

# Recent advances in postoperative pulmonary rehabilitation of patients with non-small cell lung cancer (Review)

XUE-E SU<sup>1</sup>, WAN-PING HONG<sup>1</sup>, HE-FAN HE<sup>1</sup>, SHU LIN<sup>2,3</sup>, SHAN-HU WU<sup>1</sup>, FANG LIU<sup>4</sup> and CUI-LIU LIN<sup>2</sup>

<sup>1</sup>Department of Anaesthesia, The Second Affiliated Hospital of Fujian Medical University;

<sup>2</sup>Centre of Neurological and Metabolic Research, The Second Affiliated Hospital of Fujian Medical University,

Quanzhou, Fujian 362000, P.R. China; <sup>3</sup>Group of Neuroendocrinology, Garvan Institute of Medical Research,

Sydney NSW2010, Australia; <sup>4</sup>Department of Nursing, Fujian University of Traditional

Chinese Medicine, Fuzhou, Fujian 350100, P.R. China

Received August 11, 2022; Accepted October 19, 2022

DOI: 10.3892/ijo.2022.5446

**Abstract.** Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases and has high morbidity and mortality rates. Over the past decade, treatment strategies for NSCLC have progressed rapidly, particularly with the increasing use of screening programs, leading to improvements in the initial diagnosis and treatment of early-stage and preinvasive tumors. Surgical intervention remains the primary treatment for early-stage NSCLC. Thoracoscopic lobectomy has become the main treatment for early-stage NSCLC, as it results in less postoperative bleeding and pain and fewer complications. However, the complication rate for thoracoscopic lobectomy due to sputum retention and weakened respiratory muscle strength remains as high as 19-59%. Treating NSCLC remains challenging in terms of postoperative pulmonary rehabilitation. In the present review,

recent advances in postoperative pulmonary rehabilitation for patients with NSCLC were presented in order to assist researchers in developing improved treatments to enhance postoperative pulmonary rehabilitation for such patients.

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*Correspondence to:* Professor Cui-Liu Lin, Centre of Neurological and Metabolic Research, The Second Affiliated Hospital of Fujian Medical University, 34 North Zhongshan Road, Quanzhou, Fujian 362000, P.R. China  
E-mail: 417851151@qq.com

Professor Fang Liu, Department of Nursing, Fujian University of Traditional Chinese Medicine, 1 Qiuyang Road, Shangjie Town, Minhou County, Fuzhou, Fujian 350100, P.R. China  
E-mail: liufang5511234@163.com

**Abbreviations:** CRF, cancer-related fatigue; EGFR, epidermal growth factor receptor; ERAS, enhanced recovery after surgery; IL, interleukin; IMT, inspiratory muscle training; NSCLC, non-small cell lung cancer; OLV, one-lung ventilation; OS, overall survival; PBMC, peripheral blood mononuclear cell; PC, pressure-controlled; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial; TCC, Tai Chi Chuan; TCE, traditional Chinese exercise; TCM, traditional Chinese medicine; TNM, tumor-node-metastasis; VATS, video-assisted thoracic surgery

**Key words:** non-small cell lung cancer, pulmonary rehabilitation, postoperative, thoracoscopic surgery, recovery

## 1. Introduction

Lung cancer has the highest mortality rate worldwide and seriously affects patients' health (1). According to National Cancer Center of China statistics, 733,300 new cases of NSCLC were reported in 2015 and there were ~610,200 related deaths (2). According to GLOBOCAN 2020, 820,000 new cases of lung cancer were reported in China in 2020, accounting for ~18% of all new cancer cases. In addition, the total number of lung cancer deaths far exceeded that of other cancer types, comprising ~23.8% of the total number of cancer-associated deaths (1). Over the past decade, the increase in lung cancer-related deaths in China has exceeded the global average (3,4).

Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases and is the most common pathological type of lung cancer, including adenocarcinoma and squamous cell carcinoma (5). Surgery is the main treatment modality for early-stage NSCLC (6). With recent developments in modern medicine, continuous promotion of lung cancer screening and improvements in health awareness, early-stage lung cancer has been more readily detected. Thus, patients' operative and survival rates have also improved. Furthermore, more attention has been paid to improving the quality of life of patients postoperatively (7). In recent years, thoracoscopy technology

has developed rapidly and has considerable diagnostic and therapeutic benefits in treating various respiratory diseases. Thoracoscopy is the first choice of treatment for lung cancer due to its low postoperative pain and complications. Among the treatment methods, thorascopic lobectomy has become the main treatment method for early-stage NSCLC, as it results in less intraoperative bleeding and pain and comparatively fewer complications (8-10).

Although thorascopic lobectomy is more conducive to patient recovery, the probability of various complications after thorascopic surgery remains high at 15.8-31.7%, mainly involving pulmonary air and pleural effusion such that, when taking into account the different stages of cancer, 25-70% of patients eventually relapse (11-13). The complication rate for thorascopic lobectomy due to sputum retention and weakened respiratory muscle strength is as high as 19-59%, which seriously affects patient recovery (14). Given pulmonary rehabilitation of patients with NSCLC is currently sub-optimal, the present study aimed to summarize the existing pulmonary rehabilitation programs to help clinicians determine better rehabilitation methods for patients with NSCLC.

## 2. NSCLC stages and status of lung cancer surgery

The lung cancer stage, which is closely related to the surgical method, determines whether a patient may undergo surgery and affects surgical outcomes.

