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Original Article

Clinical predictors of lymph node metastasis in lung adenocarcinoma: an exploratory study

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Abstract: Objective: To investigate whether patients with lung adenocarcinoma require systematic lymph node dissection (LND) of lymph node metastasis and to identify the predictive factors of lymph node metastasis. Methods: Lymph node metastasis status was retrospectively analyzed in 198 lung adenocarcinoma patients with small peripheral nodules. The patients' clinical factors were analyzed. Maximum standardized uptake values (SUV_{max}) in patients who underwent positron emission computed tomography (PET-CT) were recorded. Univariate and multivariate analyses were used to determine significant clinical factors of lymph node metastasis. Results: Lymph node metastasis was not found in the 34 cases with pure ground-glass opacity (pGGO). Of the 72 patients with mixed ground-glass opacity (mGGO), 67 (93.1%) had no lymph node metastasis, whereas 5 (6.9%) had lymph node metastasis. Of the 92 patients with solid opacity, 29 (31.5%) had lymph node metastasis, and there was a significant difference ($P < 0.01$). In the univariate analysis, tumor diameter > 1 cm, mixed/solid nodules, and carcinoembryonic antigen (CEA) level > 5 μg/L were important predictors of lymph node metastasis. In addition, in the analysis of the SUV_{max} in the patients who underwent PET-CT, the patients with $SUV_{max} > 5$ showed a higher lymph node metastasis potential, with a statistically significant difference ($P < 0.05$). For such patients, LND is necessary. Conclusion: Lymph node metastasis is rare in lung adenocarcinoma patients with pGGO on high-resolution CT imaging. Patients with tumors > 1 cm in diameter, mixed/solid nodules on CT, CEA levels > 5 ng/mL, $SUV_{max} > 5$ on PET-CT are more prone to lymph node metastasis, suggesting that these patients require systematic LND.

Keywords: Lung cancer, lymph node metastasis, clinical predictors

Introduction

In recent years, given the rapid development of imaging technology, high-resolution computed tomography (CT) and positron emission computed tomography (PET-CT) have been widely used, improving the detection rate of pulmonary nodules and, in turn, improving the detection rate of lung adenocarcinoma. The main treatment regimens for lung adenocarcinoma are lobectomy and pulmonary segment resection [1]. A controversial issue is whether lymph node dissection (LND) during surgery is necessary for patients with lung adenocarcinoma. Therefore, effective prediction of lymph node metastasis is of great significance for lung adenocarcinoma patients who mainly present with small pulmonary nodules [2]. In this study, in order to identify effective predictors of lymph node metastases, which will help to avoid unnecessary injury from LND in patients, we analyzed the clinical data of 198 cases.

Materials and methods

Clinical data

We selected and retrospective evaluated 1783 patients with lung cancer who underwent surgical treatment. Among these patients, 198 who were diagnosed with peripheral small lung adenocarcinoma were included in this study, including 105 men and 93 women, whose ages ranged from 32 to 85 years (mean ± SD age, 61.6 ± 9.8 years). In our retrospective study, from among 198 patients who underwent surgery, we identified 121 patients who underwent video-assisted thoracoscopy, including 22 cases of pulmonary segment resection, 90 cases of lobectomy, and 9 cases of wedge resection, and 77 patients who underwent conventional thoracotomy, including 55 cases of

Table 1. Univariate analysis of the predictors of lymph node metastasis in the patients with lung adenocarcinoma

