Original Article

Bronchial morphological changes are associated with postoperative intractable cough after right upper lobectomy in lung cancer patients

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Background: To date, postoperative intractable cough (PIC) has not received adequate attention, and the complex perioperative factors when performing pulmonary resection often prevent researchers from addressing this issue. This study aimed to investigate the clinicopathological and radiographic indicators related to PIC in lung cancer patients.

Methods: In all, 112 patients who had had right upper lobectomy for primary lung cancer from January 2019 to December 2020 were retrospectively reviewed. We collected data via the electronic medical database of our department. Bronchial morphological features were investigated comprehensively via three-dimensional chest computer tomography reconstruction images.

Results: During outpatient follow-up visits, 41 (36.6%) patients complained about persistent dry cough after surgery. Compared with the non-cough group, patients in the refractory cough group showed significant differences in smoking history, right upper lobe stump length, changes of right bronchus intermedius (RBI) diameter, changes of right lower lobe (RLL) basal bronchus diameter, changes of RBI/RLL bronchial angle, and bronchial kink. However, according to multivariable regression analysis, stump length, bronchial kink, and diameter change of the right lower lobe basal bronchus were independently associated with postoperative refractory cough. A nebulization drug was prescribed for the 41 patients diagnosed with PIC, and 33 (80.5%) patients had improved by the next visit.

Conclusions: After right upper lobectomy, the morphology of the remaining bronchial tree in the residual lung changed significantly. The bronchial morphological alterations were independent risk factors for PIC.

Keywords: Postoperative cough; risk factor; bronchial morphology; right upper lobectomy; lung cancer

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Introduction

Lobectomy and systematic lymph node dissection are standardized treatments for invasive lung cancer (1). Due to improved recovery after surgery, the average length of stay for lobectomy has decreased to 1 to 2 days postoperatively. New-onset, persistent, nonproductive cough after pulmonary resection is not uncommon. The reported incidence in the literature is as high as 50% following pulmonary resection (2). Refractory cough is painful. Once it begins, most patients are unwilling to leave the hospital and cannot typically to return to their work and life.

To date, postoperative intractable cough (PIC) has not yet received adequate attention. The often complex perioperative factors when performing pulmonary resection prevent researchers from addressing the issue of PIC. A range of reasons are assumed to account for this, including airway infection, asthma, end-bronchial sutures, lymph node dissection, gastrointestinal reflux, postoperative physical deconditioning, and bronchial kink (3,4). Following right upper lobectomy (RUL), the remaining trachea and lungs need to adapt to the new conditions. The upward movement of the middle and lower lobes are physiological, but sometimes bronchial remodeling induces excessive deformation leading to symptoms and functional problems after lung resection (5).

In this study, we focused on patients with lung cancer who underwent right upper lobectomy to investigate the association between PIC and clinicopathological features and radiographic indicators.

Methods

Participants

In all, 112 patients who underwent RUL for primary lung cancer at our institute from January 2019 to December 2020 were retrospectively reviewed. We collected data via the electronic medical database of our department. The inclusion criteria were as follows: (I) non-small cell lung cancer (NSCLC) patients (II) tumor(s) located in the right upper lobe, (III) history of RUL and systematic mediastinal lymph node dissection, (IV) no obvious preoperative cough, (V) complete (R0) resection, (VI) no neoadjuvant antitumor treatment, and (VII) no recent neck surgery. The exclusion criteria were as follows: (I) combined surgical procedures, such as a wedge resection in other lobe; (II) major respiratory complications, such as postoperative pneumonia or respiratory failure; and (III) an incomplete hospital record. The flowchart of patient selection for the study is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Renmin Hospital of Wuhan University Review Board for Clinical Research. The informed consent requirement was waived because of the retrospective study design.

Operative techniques

Both video-assisted thoracoscopic surgery (VATS) and thoracotomy were used for RUL. The typical VATS procedures in our department are conducted via 2 ports. For central type lung carcinoma or giant tumors (more than 5 cm in diameter), a right anterolateral thoracotomy is preferred. We used a single-direction approach to perform the RUL. The bronchi and vessels were resected using endoscopic staplers (Articulating Endoscopic Linear Cutter PSE45A; Ethicon Endo-Surgery, LLC; Johnson & Johnson, New Brunswick, NJ, USA). In some patients, surgeons sutured the bronchial stumps (4-0 Prolene, Ethicon Endo-Surgery) based on the surgeon's discretion. The 2R, 4R, 7, 8, 9, and 10 groups of lymph nodes were sampled and dissected. Before closing the incision, a 26F chest tube was placed towards the thoracic apex, and a 19F fine drainage tube was placed towards the costodiaphragmatic sinus.