*Clinical staging of patients with NSCLC.* Accurate lung cancer staging is an important aspect of patient treatment, with early diagnosis and lung cancer stage being the most important factors influencing the treatment plan (15). Between 1943 and 1952, Denoix conceptualized tumor-node-metastasis (TNM) staging (16). The International Association for the Study of Lung Cancer is the only global organization dedicated to lung cancer study and is responsible for collating, analyzing and updating cancer data (17). TNM staging for lung cancer is currently in its 8th edition, with data collected from 1999 to 2010 and the newest edition released in 2017. Compared with the 7th edition, the main differences are in relation to tumor size, the extent of involvement and subclassification of extra-thoracic metastases (18). T staging is determined according to the size of the tumor and its relationship with adjacent structures, lymph node staging is determined by assessing the regional hilar and mediastinal lymph nodes and M staging indicates whether there is metastasis outside of the regional lymph nodes (19).

In summary, the clinical stages of NSCLC may be divided into four stages, according to the 8th edition of TNM lung cancer staging: Stages I and II are early-stage NSCLCs, which include  $T_{1-3}N_0M_0$  and  $T_{1-2}N_1M_0$ . Stages III and IV are locally advanced and advanced NSCLCs, which include  $T_4N_0M_0$ ,  $T_{3-4}N_{1-3}M_0$ , and  $T_{1-4}N_{0-3}M_{1a-1c}$  (20,21). The appropriate treatment strategy depends on the degree of mediastinal lymph node involvement, which determines whether the tumor is resected alone or in combination with chemoradiotherapy or immunotherapy (Table I) (22-26). The sharp increase in the number of patients with early-stage NSCLC and the reduction in the number of patients with locally advanced and advanced NSCLC may be explained as follows: With increased health awareness, there

has been an increase in the number of patients undergoing physical examinations. However, improved medical care also depends on high computed tomography resolution and the use of other advanced instruments and equipment.

*Overview of NSCLC surgery.* In thorascopic lobectomy, the surgeon uses a thoracoscope to observe the status of the chest cavity in real-time on a television screen. Surgery is performed using between one and four incisions  $\leq 5$  cm (without opening the ribs) with complete lobectomy (27,28). Video-assisted thoracic surgery (VATS) lobectomy has become the technique of choice for resection of early-stage lung cancer at numerous institutions. In the National Comprehensive Cancer Network NSCLC guidelines, there is a call for 'strong consideration' of VATS lobectomy (27,29). Treatment-intent pneumonectomy should be considered for stage I lung cancer. Several studies have suggested that segmentectomy should be strongly considered for tumors  $< 2$  cm in size, as the results are comparable to lobectomy and the approach is similar for tumors measuring 2.1-3 cm (30-33). In addition, certain studies have demonstrated the efficacy of sublobar resection for solid predominant tumors  $\leq 2$  cm (34,35). Patients with stage II lung cancer also benefit from surgical resection; however, there is insufficient evidence concerning the optimal extent of surgical resection, and adjuvant chemotherapy with a platinum-containing dual-drug regimen as a treatment for stage IIB lung cancer has also been recommended (36). A recent retrospective study provided inconclusive results regarding sublobar resection vs. lobectomy in this patient population (37). Patients with stage III lung cancer benefit from a multidisciplinary evaluation, including pneumonectomy, neoadjuvant therapy and immunotherapy, which is a comprehensive treatment regime (38,39). For locally advanced lung cancer or patients with stage IV disease, where lobectomy, bilobectomy or sleeve lobectomy cannot completely resect tumors, VATS pneumonectomy is the first treatment of choice, which is similar to open pneumonectomy, or opting for an integrated and personalized application of immunotherapy (40). While guidelines or expert consensus provide reference standards, each patient differs and should be considered on an individual basis.

*Overview of VATS.* VATS is a thoracic surgical procedure that uses a small camera to enter a patient's chest through a small incision. It is currently the main surgical method in thoracic surgery (41). In a comparison of VATS with open lobectomy, VATS was indicated to have several advantages. VATS has been associated with reduced pain and blood transfusions, a shorter duration of chest tube intubation and hospital stay, and fewer perioperative complications and arrhythmias. VATS is one of the most recommended surgical methods for treating lung cancer (Table II) (42,43). Compared to the open lobectomy in terms of rehabilitation, thorascopic lobectomy has more advantages in length of stay (6 vs. 4 days) and chest tube duration (4 vs. 3 days). In 2007, in relation to treating phase I and II NSCLC, the American College of Chest Physicians identified VATS lobectomy as an acceptable alternative to thorascopic surgery (44).

With recent developments in thoracoscopy technology, surgeons performing VATS have gradually switched from the use of multiple incisions to double incisions, with one

Table I. Summary of staging and status of NSCLC.

Clinical stage	TNM stage	Survival rate (Refs.)	Intervention mode (Refs.)
<b>I</b>			
IA1	T1a ( $\leq 1$ cm) N0M0	5-year OS, 87.3% (60)	Sublobar resection (34,35)
A2	T1b ( $>1-2$ cm) N0M0	5-year OS, 87.3% (60)	Sublobar resection (34,35)
IA3	T1c ( $>2-3$ cm) N0M0	5-year OS, 84.8% (60)	Thoracoscopic pulmonary lobectomy (27)
IB	T2a ( $>3-4$ cm) N0M0	5-year OS, 84.8% (60)	Thoracoscopic pulmonary lobectomy (27)
<b>II</b>			
IIA	T2b ( $>4-5$ cm) N0M0	5-year OS, 84.8% (60)	Thoracoscopic pulmonary lobectomy (27)
IIB	T3 ( $>5-7$ cm) N1M0, T1a-2N1M0	5-year OS, 84.8% (60)	Thoracoscopic pulmonary lobectomy + adjuvant chemotherapy (27,36)
<b>III</b>			
IIIA	T4N0M0, T3-4N1M0, T1a-2N2M0	5-year OS, 15-35% (55)	Surgery + adjuvant (55) Chemotherapy + aggressive chemoradiotherapy; nonbulky ( $<3$ cm), discrete or single-level N2 involvement (24)
IIIB	T3-4N2M0, T1a-2N3M0	5-year OS, 5-10% (55)	Surgery + adjuvant (55) Chemotherapy + aggressive chemoradiotherapy; N2 involvement is at least moderate, such as tumors with central location or size $>3$ cm, a thorough preoperative staging workup is mandatory (25)
IIIC	T3-4N3M0	15.8% (3 years) (69)	Multidisciplinary team discussion + aggressive concurrent chemoradiotherapy (41)
<b>IV</b>			
IVA	T1a-4N0-3M1a-1b	Median survival, 10.2-23 months (82)	Molecular tests were performed and treatment was guided according to molecular typing (41)
IVB	T1a-4N0-3M1c	Median survival, 10.2-23 months (82)	Targeted therapies, biomarker-directed treatments (55)

