frontiers | Research Topics

Current trends in endoscopic thoracic surgery: Insights from the XXI SIET national meeting

Edited by
Federico Raveglia, Filippo Lococo, Sara Ricciardi, Giuseppe Cardillo, Cecilia Pompili, Franca Melfi and Ugo Cioffi

Published in
Frontiers in Surgery

ISSN 1664-8714
ISBN 978-2-8325-3004-7
DOI 10.3389/978-2-8325-3004-7

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Current trends in endoscopic thoracic surgery: Insights from the XXI SIET national meeting

Topic editors

Federico Raveglia — Thoracic Surgery, ASST-Monza, Italy
Filippo Lococo — Agostino Gemelli University Polyclinic (IRCCS), Italy
Sara Ricciardi — Department of Thoracic Surgery, San Camillo Forlanini Hospital, Italy
Giuseppe Cardillo — San Camillo Forlanini Hospital, Thoracic Surgery, Italy
Cecilia Pompili — University of Leeds, United Kingdom
Franca Melfi — University of Pisa, Italy
Ugo Cioffi — University of Milan, Italy

Citation

Raveglia, F., Lococo, F., Ricciardi, S., Cardillo, G., Pompili, C., Melfi, F., Cioffi, U., eds. (2023). *Current trends in endoscopic thoracic surgery: Insights from the XXI SIET national meeting*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3004-7

Table of contents

frontiers | Frontiers in Surgery

TYPE Editorial
PUBLISHED 30 June 2023
DOI 10.3389/fsurg.2023.1237928

OPEN ACCESS

EDITED AND REVIEWED BY
Dennis Paul Orgill,
Harvard Medical School, United States

*CORRESPONDENCE
Federico Raveglia
federico.raveglia@irccs-sangerardo.it

RECEIVED 10 June 2023
ACCEPTED 22 June 2023
PUBLISHED 30 June 2023

CITATION
Raveglia F, Melfi F, Cioffi U, Lococo F, Ricciardi S, Pompili C and Cardillo G (2023) Editorial: Current trends in endoscopic thoracic surgery: insights from the XXI SIET national meeting.
Front. Surg. 10:1237928.
doi: 10.3389/fsurg.2023.1237928

Editorial: Current trends in endoscopic thoracic surgery: insights from the XXI SIET national meeting

Federico Raveglia[1]*, Franca Melfi[2], Ugo Cioffi[3], Filippo Lococo[4], Sara Ricciardi[5], Cecilia Pompili[6] and Giuseppe Cardillo[5]

[1]Thoracic Surgery, IRCCS San Gerardo, Monza, Italy, [2]Thoracic Surgery, Robotic Multispecialty Centre for Surgery; Minimally Invasive and Robotic Thoracic Surgery; University Hospital of Pisa, Pisa, Italy, [3]Thoracic Surgery, University of Milan, Milano, Italy, [4]Thoracic Surgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy, [5]Thoracic Surgery, San Camillo Forlanini Hospital, Roma, Italy, [6]Thoracic Surgery, Leeds Institute of Cancer & Pathology-University of Leeds, Leeds, United Kingdom

KEYWORDS

SIET, thoracic surgery, endoscopy, airways, national meeting, lung cancer, COVID-19

Editorial on the Research Topic
Current trends in endoscopic thoracic surgery: insights from the XXI SIET national meeting

Introduction

The Italian Society of Thoracic Endoscopy (SIET) was founded in 1980 to support research and innovation in endoscopic thoracic surgery by promoting its development and application nationally and internationally. SIET also promotes the training of young people through courses in collaboration with universities and scientific societies with similar aims. The SIET national meeting is tool for information and training exchange with the aim of creating a cohesive and active scientific community. The meeting takes place every two years and welcomes specialists in different disciplines (thoracic surgeons, pulmonologists, oncologists, radiologists). During the event, different topics are addressed among the most current in the field of minimally invasive thoracic surgery.

