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ORIGINAL ARTICLE

Clinical analysis of sixty-four patients with T1aN2M0 stage non-small cell lung cancer who had undergone resection

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Abstract

Background: The aim of this study was to evaluate the clinical features of T1aN2M0 stage non-small cell lung cancer (NSCLC).

Method: From November 2008 to May 2013, 498 patients with T1a-stage NSCLC who visited the Shanghai Cancer Center were included in the study. All patients underwent a lobectomy or segmentectomy with systematic nodal resection for primary lung cancer. Analyses of gender, smoking history, primary tumor site, tumor location, tumor size, pathological classification, cancer gene, pleural invasion, number of positive lymph nodes, skip N2, single or multiple station N2, progression-free survival (PFS), and overall survival (OS) were performed.

Result: There were significant differences in tumor size, tumor size distribution, adenocarcinoma subgroup, and number of positive lymph nodes between patients at T1aN2M0 and T1aN0M0 stages. The most common histology of the T1aN2M0 subgroup was adenocarcinoma. Epidermal growth factor receptor mutations were the most common gene mutation in T1aN2M0 stage NSCLC. There were significant differences in five-year OS and PFS rates between patients with T1aN2M0, T1aN0M0, and T1aN1M0 stages. Multivariate analyses of mediastinal lymph node metastasis showed that gender, tumor size distribution, and histology type were significant predictive factors. Multivariate analyses of OS and PFS rates in the T1aN2M0 subgroup showed that the number of positive lymph nodes was a significant predictive factor.

Conclusion: Gender, tumor size distribution, and histology type were independent predictors of mediastinal lymph node metastasis in patients with T1a stage. The number of positive lymph nodes was significantly associated with OS and PFS rates in patients with T1aN2M0 stage NSCLC.

Introduction

Lung cancer is currently the leading cause of cancer-related death in China. It is generally accepted that early diagnosis and treatment of patients with non-small cell lung cancer (NSCLC) has a very important impact on their prognosis. Many researchers have focused their studies on lung cancer sized 2 cm or less.[1–3] Mediastinal lymph node metastasis can sometimes be detected in patients with tumors smaller than 2 cm, which is why many reports suggest that systematic mediastinal lymph node dissection should be performed, even in these patients.[4,5] Recent reports have mainly focused on whether lobectomy or sublobectomy and systematic mediastinal lymphadenectomy or mediastinal lymph node sampling should be used to cure patients with T1a-stage.[6–8] However, there have been few observational studies on the clinical features of tumors in the T1aN2M0 subgroup. The factors that are associated with mediastinal lymph node metastasis in T1a lung cancer are currently unclear. Useful markers that could be utilized to guide surgical procedures may exist, such as the extent of mediastinal dissection.

The purpose of the present retrospective study was to conduct a comprehensive observation of the clinical features of T1aN2M0 stage NSCLC.

Patients and methods

Patients

From November 2008 to May 2013, 598 patients with pulmonary lesions sized 2 cm or less who visited the Shanghai Cancer Center were included in the study. Clinical and pathologic data, including gender, smoking status, age, pathologic stage, primary tumor site, tumor location, pleural invasion, histology type, gene status, single or multiple station N2, skip N2, and number of positive lymph nodes were prospective collected. Of the 598, 498 T1a stage NSCLC patients underwent a lobectomy or segmentectomy with systematic nodal resection for primary lung cancer. Exclusion criteria included patients with: benign pulmonary masses; tumors of Tx, T0, or Tis-stage; or distant metastases. Evaluation before surgery included physical examination, computed tomography (CT) of the chest, two-dimensional ultrasound of the abdomen and supraclavicular and axillary lymph nodes, magnetic resonance imaging (MRI) of the brain, bone scintigraphy examinations, and a pulmonary function test. Positron emission tomography (PET) scans and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were also performed in some patients, but were not part of the routine examination. If a pulmonary lesion had standardized uptake values (SUV) of >2.5 on PET imaging, it was considered a malignant tumor.

The histopathologic types of these patients' tumors were confirmed by two pathologists after surgery. Lung cancer stage was based on the 2009 7th edition of the Tumor Node Metastasis (TNM) Classification.

