ORIGINAL ARTICLE

Analysis of factors related to chronic cough after lung cancer surgery

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Abstract

Background: In this study, we investigated the relationship between chronic cough and clinicopathological features in postoperative patients with non-small cell lung cancer (NSCLC) and evaluated the effectiveness of acupuncture therapy for the treatment of postoperative chronic cough in patients with NSCLC.

Methods: We retrospectively evaluated 171 patients with NSCLC who received lobectomy at our center between September 2017 and February 2018. The Mandarin Chinese version of the Leicester Cough Questionnaire (LCQ-MC) was used to evaluate the degree of cough in patients. Postoperative cough was assessed by a visual analog scale (VAS).

Results: The total LCQ-MC score for the whole group was 19.79 ± 0.53 before surgery and 18.40 ± 0.70 after surgery (p < 0.001). Logistic regression analysis showed that right lung cancer, difficult airway, acute cough and history of COPD were independent predictors of chronic cough. Of the 68 patients diagnosed with chronic cough, 41 received acupuncture therapy (acupuncture therapy group), and 27 received no acupuncture therapy (no therapy group). No significant difference was found between the two groups in terms of their LCQ-MC scores at eight weeks after surgery (p = 0.756). However, the acupuncture therapy group had a significantly higher LCQ-MC score than the no therapy group at 10 weeks after surgery (p = 0.002).

Conclusions: Right lung cancer, difficult airway, acute cough, and history of COPD are independent predictors of chronic cough after surgery. For patients with chronic cough, acupuncture therapy can shorten the recovery time and improve quality of life after surgery.

Introduction

Lung cancer is the leading cause of cancer death worldwide.[1,2] Surgical resection is the main treatment for resectable non-small cell lung cancer (NSCLC). Lobectomy and systemic mediastinal lymph node dissection are standard surgical methods for lung cancer treatment. Approximately 25–50% of patients have been reported to experience cough after lung cancer surgery.[3–5] Postoperative cough is known to be related to mediastinal lymph node resection, history of chronic obstructive pulmonary disease (COPD), loss of lung volume, and bronchial scarring.[6–8] Postoperative cough may last for an extended period after surgery and can reduce patient quality of life (QOL).

In this study, we investigated the relationship between chronic cough and clinicopathological features in postoperative patients with NSCLC. The Mandarin Chinese version of the Leicester Cough Questionnaire (LCQ-MC) and a

visual analog scale (VAS) were employed to evaluate postoperative cough in patients with lung cancer as well as the effectiveness and safety of acupuncture therapy for postoperative chronic cough.

Methods

Patient selection

This study was approved by the Ethics Committee of the First Hospital of the University of Science and Technology of China. Written informed consent was obtained from all patients prior to the operation. We retrospectively evaluated 523 consecutive patients with NSCLC who underwent lobectomy and systemic lymph node dissection between September 2017 and February 2018. We verified and updated the clinical data through September 2018 using the medical database. Patients were selected based on the following criteria: (i) histopathologically confirmed NSCLC; (ii) lobectomy and systemic lymph node dissection; (iii) R0 resection; (iv) no neoadjuvant therapy; and (v) an understanding of the LCQ-MC and provision of consent. The exclusion criteria were as follows: (i) diagnosis of acute respiratory disease within one month, (ii) diagnosis of pneumonia with a positive chest X-ray; and (iii) incomplete medical records. Based on the above criteria, 171 patients were ultimately enrolled for analysis in this retrospective study (Fig 1).