The 2022 XXI SIET national meeting was mainly focused on the management of lung and airways diseases with particular attention to the most challenging ongoing topics, each addressed by national and international experts presenting their personal experiences. COVID-19 related tracheal injuries, transition to RATS, innovative preoperative systemic therapies for lung cancer and awake surgery have been identified among the highly significant topics.

The goal of the current Research Topic was to promote the most interesting abstracts presented during the meeting, giving the opportunity to develop a full article manuscript.

COVID-19 related tracheal injuries

The recent pandemic has worldwide impacted the healthcare system over the last 3 years, particularly involving pulmonologists and thoracic surgeons. An increasing number of

patients have been subjected to prolonged invasive mechanical ventilation due to COVID-19 infection, leading to a significant number of post-intubation/tracheostomy upper airways lesions (stenosis or laceration) that needed endoscopic and/or surgical management (1).

In their review article Orlandi et al. focused on the different strategies to manage COVID-19-induced tracheal stenosis that may become a relevant pathology in the coming years. They conclude that this condition has distinctive features which differentiate it from other-causes stenosis and underline how the prognosis is related to (1) early diagnosis, (2) personalized and tailored treatments on each patient (through multidisciplinary discussion) (3) experienced tertiary centers referral. Therapeutic options consist of endoscopic or surgical procedures, which could provide high success and low complication rates when performed on selected patient at the right time.

Futhermore, Conforti et al. reported their meaningful experience with post intubation tracheal stenosis in COVID-19 patient with particular attention to relapses management. Their data confirm the prominent role of endoscopic therapy in the most of these challenging cases.

In turn, Passera et al. focused on post-intubation iatrogenic tracheobronchial injury (ITI) underlining that procedural and instrumental innovation, as well as medical development, have likely revolutionized the traditional management of post-intubation ITIs, broadening the use of conservative treatment and introducing the opportunity of the endoscopic approach, with interesting success and acceptable complications rates. Authors suggested the adoption of the risk-stratified morphological classification as that proposed by Cardillo et al. Cardillo et al. in particular, based on the personal experience with 62 patients affected by post-intubation tracheal laceration has confirmed the validation of the morphological classification, yet established by his team, as the major tool for defining the type of treatment. In addition, Brascia et al. presented their solid experience in the management of both tracheal stenosis and tracheal iatrogenic injuries COVID-19 related. This paper is very interesting since show the role of combined endoscopy and surgery in the most severe cases.

To conclude Tombelli et al. presented an innovative technique for tracheal laceration repairing with a hybrid mini-cervicotomic/endoscopic approach.

Transition to RATS

In the last decade robot-assisted thoracoscopic surgery (RATS) has emerged as an alternative to video-assessed thoracoscopic surgery (VATS) for the treatment of lung cancer but concerns still exist regarding its learning curve and the high associated costs (2). Palleschi et al. reported their experience of transition from uniportal VATS to RATS with da Vinci Xi for lung resections. Their data investigated different variables such as number of nodes sampled, margins, conversion rate, complication and mortality rate, observing several practical advantages over VATS. In turn Harrison et al. presented a cost analysis of robotic vs. video-assisted thoracic surgery investigating the impact of the learning curve and the COVID-19 pandemic. Their results offered some evidence that the initial increased costs associated with RATS lung resection may be gradually offset as a program progresses.

Awake surgery

Awake minimally invasive Uniportal Video Assisted Thoracic Surgery (U-VATS) has emerged as the last challenge in thoracic surgery that could change the future scenario for high comorbidity patients with early-stage lung cancer (3). Gonfiotti and co-workers presented a series of 10 high morbidity cases who underwent awake lung resection. Their results confirm recent literature data in favor of this technique and prompt further larger studies to reach stronger evidences to support it.

Innovative preoperative systemic therapies for the lung

Nowadays, the role of immunotherapy and target therapy as induction or adjuvant therapy for resectable lung cancer in the set of a multimodal approach is the hottest topic in oncology thanks to recent trials encouraging results (4). Lampridis et al. have designed an updated overview of recent phase 3 randomized clinical trials on adjuvant and neoadjuvant immunotherapy or targeted therapy with an eye on some meaningful unresolved clinical issues, such as optimal duration of treatment, scheduling with respect to surgery and potential combinations of different systemic therapies.

