Risk Factors for Lymph Node Metastasis in Clinical Stage IA3 Lung Adenocarcinoma Patients

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Abstract

Background: lymph node metastasis is a poor prognostic factor for lung cancer; however, the risk of lymph node metastasis has not been clarified yet, so it is controversial to conduct systematic lymph node dissection for early lung cancer. Therefore, this study aimed to focus on analyzing the predictive factors for lymph node metastasis in patients with clinical stage IA3 lung adenocarcinoma.

Methods: Our study group retrospectively analyzed all surgical patients admitted to our hospital from January 1, 2017 to June 2021, and these patients were considered having stage IA3 lung adenocarcinoma. A total of 334 patients underwent lobectomy combined with systematic lymph node dissection. Univariate and multivariate logistic regression analysis were adopted to predict the risk factors of lymph node metastasis.

Results: Among the 334 patients eligible for this study, the overall mediastinal lymph node metastasis rate was 15.27%. There were 45 cases of N1 metastasis and 11 cases of N2 metastasis, 5 cases had both N1 and N2 metastasis at the same time. The patients were divided into three groups according to consolidation tumor ratio (CTR) values (<0.25 , $0.25-0.5$, >0.5). The lymph node metastasis rates in each CTR group were 1.8% (2/112), 11.7% (17/145) and 41.6% (32/77), respectively. The mediastinal lymph node metastasis rate in patients with carcinoembryonic antigen (CEA $>5\text{ng/ml}$) was 57.89% (22/38). The receiver operating characteristic curve (ROC) showed that the area under the curve (AUC) of CTR, pathological type and CEA were 0.790 [95% confidence interval (CI): 0.727 – 0.853; $P<0.001$]; 0.800 [95% CI: 0.735–0.865; $P<0.001$]; 0.682 [95% CI: 0.591–0.773, $P<0.001$]; respectively. Multivariate regression analysis showed that these listed factors were significantly correlated with lymph node metastasis of clinical stage IA3 lung adenocarcinoma: CEA [Odds Ratio (OR)=3.05, $P=0.016$], CTR 0.25 to 0.5 (OR=14.12, $P<0.017$), CTR >0.5 (OR=7.75, $P=0.015$), micropapillary adenocarcinoma (OR=15.704, $P<0.001$), and solid adenocarcinoma (OR=8.971, $P=0.001$).

Conclusions: CEA ($>5\text{ng/ml}$), histologic subtype and CTR (>0.25) are important predictors of lymph node metastasis in clinical stage IA3 lung adenocarcinoma, systematic lymph node dissection should be the prior choice for patients with clinical stage IA3 incorporated with risk factors. The lymph node dissection method in stage IA3 should be alternative from those in stage IA1 and IA2.

Introduction

Currently, surgery is still the main standard treatment for early lung cancer, the lymph node metastasis being known by intraoperative lymph node dissection during operation however, anatomical lobectomy combined with systematic lymph node dissection for early lung cancer treatment is controversial within the academic field¹. The long-term follow-up results of JCOG0804 in Japan showed that most patients do not even need systematic lymph node dissection², in addition, many studies have shown that the pathological types of adenocarcinoma in situ and microinvasive adenocarcinoma will not have lymph nodes^{3,4}. In particular, Stage IA has been subdivided into stage IA1, IA2 and IA3 in the 8th Edition

International Association for the Study of Lung Cancer (IASLC), and the risk of lymph node metastasis in clinical stage IA1 and IA2 lung cancer is relatively low⁵, however, the risk factors of lymph node metastasis in IA3 lung adenocarcinoma are undetermined, and there are few studies related to discuss or clarify the risk. At present, the research results of stage IA3 in JCOG1211 in Japan have not been published yet⁶. Therefore, it is necessary to predict the risk factors of lymph node metastasis of clinical stage IA3 lung adenocarcinoma, in order to important clinical reference value for the choice of lymph node dissection in stage IA3 of lung adenocarcinoma.

Patients And Methods

Patients

The retrospective study was approved by the ethics committee of Wenzhou Central Hospital (L2021-12-42). As the study was retrospective, it was not necessary to obtain the written informed consent of each patient. During the period between January 2017 and June 2021, 334 patients with clinical stage IA3 lung adenocarcinoma were included in the study.