Surgical technique

Double-lumen endotracheal intubation and single-lung ventilation were performed with the patient in the lateral position on the unaffe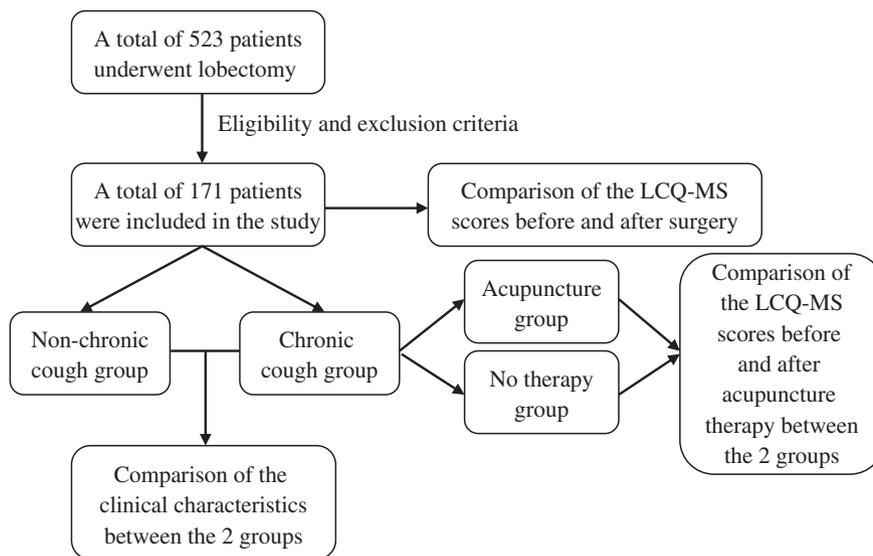cted side. All patients received minimally invasive or thoracotomy lobectomy combined with mediastinal lymph node dissection. For right lung cancer, the 2R, 3A, 3P, 4R, 7, 8, 9, 10 groups and intrapulmonary lymph nodes were routinely probed and resected. For left lung cancer, the 4L, 5, 6, 7, 8, 9, 10 groups and intrapulmonary lymph nodes were routinely probed and resected. A 28F chest tube was placed after the surgery. The chest tube was removed according to the following criteria: (i) the volume of daily chest drainage was less than 200 mL without air leakage; and (ii) no pneumothorax or localized pleural effusion was observed on chest X-ray.

The 2003 Practice Guidelines from the American Society of Anesthesiologists (ASA) suggested using at least four descriptors of difficult airway events (ASA 2003), which can be summarized as follows: Difficult face mask ventilation: It is not possible to provide adequate face mask ventilation. Difficult laryngoscopy: Even with multiple attempts, it is not possible to visualize any portion of the vocal cords during conventional laryngoscopy. Difficult tracheal intubation: Tracheal intubation requires multiple attempts. Failed intubation: Placement of the tracheal tube fails after multiple intubation attempts.[9]

Evaluation methods and diagnostic criteria for cough

The LCQ-MC was used to evaluate the degree of cough in patients. The LCQ-MC is divided into three dimensions: physical, psychological and social. There are a total of 19 questions, and each question has seven options (positive scoring, grades 1–7; the higher the score is, the lighter the cough). The scores of each dimension are averaged by the scores of each question in the dimension, and the total score is the sum of the scores of the three dimensions.[10]

Figure 1 Flow diagram of the study. LCQ-MC: Mandarin Chinese version of the Leicester Cough Questionnaire.

Postoperative cough was assessed by a VAS. When the scale was longer than or equal to 60 mm (range of 0–100 mm), the patient was diagnosed with cough (diagnostic criteria were used for all acute and chronic cough).[11] According to the criteria for the diagnosis and treatment of cough established by the American College of Chest Physicians (ACCP), cough symptoms lasting for eight weeks constitute a chronic cough.[12]

All patients in this study were subjected to the VAS assessment and filled the LCQ-MC one day before surgery, three days after surgery, eight weeks and 10 weeks after surgery, respectively. The LCQ-MC was used to evaluate cough before and after acupuncture intervention. The questionnaire was completed eight weeks after surgery and two weeks after treatment.

Acupuncture therapy

All patients who were diagnosed with chronic cough were routinely recommended acupuncture therapy. Of the 68 patients who were diagnosed with chronic cough, 41 patients received acupuncture therapy at eight weeks after surgery. The standardized acupuncture points used in the present study were as follows: (i) LU7 (Lieque) and (ii) LU9 (Taiyuan) in the lung meridian; (iii) LI4 (Hegu) in the large intestine meridian; (iv) ST36 (Zusanli) in the stomach meridian; and (v) BL13 (Feishu) in the bladder meridian.[13,14]

Statistical analyses

Statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed data are shown as the mean ± standard deviation, and independent samples t-tests were used to compare groups. χ^2 tests and Student's t-test were used to compare two groups. Pearson's χ^2 test was used to conduct single-factor correlation analysis. Logistic regression was used to analyze the factors influencing chronic pain, and differences were statistically significant when $p < 0.05$.

Results

The study group comprised 97 (56.7%) men and 74 (43.3%) women with NSCLC (ages ranging from 43–75 years (mean: 65 years)). All of the patients had a Karnofsky score greater than or equal to 80. TNM staging was based on the International Association for Lung Cancer Research (IASLC), 8th edition. This study included 93 patients with stage I disease, 49 patients with stage II disease, and 29 patients with stage III disease.