incision used as an observation hole and the other used to perform the procedure. In single utility port thoracoscopic surgery, one surgical incision is made for observation and to perform the operation. In general, the efficacy of VATS in the treatment of lung cancer is comparable to standard thoracotomy (45-47). Single utility port thoracoscopic surgery is suitable for T-stage T<sub>1</sub>-T<sub>3</sub> (grade II) and N-stage N<sub>0</sub>-N<sub>2</sub> (grade I) lung cancer (43,48). Single utility port thoracoscopic lung surgery has the following advantages: Less bleeding, a shorter operative time and faster recovery than standard multi-port thoracoscopic surgery (49,50). However, the postoperative complication rate for single utility port thoracoscopic surgery has been reported to be between 3 and 40% (51). Several recent studies have investigated how to best select the location of the single-hole thoracoscopic incision and whether to place a drainage tube to improve the surgical effect (52-55). Decisions made concerning whether to perform single or multiple incisions or whether to place a drainage tube or not vary from patient to patient, in relation to promoting rapid recovery.

### 3. Postoperative pulmonary rehabilitation for patients with NSCLC

*Pathogenesis of lung cancer.* Obtaining an in-depth understanding of the pathogenesis of lung cancer facilitates the diagnosis and treatment of NSCLC, and the rehabilitation efficacy and prognosis of patients with NSCLC would be likely to improve. The pathogenesis of lung cancer is related to smoking, radon exposure, air pollution and gene mutation (Fig. 1).

*Smoking.* Smoking is known to be the most important risk factor for lung cancer (56). A global study reported that, in 2017, smoking was associated with 63.17% of lung cancer-related deaths (57). The incidence of postoperative complications was also indicated to be high among patients who were smokers. A study reported that smoking cessation improved overall survival (OS) of patients with lung cancer (58). Tobacco control, which was implemented in the 1960s, has reduced lung cancer rates. However, ongoing smoking cessation efforts

Table II. Summary of thoracoscopic lobectomy vs. open lobectomy in terms of rehabilitation.

Surgery type	Rehabilitation program					Author, year	(Refs.)
	Length of stay, days	Chest tube duration, days	Cardiac arrhythmias, %	Perioperative complications, %	Blood transfusions, %		
Thoracoscopic lobectomy	4	3	7	26	2	Paul, 2010	(42)
Open lobectomy	6	4	12	35	5	Han, 2020	(43)