Inclusion criteria: preoperative clinical staging was based on TNM staging (IASLC 8th Edition); Single tumor with diameter (>2-3cm); Malignant tumor without previous chemotherapy or radiotherapy treatment; Performance status of 0 or 1; Sufficient organ function; Intraoperative pathology confirmed invasive adenocarcinoma; Preoperative examination excluded distant organ metastasis. Exclusion criteria: Incomplete case records; Severe emphysema, pulmonary fibrosis, interstitial pneumonia; history of severe heart failure, myocardial infarction, heart disease within the past 6 months; Pleural dissemination; The short axis of mediastinal lymph nodes was greater than 1cm or positron emission tomography-computer tomography (PET-CT) considered lymph node metastasis; Preoperative neoadjuvant radiotherapy or chemotherapy.

Methods

All patients had completed listed medical tests before operation, including contrast-enhanced thoracic CT, head magnetic resonance imaging, abdominal CT, echocardiography, pulmonary function and CEA. Some patients completed PET-CT examination. No puncture biopsy was performed before operation. Lobectomy combined with systemic lymph node dissection was performed, Systematic lymph node dissection for right-side tumors contained 2R, 4R, 7-12 stations, while 4-12 stations were required for left side tumors, the lymph node classification comply with the IASLC (8th Edition). Age, sex, smoking, preoperative serum CEA level, CTR, histopathological subtypes (lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant), epidermal growth factor receptor

(EGFR) mutation, PET-CT, and spread through air spaces (STAS) are medical records and pathological data taken into account in the analysis.

Statistical analysis

Univariate analysis and multivariate logistic regression analysis were performed by SPSS (version 23.0, Inc, Chicago, IL), to identify the risk factors of lymph node metastasis. Univariate analysis used Fisher's exact test or χ^2 test, and the categorical variables with univariate analysis $P < 0.1$ were included in multivariate regression analysis, where $P < 0.05$ was statistically significant.

Results

190 males and 144 females constitute the 334 patients eligible for the study. According to the postoperative pathological diagnosis, 51 patients had mediastinal lymph node metastasis, which the rate was 15.27% (51/334), 45 patients showed N1 positive lymph nodes, 11 patients showed N2 positive lymph nodes, 5 patients had both N1 and N2 positive lymph nodes. The mediastinal lymph node metastasis rate in patients with CEA ($>5\text{ng/ml}$) was 57.89% (22/38).

Figure 1A shows lymph node status according to histologic subtype, N1 lymph node metastasis occurred in 5 cases (3.8%) of lepidic predominant, 6 cases (6.2%) of acinar predominant, 5 cases (13.9%) of papillary predominant, 15 cases (53.6%) of micropapillary predominant and 14 cases (31.7%) of solid predominant, N2 lymph node metastasis occurred in all pathological types except lepidic predominant. Figure 1B shows lymph node status according to CTR. When $\text{CTR} < 0.25$, only 2 cases (1.8%) had N1 metastasis, and there was no N2 lymph node metastasis. With $\text{CTR} > 0.5$, 28 cases (36.4%) had N1 lymph node metastasis and 7 cases (9.1%) had N2 lymph node metastasis.

After univariate factor analysis, the following 6 factors were identified as important predictors for mediastinal lymph node metastasis: CTR ($p < 0.001$), PET-CT ($p = 0.013$), CEA level ($p < 0.001$), Pathologic type ($p < 0.001$), EGFR mutation ($p < 0.001$) and STAS ($P = 0.001$). Age, gender and smoking were not identified as significant predictors (Table 1). Six predictive factors mentioned at the beginning were included in multivariate analysis, and the results showed that mediastinal lymph node metastasis had the following three vital risk factors: preoperative CEA level > 5 (ng/ml) (OR: 3.05, 95% CI: 1.226-7.586, $P = 0.016$); CTR 0.25 to 0.5 (OR: 6.413, 95% CI: 1.396-29.458, $P = 0.017$), CTR > 0.5 (OR: 7.750, 95% CI: 1.489-40.343, $P = 0.015$); micropapillary predominant (OR: 15.704, 95% CI: 3.785-65.155, $P < 0.001$) and solid predominant (OR: 8.971, 95% CI: 2.382-33.790, $P = 0.001$).