A total of 94 patients (55.0%) were diagnosed with acute cough (VAS > 60 mm), and 68 patients (39.8%) were

diagnosed with chronic cough. The total LCQ-MC score for the whole group was 19.79 ± 0.53 before surgery and 18.40 ± 0.70 after surgery (p < 0.001) (Table 1). Patients with lung cancer have different degrees of cough after surgery. Univariate analysis showed that right lung cancer, difficult airway, acute cough, history of COPD, and smoking history were associated with chronic cough (Table 2). Next, chronic cough was used as a dependent variable, and other clinical pathological features were used as covariates for logistic regression analysis. The results showed that right lung cancer, difficult airway, acute cough and a history of COPD were independent predictors of chronic cough after surgery (Table 3).

Of the 68 patients diagnosed with chronic cough, 41 received acupuncture therapy on the 8th week after surgery (acupuncture therapy group), and 27 received no acupuncture treatment (no treatment group). The two groups were similar in terms of age, sex, smoking history, history of COPD, tumor location, tumor diameter, TNM staging and incidence of acute cough (p > 0.05). The LCQ-MC score at eight weeks after surgery in the acupuncture therapy group and the no therapy group was 17.31 ± 1.19 and 17.23 ± 1.07, respectively. No significant difference was found between the two groups (p = 0.756). However, at 10 weeks after surgery, the LCQ-MC score was 18.29 ± 0.74 and 17.74 ± 0.59 in the acupuncture therapy group and the no therapy group, respectively. The score for the acupuncture therapy group was significantly higher than that for the no therapy group (p = 0.002) (Table 4).

Discussion

As an invasive treatment, surgery can be used to remove lesions, treat disease and improve prognosis but inevitably produces physical and psychological trauma that affects patient QOL after the operation. Cough is a protective respiratory reflex of the body that removes secretions or foreign bodies in the airway. According to the 2015 edition of the diagnosis and treatment guidelines for cough, chronic cough usually refers to a cough that lasts for more than eight weeks, primarily manifests as cough symptoms, has no abnormality on X-ray, is not affected by

Table 1 The mean LCQ-MC score before and after surgery

| | LCQ-MC score | | | |
	Preoperative	Postoperative	t	p value
Physical	6.64 ± 0.23	5.34 ± 0.42	35.15	<0.001
Psychological	6.56 ± 0.32	6.53 ± 0.33	0.74	0.459
Social	6.60 ± 0.43	6.53 ± 0.44	1.42	0.156
Total	19.79 ± 0.53	18.40 ± 0.70	20.60	<0.001

LCQ-MC: Mandarin Chinese version of the Leicester Cough Questionaire

Table 2 Clinical characteristics of the patients

Characteristics	chronic cough (n = 68)	non- chronic cough (n = 103)	χ^2/t	p value
Sex			0.018	0.893
Male	39(57.4%)	58(56.3%)		
Female	29(42.6%)	45(43.7%)		
Age (years)			0.032	0.858
≤65	40(58.8%)	62(60.2%)		
>65	28(41.2%)	41(39.8%)		
Smoking			12.857	<0.001
Yes	28(41.2%)	17(16.5%)		
No	40(58.8%)	86(83.5%)		
History of COPD			16.832	<0.001
Yes	24(35.3%)	10(9.7%)		
No	44(64.7%)	93(90.3%)		
Tumor location			9.876	0.002
Right lung	47(69.1%)	46(44.7%)		
Left lung	21(30.9%)	57(55.3%)		
Tumor diameter(cm)			0.696	0.404
≤3	42(61.8%)	70(68.0%)		
>3	26(38.2%)	33(32.0%)		
Difficult airway			10.020	0.002
Yes	15(22.1%)	6(5.8%)		
No	53(77.9%)	97(94.2%)		
TNM staging			0.403	0.817
I	35(51.5%)	58(56.3%)		
II	21(30.9%)	28(27.2%)		
III	12(17.6%)	17(16.5%)		
Operation			0.016	0.900
VATS	61(89.7%)	93(90.3%)		
Open	7(10.3%)	10(9.7%)		
Acute cough			21.082	<0.001
Yes	52(76.5%)	42(40.8%)		
No	16(23.5%)	61(59.2%)		
No. of DN	15.75 ± 2.8	15.99 ± 2.91	0.539	0.590

COPD: chronic obstructive pulmonary disease VATS: Video-assisted Thoracoscopic Surgery DN: dissected nodes

Table 3 Logistic regression analysis of influencing fators of chornic cough postoperative

