38%.[7-10] Surgery is beneficial in early stage NSCLC[27] but still controversial in stage IIIA-N2, reflecting the general trend away from surgery.[28,29] Pneumonectomy for lung cancer also results in poor prognosis and followed by several post operative complication[30], since then this operation is less performed. Comparison of the survival rate showed that in our series, patients who had received adjuvant chemo-radiation therapy had a better survival rate than the others ($p = 0.011$). Pathological N2 disease indicates a systemic spreading, and like in a previous study, it was found that systemic therapy tends to play a more important role and improve survival more than surgery alone[31-33], whereby we found a correlation to distant metastases in 71 patients (56.8%), with a significant difference in the survival comparison ($p = 0.003$). The multivariate analysis results also supported that CMT/RT and distant metastases are independent factors for survival.

There are several limitations of this study to note. First, the study population only involved a single group of clinical N0/N1 patients with unexpected N2 disease, and we did not compare the overall survival rates of early stage (stage I–II) patients. Second, as a result of the limited population, IMS results showing false negatives were analyzed with the unexpected N2 base patients, and so the overall IMS information was inadequate. Other than that, in general, adjuvant chemotherapy is considered in all patients with N2 disease, despite complete resection previously being performed. However, in our study, it depended on the patient preference. In particular, some patients who were diagnosed distant metastases after complete re-staging declined receiving adjuvant therapy, which might have resulted in a different survival rate.

CONCLUSION

The overall 5-year survival rate of unexpected N2 patients was low despite complete pulmonary resection and mediastinal lymphadenectomy being achieved. Adjuvant chemo-radiation therapy seems to improve survival for those with unexpected N2 metastasis as it is a systemic disease. However, not all patients received IMS, and those who did it was mostly by EBUS and which had a high false negative, leading to underestimating the staging. Other modalities, such as cervical mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA) or open biopsy should be considered for the adequate evaluation of N2 metastasis, nonetheless further study is still needed to compare each methods.

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