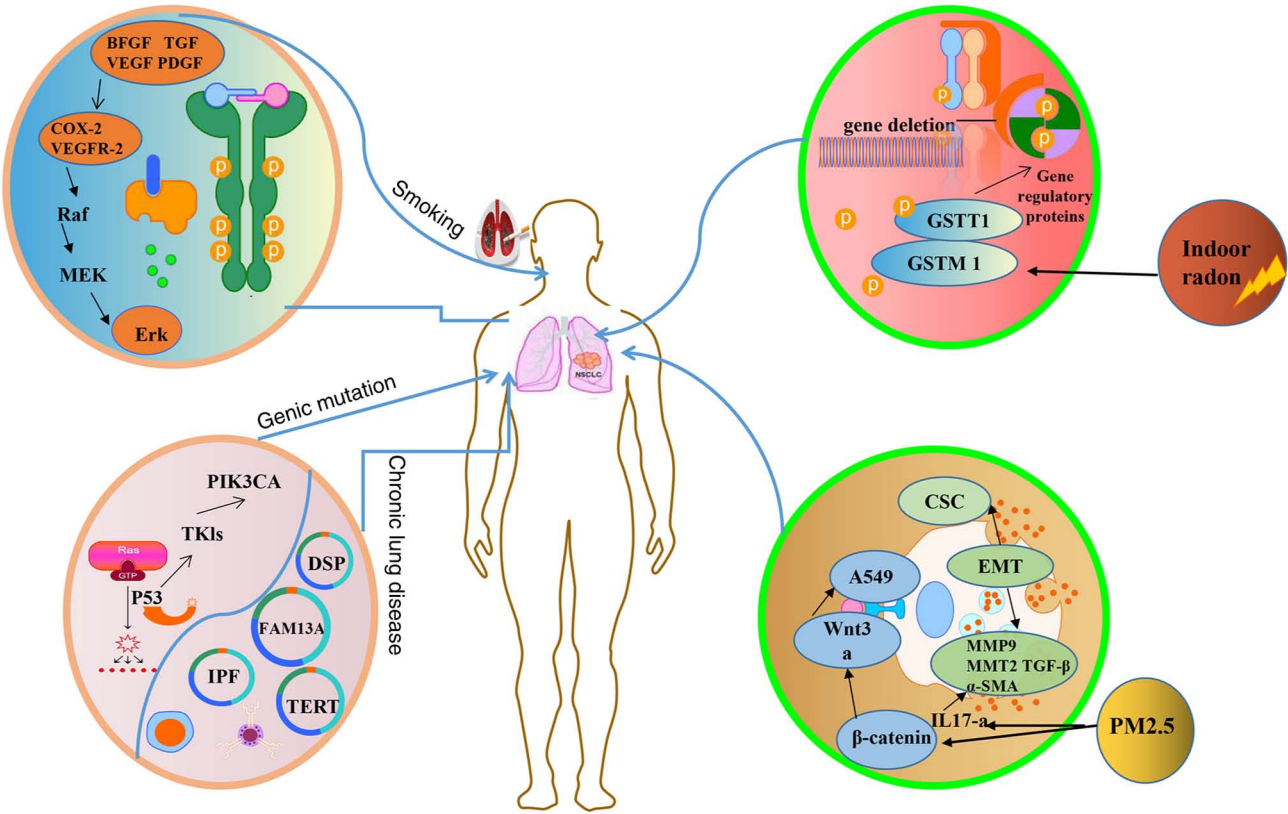


Figure 1. Pathogenesis of NSCLC. The pathogenesis of lung cancer is related to smoking, indoor radon exposure, air pollution, chronic lung disease and gene mutations, which act on airway epithelial cells guided by related signaling pathways. EGFR gene mutation is a common mutation in NSCLC, which is one of the most common driver gene mutations in NSCLC in East Asian populations. TP53 is a gene that accounts for >50% of the mutation frequencies in lung cancer. In the EGFR signaling pathway, multiple proteins are associated with tyrosine phosphorylation, the downstream proteins are activated and the associated signaling pathways are RAS-RAF-MAPK and PI3K-AKT. NSCLC, non-small cell lung cancer; EMT, epithelial to mesenchymal transition; CSC, cancer stem cell.

are required to consolidate this result and reduce the lung cancer burden worldwide.

**Indoor radon exposure.** Radon, a chemically inert radioactive gas of natural origin, produced from uranium and radium in crustal rocks and soils, is the second most common cause of lung cancer (59,60). Inhalation of high levels of indoor radon has been demonstrated to cause DNA mutations and increases risks through depositing decay products in lung epithelial cells (61-63).

**Air pollution.** Air pollution is a risk factor for lung cancer, as it induces adverse effects on the respiratory system, especially after exposure to fine particulate matter (PM2.5). PM2.5 exposure leads to lung injury through inflammation, oxidative stress and apoptosis, which increases the morbidity and

mortality of respiratory and circulatory diseases (64). PM2.5 promotes the occurrence and development of lung cancer. Compared with tumor-bearing mice in a normal environment, mice exposed to PM2.5 have been indicated to have a higher number of tumor nodules and higher matrix metalloproteinase-1 and vascular endothelial growth factor protein levels, leading to the occurrence of lung cancer (65,66).

**Chronic lung diseases.** Chronic lung diseases such as tuberculosis and bronchiectasis increase the risk of lung cancer. Several studies have indicated that respiratory diseases are closely related to the morbidity rate of lung cancer (67,68).

**Gene mutation.** With the rapid development of modern biomedicine, it has become increasingly important to explore the differentially expressed genes in NSCLC. Epidermal

growth factor receptor (EGFR) gene mutation is a common gene mutation in NSCLC (69). EGFR gene mutation is a common driver of gene mutations in East Asian populations with NSCLC. TP53 is a tumor suppressor. Previous studies have indicated that TP53 mutations exist in 35-60% of patients with NSCLC, accounting for >50% of the mutation frequency in lung cancer (70). In addition, studies of microRNAs have also broadened the understanding of the pathogenesis of lung cancer.

NSCLC is a chronic disease that frequently requires rehabilitation. Achieving smoking cessation is never too late for patients with NSCLC. Patients should seek to inhale fresh air and increase their exercise levels in a natural environment. Further studies concerning the identification of molecular mechanisms underlying lung cancer metastasis are required, which may then provide new opportunities to eradicate lung cancer metastasis and guide further research and rehabilitation. A better understanding of the pathogenesis of lung cancer is likely to be helpful in developing a multimodal treatment approach that combines lifestyle changes, exercise programs and nutritional support to address rehabilitation challenges faced by patients with NSCLC.

*Current status of NSCLC.* Although the surgical treatment of NSCLC has demonstrated certain progress, its postoperative complications and recurrence rates remain unsatisfactory. For completely resected stage I NSCLC, local or distant recurrence occurs in 20-40% of patients, with a high risk of recurrence per patient annually, namely, 6-7% in the first four years (71,72). Despite the use of adjuvant chemotherapy, the risk of developing stage I and III disease has been reported to range from 45 to 76% (73). Three- and five-year OS rates after open lobectomy are ~82 and 66%, respectively (74). Table II provides the five-year OS rates for sublobar, lobectomy, stage III and advanced NSCLCs (75-80). Molecular testing was performed for nonsurgical and stage IV NSCLC and treatment was guided according to molecular typing. Despite current surgical techniques and skilled nursing, 19-59% of patients experience postoperative lung complications (14), which then increase hospital stays and hospitalization costs, and may result in poor quality of life. Previous studies have indicated that dyspnea, physical activity tolerance, stair-climbing ability and quality of life may worsen and persist for ≥6 months postoperatively (81-83). Based on these findings, rehabilitation after NSCLC is essential and continued efforts are required to reduce these high complication and recurrence rates.