Alongside these main topics, other emerging topics have been addressed by our experts in the field such as the surgical management of compensatory sweating after sympathectomy in hyperhidrosis or the role of surgery and medical approach in catamenial pneumothorax.

To conclude, during the 2022 SIET annual meeting thoracic surgeons and pulmonologists have discussed and reported their experience concerning advanced in thoracic pathologies with particular attention on new techniques and their impact on clinical practice. A picture has emerged showing that a continuous innovation in the field of surgery and interventional endoscopy is characterizing our days. Our research topic represents an insight in the hottest ongoing topics based on new data from the maximal experts in the field and an accurate literature review.

Author contributions

FR contributed to conception and design of the study. FM and GC wrote the first draft of the manuscript. FL, UC, CP and SR

wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We thank Gerardo Cioffi, native speaker, for reviewing the English language.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Piazza C, Filauro M, Dikkers FG, Nouraei SAR, Sandu K, Sittel C, et al. Long-term intubation and high rate of tracheostomy in COVID-19 patients might determine an unprecedented increase of airway stenoses: a call to action from the European laryngological society. *Eur Arch Otorhinolaryngol.* (2021) 278(1):1–7. doi: 10.1007/s00405-020-06112-6

2. Novellis P, Maisonneuve P, Dieci E, Voulaz E, Bottoni E, Di Stefano S, et al. Quality of life, postoperative pain, and lymph node dissection in a robotic approach compared to VATS and OPEN for early stage lung cancer. *J Clin Med.* (2021) 10 (8):1687. doi: 10.3390/jcm10081687

3. Grott M, Eichhorn M, Eichhorn F, Schmidt W, Kreuter M, Winter H. Thoracic surgery in the non-intubated spontaneously breathing patient. *Respir Res.* (2022) 23(1):379. doi: 10.1186/s12931-022-02250-z

4. Mamdani H, Matosevic S, Khalid AB, Durm G, Jalal SI. Immunotherapy in lung cancer: current landscape and future directions. *Front Immunol.* (2022) 13:823618. doi: 10.3389/fimmu.2022.823618

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 October 2022
DOI 10.3389/fmed.2022.972066

OPEN ACCESS

EDITED BY
Federico Raveglia,
ASST-Monza, Italy

REVIEWED BY
Takeshi Yokoyama,
Kyushu University, Japan
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

*CORRESPONDENCE
Jianming Liu
liujianming@126.com

SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 17 June 2022
ACCEPTED 03 October 2022
PUBLISHED 31 October 2022

CITATION
Zhou Y, Wu W, Zhu Y, Lv X and Liu J (2022) Inhibition of stress and spontaneous respiration: Efficacy and safety of monitored anesthesia care by target-controlled infusion remifentanil in combination with dexmedetomidine in fibreoptic bronchoscopy for patients with severe tracheal stenosis.
Front. Med. 9:972066.
doi: 10.3389/fmed.2022.972066

Inhibition of stress and spontaneous respiration: Efficacy and safety of monitored anesthesia care by target-controlled infusion remifentanil in combination with dexmedetomidine in fibreoptic bronchoscopy for patients with severe tracheal stenosis

Yi Zhou[1,3], Wei Wu[2], Yuanjie Zhu[2], Xin Lv[2] and Jianming Liu[2]*

[1]School of Life Sciences and Technology, Tongji University, Shanghai, China, [2]Department of Anesthesiology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China, [3]Department of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai, China

Objective: This study aimed to determine the effective concentration of target-controlled infusion (TCI) of remifentanil used to inhibit stress during the treatment of severe tracheal stenosis with fibreoptic bronchoscopy and to evaluate the monitored anesthesia care (MAC) by remifentanil.