Figure 2 shows ROC curves generated according to the distributions of each important variable of mediastinal lymph node metastasis. The area under ROC curve values for CTR, CEA level and pathological type were 0.790 (95% CI: 0.727-0.853), 0.682 (95% CI: 0.591-0.773), 0.800 (95% CI: 0.735-0.865), respectively.

Discussion

Many studies have shown that mediastinal lymph node metastasis may occur even in early non-small cell lung cancer^{7,8}. If lymph node metastasis can be identified before surgery, these patients will benefit from surgical resection after neoadjuvant therapy⁹. However, it is difficult to evaluate mediastinal lymph node metastasis by enhanced CT or PET-CT before operation. This study excluded patients with mediastinal lymph node metastasis considered by preoperative PET-CT. Nevertheless, 17.96% (46/256) of patients with mediastinal lymph node metastasis were not found by PET-CT before operation, which explained the limitations of PET-CT in evaluating mediastinal lymph node metastasis.

In this study, mediastinal lymph node metastasis occurred in any pathological subtype of IA3 lung invasive adenocarcinoma, but Ye et al¹⁰ suggested that no mediastinal lymph node metastasis in stage IA lepidic predominant taking place, which may due to the small sample size. In our study, the total metastasis rate of mediastinal lymph nodes in IA3 stage was 15.27%, but Koike et al¹¹ reported that the overall mediastinal lymph node metastasis rate in patients with stage IA non-small cell lung cancer was only 7.5%, Ye et al¹⁰ showed that the overall mediastinal lymph node metastasis rate in patients with stage IA lung adenocarcinoma was 10.6%, Ding et al¹² showed that only 8.5% of patients with stage IA had mediastinal lymph node metastasis. The latest research results in Japan show that the lymph node metastasis rate of stage IA lung adenocarcinoma is only 4.9%¹³. The above results showed that the proportion of mediastinal lymph node metastasis in IA3 stage was significantly higher than that in IA stage during clinical research, implying that the size of the tumor possibly affects the occurrence of mediastinal lymph node metastasis. The mediastinal lymph node metastasis rate in stage IA3 was higher than that stage IA, so the lymph node dissection method in stage IA3 should be different from that in stage IA1 and IA2, suggesting that further refinement of clinical staging may help to optimize mediastinal lymph node dissection.

Lee et al¹⁴ have shown that the abnormal CEA level is closely related to the distant metastasis of non-small cell lung cancer. Our results showed that the mediastinal lymph node metastasis rate in patients with CEA (>5ng/ml) was 57.89% (22/38), however, Wang et al¹⁵ reported mediastinal lymph node metastasis rate in patients with CEA (>5ng/ml) was 15.25%, and it was a risk factor for lymph node metastasis (OR=1.574, P=0.001). Ye et al¹⁰ also showed that the lymph node metastasis rate of CEA (>5ng/ml) was 19.16%, and it was a risk factor for lymph node metastasis in stage IA lung adenocarcinoma (OR=3.923, P<0.001), Koike et al¹¹ revealed that preoperative CEA(>3.5ng/ml) was a risk factor for mediastinal lymph node metastasis of clinical stage IA non-small cell lung cancer. All the results mentioned above were consistent with our study (OR=3.05, P=0.016). In clinical stage IA3 lung adenocarcinoma, the mediastinal lymph node metastasis rate of CEA (>5ng/ml) was significantly higher than that in previous stage IA studies, it shows that preoperative CEA abnormality is an important risk factor for mediastinal lymph node metastasis of lung cancer, the lymph node dissection of stage IA3 lung adenocarcinoma should be alternative from those in stage IA1 and IA2, systemic lymph node dissection should be preferably choice for patients with stage IA3 lung adenocarcinoma with CEA (>5ng/ml).