*Importance of pulmonary rehabilitation.* Pulmonary rehabilitation is defined as 'comprehensive intervention based on a thorough patient assessment after patient-tailored treatment, including but not limited to exercise training, education and behavioral modification, aimed at improving the physical and mental well-being of patients with chronic respiratory disease and promoting long-term adherence to health-promoting behaviors' (84). Pulmonary rehabilitation includes exercises to strengthen respiratory muscles and educational programs which, in combination, may be expected to contribute to improved rehabilitation outcomes (85-88). Pulmonary rehabilitation is essential in a variety of clinical situations, and National Institute for Health and Clinical Excellence

guidelines state that it may reduce mortality and pulmonary complication rates and may improve lung function (89,90). Several studies have indicated that pulmonary rehabilitation may also improve quality of life, forced expiratory volume in 1 sec and forced vital capacity, and reduce lung cancer complication and mortality rates (91-94). The value of pulmonary rehabilitation for patients with NSCLC after surgery merits increased attention.

#### **4. Current pulmonary rehabilitation for patients with NSCLC**

Poor pulmonary rehabilitation affects quality of life and imposes a heavy burden on societies and families. To date, no specific treatment program has been approved to enhance pulmonary rehabilitation. Current evidence in relation to advances in interventions and strategies for pulmonary rehabilitation are summarized in the following sections (Figs. 2 and 3).

*Rehabilitation programs in advanced Western countries.* Medical rehabilitation programs in advanced Western countries have demonstrated great potential for rehabilitation and have a positive role in improving rehabilitation outcomes (Table III).

*Respiratory muscle strength training.* Studies have indicated that respiratory muscle strength training, particularly inspiratory muscle strength training, may significantly improve respiratory function, enhance exercise capacity and reduce dyspnea. Studies on prospective pulmonary rehabilitation have indicated that a routine postoperative pulmonary rehabilitation program led by a physical therapist (including breathing pattern, positive pressure breathing, resistance, abdominal wall and respiratory muscle strength training) for 1-6 months has a positive effect on lung function, quality of life, exercise tolerance and emotional disorders (95). A study of respiratory muscle strength preservation with inspiratory muscle training (IMT) demonstrated that IMT did not preserve respiratory muscle strength but improved oxygenation in high-risk patients postoperatively (96). In another study, six weeks of IMT and aerobic exercise in postoperative patients with lung cancer were reported to improve respiratory muscle strength and exercise capacity after VATS (97). Based on these studies, respiratory muscle strength training appears to be a useful rehabilitation measure for complications such as postoperative dyspnea and cough, and may have an important role in preventing postoperative complications.

*Interventions in terms of ventilation modes.* With advances in mechanical ventilation studies and continuous improvements in ventilation modes, significant attention has been paid to the use of lung protective ventilation strategies in treatment. Surgery causes a variety of lung injuries. One-lung ventilation (OLV) is the most commonly used technique for maintaining intraoperative ventilation and oxygenation. However, selecting an appropriate mechanical ventilation strategy to minimize lung injury and other adverse clinical outcomes remains challenging.

Extensive investigations have been performed to determine the most appropriate modality of mechanical ventilation. One systematic review provided recommendations for each



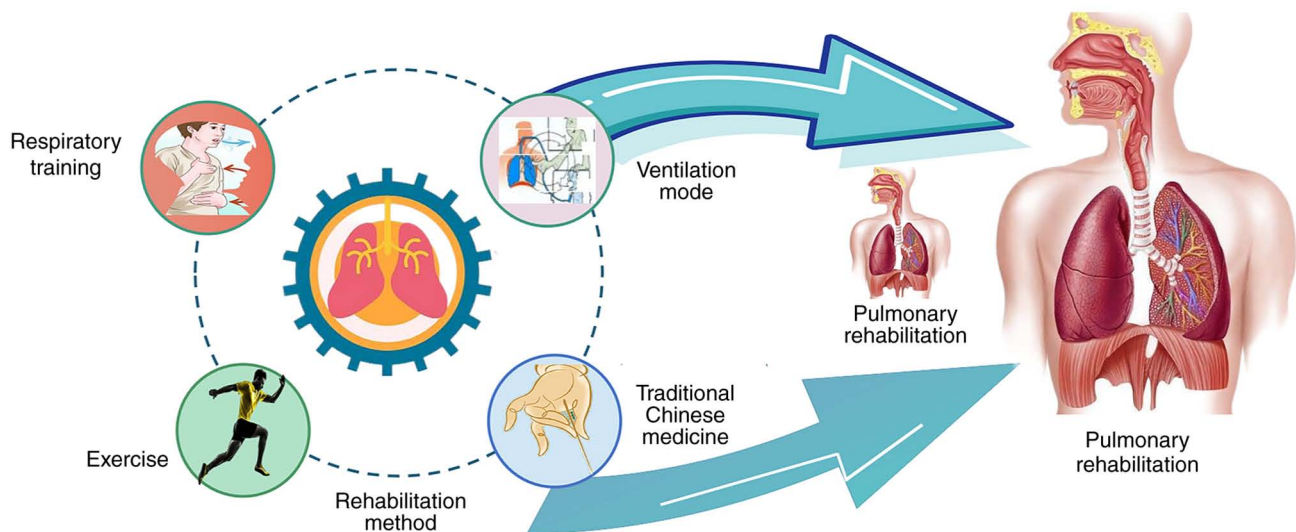


Figure 2. Schematic diagram indicating the rehabilitation approaches for patients with NSCLC. There are currently four main rehabilitation approaches for patients with NSCLC, namely respiratory muscle training, interventions in ventilation modes, acupuncture therapy and 'enhanced recovery after surgery' management, which is focused on exercise, including traditional Chinese exercise. NSCLC, non-small cell lung cancer.