Materials and methods: 60 patients with severe tracheal stenosis who underwent fibreoptic bronchoscopy was performed. Dexmedetomidine was initially administered at a bolus dose (0.8 mcg/kg), followed by a 0.5 mcg/(kg·h) continuous infusion. Remifentanil was administered by TCI. The effective concentration (EC) of remifentanil was titrated by the improved sequential method, and 30 patients were included. The EC95 of remifentanil was set as the plasma target concentration to evaluate the safety of the MAC, and another 30 patients were included.

Results: The half effective effect-chamber concentration of remifentanil (EC50) was 2.243 ng/ml, and the EC95 was 2.710 ng/ml. Among the 30 patients who received an EC95 of remifentanil as the target concentration, one patient was remedied by injecting propofol, the score of Ramsay sedation was three. The incidence of subclinical hypoxemia (SPO_2 of 90–95%) was 30%, the incidence of moderate hypoxemia (SPO_2 of 75–89%, $\leq$60 s) was 20 and 86.7% of patients with oxygen saturation was less than 95% returned

to normal by awakening. The satisfaction score of the operator was nine, the satisfaction score of the anesthesiologist was eight, the satisfaction score of the patients was 10, the rate of patient willingness to re-accept the procedure was 93.3% and the circulation was stable during the operation.

Conclusion: MAC using TCI of remifentanil with continuous pumping dexmedetomidine can effectively inhibit the stress response to fibreoptic bronchoscopy in patients with severe tracheal stenosis while maintaining spontaneous breathing. Under the anesthesia management of an experienced anesthesiologist, it provides a reference to tracheoscopic anesthesia of autonomous breathing.

Clinical trial registration: [http://www.chictr.org.cn/], identifier [ChiCTR 2100043380].

KEYWORDS

remifentanil, effect concentration, monitored anesthesia care, severe tracheal stenosis, fibreoptic bronchoscopy, spontaneous breathing

Introduction

With the development of endoscopic technology, interventional treatment *via* fibreoptic bronchoscopy has become one of the main methods of diagnosis and treatment for patients with benign and malignant tracheal stenosis, and the demand for fibreoptic bronchoscopic interventional treatment for patients with severe tracheal stenosis continues to increase (1–3). Compared with ordinary patients, severe patients tend to be anxious and exhibit obvious difficulty breathing, tachycardia, hypersecretion or expectoration of sputum, and lung infections, and they must often be placed in unnatural postures to maintain airway patency. Even if apnoea occurs, most conscious patients cannot tolerate the diagnosis and treatment of fibreoptic bronchoscopy, which could improve airway obstruction (4).

Effective and safe anesthesia management technology can inhibit the stress response to fibreoptic bronchoscopy in severe patients, reduce the occurrence of choking cough and laryngeal spasm, and reduce serious complications that may be life-threatening, such as asphyxia, massive bleeding, and malignant arrhythmia (5, 6). There is no compressed air in the respiratory endoscopy center of our hospital, so, laryngeal mask general anesthesia can only provide pure oxygen during mechanical ventilation, which is more likely to cause airway fire and damage during laser cauterization. MAC with spontaneous respiration has significant advantages over local anesthesia and laryngeal mask general anesthesia (7–11). However, there are few studies about MAC on anesthesia management techniques for such severe patients at home and abroad. In our study, on the basis of sedation with dexmedetomidine, the effective concentration of remifentanil for inhibiting the stress response was titrated through a modified sequential method during fibreoptic bronchoscopy of patients with severe tracheal stenosis, and the safety of the MAC regimen with remifentanil was evaluated.

Materials and methods

Study design and population

This prospective interventional study was conducted at the respiratory endoscopy center of Shanghai Pulmonary Hospital affiliated with Tongji University from February 2021 to May 2021. The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University, China (K19-122) and registered in the Chinese Trial Registry (12/02/2021, ChiCTR2100043380). All patients enrolled in this study received written informed consent.

