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Risk analyses of N2 lymph-node metastases in patients with T1 non-small cell lung cancer: a multi-center real-world observational study in China

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Abstract

Purpose N2 lymph-node metastases occur in approximately 6–17% of the patients with T1-2 non-small cell lung cancer (NSCLC). However, the clinical characteristics of N2 patients are not fully understood.

Methods This retrospective, multi-center analysis included T1 NSCLC patients receiving surgical resection during a period from Jan 2nd, 2014 to Dec 27th, 2017. The diagnosis was pathologically verified in all cases. Univariate and multivariate logistic regression analyses were conducted to analyze the factors that are associated with pN2 lymph-node metastases.

Results A total of 10,885 patients (48.4% men; 84.7% adenocarcinoma) were included in the analysis. The mean age was 59.0 ± 9.9 years. The mean tumor size was 1.8 ± 0.8 cm. Of the patients, 3260 (29.9%) were smokers or ex-smokers. Lymph-node metastases were verified in 1808 (16.6%) patients, and 1167 (10.7%) patients had N2 lymph-node metastases. The multivariate analyses indicated that larger tumor size, lower differentiation, CEA level ≥ 5 ng/mL, vascular invasion (+), and pleural involvement (+) were associated with higher percentages of N2 lymph-node metastases ($p < 0.001$ for all).

Conclusions This study demonstrated the significant association between N2 lymph-node metastases and tumor size and differentiation, CEA levels, and status of vascular invasion and pleural involvement.

Keywords T1 non-small cell lung cancer · N2 lymph-node metastases · Risk factors · Chinese patients · Observational study

Introduction

Lung cancer, mostly non-small cell lung cancer (NSCLC), is the most common cancer worldwide. It was estimated that there were 2.1 million new cases and 1.8 million deaths in 2018 according to the latest data showed in GLOBOCAN 2018, which account for 11.6% of all new cancer diagnosis and 18.4% of all cancer deaths, respectively (Bray et al. 2018; Zakaria et al. 2017). The recent advancements in medical and public health awareness have resulted in an increased diagnosis of early stage NSCLC. As per the eighth edition of the tumor, node, and metastasis (TNM) classification for NSCLC, early stage T1 NSCLC is defined by tumor size at ≤ 3 cm in the greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus, and with a relatively better prognosis (Goldstraw et al. 2016), whereas the risk of metastasis is developed in T1 NSCLC, with different prognosis among patients. The prevalence of nodal metastases was 21% in Canadian patients with T1 NSCLC, as reported by Seely JM et al. (1993). In addition, Kim BT et al. pointed out that lymph-node involvement was observed in 23% of Korean patients with pathological T1 NSCLC (Kim et al. 2006). In Chinese T1 NSCLC patients, the incidence of lymph nodal metastasis was reported to be 19% (Kim et al. 2006; Zhang et al. 2017). Notably, 16.8% of the Chinese T1 patients had pathologic N2 lymph-node metastases, which was approximately 10% higher than that of American and Italian patients (6.1% and 7%, respectively) (Casiraghi et al.

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2011; Defranchi et al. 2009; Zhang et al. 2012). The 5-year survival rate in pT1 N0/N1 NSCLC patients was reported to be 46%, while decreased to 36% in patients with N2 disease (Defranchi et al. 2009).

Currently, the risk factors for predicting lymph-node metastasis, especially for N2 disease, in NSCLC patients remain controversial. Several previous studies reported that clinical and pathological features, such as age, sex, histologic subtype, tumor size, type of surgery, etc. may not be associated with N2 lymph-node metastasis in NSCLC patients (Bertoglio et al. 2018; Casali et al. 2005; Haager et al. 2018). However, other studies have suggested that age, smoking history, histologic subtype, tumor size, etc. had the potential to predict N2 lymph-node metastasis in NSCLC patients (Chen et al. 2015; Tamura et al. 2016; Zhang et al. 2012). Thus, further evidence is necessary to confirm the risk factors for N2 lymph-node metastasis in NSCLC patients, especially those with T1 stage. The aim of the current study was to collect real-world evidence on the clinical characteristics of Chinese T1 NSCLC patients with N2 lymph-node metastases and to assess risk factors that could predict N2 lymph-node metastases.

Methods

Patients

This nationwide multi-center observational study included Chinese patients with pathologically confirmed T1 NSCLC undergoing surgical resection in ten Class 3A hospitals during a period from Jan 2nd, 2014 to Dec 27th, 2017. Patients receiving chemotherapies, radiotherapies, biotherapies, or other intervention therapies before surgery were excluded. Patient diagnosis and surgical procedures followed the clinical practice and physicians' discretion. Patients were preoperatively evaluated and staged according to the routine protocol, including enhanced chest CT scan, enhanced brain MRI or CT, abdominal CT or ultrasonography, bone scanning, electronic fiber bronchoscopy, and cardiopulmonary tests (CSCO 2018). Clinical stage was assessed mainly by chest CT scan. Whereas, PET–CT was performed on highly suspicious patients with bulky mediastinal mass (Song et al. 2017; Zheng et al. 2018). Before the study was initiated, the study designs and hypotheses were reviewed and approved by the Institutional Ethics Committee and were registered at www.clinicaltrials.gov (NCT03413956).

Data evaluation

Clinicopathological factors including age, sex, body mass index (BMI), pathologic type, tumor types, N2 lymph-node metastases, tumor size, location, differentiation, smoking history, serum preoperative carcinoembryonic antigen (CEA) levels, vascular invasion, number of lymph node dissected and lymph-node stations explored, pleural involvement, and EGFR status were retrospectively collected from the electronic medical database (LinkDoc, Beijing, China). The data were used to evaluate the risk factors associated with N2 lymph-node metastases and to compare the percentages of the patients with N2 lymph-node metastases in the subpopulations.

Statistical analyses

Continuous variables were presented as mean (SD). Categorical variables were presented as frequency and percentage. Univariate and multivariate logistic regression analyses were conducted to examine the risk factors associated with N2 lymph-node metastases. Results were summarized as odds ratios (ORs) and two-side 95% confidential intervals (CIs). Independent variables in the multivariate analysis were selected using a step-wise approach; all variables with $p \leq 0.2$ were retained in the final model. All statistical analyses were two-sided and were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

A total of 10,885 eligible patients were enrolled, 5265 (48.4%) were men. The mean age of the patients was 58.96 ± 9.91 years. Demographic and baseline characteristics are shown in Table 1. Among the 10,885 patients, 1808 (16.6%) had pathological lymph-node metastases, and 1167 (10.7%) had pathological N2 (pN2) lymph-node metastases. Overall, 15.2% of the patients were ex-smokers and 15.4% were smokers in the whole population, corresponding to 20.4% and 20.4% in the N2 population, respectively. Over 40% of patients in the N2 group had baseline CEA level ≥ 5 ng/mL, whereas only 15.3% in the overall sample. The number of lymph-node dissected was 12.7 ± 8.0 in the whole population and 17.0 ± 9.4 in the N2 population. Overall, 91.7% and 93.8% of patients had at least three stations of lymph-node stations explored in the whole population and N2 population, respectively.

As shown in Table 2, most patients (9216, 84.7%) had adenocarcinoma. Tumor differentiation was low in 31.0% and middle in 55.9% of the overall patients, while 60.6% and 37.6% in the N2 population, respectively. Mean tumor size was 1.8 ± 0.8 cm in the overall sample and 2.32 ± 0.65 cm in the N2 population. Most of the tumors were located at the upper lobe of the lungs (60.1% in the overall sample, 57.2%

Table 1 Demographic and clinical characteristics

	pT1 NSCLC patients	
	Total ($n = 10,885$)	pN2 positive ($n = 1167$)
Age (years), mean (SD)	59.0 (9.9)	59.8 (9.0)
Sex, males	5265 (48.4%)	642 (55.0%)
Body mass index, mean (SD)	23.5 (3.1)	23.5 (3.1)
Smoking status		
Non-smokers	7363 (69.3%)	673 (59.3%)
Ex-smokers	1620 (15.2%)	231 (20.4%)
Smokers	1640 (15.4%)	231 (20.4%)
Baseline CEA levels		
< 5 ng/mL	5560 (84.7%)	427 (59.3%)
≥ 5 ng/mL	1004 (15.3%)	293 (40.7%)
Number of LN dissected, mean (SD)	12.7 (8.0)	17.0 (9.4)
Number of LN station dissected		
Single station	318 (2.9%)	12 (1.0%)
Two stations	584 (5.4%)	25 (2.1%)
Multiple stations (≥ 3)	9983 (91.7%)	1130 (93.8%)