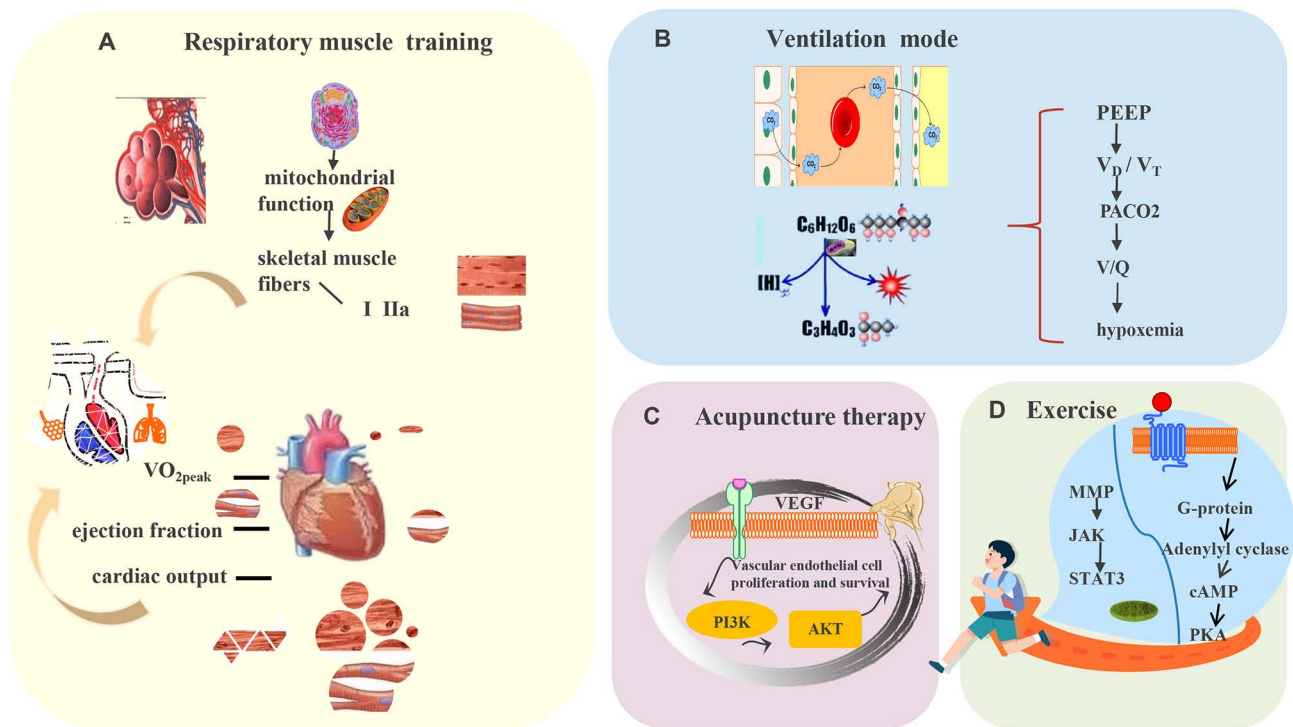


Figure 3. Schematic diagram indicating the mechanisms of the effects of NSCLC rehabilitation approaches for patients. (A) Respiratory muscle training increases the oxygen supply and improves mitochondrial function and aerobic exercise capacity in skeletal muscle, increases the cross-sectional area of skeletal muscle fibers and decreases the proportion of glycolytic muscle fibers, particularly reducing the proportion of type IIb muscle fibers. It also has therapeutic effects, such as improving the  $VO_{2peak}$  and increasing the ejection fraction and the output per stroke, and practice improves the ability and work efficiency of patients with NSCLC to cope with the heart and lung exercise load. (B) Interventions in ventilation modes change the PEEP, which leads to a physiologic dead space to  $VD/VT$  increase, a rise in  $PACO_2$  and then  $V/Q$  regulation, causing hypoxemia. Exercise may activate the JAK/STAT3 signaling pathway through increasing MMP levels, and also activate the cAMP-PKA signaling pathway, finally improving a patient's exercise endurance capacity. (C) Acupuncture may inhibit the PI3K/AKT signaling pathway through inhibition of airway smooth muscle cell proliferation. (D) Exercise may activate the JAK/STAT3 signaling pathway through increasing MMP levels and also activate the cAMP-PKA signaling pathway, thus improving a patient's exercise endurance capacity. NSCLC, non-small cell lung cancer; PEEP, positive end-expiratory pressure;  $VD/VT$ , tidal volume ratio;  $PACO_2$ , partial pressure of carbon dioxide in arterial blood;  $V/Q$ , ventilation-perfusion ratio;  $VO_2$ , volume of consumed oxygen.

grade. Specifically, recommendations were made to maintain a partial pressure of carbon dioxide of 50-70 mmHg, a pressure volume with a tidal volume ( $V_t$ ) of 6-8 ml/kg and a

positive end-expiratory pressure (PEEP) of 5 cmH<sub>2</sub>O. It was also recommended to control mechanical ventilation using an inhalation to exhalation ratio of 1:1, with pressure-controlled

Table III. Summary of rehabilitation programs.