Variables	OR	OR (95%CI)	p value
Chronic cough			
Acute cough	0.233	0.106–0.511	<0.001
Difficult airway	0.317	0.103–0.976	0.045
Tumor Location	0.395	0.187–0.835	0.015
History of COPD	0.224	0.075–0.669	0.007
Sex	1.212	0.568–2.589	0.619
Age	0.632	0.295–1.351	0.236
Smoking	0.804	0.309–2.097	0.656
Tumor diameter	0.673	0.314–1.443	0.308
TNM staging	0.818	0.507–1.320	0.411
Operation	0.720	0.203–2.560	0.612
Constant	56.649		0.001

COPD: chronic obstructive pulmonary disease

Table 4 The mean LCQ-MC score(total) with or without acupuncture therapy

	LCQ-MC score			
	Acupuncture group (n = 41)	Non- acupuncture group (n = 27)	t	p value
Eight weeks after surgery	17.31 ± 1.19	17.23 ± 1.07	0.312	0.756
10 weeks after surgery	18.29 ± 0.74	17.74 ± 0.59	3.261	0.002

LCQ-MC: Mandarin Chinese version of the Leicester Cough Questionnaire

conventional treatment, and has an unknown etiology.[12] The results of this study indicate that right lung cancer, difficult airway, acute cough and a history of COPD are independent predictors of chronic cough. Additionally, for patients with chronic cough, acupuncture therapy can significantly shorten the recovery time and improve QOL after surgery.

There are few studies on the pathogenesis of chronic cough after lung cancer surgery. Based on these studies, airway inflammation is a common feature of patients with chronic cough.[4,15] According to a previous study,[15–17] the mechanism of chronic cough caused by surgery mainly includes the following: (i) local inflammation caused by surgery in lung tissues and peripheral nerves; (ii) physical changes to small airways after surgery, such as local torsion caused by poor ventilation; (iii) surgical scars and chronic stimulation from foreign bodies, such as sutures in the trachea; and (iv) local pleurisy and pleural effusion. In this study, we found that right lung cancer, difficult airway, acute cough and a history of COPD are independent predictors of chronic cough after surgery. Right lung cancer dissection and extensive lymph node dissection of the superior mediastinum, damage to vessels and nerves on the anterior wall of the trachea and partial cavity formation after surgery are the main causes of chronic cough. Difficult airway can lead to prolonged intubation time. Furthermore, repeated stimulation of the tracheal mucosa is the main cause of increased acute cough, and poor control of acute cough and COPD leads to chronic inflammation. Notably, COPD is an important cause of chronic cough.

Acupuncture therapy is a vital component of traditional Chinese medicine. As previously reported, acupuncture can reduce the postoperative inflammatory response in patients with lung cancer, thereby reducing postoperative pulmonary complications. Moreover, acupuncture has been found to be effective and safe in the management of a variety of pulmonary diseases.[18,19] Liu *et al.*[14] found that patients undergoing lung cancer surgery have significantly reduced lung-related complications after electroacupuncture, and the mechanism might be related to the regulation of inflammatory reactions and a reduction in the proinflammatory factors in plasma

by acupuncture. Additionally, a recent study by Tu *et al.*[13] suggested that transcutaneous electrical acupoint stimulation was beneficial for accelerating postoperative recovery and improving patient prognosis. In the present study, among the 68 patients diagnosed with chronic cough, patients who received acupuncture therapy had significantly higher scores than patients who received no therapy, which is consistent with the findings reported in previous studies.

The question of how to prevent and reduce chronic cough in lung cancer patients after surgery remains unsolved. The main aspects to consider include the following: First, tubeless anesthesia technology can be used to minimize the stimulation of airways in some patients. Second, when cleaning lymph nodes, more attention should be paid to protect nerves and vessels around the trachea and bronchi and to reduce postoperative scar formation. Third, early intervention for patients with acute cough may reduce the incidence of chronic cough. Fourth, for patients who are diagnosed with chronic cough, acupuncture therapy can be administered to relieve symptoms.

Nevertheless, this study does have some limitations. First, there is a potential for selection bias because of the retrospective nature of the study. Second, the sample size was small. Third, the reason why acupuncture helps to reduce chronic cough is unknown, which should be the focus of future work.

In summary, the probability of acute and chronic cough in patients with lung cancer is relatively high. Right lung cancer, difficult airway, acute cough, and history of COPD are independent predictors of chronic cough after surgery. Meanwhile, for patients with chronic cough, acupuncture therapy can shorten the recovery time and improve QOL after surgery.

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Disclosure

No authors report any conflict of interest.

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