CEA carcinoembryonic antigen, *LN* lymph node

Table 2 Tumor characteristics

	pT1 NSCLC patients	
	Total ($n = 10,885$)	pN2 positive ($n = 1167$)
Tumor size (cm)		
> 0 and ≤ 1 cm	2779 (25.5%)	71 (6.1%)
> 1 and ≤ 2 cm	4766 (43.8%)	400 (34.3%)
> 2 and ≤ 3 cm	3340 (30.7%)	696 (59.6%)
Pathologic type		
Adenocarcinoma	9216 (84.7%)	898 (76.9%)
Squamous cell carcinoma	1271 (11.7%)	189 (16.2%)
Others	398 (3.7%)	80 (6.9%)
Tumor types		
Central type	305 (13.8%)	90 (20.7%)
Peripheral type	1904 (86.2%)	345 (79.3%)
Tumor differentiation		
Un-differentiated	4 (0.1%)	1 (0.2%)
Low	1761 (31.0%)	397 (60.6%)
Middle	3180 (55.9%)	246 (37.6%)
High	742 (13.0%)	11 (1.7%)
Tumor location		
Upper lobe	6544 (60.1%)	667 (57.2%)
Middle lobe	820 (7.5%)	85 (7.3%)
Lower lobe	3521 (32.3%)	415 (35.6%)
N2 nodal station		
Single station	–	619 (53.0%)
Two stations	–	325 (27.8%)
Multistations (≥ 3)	–	223 (19.1%)
Vascular invasion (+)	381 (3.5%)	141 (12.1%)
Pleural involvement (+)	2198 (20.2%)	420 (36.0%)

in the N2 population). Vascular invasion was presented in 3.5% of the overall patients and 12.1% of the N2 population. A total of 2198 (20.2%) patients were documented to have pleural involvement, while, in the N2 patients, 420 (36.0%) had pleural involvement.

Univariate analysis of risk factors for N2 lymph-node metastases

Univariate logistic regression analysis was performed to identify potential factors that may associate with N2 lymph-node metastases. As shown in Fig. 1, male patients were more likely to have N2 lymph-node metastasis (OR 1.35, 95% CI 1.193–1.523, $p < 0.001$). Patients who were ex- or current smokers were more often associated with N2 lymph-node metastasis (OR 1.64, 95% CI 1.447–1.862, $p < 0.001$). The patients with larger tumor size or lower differentiated tumor had higher rate of N2 lymph-node metastases ($p < 0.001$): in the patients with $2 < $ tumor size ≤ 3 cm, the rate of N2 lymph-node metastases (20.8%) was higher than that in $0 < $ tumor size ≤ 1 cm group (2.6%) (OR 10.04, 95% CI 7.819–12.891, $p < 0.001$) and $1 < $ tumor size ≤ 2 cm group (8.4%) (OR 2.87, 95% CI 2.518–3.279, $p < 0.001$); 22.5% of the patients with low-differentiated tumors had N2 lymph-node metastases, whereas 7.7% and 1.5% of the patients with middle- and high-differentiated tumors had N2 metastasis (middle- vs. low-differentiated: OR 0.29, 95% CI, 0.243–0.342, $p < 0.001$; high- vs. low-differentiated: OR 0.05, 95% CI, 0.028–0.095, $p < 0.001$). The percentage of patients with N2 lymph-node metastases was higher in patients with CEA level ≥ 5 ng/mL (29.2%) than those with CEA < 5 ng/mL (7.7%) (OR 4.95, 95% CI