Type of training/method	Author, year	Main outcomes/features	Study type	(Refs.)
Respiratory muscle strength training				
Breathing mode training	Tenconi, 2021	Improved exercise capacity; reduction of the decrease in exercise tolerance observed; influence on the incidence of postoperative complications	Randomized controlled trial	(95)
Positive pressure breathing training	Brocki, 2016	Improved oxygenation in high-risk patients after lung cancer surgery	Randomized controlled trial	(96)
Resistance training	Liu, 2021	Improved respiratory muscle strength and exercise capacity	Randomized controlled trial	(97)
Intervention regarding ventilation mode				
Mechanical ventilation management	Gao, 2017	PV with tidal volume of 6-8 ml/kg; PEEP of 5 cm H <sub>2</sub> O	Review	(98)
Mechanical ventilation management	Marret, 2018	Controlled mechanical ventilation with I:E ratio of 1:1; PC, PCV-PG or CPAP Combination of low VT ventilation and moderate-to-high PEEP ( $\geq 5$ cm H <sub>2</sub> O)	Meta-analysis	(100)
ERAS management				
Personalized home-based physical activity	Mittaz, 2019	Improvement in several aspects of QoL	Randomized controlled trial	(107)
Nordic walking	Skórkowska-Telichowska, 2016	Improvement of patients weight and body mass; prevention of muscle attenuation	Randomized controlled trial	(108)
Anesthesia management and surgical intervention	Xian, 2022;	Intraoperative paravertebral or intravenous lidocaine during lung resection surgery, and non-intubated thoracoscopic surgery	Randomized controlled trial	(109)
Acupuncture therapy	Yang, 2020; Kuang, 2021	Relief of pain, reduced expression of tumor necrosis factor- $\alpha$ , IL-1 $\beta$ and IL-6	Meta-analysis	(112,113)
Traditional Chinese medicine exercise: Tai Chi Chuan	Liu, 2015; Zhang, 2016	Effective impact on the proliferative and cytolytic/tumoricidal activities of peripheral blood mononuclear cells; Reduced fatigue and increased vitality	Randomized controlled trial	(122,123)

PEEP, positive end-expiratory pressure; ERAS, enhanced recovery after surgery; QoL, quality of life; PC, pressure-controlled; I:E, inhalation to exhalation ratio; PV, protective ventilation; VT, tidal volume; CPAP, continuous positive airway pressure; PCV-PG, pressure-controlled ventilation pressure-guaranteed.

(PC) or PC ventilation-polygraphy recommended rather than volume-controlled ventilation, as well as ensuring continuous positive airway pressure, which is beneficial for improving

short-term oxygenation (98). A previous study suggested that protective ventilation and flurbiprofen ester pretreatment may alleviate stress-induced immunosuppression, providing

further options for clinical treatment (99). One study indicated that lung protective ventilation combined with low Vt and PEEP during anesthetic induction in lung cancer surgery resulted in improved postoperative outcomes compared with high Vt without PEEP (100). Two other studies reported similar results (101,102). The benefits of low Vt strategies and PEEP values during OLV for better clinical outcomes have been discussed in certain studies; however, the benefits were not found to be statistically significant (103,104). One study reported that a combination of low Vt ventilation and moderate-to-high PEEP ( $\geq 5$  cm H<sub>2</sub>O) provided good lung protection for surgical patients receiving general anesthesia (105).

*Enhanced recovery after surgical management (ERAS).* The first external validation of the ERAS Society thoracic guidelines suggested that the thoracic ERAS program for lung resection reduced the length of stay, morbidity rate, opioid use and direct costs without a change in readmission (106). Exercise tolerance declines during the complex postoperative period. A recent study found a strong and significant association among peak aerobic capacity, quadriceps muscle function and lung diffusing capacity, suggesting that lower extremity muscle function is a determinant of exercise tolerance in patients with lung cancer after pneumonectomy (7). This finding provides a good indication for rapid postoperative recovery. Exercise also has an important role in recovery after lung cancer surgery. A study on the effects of supervised exercise training on athletic performance, physical activity and sedentary behaviors suggested that clinical populations may benefit from participating in exercise training programs (21). Similarly, personalized home physical activity has also been reported to improve postoperative quality of life and cancer biomarkers in patients with NSCLC (107). Skórkowska-Telichowska *et al* (108) indicated that Nordic walking is an effective exercise to increase patients' body weight and prevent muscle decay, which supported the beneficial effects of aerobic exercise on rapid recovery in patients with lung disease. The attention of physicians is primarily focused on intraoperative anesthetic management and surgical intervention. For instance, intraoperative paravertebral or intravenous lidocaine or non-intubated thoracoscopic surgery have been attempted in lung resection (109).

*Traditional Chinese medicine (TCM) rehabilitation programs.* TCM also has a role in the prevention and treatment of chronic diseases. Specifically, since the outbreak of Coronavirus disease-2019 in 2020, TCM has been used throughout the entire treatment process and has made positive contributions. These findings support the innovative use of TCM and indicate that TCM supports the recovery of patients with NSCLC.

*Acupuncture therapy.* Acupuncture therapy is a characteristic therapy of TCM. Directly acting on acupoints may effectively improve the respiratory reflex center, remove harmful air in the body, promote physical recovery and improve physical function. Patients with lung cancer inevitably experience pain due to tumor location and spread, as well as from surgical treatment, which seriously affects their quality of life (110,111). Two systematic reviews have indicated that acupuncture may effectively relieve pain, regulate inflammation by stimulating the central nervous system and

significantly reduce the expression of tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6 (112,113). Up to 90% of patients with lung cancer experience side effects such as fatigue after chemotherapy (114). Currently, there is a lack of effective pharmacological interventions for the treatment of cancer-related fatigue (CRF). Hence, complementary and alternative medicine is gaining popularity among patients with cancer and is frequently used to manage cancer-related side effects. Another systematic review and meta-analysis indicated that acupuncture and auricular acupressure combination treatment worked better than acupuncture alone to relieve CRF in patients with lung cancer (115). According to a study by Wei *et al* (116), the incidence rate of cancer-related insomnia in patients with lung cancer has increased to 68.4%. A recent randomized controlled trial (RCT) reported the efficacy and safety of acupuncture in the treatment of insomnia in patients with lung cancer, with acupuncture potentially providing a promising therapeutic intervention for the clinical treatment of insomnia in lung cancer survivors (117). For NSCLC, postoperative pain, anxiety, insomnia, fatigue and other symptoms affecting the quality of life of patients are conventionally treated with medication to relieve patients' symptoms (118,119). Recently, acupuncture, as a medical alternative therapy, has been extensively applied to improve the postoperative rehabilitation of patients with NSCLC.