Postoperative management

Patients received antibiotics and Mucosolvan therapies for about 3 to 5 days. The chest tube was removed if the following conditions were met: (I) good expansion of remaining lung, (II) no obvious pleural effusion, (III) no air leakage, and (IV) plasma drainage fluid of less than 200 mL/d.

For patients with dry cough after surgery, our protocol was initial administration of symptomatic therapies, including methoxamine and pectoral syrups. For patients who failed to respond to the above 2 drugs, A neubilization drug (SYMBICORT®, Budesonide and formoterol powder for inhalation; AstraZeneca AB, Stockholm, Sweden) was prescribed.

Outpatient records

Patients were followed up in our outpatient center after discharge. Routine visits were scheduled at 2 weeks, 1 month, and then every 3 months during the first year and

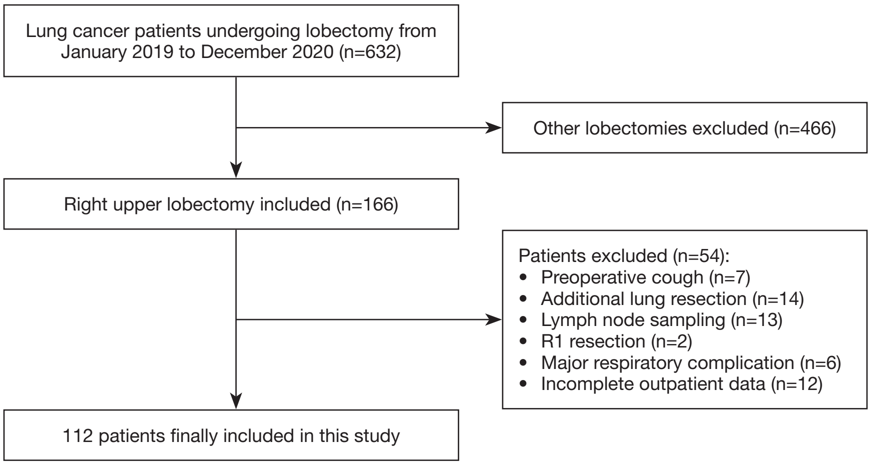

Figure 1 Flowchart of patient selection for inclusion in the study.

every 6 months thereafter. Outpatient medical records were checked and collected, including symptoms, radiological examinations, and medications.

The definition of postoperative intractable cough in this study was (I) new-onset dry cough after lung resection, (II) clear etiology with postnasal drip syndrome (PNDS) being excluded, (II) cough lasting more than 3 weeks after surgery, and (IV) normal blood tests and chest radiographs.

X-ray-based measurement

Chest X-ray (posterior-anterior position) was used to evaluate the dead space of the right thoracic cavity and whether there was obvious pleural effusion. The ratio of dead space was measured according to the method introduced by Matsuoka *et al.* (6).

Three-dimensional (3D) chest computer tomography reconstruction-based measurement

The 1-month follow-up visit included a routine thin-slice chest computer tomography (CT) examination. Three-dimensional reconstructions of CTs for each patient were conducted by two authors (XFL and XPM) using the Materialise Mimics V. 20.0 software (Materialise LLC, Leuven, Belgium) for both preoperative and postoperative images. The following indicators of bronchial morphological changes were investigated: (I) changes of bronchial diameters at different levels, (II) changes of the angles between different bronchi, (III) bronchial kink, and (IV) the lengths of the upper lobe bronchial stumps. Measurement of the bronchial diameters and angles was performed manually for the coronal and transverse planes of the 3D reconstruction images (*Figure 2*). The final values were the averages of the 2 data collectors. If the differences were too substantial, a third researcher was consulted. The definition of bronchial kink was the presence of bronchial angulation resulting in severe airway narrowing as reported by Ueda *et al.* (7) and as shown in *Figure 3*. The postoperative major (a) and minor (b) diameters of the bronchi and corresponding preoperative diameters (A and B) were measured in 3D reconstructive images. Severe bronchial narrowing was defined as more than 75% (narrowing index =1 – ab/AB).