Methods

Lymph nodes were classified into two groups according to their location. Mediastinal lymph nodes included lymph nodes of stations 1–9. Intrapulmonary lymph nodes included those of stations 10–14. Patients with mediastinal lymph nodes larger than 1 cm on the short axis underwent EBUS-TBNA. If mediastinal lymph node disease was confirmed, the patient received neoadjuvant chemotherapy and was excluded from the study. During surgery, if the tumor specimen was confirmed to be malignant and was not diagnosed from frozen sections as carcinoma in situ, systematic lymph node dissection was then performed. Systematic lymph node dissection on the right mediastinum includes complete resection of stations 2R, 4R, 7, 8, and 9, while on the left includes removal of stations 4L, 5, 6, 7, 8, and 9. All 498 patients were divided into three groups of patients at T1aN2M0, T1aN0M0, and T1aN1M0 stages according to lymph node metastasis status. Patients with positive lymph nodes received chemotherapy three weeks after surgery. All patients were followed up through direct patient or family contact. Data for each group, including gender, age, smoking history, primary tumor site, tumor location, pleural invasion, tumor size, histology type, gene status, number of positive lymph nodes, skip N2, single or multiple station N2, progression-free survival (PFS), and overall survival (OS), were collected. PFS duration was defined as the time between the date of surgery and the date of the first recurrence or last follow-up. OS duration was defined as the interval from surgery to death or to the date of the last follow-up.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Patient characteristic data were expressed as means and standard deviations. A Pearson's $\chi 2$ test was used to test for differences in categorical variables and the *t*-test was used for quantitative data. Survival curves were plotted according to the Kaplan–Meier method and compared with the log-rank test. Multivariable logistic regression analyses were used to determine the factors that influenced lymph node metastasis. Cox regression analyses were used to determine the factors that influenced PFS and OS. *P* values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

There were 498 patients included in this retrospective study. Tumor status of the patients studied included: 64 (12.9%) at T1aN2M0, 400 (80.3%) at T1aN0M0, and 34 patients (6.8%) at T1aN1M0, according to the 2009 7th edition of the TNM Classification. Patient characteristics are shown in Table 1. Tumor size in the T1N0M0 group was smaller than in the T1aN2M0 ($P < 0.01$) and T1aN1M0 groups ($P < 0.01$). Regarding tumor size distribution, the ratio of tumor diameters greater than 1.5 cm but less than or equal to 2 cm in the T1aN0M0 group was less than that of the T1aN2M0 ($P < 0.01$) and T1aN1M0 groups ($P < 0.05$). The ratio of pleural invasion in the T1aN2M0 group was higher than in the T1aN0M0 group ($P < 0.05$). The ratio of adenocarcinoma in the T1aN2M0 group (95.3%) was higher than that of the T1aN0M0 group (90.8%). In the subgroup of adenocarcinoma cases, the ratios of acinar adenocarcinoma and solid adenocarcinoma in the T1aN2M0 group (65.6%, 21.3%) were higher than those in the T1aN0M0 (48.8%, 6.9%) and T1aN1M0 groups (48.1%, 14.8%). The number of single-station N2 and skip N2 of the T1aN2M0 group was 37 and 27, respectively. The number of positive lymph nodes in the T1aN2M0 group was much higher than in the other two groups. In regard to gene status, the ratio of echinoderm microtubule associated protein like 4-anaplastic lymphoma

Table 1 Patient characteristics ($n = 498$)

	T1aN2M0 (n=64)	T1aN0M0 (n=400)	T1aN1M0 (n=34)	P N0:N2/N0:N1
Gender				0.484/0.004
Male	26	158	22	
Female	38	242	12	
Age	59.2±10.1	59.5±14.5	57.7±7.2	0.906/0.473
Smoking history				0.092/0.003
Smoker	22	102	17	
Non-smoker	42	298	17	
Tumor location				0.241/0.598
Right upper lobe	17	137	11	
Right middle lobe	6	29	2	
Right lower lobe	8	79	6	
Left upper lobe	21	90	11	
Left lower lobe	12	65	4	
Primary tumor site				0.259/0.152
Central	3	32	5	
Peripheral	61	368	29	
Tumor size(cm)	1.70±0.32	1.56±0.39	1.77±0.32	0.004/0.001
Tumor size distribution				0.001/0.013
d≤1	2	71	1	
1<d≤1.5	24	144	8	
1.5<d≤2	38	185	25	
Histology type				0.067/0.051
Squamouscell carcinoma	1	33	7	
Adenosquamous carcinoma	2	4	0	
Adenocarcinoma	61	363	27	0.000/0.006
IMA	2	16	1	
MIA	0	15	0	
Lepidic predominant	0	83	1	
Acinar predominant	40	177	13	
Papillary predominant	6	44	6	
Micropapillary predominant	0	3	2	
Solid predominant	13	25	4	
Pleural invasion (+/–)	20/44	80/320	4/30	0.034/0.174
Gene status				
EGFR (+/–)	40/24	270/130	16/18	0.257/0.015
KRAS (+/–)	4/60	29/371	4/30	0.512/0.252
HER2 (+/–)	0/64	6/394	0/34	0.108/0.611
BRAF (+/–)	0/64	3/397	0/34	0.640/0.782
ALK (+/–)	6/58	10/390	5/29	0.014/0.004
RET (+/–)	2/62	7/393	0/34	0.359/0.563
ROS1 (+/–)	0/64	2/398	1/33	0.743/0.218
Single or multiple station N2 (single/multiple)	37/27	–	–	
Skip N2 (+/–)	27/37	–	–	
Number of positive LN	5.3±4.7	0	1.8±1.1	0.000/0.000

ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; d, diameter; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IMA, invasive mucinous adenocarcinoma; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LN, lymph node; MIA, minimally invasive adenocarcinoma; RET, ret proto-oncogene; ROS, ROS proto-oncogene 1.

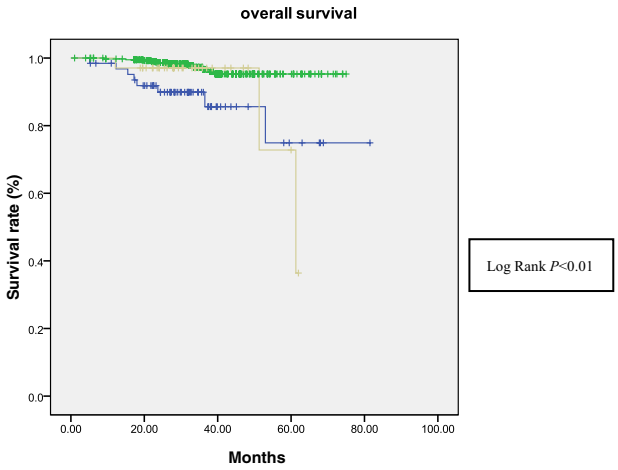

Figure 1 Overall survival rates. ⌐, T1aN2M0; ⌐, T1aN0M0; ⌐, T1aN1M0; ⊢, T1aN2M0-censored; ⊢, T1aN0M0-censored; ⊢, T1aN1M0-censored.

kinase (*EML4-ALK*) fusion in the T1aN0M0 group was lower than the T1aN2M0 ($P < 0.05$) and T1aN1M0 groups ($P < 0.01$; Table 1).

Progression-free survivial (PFS) and overall survival (OS)

The median follow-up time was 33.5 months (range 5.1–81.5). The five-year OS rate of all 498 patients was 95.8%, while that of patients at T1aN2M0, T1aN0M0, and T1aN1M0 stages were 89.1%, 97.3%, and 85.3%, respectively ($P < 0.01$).The five-year PFS rate of patients at T1aN2M0, T1aN0M0, and T1aN1M0 stages was 68.8%, 90.3%, and 76.5%, respectively($P < 0.01$, Figs 1 and 2).

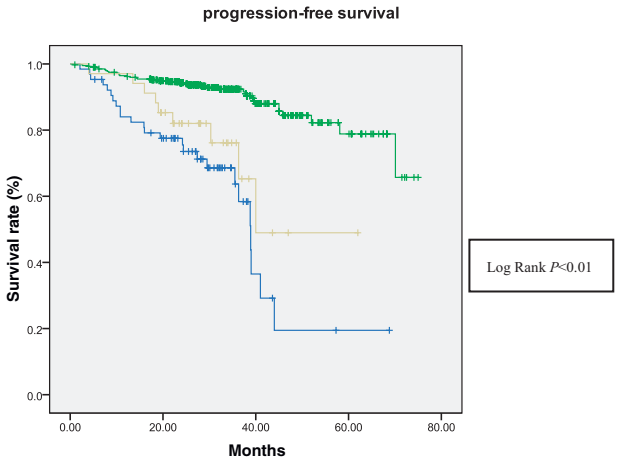

Figure 2 Progression-free survival. ⌐, T1aN2M0; ⌐, T1aN0M0; ⌐, T1aN1M0; ⊢, T1aN2M0-censored; ⊢, T1aN0M0-censored; ⊢, T1aN1M0-censored.

Factors affecting lymph node metastasis, OS, and PFS

Tumor size distribution, history type, gender, pleural invasion positivity, and ALK positivity were statistically significantly associated with mediastinal lymph node metastases in the T1a stage in univariate analyses. Multivariable logistic regression analysis of these five factors showed that only gender, tumor size distribution, and histology type were significant predictors of mediastinal lymph node metastases. In the adenocarcinoma subgroup, acinar predominant and solid predominant tumors were significant predictors of mediastinal lymph node metastases.