*Traditional Chinese exercise (TCE).* According to the Chinese State Council's 'Healthy China 2030' Program (120), exercises that are popular should be vigorously developed, the development of sports suitable for different groups and regions should be encouraged and traditional sports, such as Tai Chi Chuan (TCC) and Qigong, should be supported and promoted. TCE has been an important cultural factor in the health culture of TCM for thousands of years. TCC, Baduanjin and Qigong are important components of TCE. TCE has gradually become one of the most widespread complementary therapies for tumor treatment and rehabilitation in China. A systematic review has summarized the current RCTs outlining the effects of TCE in patients with cancer. Although certain studies included had methodological limitations and a relatively high risk of bias, evidence was found for the positive effect of TCE on physical, psychological and physiological parameters in relation to cancer-related health outcomes (121). TCC is a TCE that is beneficial to physical and mental health. Liu *et al* (122) investigated the positive effects of 16 weeks of TCC exercise on the proliferation and cytolytic/tumoricidal activities of peripheral blood mononuclear cells (PBMCs) in postsurgical patients with NSCLC. Regular TCC enhanced PBMC proliferation and cytolytic activity in patients with NSCLC (122). Another study on TCC also concluded that TCC was an effective intervention in the treatment of CRF in patients with lung cancer receiving chemotherapy, particularly in terms of reducing general and physical fatigue and enhancing vitality (123).

These studies have involved postoperative or perioperative rehabilitation programs; however, the role of preoperative rehabilitation has yet to be fully elucidated. In one study involving a preoperative pulmonary rehabilitation program, preoperative resistance training in addition to breathing exercises improved patients' preoperative condition and possibly prevented postoperative functional decline (124). Similarly, a systematic review indicated that preoperative exercise therapy



may have beneficial effects on various constitutional variables and postoperative complications in patients with lung cancer planning surgery (66,97). It remains to be elucidated whether preoperative intervention may lead to the deferral of an operation to a more appropriate time and further studies are recommended. However, it would appear that preoperative rehabilitation may be a useful adjunct with numerous advantages and certain disadvantages. Overall, it is important that a patient's freedom of choice is respected when being advised by a physician.

## 5. Limitations of postoperative pulmonary rehabilitation

With regard to NSCLC, there are consensus guidelines concerning the identification of important factors and the grade of perceived risk; however, the implementation of postoperative rehabilitation measures remains unclear. Currently, various respiratory training methods are used in patients with NSCLC. However, the training method, timing and duration are not uniform, and the guidelines do not clearly indicate the best rehabilitation plan for patients undergoing lung cancer surgery. It remains unclear whether short-term preoperative pulmonary rehabilitation improves the clinical prognosis of patients. Questions remain, such as whether it may help promote ineligible patients with lung cancer to meet surgical requirements or whether it reduces postoperative complications in high-risk patients with lung cancer. Currently, accelerated rehabilitation surgery management is widely used in thoracoscopic lung cancer surgery; however, numerous measures are limited to the perioperative period, and rehabilitation quantity and quality after discharge require to be further improved. In addition, physical activity potentially improves postoperative outcomes; however, the available evidence is weak and larger longitudinal studies are required. A multidisciplinary team approach is crucial in the management of all stages of lung cancer; however, the optimal rehabilitation program remains to be determined.

## 6. Conclusion and perspectives

Studies on postoperative pulmonary rehabilitation of patients with NSCLC range from conventional research to TCM. The current study first presented the basic epidemiology of lung cancer. Lung cancer TNM stages (according to the 8th edition) and surgical approaches were then examined, including thoracoscopic surgery, which provided a context of postoperative rehabilitation in patients with NSCLC. Finally, the current conventional medical and TCM rehabilitation programs that may achieve better rehabilitation effects were discussed.

With the rapid development of modern medical and examination techniques, a significant number of NSCLCs are detected early and treated surgically. However, with population aging, it remains challenging to determine how to effectively improve the prognosis and quality of life of patients with NSCLC after surgery. It is necessary to optimize the current health management model to ensure efficient care for patients with NSCLC. Various types of respiratory training have differing effects. However, if a training method is complex, patients may experience difficulties and adherence to exercise may be reduced, which is likely to negatively

affect their rehabilitation. Therefore, future studies are recommended to determine tailored breathing training methods and the selection and duration of these training methods, in accordance with an individual's characteristics. With the development of TCM, its advantages have become gradually clearer. However, patients undergoing acupuncture and auricular points are frequently restricted owing to the rehabilitation cycle, location and cost, and may not be able to meet all of their long-term rehabilitation needs. Therefore, TCM supplementary therapies that are not affected by location and have low cost and good effects, such as TCC, the six-character formula and Baduanjin, should be encouraged (125). Furthermore, the positive effect of certain single TCM interventions remains elusive and a combination of TCM may be more effective, which is a recommended area for further research. Clinical trials with large sample sizes and multicenter, randomized and accurate statistical analysis methods are required.

The present study systematically analyzed the importance of pulmonary rehabilitation and the rehabilitation measures applied in integrated TCM and in conventional medicine. The advantages and disadvantages of current treatment strategies were also summarized. Although there has been clear progress, certain challenges remain. Further research to improve pulmonary postoperative rehabilitation programs for patients with NSCLC is required.

## Acknowledgements

Not applicable.

## Funding

This work was supported by the Nursery Fund Project of the Second Affiliated Hospital of Fujian Medical University (grant no. 2021MP25).

## Availability of data and materials

Not applicable.

## Authors' contributions

XES, CLL and FL were involved in the conception of the review; HFH, SL and SHW reviewed and edited the final manuscript. XES and WPH drafted the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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