Statistical analysis

Data are presented as either mean ± standard deviation or percentages. The Student's *t* test and Mann-Whitney test were used for continuous and discrete variables. The chi-square test was used for categorical variables. Statistical significance was set at a P value less than 0.05. Risk factors for intractable cough were investigated using logistic regression model analysis. The SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used.

Results

Patient characteristics

There were 66 (58.9%) males with a median age of 61 years. Nearly half of all patients (46.4%) had a history of smoking; however, only 9.8% of patients had chronic

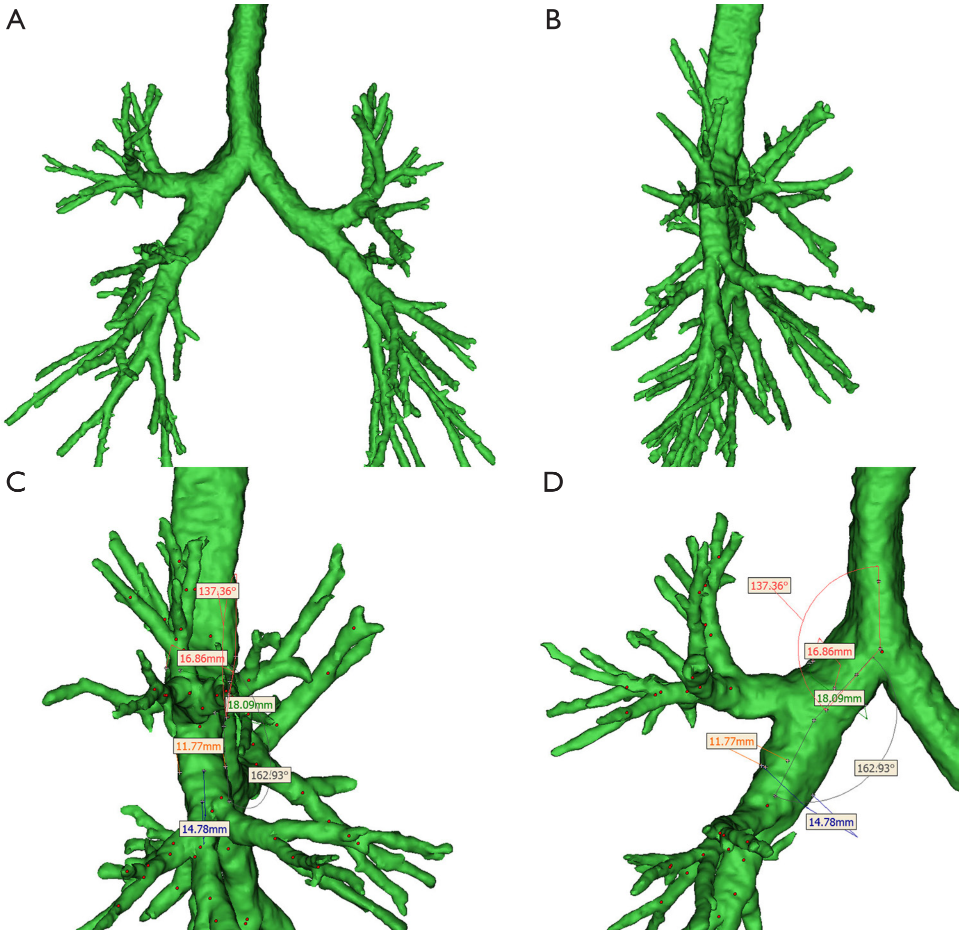

Figure 2 Three-dimensional (3D) chest CT reconstruction images on the coronal (A)/transverse (B) planes and examples of measurement of the bronchial diameters and angles on the coronal (C)/transverse (D) planes.