Variables		Cases (*n* = 198)	pN0 (*n* = 164)	pN1 (*n* = 19)	pN2 (*n* = 15)	*P*
Age (years)	≤ 59	115	90	11	14	0.412
	> 59	83	74	8	1	
Sex	Male	105	89	11	5	0.109
	Female	93	75	8	10	
Smoking history	Absence	121	102	10	9	0.62
	Presence	77	62	9	6	
Symptom	Absence	107	89	10	8	0.41
	Presence	91	75	9	7	
Tumor size (cm)	≤ 1.0	53	52	1	0	0.003
	1.1-2.0	145	112	18	15	
Imaging features	pGGO	34	21	0	0	< 0.001
	mGGO	72	67	4	1	
	Solid nodules	92	63	15	14	
Pleural invasion	Absence	117	102	6	9	0.332
	Presence	81	62	9	10	
Air bronchogram	Absence	121	111	5	5	0.093
	Presence	77	53	14	10	
CEA (μg/L)	≤ 5	124	116	5	3	< 0.001
	> 5	74	48	14	12	

Table 2. Multivariate analysis of the predictors of lymph node metastasis in the patients with lung adenocarcinoma

	OR	95% CI for OR	*P*
Tumor size, 1.1-2.0 cm	12.61	8.33-19.08	< 0.001
Imaging features mGGO	3.92	2.94-5.23	< 0.001
Solid nodules	10.25	9.15-1.49	< 0.001
Air on pouchography	2.04	1.49–2.81	0.03
CEA (ng/mL)	5.12	4.48-5.86	< 0.001

OR, Hazard Ratio; CI, Confidence Interval.

Table 3. The SUV_{max} in the patients with lymph node metastasis

SUV_{max}	Cases (*n* = 73)	pN0 (*n* = 62)	pN1 (*n* = 7)	pN2 (*n* = 4)	*P*
≤ 5	28 (38.4)	25 (40.3)	2 (28.6)	1 (25)	< 0.001
> 5	45 (61.6)	37 (59.7)	5 (71.4)	3 (75)	

lobectomy, 17 cases of pulmonary segments resection, and 5 cases of wedge resection.

Inclusion and exclusion criteria

Inclusion criteria: ① Peripheral pulmonary nodule diameter < 2 cm on CT, no nodules in both lungs, and nodules pathologically diagnosed as adenocarcinoma; ② No segmental and upper bronchus invasions; ③ No detected metastasis; and ④ Had undergone segmental or lobe resection, and systemic LND (i.e., at least 6 hilar and mediastinal lymph nodes resected). Exclusion criteria: ① Preoperatively suspected with thoracic or distant metastasis; ② History of preoperative chemotherapy; ③ History of malignant tumor; and ④ No systematic LND during surgery.

Classification

Based on histological and CT imaging features, the nodules were divided into the following three categories according to the 2011 International Classification of Lung Adenocarcinoma: ① Pure ground-glass opacity (pGGO); ② Mixed ground-glass opacity (mGGO); and ③ Solid nodules [3].

Research methods

The related clinical factors in the 198 cases were analyzed. The risk factors of lymph node metastasis that were identified in the univariate analysis were subjected to a multivariate analysis in order to identify independent predictors. Then, the clinical predictors of lymph node metastasis in the lung adenocarci-

Table 4. Imaging manifestation and surgical clinicopathological features of the 198 patients

Surgical pathological features		pGGO (*n* = 34)	mGGO (*n* = 72)	Solid opacity (*n* = 92)	P
Surgical method	Wedge resection	5	8	1	
	Segment lobectomy	15	21	3	
	Lobectomy	14	43	88	< 0.001
Lymph node metastasis	N0	34	67	63	
	N1	0	4	15	
	N2	0	1	14	< 0.001
Histological type	AAH	10	0	0	
	AIS	24	1	0	
	MIA	0	43	20	
	IA	0	45	72	< 0.001

noma patients with small peripheral nodules were determined. In addition, univariate analyses of standardized uptake value (SUV) and lymph node metastasis were performed for the patients who underwent PET-CT.

Statistical analyses

All statistical analyses were performed by using SPSS 13.0 (SPSS Inc, Chicago, IL, USA). The Fisher exact probability test was used for data analysis. Influence factors were analyzed by using logistic regression analysis. Counting data were analyzed by performing a chi-square test. A $P < 0.05$ was considered statistically significant.

Results

The 198 patients were clinically followed up for up to 9-15 months (mean, 13 months). None of the patients died of disease during the follow-up period. All predictive variables of lymph node metastasis were included in the univariate analysis, and results are presented in **Table 1**. The results of the analysis of risk factors of lymph node metastasis after exclusion of the other factors are listed in **Table 2**.

Of the 198 patients, 73 underwent PET-CT examination and measurement of SUV_{max} (**Table 3**). The results of the analysis of the imaging and surgical clinicopathological features of the 198 patients are shown in **Table 4**.

Discussion

With the rapid development of imaging technology, high-resolution computed tomography (CT) has become widely used in early cancer detection [4]. Lung cancer is one of the most common malignant tumors in the world. As the most common histological type of lung cancer, lung adenocarcinoma accounts for about 50% of all lung cancers. According to the 2011 International Classification of Lung Adenocarcinoma, including adenocarcinoma in situ (AIS) and micro infiltrating adenocarcinoma (MIA), clinical manifestations are consistent with pathology. Therefore, preoperative imaging judgment can reflect the pathological types more accurately [5].

The lymph nodes are one of the main metastatic sites of lung cancer. The presence of lymph node metastasis is the basis of lung glandular staging and an important factor to consider in the choice of a standardization treatment and prognosis evaluation. However, the clinical significance of LND for early lung cancer remains controversial [6]. The purposes of LND for lung cancer are as follows: to determine the pathological stage of lung cancer and to provide radical cure and prevent postoperative local recurrence of the disease. Wedge-shaped lesion resection is performed as the main clinical surgery for lung cancer, for rapid pathological judgment of benignity and malignancy, and in pulmonary segment or lobe resection for malignant tumors [7]. Furthermore, the surgeon needs to decide whether systemic LND is needed. Surgeons generally believe that lymph nodes require systematic cleaning based on tumor diameter. Systemic LND, of course, will increase the risk of surgery, which, in turn, extends surgical time, increase the risk of complications, such as cardiac arrhythmias, increased postoperative chest drainage volume, and chylothorax. These result in adverse effects on patients and increase their risk of mortality [8-10]. Many studies have shown that

if no lymph node metastasis is detected, LND is not necessary for patients with early-stage cancers. Thus, the method of determining lymph node metastasis status according to clinical factors is an important research factor [11, 12]. Based the results of the regression analysis of the 198 clinical cases, we identified the preoperative predictors of lymph node metastasis and provided indications for performing LND during surgery.

Of the 198 patients in this study, 34 had pGGO imaging types, including 10 cases of atypical adenomatous hyperplasia and 24 cases of AIH. None of the patients had lymph node metastasis in the early-stage of their disease, which suggests that patients with early-stage disease can avoid of systematic LND. Lymph node metastasis was present in 5 (6.9%) of the 72 patients with an mGGO imaging type and in 29 (31.5%) of the 92 patients with solid nodules, with significant difference between the two groups ($P < 0.01$). These data verified that the new adenocarcinoma staging was useful in determining the progression of lung adenocarcinoma from AAH, AIS, and MIA to IA. The rate of lymph node metastasis increased along with the progression of the disease.

In the univariate analysis, the predictive factors of lymph node metastasis are tumor diameter, imaging type (i.e., pathological classification), and CEA levels. Tumor diameter > 1 cm, mixed/solid nodules, and CEA level > 5 g/L are important predictors of lymph node metastasis. In addition, the results of the analysis of SUV_{max} in the patients who underwent PET-CT showed that the incidence of lymph node metastases was higher in the patients with $SUV_{max} > 5$ ($P < 0.05$), with a statistically significant difference. LND is necessary for these patients.

Owing to its retrospective nature, this study has some limitations. A wide range of prospective, randomized, and controlled studies are needed to identify the predictors of LND in patients with tumors < 2 cm in size. A certain follow-up duration is required to validate important evaluation indexes. Thus, our results should be validated in a large-scale and long-term study.

Disclosure of conflict of interest

None.

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