In the T1aN2M0 stage, the number of positive lymph nodes, smoking history, and gender were statistically significantly associated with OS in univariate analysis, while for PFS, the significant factors were positive lymph nodes, smoking history, gender, and primary tumor site. Only the number of positive lymph nodes was significantly associated with OS and PFS rates in multivariate analysis (Table 2).

Discussion

In the 2009 7th edition of the TNM Classification, T1 stage tumors were subdivided into tumors at T1a and T1b stages. Current research has focused on the treatment and prognosis of NSCLC patients with T1a stage. Consequently, there are few clinical analyses of lung cancer at T1aN2M0 stage.

Because mediastinal lymph node metastasis has a significant impact on prognosis in NSCLC patients, many researchers have suggested that systematic lymph node dissection is necessary for T1a stage NSCLC patients.[9–11] However, researchers have also reported that the outcomes of T1a patients who underwent lymph node sampling were not significantly different from patients who underwent systematic lymph node dissection.[12,13] We found that these researchers seldom analyzed the impact of tumor size and histology type on mediastinal lymph node metastases. Table 2 shows the results of multivariable logistic regression analysis, in which gender, tumor size distribution, and histology type are significant predictors of mediastinal lymph node metastases in patients with T1a stage tumors. This means that during surgery, systematic lymph node dissection may be necessary for patients with T1a stage cancer if the patient is female, the tumor diameter is greater than 1 cm, or the tumor specimen is confirmed by frozen sections to be adenocarcinoma. Further research is required to determine whether the prognosis of patients who undergo systematic lymph node dissection is better than those who undergo lymph node sampling.

Tumor size is considered to be associated with the prognosis of T1a stage cancer NSCLC patients. Shi *et al*. reported five-year survival rates in patients with tumors 1.6–2.0 cm, 1.0–1.5 cm, and less than 1.0 cm in diameter of 80.20%,

Table 2 Multivariable logistic regression analyses for factors affecting mediastinal lymph node metastases. Cox regression analyses for OS and PFS in T1a stage

	UVA		MVA	
Variable	*P* value	Risk ratio	95% CI	*P* value
Factors affecting mediastinal lymph node metastases in T1a stage				
Gender	0.000	0.404	0.297–0.548	0.000
Tumor size distribution	0.012	2.006	1.247–3.227	0.004
Histology type	0.000	1.297	1.102–1.528	0.002
Adenocarcinoma subtype				
Acinar predominant	0.005	2.643	1.451–4.812	0.001
Solid predominant	0.001	2.588	1.171–5.718	0.019
IMA	0.892	Not included in MVA		
MIA	0.999	Not included in MVA		
Lepidic predominant	0.996	Not included in MVA		
Papillary predominant	0.649	Not included in MVA		
Micropapillary predominant	0.999	Not included in MVA		
Pleural invasion+	0.031	1.713	0.906–3.238	0.098
ALK+	0.035	2.734	0.909–8.225	0.073
EGFR+	0.745	Not included in MVA		
Age	0.964	Not included in MVA		
Smoking history	0.249	Not included in MVA		
Tumor location	0.139	Not included in MVA		
Primary tumor site	0.323	Not included in MVA		
Factors affecting OS in T1aN2M0 stage subgroup.				
Number of positive LNs	0.012	1.143	1.002–1.143	0.047
Smoking history	0.039	1.996	0.268–14.890	0.500
Gender	0.037	0.235	0.017–3.250	0.280
Single or multiple station N2	0.110	Not included in MVA		
Skip N2	0.253	Not included in MVA		
Tumor size distribution	0.390	Not included in MVA		
Age	0.195	Not included in MVA		
Tumor location	0.432	Not included in MVA		
Histology type	0.243	Not included in MVA		
Primary tumor site	0.304	Not included in MVA		
Pleural invasion+	0.484	Not included in MVA		
EGFR+	0.977	Not included in MVA		
ALK+	0.560	Not included in MVA		
Factors affecting PFS in T1aN2M0 stage subgroup.				
Number of positive LNs	0.006	1.106	1.005–1.217	0.039
Smoking history	0.04	1.563	0.536–4.559	0.413
Gender	0.027	0.701	0.224–2.192	0.541
Primary tumor site	0.008	0.279	0.075–1.035	0.056
Single or multiple station N2	0.116	Not included in MVA		
Skip N2	0.679	Not included in MVA		
Tumor size distribution	0.236	Not included in MVA		
Age	0.096	Not included in MVA		
Tumor location	0.19	Not included in MVA		
Histology type	0.498	Not included in MVA		
Pleural invasion+	0.098	Not included in MVA		
EGFR+	0.985	Not included in MVA		
ALK+	0.408	Not included in MVA		