Previous JCOG series studies have shown that CTR will affect the long-term survival of lung cancer patients^{2,16}. The results of JCOG0201 suggest that small-sized (<2cm) patients with CTR (<0.25) should be classified as non-invasive adenocarcinoma¹⁶. JCOG0804 study further showed that most patients with CTR (<0.25) did not need systematic lymph node dissection, and their 5-year Disease-free survival (DFS) reached 99.7% (95% CI: 98.3-99.9%)². In our study, the rate of lymph node metastasis in patients with tumor size (<2-3cm) and CTR (<0.25) was only 1.8% (2/112). Although the results did not receive long-term follow-up, it still showed that CTR (<0.25) was not prone to mediastinal lymph node metastasis occurrences. The probability of mediastinal lymph node metastasis significantly increased in CTR (>0.25), exhibiting 22.07% (49/222) in our study. In addition, Koike et al¹¹ showed that CTR (>0.75) is an important risk factor for mediastinal lymph node metastasis (OR=1.126, P<0.001). Another study by Chen et al¹⁷ suggested that CTR (>0.62) is an important risk factor for mediastinal lymph node metastasis (OR=12.723, P=0.002). These results reflect that the value of CTR is a high-risk factor for mediastinal lymph node metastasis. In our study, patients with stage IA3 lung adenocarcinoma were included, and their CTR (>0.25) was the high-risk factor of mediastinal lymph node metastasis. For these patients, systematic lymph node dissection was preferably recommended.

Lu et al¹⁸ have shown that the pathological subtype of lung adenocarcinoma is an important indicator for long-term prognosis and survival of lung cancer. Kim et al¹⁹ reported that the 5-year disease-free recurrence risk of papillary predominant (OR= 2.49, P<0.001) and solid predominant (OR=1.99, P=0.003) is higher than that of other types of lung adenocarcinoma. Wang et al¹⁵ (OR=1.574, P=0.001) and Ye et al¹⁰ (OR=2.493, P=0.004) showed that pathological subtype was an important risk factor for mediastinal lymph node metastasis of stage IA lung adenocarcinoma, complying with the results of our study. For these two special types of lung adenocarcinoma above, systematic lymph node dissection should be the prior choice. In the ROC analyses, the pathological subtype showed the highest area value under the AUC curve of 0.800, being considered to be the most accurate predictor among the three predictors. In addition, another study found that patients with pathological subtype of micropapillary or solid adenocarcinoma should be followed with adjuvant therapy after operation⁹. As for patients with stage IA3 lung adenocarcinoma combined with micropapillary or solid adenocarcinoma, the necessity of postoperative adjuvant treatment should be evaluated by the results of long-term follow-up.

Dai et al²⁰ have shown that STAS has relatively little effect on the prognosis of lung adenocarcinoma (<2cm), while STAS can cause obvious poor prognosis in patients with lung adenocarcinoma (>2-3cm). Therefore, this study included STAS in multivariate analysis and did not find that it was a risk factor for mediastinal lymph node metastasis. The possible reason is that different evaluation methods and standards may lead to different evaluation results. Moreover, the sample capacity included in this study is small, and whether the sample is related to mediastinal lymph node metastasis needs further research.

Wang et al²¹ revealed that patient with advanced lung cancer with EGFR gene mutation were more prone to distant brain metastasis, while Nie et al²² reported that there was no significant difference in the rate of mediastinal lymph node metastasis between EGFR gene mutation and EGFR gene wild type.

Nonetheless, above two studies did not show statistical significance, for they were carried out in locally advanced lung cancer. However, there are only a few studies on whether EGFR gene mutation is related to lymph node metastasis in patients with early lung cancer. In our study, we included EFGR gene mutation into multivariate analysis and did not find that whether EGFR gene mutation was a risk factor for mediastinal lymph node metastasis.

Our study had some limitations. First, it was a retrospective study and single-center with a relatively small number of cases, therefore, patient-selection bias may be existed. Prospective multi-institutional trials are required for a definitive conclusion. Secondly, the long-term follow-up outcome was not known. And the advantage of this study was that the authors performed lobectomy and mediastinal lymph node dissection in all cases, we believe that our results will be helpful in identifying the mediastinal lymph node dissection of IA3 lung adenocarcinoma.