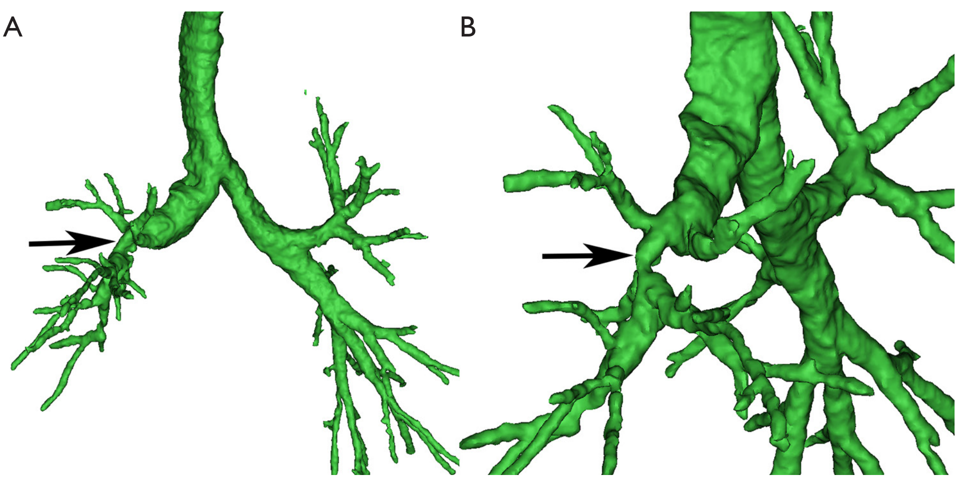

Figure 3 Three-dimensional bronchographic images showing postoperative bronchial kink (arrow; *Figure 2* and *Figure 3* are from the same patient).

Table 1 Preoperative and perioperative patient characteristics

Characteristics	Data
No. of patients	112
Age (years)	61.2±9.8
Male	66 (58.9)
Smoking history	52 (46.4)
COPD	11 (9.8)
Surgical approach	
VATS	13 (11.6)
Thoracotomy	99 (88.4)
Reinforcement of bronchial stump	14 (12.5)
Pathology	
Adenocarcinoma	104 (92.9)
Squamous carcinoma	8 (7.1)
T stage	
1	98 (87.5)
2	11 (9.8)
3	3 (2.7)
4	0
N stage	
0	102 (91.1)
1	7 (6.3)
2	3 (2.7)

Data are presented as mean ± standard deviation or percentage (%). COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery.

obstructive pulmonary disease (COPD). The majority (88.4%) of patients underwent right upper lobectomy via a thoracoscopy approach. The stumps of the right upper bronchus were sutured using 4-0 Prolene in 14 (12.5%) patients. The pathological findings revealed that 92.9% patients had an adenocarcinoma. With regard to the tumor, nodes, and metastases (TNM) classification, 87.5% were T1, 9.8% T2, and 2.7% T3, while 91.1% were N0, 6.3% N1, and 2.7% N2. The preoperative and perioperative characteristics of patients are summarized in *Table 1*.

Outpatient outcome of intractable cough

During the first postoperative visit, half of all patients exhibited a cough of different degrees of severity. One month after surgery, 41 (36.6%) patients complained of persistent dry cough during their visits.

Bronchial morphological changes in radiology

Based on the 3D reconstruction images, we found that the average lumen diameters of all the bronchi decreased significantly after surgery. The bronchial angle, changes in the trachea and right principal bronchus (trachea/RPB) angle increased slightly; however, other angles between different bronchi, such as the right principal bronchus/right bronchus intermedius (RPB/RBI) angle and right bronchus intermedius/right middle lobe (RBI/RML) bronchus angle, were all significantly reduced. The RUL stumps ranged from 1.6 to 10.1 mm with a mean value of 3.1 mm. The detailed data of bronchial morphological changes are summarized in *Table 2*. In addition, it is worth mentioning that 27 (24.1%) patients demonstrated bronchial kink in 3D reconstruction images. Tortile bronchi were found in 14 patients in the RLL basal bronchus, 6 in the RLL dorsal bronchus, and 7 in the RML bronchus.

Univariate and multivariate analyses of risk factors

Variables that likely influenced postoperative intractable cough were analyzed between groups (*Table 3*). Compared with the non-cough group, patients in the refractory cough group showed significant differences in smoking history, RUL stump length, changes of RBI diameter, changes of RLL basal bronchus diameter, changes of RBI/RLL bronchial angle, and bronchial kink. The above indicators were then entered into a multivariable regression model, and RUL stump length, bronchial kink, and diameter change of RLL basal bronchus were independently associated with postoperative refractory cough (*Table 4*).

Potential benefit of nebulization drugs

When the 41 patients who did not respond to common antitussive drugs complained of refractory cough during the 1-month visit, the nebulization drug Symbicort was offered. During the next visit, cough was alleviated in 33 (80.5%) patients according to medical records. We analyzed the clinical demographics of all 41 PIC patients. Unfortunately, no indicators showed a statistically significant difference between the cough improvement and no-improvement groups, probably due to the relatively small number of cases.