The reference groups of the various factors were, male(gender), d ≤ 1 (tumor size distribution), non-smoker (smoking history), no invasion(pleural invasion), ALK-(ALK+), EGFR-(EGFR+), right upper lobe (tumor location), central (primary tumor site), squamous cell carcinoma (history type),single(Single or multiple station N2) and noskip N2(skip N2).ALK, anaplastic lymphoma kinase; CI, confidence interval; d, diameter; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; LN, lymph node; MIA, minimally invasive adenocarcinoma; MVA, multivariate analysis; UVA, univariate analysis.

85.07%, and 100%, respectively; the differences between these were significant.[4] Kudo *et al*. determined that in T1a stage NSCLC patients, tumor size is a prognostic factor.[14] On the contrary, Kobayashi *et al*. and Nitadori *et al*. suggested that tumor size was not significantly associated with the OS of patients with T1a stage cancer.[15,16] However, these researchers did not subdivide their cases according to the status of lymph node metastasis.

There have been few detailed analyses to determine whether tumor size is a prognostic factor in patients with T1aN2M0 stage cancer. Our results determined that tumor size distribution was significantly associated with mediastinal lymph node metastasis in patients with T1a stage cancer (Table 2). However, for patients in the T1aN2M0 subgroup, tumor size distribution was not a significant predictor of OS and PFS, which might mean that postoperative follow-up for patients with tumors > 1 cm in diameter should be no different than that for patients with tumors ≤ 1 cm. Because there was a small number of T1aN2M0 cases in our sample, further research is required to determine whether tumor size is a prognostic factor for T1aN2M0 stage patients.

The number of positive lymph nodes is considered to be a prognostic factor for NSCLC. Jonnalagadda *et al*. performed an analysis of patients with N1 NSCLC and found that the number of positive lymph nodes is an independent prognostic factor of survival in these patients.[17] Jeon and Dehing-Oberije expressed a similar view in their research on clinical IA stage NSCLC patients and patients with inoperable NSCLC treated with (chemo)radiation.[18,19] However, other authors have expressed different opinions. Haney *et al*. showed that the number of positive lymph nodes was not significantly associated with the prognosis of patients with surgically resected stage II NSCLC.[20] None of these researchers considered the impact of the number of positive lymph nodes in the T1aN2M0 subgroup. Our research showed that the number of positive lymph nodes was a significant predictor of not only OS, but also PFS, in patients with T1aN2M0 stage NSCLC, which might mean that a longer postoperative follow-up is needed for patients with greater numbers of positive lymph nodes.

Epidermal growth factor receptor (*EGFR*) mutations and *ALK* fusions are thought to be associated with the prognosis of NSCLC patients. Jeon *et al*. indicated that the presence of an *EGFR* mutation is an independent prognostic factor for PFS, and selecting patients for EGFR-TKI therapy according to *EGFR* mutation status may lead to better prognoses in patients with recurrent pulmonary adenocarcinoma.[21] Li *et al*. performed an analysis on *EGFR* T790M mutations in NSCLC patients and found that although primary *EGFR* T790M mutations are rare in NSCLC cases, they are a predictor of a poorer prognosis.[22] However, there are also different points of view about the relationship between *EGFR* mutation status and NSCLC prognosis. Fang and Wang analyzed the relevant research of the past 20 years and concluded that the prognostic and predictive value of *EGFR* mutation status in NSCLC remains uncertain.[23] We found that most of these studies had not considered the T1aN2M0 subgroup. Our research showed that *EGFR* and *ALK* status were not significant predictors of OS and PFS rates in patients of the T1aN2M0 subgroup, nor were they independent predictors of mediastinal lymph node metastasis. Existing research has confirmed that molecular-targeted therapy is effective for NSCLC patients with EGFR and ALK-positive tumors.[24,25] Even if EGFR and ALK status are not independent predictors of OS in patients with T1aN2M0 stage cancer, genetic testing may still be very important for the individualized treatment of these patients.

In conclusion, we found that patients with T1aN2M0 stage NSCLC had poorer PFS and OS rates than those with T1aN0M0 or T1aN1M0 stage NSCLC. Gender, tumor size distribution, and histology type were independent factors of mediastinal lymph node metastasis in T1a stage patients. The number of positive lymph nodes was significantly associated with OS and PFS of patients in T1aN2M0 stage. The next step is to evaluate the best treatment for T1aN2M0 NSCLC patients.

Disclosure

No authors report any conflict of interest.

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