	Number of Patients with N2 Lymph Node Metastases (+) (%) (n (%) vs m (%))		OR (95% CI)	P-Value
Univariate Analysis				
Age (years) (>65 vs <=65)	330 (10.7) vs	837 (10.7)	0.99 (0.869,1.139)	0.9414
Gender (Male vs Female)	642 (12.2) vs	525 (9.3)	1.35 (1.193,1.523)	<.0001
Smoking History (Yes vs No)	462 (14.2) vs	673 (9.1)	1.64 (1.447,1.862)	<.0001
Pathological Types				<.0001
SCC vs Others	189 (14.9) vs	80 (20.1)	0.69 (0.520,0.928)	0.0136
Adenocarcinoma vs Others	898 (9.7) vs	80 (20.1)	0.43 (0.333,0.554)	<.0001
Adenocarcinoma vs SCC	898 (9.7) vs	189 (14.9)	0.62 (0.522,0.732)	<.0001
Tumor Location (Right vs Left)	672 (10.5) vs	495 (11.0)	0.95 (0.844,1.080)	0.4622
Tumor Location				0.0454
Middle vs Upper	85 (10.4) vs	667 (10.2)	1.02 (0.803,1.293)	0.8772
Lower vs Upper	415 (11.8) vs	667 (10.2)	1.18 (1.034,1.341)	0.0139
Lower vs Middle	415 (11.8) vs	85 (10.4)	1.16 (0.903,1.479)	0.2514
Tumor Differentiation				<.0001
Middle vs Low	246 (7.7) vs	397 (22.5)	0.29 (0.243,0.342)	<.0001
High vs Low	11 (1.5) vs	397 (22.5)	0.05 (0.028,0.095)	<.0001
High vs Middle	11 (1.5) vs	246 (7.7)	0.18 (0.098,0.330)	<.0001
Tumor Size (Pathological)				<.0001
>1 and <=2 cm vs >0 and <=1 cm	400 (8.4) vs	71 (2.6)	3.49 (2.702,4.518)	<.0001
>2 and <=3 cm vs >0 and <=1 cm	696 (20.8) vs	71 (2.6)	10.04 (7.819,12.891)	<.0001
>2 and <=3 cm vs >1 and <=2 cm	696 (20.8) vs	400 (8.4)	2.87 (2.518,3.279)	<.0001
CEA Levels (>=5 ng/ml vs <5 ng/ml)	293 (29.2) vs	427 (7.7)	4.95 (4.187,5.861)	<.0001
Tubular Cancer Thrombus (+ vs -)	141 (37.0) vs	1026 (9.8)	5.42 (4.358,6.736)	<.0001
Pleural involvement (+ vs -)	420 (19.1) vs	747 (8.6)	2.51 (2.208,2.864)	<.0001

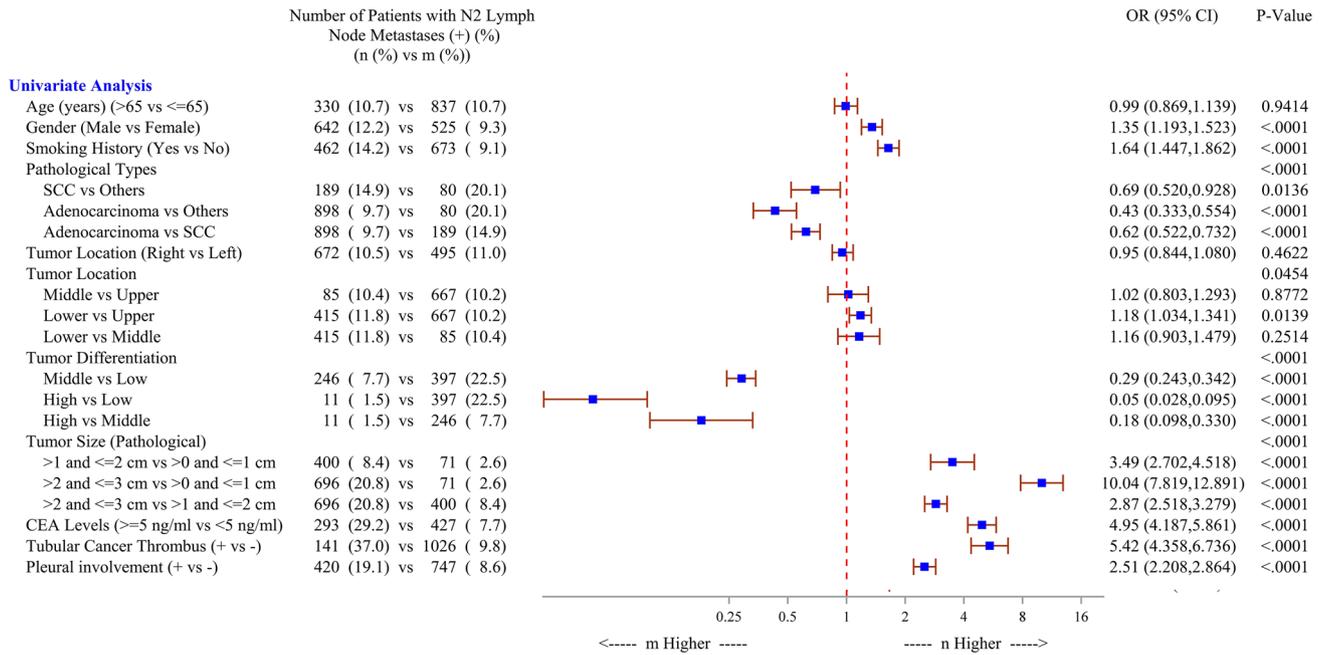<----- m Higher -----   ----- n Higher ----->