Table 2 Radiological findings of bronchial morphological changes after surgery

Morphological indicators	Preoperative	Postoperative	P value
RUL stump length (mm)	N/A	3.1±1.7	N/A
Lumen diameter (mm)			
RPB (major axis)	13.7±2.9	12.0±2.0	<0.001
RPB (minor axis)	11.8±2.6	9.5±1.4	<0.001
RBI (major axis)	11.7±2.5	10.6±1.6	<0.001
RBI (minor axis, cm)	8.6±2.3	8.3±1.7	0.015
RML bronchus (major axis)	6.5±0.6	5.5±0.8	<0.001
RML bronchus (minor axis)	5.8±0.6	5.1±0.8	<0.001
RLL bronchus (major axis)	8.4±1.6	8.0±1.2	0.001
RLL bronchus (minor axis)	7.0±1.2	6.8±1.1	0.015
RLL dorsal bronchus (major axis)	6.6±1.4	5.9±1.7	<0.001
RLL dorsal bronchus (minor axis)	5.6±1.2	4.9±1.4	<0.001
RLL basal bronchus (major axis)	5.0±1.1	4.4±0.9	<0.001
RLL basal bronchus (minor axis)	4.2±0.9	3.9±0.8	<0.001
Bronchial angle (°)			
Trachea/RPB	136.5±3.6	139.0±4.7	<0.001
RPB/RBI	167.1±4.7	162.0±4.4	<0.001
RBI/RML bronchus	135.6±4.2	126.9±6.2	<0.001
RBI/RLL bronchus	161.7±5.9	155.2±6.2	<0.001
RLL/RLL basal bronchus	160.5±6.0	1143.0±4.9	<0.001
RLL/RLL dorsal bronchus	120.5±5.8	115.4±7.9	<0.001

Data are presented as mean ± standard deviation. RUL, right upper lobe; N/A, not available; RPB, right principal bronchus; RBI, right bronchus intermedius; RML, right middle lobe; RLL, right lower lobe.

Table 3 Variables influencing postoperative intractable cough

	Postoperative intractable cough		P value
	Yes (n=41)	No (n=71)	
Age (years)	53.1±11.4	54.4±9.4	0.711
Female	12 (29.3)	34 (47.9)	0.073
Smoking history	25 (61.0)	27 (38.0)	0.019
COPD	5 (12.2)	6 (8.5)	0.743
VATS	37 (90.2)	62 (87.3)	0.765
Reinforcement of stump	5 (12.2)	9 (12.7)	1.000
Adenocarcinoma	37 (90.2)	67 (94.4)	0.461

Table 3 (*continued*)

Table 3 (*continued*)

	Postoperative intractable cough		P value
	Yes (n=41)	No (n=71)	
T stage			
1	36 (87.8)	62 (87.3)	1.000
2	4 (9.8)	7 (9.9)	
3	1 (2.4)	2 (2.8)	
N stage			
0	37 (90.2)	65(91.5)	1.000
1	3 (7.3)	4 (5.6)	
2	1 (2.4)	2 (2.8)	
Dead space rate (%)	2.1±8.4	0.4±1.9	0.113
Pleural effusion	5 (12.2)	3 (4.2)	0.140
RUL stump length (mm)	3.8±2.3	2.6±0.8	<0.001
Lumen diameter (mm)			
Δ RPB (major axis)	−1.9±1.2	−1.5±1.4	0.160
Δ RPB (minor axis)	−2.7±1.9	−2.1±1.9	0.089
Δ RBI (major axis)	−1.6±1.5	−0.8±1.6	0.009
Δ RBI (minor axis, cm)	−0.7±1.5	−0.2±1.6	0.115
Δ RML bronchus (major axis)	−1.2±1.2	−1.2±1.1	0.764
Δ RML bronchus (minor axis)	−0.9±1.3	−0.8±1.0	0.589
Δ RLL bronchus (major axis)	−0.6±1.3	−0.3±1.2	0.197
Δ RLL bronchus (minor axis)	−0.4±1.3	−0.2±1.0	0.415
Δ RLL basal bronchus (major axis)	−1.7±2.1	−0.3±0.9	<0.001
Δ RLL basal bronchus (minor axis)	−1.7±1.9	−0.2±0.8	<0.001
Δ RLL dorsal bronchus (major axis)	−0.8±1.0	−0.6±0.7	0.358
Δ RLL dorsal bronchus (minor axis)	−0.5±0.9	−0.3±0.7	0.062
Bronchial angle (°)			
Δ Trachea/RPB	2.1±6.8	2.7±5.9	0.585
Δ RPB/RBI	−5.9±7.5	−6.0±8.3	0.961
Δ RBI/RML bronchus	−8.9±7.2	−8.6±7.6	0.802
Δ RBI/RLL bronchus	−8.9±7.7	−5.2±7.1	0.012
Δ RLL/RLL basal bronchus	−17.1±6.9	−17.7±7.0	0.645
Δ RLL/RLL dorsal bronchus	−5.3±11.0	−5.0±8.7	0.851
Bronchial kink	22 (53.7)	5 (7.0)	<0.001