Conclusion

Systematic lymph node dissection should be the prior choice for patients with clinical stage IA3 incorporated with risk factors such as CTR, CEA and pathological subtypes. The overall occurrence rate of mediastinal lymph node metastasis in IA3 lung adenocarcinoma is high, so the lymph node dissection method of stage IA3 should be alternative from those in stage IA1 and IA2.

Abbreviations

Consolidation tumor ratio: CTR; Carcinoembryonic antigen: CEA; Receiver operating characteristic curve: ROC; Area under the curve: AUC; Confidence interval: CI; Odds Ratio: OR; International Association for the Study of Lung Cancer: IASLC; Positron emission tomography-computer tomography: PET-CT; Epidermal growth factor receptor: EGFR; Spread through air spaces: STAS.

Declarations

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The paper is the result of my team and I. This paper does not contain any published or written content by others, except as expressly indicated and quoted in the paper.

Author contributions:

Yuan-Liang Zheng: collected and recorded the original data; Ju Sheng and Ri-Sheng Huang: analyzed the data and was a major contributor in writing the manuscript; Jun Zhao: guided all the work.

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Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

The study has been approved by the ethic committees of the Wenzhou Central Hospital (L2021-12-42).

Consent for publication:

Not applicable.

Competing interests:

The authors reported no proprietary commercial interest in any product mentioned or concept discussed in this article.

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Tables

Table 1

clinical characteristics and univariate analysis of lymph node metastasis for patients

Variables	Total(n=334)	pN0(n=283)	pN1+pN2(n=51)	χ^2	<i>P</i>
Age(years)				1.234	0.267
£60	153	126	27		
>60	181	157	24		
Sex				0.842	0.359
Male	190	158	32		
Female	144	125	19		
Smoking history				1.426	0.232
never	184	152	32		
Current/former	150	131	19		
CTR				58.279	<0.001
£0.25	112	110	2		
0.25-0.5	145	128	17		
>0.5	77	45	32		
PET-CT				6.173	0.013
Not Performed	78	73	5		
Performed	256	210	46		
CEA level(ng/ml)				60.216	<0.001
£5	296	267	29		
>5	38	16	22		
Pathologic type				67.839	<0.001
LP	132	127	5		
AP	97	90	7		
PP	36	30	6		
MP	28	11	17		
SP	41	25	16		
EGFR mutation				40.304	<0.001
negative	113	76	37		
positive	221	207	14		

STAS				11.456	0.001
No	245	217	28		
Yes	89	63	23		
CTR=Consolidation tumor ratio, PET-CT=Positron emission tomography-computed tomography, CEA=carcinoembryonic antigen, LP=Lepidic predominant, AP=Acinar predominant, PP=Papillary predominant, MP=Micropapillary predominant, SP=Solid predominant, STAS= spread through air spaces.					

Table 2

Independent predictors of lymph node metastasis by multivariate analysis

Variable	OR	95% CI	<i>P</i>
CEA (ng/ml)	3.05	1.226-7.586	0.016
CTR			
<0.25	1.00		
0.25-0.5	6.413	1.396-29.458	0.017
>0.5	7.750	1.489-40.343	0.015
Pathologic type			
LP	1.00		
AP	3.397	0.987-11.692	0.053
PP	3.663	0.919-14.605	0.066
MP	15.704	3.785-65.155	<0.001
SP	8.971	2.382-33.790	0.001
CEA=carcinoembryonic antigen, CTR=Consolidation tumor ratio, CI= confidence interval, OR=Odds Ratio.			

Figures

Figure 1

1A: Distribution of lymph node status is shown according to CTR of clinical stage IA3 lung adenocarcinoma. CTR: Consolidation tumor ratio. (green=pN2; orange=pN1; blue=pN0)

1B: Distribution of lymph node status is shown according to pathologic types of clinical stage IA3 lung adenocarcinoma. (green=pN2; orange=pN1; blue=pN0)

Figure 2

ROC curve showed the predictability of lymph node metastasis based on CTR (A) Pathologic types (B) and CEA (C). CTR: Consolidation tumor ratio; CEA: carcinoembryonic antigen; ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval.