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ORIGINAL RESEARCH

Multivariate Analysis Of The Diagnostic Yield Of Conventional Bronchoscopy In Peripheral Lung Adenocarcinoma

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Background: The new subtypes of lung adenocarcinoma reflect local invasive growth, pulmonary alveoli, and intraluminal spreading, while the effective improvement of the diagnostic yield of bronchoscopy still remains unclear. This study aims to explore whether the subtypes of lung adenocarcinoma and other factors affect the diagnostic yield of bronchoscopy.

Methods: All patients were performed 64-row CT examination and bronchoscopy.

Results: The bronchus cutoff sign in 48 cases and the endoscopic diagnostic yield was 60.4%. The lumen of the lobes and segments was invaded in 59 cases, and the endoscopic diagnostic yield was 54.2%.The lymph node metastasis was detected in 46 cases, and the endoscopic diagnostic yield was 60.9%. In addition, 42 cases showed acinar type-predominant, and the endoscopic diagnostic yield was 28.6%. Eighteen cases showed solid type-predominant, and the endoscopic diagnostic yield was 33.3%. The micropapillary type-predominant was noted in 17 cases, with the endoscopic diagnostic yield as 94.1%. The papillary type-predominant was in 14 cases, and the endoscopic diagnostic yield was 42.9%. The lepidic type-predominant was seen in 13 cases, and the endoscopic diagnostic yield was 7.7%. The mean diameter of tumors with a positive endoscopic diagnostic yield was 4.34±2.65cm, and the mean diameter of tumors with a negative diagnostic yield was 2.83±1.47cm. Multivariate analysis showed that micropapillary lung adenocarcinoma affected the endoscopic diagnostic yield (OR=37.594, 95% CI: 4.074–346.94) .Tumor diameter affects endoscopic diagnostic yield (OR=1.39, 95% CI: 1.073–1.802), bronchus cutoff sign is easy to obtain endoscopic diagnostic yield (OR=4.86, 95% CI: 1.606–14.704), and lymph node metastasis affects the endoscopic diagnostic yield (OR=3.696, 95% CI: 1.255–10.883).

Conclusion: The micropapillary subtype lung adenocarcinoma has a certain influence on the diagnostic yield of bronchoscopy. When the lung adenocarcinoma has a large tumor diameter, bronchus cutoff sign and lymph node metastasis, it is easy to obtain a diagnostic yield of bronchoscopy.

Keywords: bronchoscopy, micropapillary type-predominant, lepidic type-predominant, bronchial lumen biopsy, bronchus cut off sign

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Introduction

Lung adenocarcinoma incidence is currently increasing, and 64-row CT examination and bronchoscopy are commonly used methods for the diagnosis of peripheral lung cancer.[1–4] The CT features are such a major reference for early diagnosis of lung adenocarcinoma, and cytology or pathology results can be obtained by bronchoscopy;

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however, we typically cannot observe the primary lesions by bronchoscopy, and the diagnostic yield of bronchoscopy is limited and variable, ranging from 16% to 80%.[5] Invasive lung adenocarcinoma under endoscopy presents intraluminal tumor and submucosal infiltration. In 2011, the new subtypes of lung adenocarcinoma reflected local invasive growth, pulmonary alveoli, intraluminal spreading, etc.,[6]while the effective improvement of the endoscopic diagnostic yield has still remained unclear. According to the definition of the correlation between CT features, pathological subtypes and the endoscopic diagnostic yield can help to improve the value of bronchoscopy in clinical diagnosis and treatment. We hope that this study can provide a reference for clinical diagnosis.

Materials And Methods

Ethics Statement

This study was approved by the medical ethical committee of Linyi City People's Hospital as a retrospective study. The requirement for patient-informed consent was waived by the ethical committee because of the retrospective nature of this study, but patient data confidentiality was protected. The ID of ethical approval was 30037 with confirmation of compliance with the Declaration of Helsinki.

Subjects

A total of 104 patients with clinically diagnosed peripheral lung adenocarcinoma admitted to the Linyi People's Hospital (Linyi, Shandong province, China) were included in this study from January 2014 to December 2016. All patients underwent 64-row CT scan, they were reconstructed by thin-slice CT on sagittal, coronal and horizontal positions, the bronchus cutoff sign was observed, and the diameter of the tumor was measured. All patients underwent BF260 electronic bronchoscopy (Olympus, Tokyo, Japan), and the methods of obtaining specimen included transbronchial lung biopsy (TBLB), endoscopic biopsy (biopsy), brushing and bronchoalveolar lavage (BAL). The specimens were routinely sent for pathological and cytological examinations. The post-operative or biopsy specimens were embedded in paraffin and lung adenocarcinoma was confirmed. Biopsy was performed for all patients with Forceps (Olympus Endojaw FB-211D alligator cup forceps; Olympus, Tokyo, Japan).

Endoscopy And Specimen Processing

Bronchoscopies were done under local or general anesthesia in an endoscopy unit. Endoscopic findings were classified as (a) a visible endoluminal lesion, (b) bronchial mucosal changes such as edema with or without stenosis, inflammation, enlarged carina, or extrinsic compression, or (c) normal. The features of metastatic bronchus were as follows: mucosal hyperemia and edema, infiltration change, polypoid change. In the case of a visible endobronchial tumor, bronchial aspirates, brushings, and several biopsies were performed. When bronchial mucosal alterations were found, aspirates, brushings, and bronchial biopsies were taken from the abnormal area. When no abnormalities were observed, BAL, brush specimens and blind transbronchial lung biopsies were undertaken at the corresponding bronchus, as shown on computed tomography (CT). BAL was carried out in all patients by 150 mL of 0.9% saline.

Fresh lavage specimens were centrifuged at 2000 rpm for 5 mins, and the resulting pellets were smeared on three different slides, fixed with methanol–acetone, and stained by the Papanicolaou (Pap) smear method. Subsequently, cell blocks were prepared using 7-μm sections and stained with hematoxylin and eosin (H & E). In a majority of patients, bronchial brushing material was rinsed in physiological saline before transportation. At the laboratory, the brushing specimens were smeared on two slides. Physiological saline was centrifuged on one slide. Then, the slides were fixed with methanol–acetone and stained by the Pap smear method. The specimens' findings were classified as endoscopic positive diagnosis if they showed malignant-looking cells.

The forceps were inserted into the bronchial trees to the level of subsegmental bronchi through the channel of the bronchoscope. In this approach, the biopsies were repeatedly performed in appropriate segmental bronchi. Eventually, five or six specimens were collected. All specimens were placed in a 10% buffered formalin solution and embedded in paraffin. Then, the slides were stained with H & E for examining histological levels.

High-Resolution CT (HRCT) Scanning

All patients underwent a 64-row enhanced CT scanning, and the characteristics of HRCT primarily included were tumor size and bronchus cutoff sign (on axial, sagittal, and coronal sections).

Evaluation Of Pathology Data

All specimens were fixed in a formaldehyde solution after resection and stained with H&E. Each of the slides was independently examined by two pathologists under a

multithreaded microscope and discussed until consensus was achieved. According to the new IASLC/ATS/ERS criteria, the subtypes of lung adenocarcinoma were divided into lepidic, acinar, papillary, micropapillary and solid, and each tumor was reviewed using the comprehensive histological subtyping, while the percentage was recorded in 5% increments for each histological component. The predominant subtype was defined as the subtype with the highest percentage.

Statistical Analysis

The statistical analysis was performed using SPSS 19.0 software (IBM, NY, USA). Categorical data were analyzed using Fisher's exact probability test, between-group comparison of numerical data with normal distribution was conducted using a two-sample *t*-test, and paired *t*-test was employed for intra-group comparison. Multivariate analysis was performed by a logistic regression method. Odds ratio (OR) and 95% confidence interval (CI) were calculated accordingly. In all the tests, two-sided P-values < 0.05 were considered as statistically significant.

Results

The cohort consisted of 49 male patients and 55 female patients with peripheral adenocarcinoma after the operation. In addition, 41 cases with preoperative endoscopic diagnoses were included, and the positive preoperative rate of bronchoscopy was 39.4%. Herein, 14 cases were confirmed by cytological analysis, 12 were merely confirmed by pathology, and 15 were diagnosed with both cytological and pathological analyses. The HRCT showed 48 cases with bronchus cutoff sign, and the endoscopic diagnostic yield was 60.4%. The lobes and segmental lumen were invaded in 59 cases, and the diagnostic yield of endoscopy was 54.2%.The lymph node metastasis was 46 cases, and the diagnostic yield of endoscopy was 60.9%.The diameter of the tumor in the endoscopy positive diagnosis group was 4.34±2.65 cm, and that in the endoscopy negative diagnosis group was 2.83±1.47 cm. The mean age of the endoscopy positive diagnosis group was 58.56±9.61 years, and that of the negative diagnosis group was 60.11±8.32 years. The pathological subtypes of invasive lung adenocarcinoma after the operation were as follows: the diagnostic yield of endoscopy of 42 cases of acinar type-predominant was 28.6%. The diagnostic yield of endoscopy of 14 cases of papillary subtype-predominant was 42.9%. The number of micropapillary type-predominant cases was 17, and the diagnostic yield of endoscopy was 94.1%. In addition, while that for 18 cases of solid type-predominant was 33.3% and 7.7% for 13 cases of lepidic subtype-predominant.

Univariate Analysis

Univariate analysis showed that the endoscopic diagnostic yield with micropapillary type-predominant was significantly higher than that of patients with a negative result ($P<0.05$). The negative results of endoscopic examination of lepidic type-predominant were higher than the positive results ($P<0.05$), albeit no significant difference was detected in the diagnostic yield of bronchoscopy between acinar type, papillary type and solid type lung adenocarcinoma ($P>0.05$).The bronchus cutoff sign, tumor diameter, lymph node metastasis and endobronchial invasion affected the endoscopic diagnosis ($P<0.05$). Also, no statistically significant difference was observed in the positive diagnosis of bronchoscopy between gender and age ($P>0.05$) (Table 1).

Multivariate Analyses

Univariate analysis showed that tumor diameter, bronchus cutoff sign, lymph node metastasis, endobronchial invasion, lepidic type-predominant adenocarcinoma, and micropapillary type-predominant adenocarcinoma affected the endoscopic diagnosis. Furthermore, multivariate analysis showed that tumor diameter, bronchus cutoff sign, lymph node metastasis and micropapillary type-predominant adenocarcinoma affected the diagnostic yield of bronchoscopy ($P<0.05$), while the endobronchial invasion and lepidic type-predominant adenocarcinoma did not exert a significant effect on the positive rate of bronchoscopy ($P>0.05$) (Table 2).

Discussion

Regarding the broad application of HRCT, the discovery of peripheral lung adenocarcinoma is remarkable. In addition, bronchoscopy is a routine preoperative examination,[7] and mainly depends on the natural bronchial lumen of the lung to reach the lesion site, and the biopsy site includes the alveolar cavity, the bronchial lumen of the lung lobe or the lung segment. Endoscopic biopsy techniques include endobronchial biopsy, TBLB, alveolar lavage, and brushing. A combination of multiple biopsy techniques makes it easy to obtain a positive diagnostic yield.[8] Previous studies reported that the endoscopic diagnosis was related to the lesion's location and bronchoscopy position in the lumen.[9,10] In this study, the effect of the pathological subtype on the diagnostic yield of endoscopy was observed from the invasiveness of lung adenocarcinoma. There was a relationship between

Table 1 Comparison Of Indicators Between The Two Groups (n=104)

Indicators		Positive Results	Negative Result	t/χ^2	P-value
Age (years)		58.56±9.61	60.11±8.32	0.873	0.385
Tumor diameter (cm)		4.34±2.65	2.83±1.47	−3.331	0.002
Gender	Man Female	21 (42.9) 20 (36.4)	28 (57.1) 35 (63.6)	0.458	0.499
Bronchus cutoff sign	Yes No	29(60.4) 12 (21.4)	19 (39.6) 44 (78.6)	16.451	0.000
Bronchial lumen invasion	Yes No	32 (54.2) 9 (20.0)	27 (45.8) 36 (80.0)	12.531	0.000
Lymph node metastasis	Yes No	28 (60.9) 13 (22.4)	18 (39.1) 45 (77.6)	15.886	0.000
Lepidic subtype-predominant	Yes No	1 (7.7) 40 (44.0)	12 (92.3) 51 (56.0)	6.264	0.012
Acinar subtype-predominant	Yes No	12 (28.6) 29 (46.8)	30 (71.4) 33 (53.2)	3.474	0.062
Papillary subtype-predominant	Yes No	6 (42.9) 35 (38.9)	8 (57.1) 55 (61.1)	0.080	0.777
Micropapillary subtype-predominant	Yes No	16 (94.1) 25 (28.7)	1 (5.9) 62 (71.3)	25.456	0.000
Solid subtype-predominant	Yes No	6 (33.3) 35 (40.7)	12 (61.1) 51 (59.3)	0.338	0.561

Table 2 Multivariate Analysis Of Diagnostic Yield From Bronchoscopy

Indicators	B	S.E	Wals	OR	95% C.I.	P-value
Bronchus cutoff sign	1.581	0.565	7.835	4.86	1.606–14.704	0.005
Tumor diameter	0.33	0.132	6.216	1.39	1.073–1.802	0.013
Lymph node metastasis	1.307	0.551	5.629	3.696	1.255–10.883	0.018
Micropapillary subtype-predominant	3.627	1.134	10.231	37.594	4.074–346.94	0.001

bronchus cutoff sign, tumor diameter, lymph node invasion, endobronchial invasion and the endoscopic diagnosis. All 104 patients with invasive adenocarcinoma diagnosed after operation were enrolled, and the endoscopic diagnostic yield in 42 patients with acinar type-predominant adenocarcinoma, a common subtype was 28.6%.The number of papillary type-predominant adenocarcinoma cases was 14, and the diagnostic yield of endoscopy was 42.9%, the diagnostic yield of endoscopy for 18 cases of solid type was 33.3%, the number of lepidic type-predominant cases was 13, and the diagnostic yield of endoscopy was 7.7%, while that of the 17 micropapillary type-predominant cases was 94.1%. Univariate analysis showed that acinar type, papillary type and solid type adenocarcinoma did not have any significant effect on the endoscopic diagnosis (P>0.05). The diagnostic yield of bronchoscopy was related to the amount of specimen obtained.[11,12] The univariate analysis also showed that micropapillary type-predominant affected the endoscopic diagnosis(χ^2=25.456, P=0.000), while multivariate analysis revealed a specific effect (OR=37.594, 95% CI: 4.074–346.94). Micropapillary adenocarcinoma is highly invasive and easily invades the alveolar structure along with the alveolar space or spreads along the bronchial lumen .[13-15]The methods such as brushing, lavage, biopsy or TBLB can easily obtain positive results, and the 5-year survival rate of patients with micropapillary type-predominant adenocarcinoma is significantly reduced.[16] Univariate analysis showed that the lepidic type-predominant of

adenocarcinoma had an effect on the diagnostic yield of endoscopy, and obtaining positive results by endoscopy was challenging (χ^2=6.264 P=0.012). Lepidic predominant adenocarcinoma in the alveolar cavity cannot easily invade the lumen, and the diameter of adenocarcinoma is <3 cm, [17] affecting the positive rate of endoscopy (especially biopsy). However, further multivariate analysis showed that the lepidic type-predominant did not have any significant effect on the positive rate of endoscopy (P>0.05).

Imaging characteristics including tumor size, bronchus cutoff sign, lymph node metastasis suggest local invasiveness of lung cancer, which is conducive to the positive rate of endoscopy, and the average diameter of patients with positive results of endoscopy is 4.34±2.65 cm. Univariate analysis showed that the diameter of the tumor affected the endoscopic diagnosis (χ^2=−3.331, P=0.002), and further multivariate analysis showed that the tumor diameter of the positive diagnostic yield of endoscopy was significantly larger than that of the negative diagnostic yield (OR=1.39, 95% CI: 1.073–1.802), which was similar to previous studies, indicating that larger the tumor diameter, easier to obtain the endoscopic diagnostic yield by routine technique or ultrasound.[9,18,19] The incidence of lymphatic metastasis in lung adenocarcinoma is high[20]; in this study, 46 patients showed postoperative lymph node metastasis, and the diagnostic yield of the endoscopic routine examination was 60.9%. The univariate analysis of lymph node metastasis patients could easily obtain the endoscopic diagnosis (χ^2=15.886, P=0.000); further, multivariate analysis showed that the endoscopic diagnosis in patients with lymph node metastasis was significantly higher than in patients without lymph node metastasis (OR=3.696, 95% CI: 1.255–10.883). Lymph node metastasis suggests that the local invasiveness of the tumor is significantly enhanced, affecting the diagnostic yield of bronchoscopy.[12] In addition, it is a major factor affecting the prognosis of patients [21] and correlates with the tumor diameter and micropapillary subtype adenocarcinoma.[22,23] The number of patients with the bronchus cutoff sign was 48 cases, and the endoscopic diagnostic yield was 60.4%. The univariate and multivariate analyses showed that endoscopic diagnostic yield could be easily obtained in patients with the bronchial cutoff sign (χ^2=16.451 P=0.000) with positive results (OR=4.86, 95% CI: 1.606–14.704), which was similar to that of Qiang et al[1]. The bronchus cutoff sign suggested that the cancer cells invaded along with the alveolar structure and peripheral bronchiole,[3,9] and the lesion is amenable to obtain endoluminal sampling with forceps or cytology brush.[9,24]

A total of 59 patients showed bronchial invasion, and 31 were diagnosed with a positive rate of 54.2%. Univariate analysis showed that intrabronchial invasion affected the diagnostic yield of bronchoscopy (χ^2=12.531 P= 0.000), which was similar to that of Roth et al[25]. But multivariate analysis showed that there was no statistically significant difference in the positive rate of bronchoscopy, when the lung lobe or lung segment was invaded (P>0.05). The possible cause was the intraluminal manifestation due to different intrabronchial invasion modes. The positive rate of biopsy is high when neoplasm is seen in the lumen, but the submucosal infiltration or stenosis is present, the positive rate of intramucosal biopsy is low[25–27]; however, the intrabronchial invasion may affect the treatment choice.[28]

Limitations

In this study, routine electronic bronchoscopy (intraluminal mucosa biopsy, TBLB, brush, local lavage) was used to blindly obtain the specimens of peripheral lung lesions. However, we did not know whether the lesions were reached. Further studies need to be performed using small ultrasound probes to improve the endoscopic diagnostic yield and to study the correlation between small specimens and lung adenocarcinoma subtypes.

In conclusion, lung adenocarcinoma involves bronchus cutoff sign, lymph node metastasis and large diameter of tumor diameter, and there is a high diagnostic yield of bronchoscopy. In addition, the micropapillary lung adenocarcinoma exerts a specific influence on the diagnostic yield of bronchoscopy. The application of electronic bronchoscopy combined with invasive of lung adenocarcinoma and characteristics of imaging is valuable in improving the positive rate of the endoscopic diagnosis and its clinical application.

Data Availability

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

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Disclosure

The authors report no conflicts of interest in this work.

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