Data are presented as mean ± standard deviation or percentage (%). "Δ" represents the changes of bronchial diameter/angle after surgery. COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery; RUL, right upper lobe; RPB, right principal bronchus; RBI, right bronchus intermedius; RML, right middle lobe; RLL, right lower lobe.

Table 4 Independent risk factors of postoperative intractable cough

Indicators	OR	95% CI	P value
Smoking history	2.345	0.609–9.036	0.215
RUL stump	1.904	1.185–3.058	0.008
Bronchial kink	20.855	4.718–92.184	<0.001
Δ RBI (major axis)	0.693	0.435–1.103	0.122
Δ RLL basal bronchus (major axis)	0.408	0.170–0.982	0.045
Δ RBI/RML bronchus	1.046	0.968–1.130	0.256

RUL, right upper lobe; RBI, right bronchus intermedius; RLL, right lower lobe; RML, right middle lobe; OR, odds ratio. "Δ" represents the changes of bronchial diameter/angle after surgery.

Discussion

Given the changes in the disease spectrum, the proportion of asymptomatic patients with early lung cancer has increased gradually in clinical practice (8). The fast-track recovery management of video-assisted thoracoscopic surgery (VATS) for lung cancer minimizes injury to and impact of the surgery on patients when a lobectomy is performed (9). Single-port VATS and multimodal analgesia relieves the refractory pain after surgery (10); however, postoperative intractable cough remains a neglected clinical issue, for which clinical features and causes are still unclear.

Postoperative refractory cough can occur after all general thoracic operations, such as pulmonary wedge resection, segmentectomy, lobectomy, esophagectomy, and even mediastinal surgery. Potential mechanisms of PIC are (I) airway inflammation or airway hyper-responsiveness after pulmonary resection; (II) anatomic and physiological changes of the air ways; (III) foreign body irritation of bronchial stump; and (IV) underlying diseases, such as cough variant asthma, upper airway cough syndrome, or gastroesophageal reflux-induced cough. The reported risk factors include female sex, history of COPD, obstructed airways, anesthesia duration, right lung cancer, mediastinal lymph node dissections, etc. (11,12). In our present study, we included only lung cancer patients who underwent right upper lobectomy and systematic lymph node dissections and found that the bronchial morphological changes, such as RUL bronchial stump length, bronchial kink, and diameter change of RLL basal bronchus, were independent predictors of PIC.

Bronchial detachment is an important part of lobectomy. It is widely accepted that the management of bronchial stump during surgery has an effect on the occurrence of PIC. Possible causes of stump-related PIC are local inflammatory reactions caused by injury of lung tissue, surgical scar of the airway mucosa, and stimulation by a foreign body, such as sutures or clips in the bronchi (13-15). In our present study, we found that bronchial stump length was an independent risk factor for PIC. However, it is unclear why suturing of the stapled stumps with Prolene was found not be associated with postoperative cough. This might be related to the high biocompatibility of titanium alloy and the nonabsorbable Prolene suture.

Surgeons are well aware of the occurrence of bronchial stenosis and deformation after lobectomy (16). It is regarded as a physiological outcome in most instances; however, unfavorable postoperative complications are occasionally associated with these changes. Limited studies have focused on this issue, especially in relation to postoperative cough. Ueda *et al.* first reported the clinical ramifications of bronchial kink after upper lobectomy in 50 patients (7). For 42% (21/50) of patients, a bronchial kink was confirmed, and significantly more patients complained of intractable cough and shortness of breath in the kink group compared to the nonkink group (76% *vs.* 21%). Arai *et al.* reviewed 100 lung cancer patients who underwent right upper lobectomy and found 23 cases with intermediate bronchial kinking after surgery. They concluded that intermediate bronchial kink correlated with postoperative respiratory symptoms (17). In our study, significant changes in bronchial morphology were demonstrated after lobectomy. As shown in *Table 2*, the diameters of bronchi and angles between different bronchi decreased significantly, which indicates that the remaining airway and lung tissues underwent a process of readjustment after upper lobectomy. Bronchial kink was verified in 27 (24.1%) cases, which is consistent with previous reports (7,17). Furthermore, we found that bronchial kink was an independent predictor of PIC, which was hypothesized but not proven with clinical data in the literature. Bronchial kink was reported to be associated with reduced functional lung volume and ventilatory capacity, and these may be related to one and the same cause (18). Bronchial stenting has been reported to treat extreme bronchial kinks that cause dyspnea and cough due to bronchial obstruction or atelectasis (19,20). Symptoms of patients were shown to be alleviated after the stenting procedure according to case reports (19,20). Gu *et al.* investigated the structural and functional alterations of the airways after left upper lobectomy. They reported that the left lower bronchus lumens reduced in most cases by 15% to 75%, and that wall pressure, airflow velocity, and pressure drop increased significantly postoperatively as measured by the virtual computational fluid dynamics method (21). Therefore, it is assumed that high-speed airflow caused by bronchial kink mechanically stimulates the rapid adapting receptors (RARs) of the major airway tract, passing through the A delta (A-δ) fiber to the cough center of the brain, thus inducing coughing. To dilate and correct the deformed airway medically, we attempted to use bronchodilators as an inhalation drug when the common antitussives were ineffective. Our result was consistent with that of Sawada *et al.* reported in 2012 (22). For a large proportion of PIC patients, symptoms were alleviated after β-agonist nebulization drugs were administered. The underlying mechanisms were likely the anti-inflammatory effect of the corticosteroid (decreasing the release of certain chemical substances, such as bradykinin, histamine or prostaglandin, and weakening the C-fiber conduction) and the bronchial relaxation effect of a β-agonist (weakening the A-δ fiber conduction) (22).

As described above, for the management of PIC, medical treatments to control symptoms are still the approach of choice. Surgical treatment mainly focuses on intraoperative prevention and improvement of surgical manipulations. Surgeons should make sure the operation is conducted with care, protecting nerves and avoiding excessive traction of tissues. The only specific preventive method is the surgical fat-filling procedure after mediastinal lymphadenectomy, as reported by Huang *et al.* (23). Their theory is based on RARs, which are the main receptors mediating cough and which are mainly located just below the carina and around the main bronchi (24). Huang *et al.* proposed filling the postlymphadenectomy residual cavities with mediastinal fat tissue or a gelatin sponge to reduce chemical and mechanical stimulation after surgery. In our case, we performed systematic lymphadenectomy for all lung cancer patients and used a medical sponge to fill the cavities to reduce the incidence of PIC. Another surgical procedure that might play a role in the management of PIC is dissecting the inferior pulmonary ligament (IPL) (25). Previous studies reported that dividing IPL might have an adverse effect on bronchial distortion and pulmonary function (26,27). Although no direct correlation between dissecting IPL and PIC has been demonstrated in the literature, bronchial deformation and worsening lung function are potential causes of dry cough after surgery. One systematic review indicated that no clear evidence is available that dissection with IPL can improve clinical outcomes and reduce complications during upper lobectomy (28); consequently, dissection of IPL is not recommended as routine procedure from the point of view of reducing postoperative cough.

Our study has several limitations. First, our study was retrospective in design, and thus there was no quantitative evaluation of patients' coughs. Second, several clinical features of the cohort, such as some surgical details and postoperative pulmonary function data, were not captured, as they were not included in the medical record database. In addition, although the data on bronchial morphology were measured by 2 authors independently based on 3D reconstructive imaging, manual manipulation might have introduced human error. The relatively small sample and the single-center study design warrant further verification in multicenter, prospective, large-scale studies both in relation to the study of risk factors of PIC and the potential benefit of nebulization drugs.

Conclusions

After right upper lobectomy, the morphology of the remaining bronchial tree in the residual lung changed significantly. Bronchial morphological alternations, such as RUL stump length, bronchial kink, and diameter change of the RLL basal bronchus were independent risk factors of postoperative refractory cough. The identification of risk factors associated with PIC can provide surgeons with new ideas for improving the quality of life of lung cancer patients after pulmonary resection.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-368). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Renmin Hospital of Wuhan University Review Board for Clinical Research. Informed consent was waived due to the retrospective nature of this study.

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