Fig. 1 Univariate analyses of N2 lymph-node metastases

4.187–5.861, $p < 0.001$), and was also higher in patients with vascular invasion (+) (37.0%) than those without vascular invasion (−) (9.8%) (OR 5.42, 95% CI 4.358–6.736, $p < 0.001$). Patients with pleural involvement were more likely to suffer from N2 lymph-node metastases (OR 2.51, 95% CI 2.208–2.864, $p < 0.001$). The univariate analyses suggested that N2 lymph-node metastases were observably correlated with male, smoking, larger size tumor, a higher CEA level, vascular invasion (+), and pleural involvement (+).

Multivariate analysis of risk factors for N2 lymph-node metastases

In multivariate analysis, as shown in Table 3, age > 65 years (OR 0.70, 95% CI 0.545–0.896, $p < 0.01$), lower differentiation (middle vs. low: OR 0.42, 95% CI 0.332–0.532, $p < 0.001$; high vs. low: OR 0.12, 95% CI 0.058–0.235, $p < 0.001$; high vs. middle: OR 0.28, 95% CI 0.138–0.557, $p < 0.001$), larger size tumor (> 2 and ≤ 3 cm vs. > 0 and ≤ 1 cm: OR 2.53, 95% CI 1.666–3.829, $p < 0.01$; > 2 and ≤ 3 cm vs. > 1 and ≤ 2 cm: OR 2.09, 95% CI 1.632–2.665, $p < 0.001$), a higher CEA level (≥ 5 ng/mL) (OR 2.31, 95% CI 1.792–2.966, $p < 0.001$), vascular invasion (+) (OR 3.26, 95% CI 1.986–5.353, $p < 0.001$), and pleural involvement (+) (OR 1.29, 95% CI 1.002–1660, $p < 0.05$) were independent risk factors for N2 lymph-node metastases.

Table 3 Multivariate analyses of the risk factors associated with pN2 lymph-node metastases

	ORs	95% CIs	p value
Age > 65 (vs ≤ 65 years)	0.70	0.545, 0.896	0.0047
Tumor location			0.1240
Middle vs upper	0.81	0.494, 1.332	0.4076
Low vs. upper	1.23	0.967, 1.565	0.0918
Low vs. middle	1.52	0.911, 2.526	0.1096
Degrees of differentiation			< 0.0001
Middle vs. low	0.42	0.332, 0.532	< 0.0001
High vs. low	0.12	0.058, 0.235	< 0.0001
High vs. middle	0.28	0.138, 0.557	0.0003
Tumor sizes (pathologic)			< 0.0001
> 1 and ≤ 2 cm vs. > 0 and ≤ 1 cm	1.21	0.792, 1.852	0.3772
> 2 and ≤ 3 cm vs. > 0 and ≤ 1 cm	2.53	1.666, 3.829	< 0.0001
> 2 and ≤ 3 cm vs. > 1 and ≤ 2 cm	2.09	1.632, 2.665	< 0.0001
CEA ≥ 5 ng/mL (vs. < 5 ng/mL)	2.31	1.792, 2.966	< 0.0001
Vascular invasion (+ vs. −)	3.26	1.986, 5.353	< 0.0001
Pleural involvement (+ vs. −)	1.29	1.002, 1.660	0.0483

CEA carcinoembryonic antigen, *CI* confidential interval, *OR* odd ratio

Discussion

Given that most published reports were single-center studies in NSCLC with lymph-node metastases (especially N2 disease) (Heon et al. 2010; Xiong et al. 2016; Zhang et al.

2012, 2017), this is the first large-scale Chinese multi-center retrospective study to show that clinical characteristics such as age, tumor differentiation, tumor size, CEA levels, and vascular invasion were risk factors for N2 lymph-node metastasis in T1 NSCLC patients.

Tumor size has been well recognized as a crucial prognostic factor for survival of early NSCLC patients and was proportional to the prevalence of lymph-node metastases, especially N2 disease (Asamura et al. 1996; Birim et al. 2005; Port et al. 2003). An early Japanese retrospective study showed no lymph-node metastasis in lung cancer patients with tumor sizes ≤ 1.0 cm, 17% lymphatic metastases in 1.1 cm > tumor sizes ≤ 2.0 cm, and 38% in 2.0 cm > tumor sizes ≤ 3.0 cm (Ishida et al. 1990). Lee et al. also reported that the incidence of N2 lymph-node metastases in American patients with clinical stage I NSCLC increased from 4.8% in tumor sizes ≤ 2.0 cm to 57.1% in tumor sizes > 6.0 cm (Lee et al. 2007). Others similar results were also observed in early stage NSCLC (Cho et al. 2014; Zhang et al. 2012). In consistent with the above reports, N2 lymph-node metastases in patients with T1 NSCLC increased greatly from 6.1% (tumor sizes ≤ 1.0 cm) to 59.6% (2.0 cm > tumor sizes ≤ 3.0 cm) in the current study, which indicated that tumor size may guide significantly for pre-operative lymph-node staging. It is warranted that patients with small T1 NSCLC, especially those with less than 1 cm, should perform the surgical resection with systematic lymphadenectomy to ensure radically resect all possible lymph-node metastases. In addition, we found that the majority of the patients with N2 lymph-node metastases were current or ex-smokers, which revealed a close association between both former and current smoking and N2 disease in patients with T1 NSCLC. In contrast to our results, Zhang et al. demonstrated a higher rate of non-smokers in patients with N2 lymph-node metastases (Zhang et al. 2012). However, they only compared N2 status (positive and negative) in non-smokers without presenting the data of current or ex-smokers. Previous studies showed different prognoses between patients with single and multiple N2 diseases (Inoue et al. 2004; Lochowski et al. 2018; Qiang et al. 2015). In the study, 53.0% of N2 patients had single N2 station involved, suggesting a potential impact on patient survival (Bertoglio et al. 2018). Future studies are needed to pay more attention to the issue of survival data.

Univariate analysis in the current study indicated an association of N2 metastasis with sex, smoking history, tumor size, differentiation and pathological type, preoperative CEA levels, and status of vascular invasion and pleural involvement. After adjusted in a multivariate analysis, age, degrees of differentiation, tumor size, CEA levels, and status of vascular invasion and pleural involvement were major independent predictive factors for N2 metastasis. Similar with our findings, Yong-Kui Zhang and his colleagues reported that positive CEA

levels and tumor sizes > 1.0 cm were remarkably associated with lymph-node involvement in T1 NSCLC patients (Zhang et al. 2017). Bao et al. showed that tumor size and CEA level were predictive factors for lymph-node metastasis in patients with small size NSCLC (Bao et al. 2014). Deng et al. reported that tumor differentiation retained independent associations with outcomes of N2 NSCLC patients in the SEER database (Deng et al. 2018). In addition, several studies have revealed that vascular invasion was an independent prognostic factor in patients with stage I NSCLC (Hamanaka et al. 2015; Okada et al. 2017; Shimada et al. 2012). A similar result was found in our study that positive vascular invasion with T1 NSCLC was more likely to appear N2 lymph-node metastases. In addition, pleural involvement was found to significantly associate with lymph-node metastasis in NSCLC patients (Hattori et al. 2012; Yu et al. 2016). Of note, 41.1% (88) of patients in pN2 patients had pleural involvement, obviously higher than those in pN0 (19.2%) and in pN1 (32.9%) patients (Yu et al. 2016). The present results extend previous observations showing that pleural involvement was significantly associated with N2 lymph-node metastases.

Our study has some potential limitations. First, this study is a retrospective study that is prone to result in some biases, such as selection bias, incomplete retrieval of medical records, and missing information for preoperative staging. Second, we did not collect patient survival due to the follow-up time of T1 NSCLC patients which is too short to show the clinical outcomes. As a result, the ultimate relevance between risk factors for N2 lymph-node metastasis and patient survival remains unknown.

Conclusions

In conclusions, clinical characteristics including sex, smoking history, tumor size, differential level, CEA levels, and status of vascular invasion and pleural involvement were associated with N2 lymph-node metastasis in the Chinese T1 NSCLC patients, which may offer some clues to preoperative assessment of lymph-node metastasis, especially of N2 lymph-node metastasis.

Compliance with ethical standards

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