Sixty patients who received fibreoptic bronchoscopy treatment were included, all of whom were diagnosed with severe tracheal stenosis for the first time. The effective concentration of remifentanil was titrated by the improved sequential method in 30 patients, the safety of the MAC protocol was evaluated using EC95 as the plasma target concentration in 30 patients, and the inclusion of patients was completed by LJM. The inclusion criteria included patients with severe tracheal stenosis (the reduced area of the tracheal cavity was more than 50%) who wanted to be treated by fibreoptic bronchoscopy, were aged 18 ∼ 65 years, and had ASA I–III status. The exclusion criteria were as follows: abnormal nasal anatomy, severe coagulation dysfunction, severe hepatic and

renal dysfunction, history of abnormal recovery from surgical anesthesia, chronic opioid treatment, substance abuse or drug use, pregnancy, history of allergy to related drugs, and no informed consent. Included patients were later excluded if general anesthesia by laryngeal-mask or endotracheal intubation was required for the operation or the operation was over 60 min in duration.

Monitored anesthesia care protocol

All patients fasted for 8 h, and water was forbidden for 4 h preoperatively. In the anesthesia preparation area, 0.03 mg/kg midazolam (Midazolam®, Nhwa, China) was given intravenously to relieve pre-procedural anxiety. Electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SpO_2) and mean arterial pressure (MAP), and respiratory rate (RR) were monitored regularly after patient entry into the operating room. Oxygen inhalation through a nasal catheter (2 L/min) was performed. A simple mask breathing apparatus and anesthesia machine were used as a standby. Dexmedetomidine (0.8 mcg/kg, Dexmedetomidine®, Yangtze River, China) was administered within 10 min using a Fresenius DPS workstation, and plasma target-controlled infusion (TCI) of remifentanil (Remifentanil®, Yichang Humanwell, China) was completed within 5 min. When the effector chamber concentration reached the target concentration, a nasopharyngeal airway (No. 6/7, Medis, UK) was placed, and oxygen was given by an anesthesia machine (6 L/min) with an adjustable pressure-limiting (APL) valve setting of 30 cm H_2O. There was no compressed air in the respiratory endoscopy center of our hospital and only pure oxygen was provided. Four milliliters of 1% lidocaine (Lidocaine®, CSPC, China) was injected through the nasopharyngeal airway for topical anesthesia, and then fibreoptic bronchoscopy was started. When the fibreoptic bronchoscope (BF-1T260/6C260, Olympus, Japan) was placed, 4 ml of 1% lidocaine was injected through the bronchoscopic tube into the acoustic gateway and subglottis for topical anesthesia. Intraoperative dexmedetomidine was pumped continuously at 0.5 mcg/(kg·h). The effective concentration of remifentanil was titrated by a modified sequential method. The plasma target concentration of remifentanil in the first patient was 2.5 ng/ml, and the difference between adjacent targets was 0.5 ng/ml. After three cycles of negative and positive reactions, the difference in adjacent target concentrations was changed to 0.2 ng/ml. The stress response was defined as positive if the change in HR or MAP exceeded 15% of the baseline or a choking cough affected the operation. Intravenous injection of 10∼20 mg propofol was used as a remedy and was used repeatedly if necessary. After obtaining the EC95 of remifentanil, the plasma target concentration was set to EC95 to evaluate the perioperative safety of the MAC during the operation.

Related events and their management: (1) definition of hypoxemia: SpO_2 < 90% at any time. The severity of hypoxemia was classified as follows: subclinical hypoxemia (SPO_2 of 90–95%), moderate hypoxemia (SPO_2 of 75–89%, ≤60 s), and severe hypoxemia (SpO_2 < 90% for >60 s or SpO_2 < 75% at any time). The treatment process for hypoxemia was as follows: stimulation and awakening, increasing the oxygen flow (10 L/min), supporting the lower jaw, mask-assisted ventilation, and mechanical ventilation with a laryngeal mask. (2) hypotension: for MAP < 80% of baseline or 60 mmHg, if necessary, an intravenous injection of norepinephrine (25∼100 μg/time) was used to maintain the blood pressure and was repeated when needed. (3) bradycardia: HR < 50 bmp, with administration of atropine as appropriate; if arrhythmia occurred, vasoactive drugs were administered by the anesthesiologist based on his or her clinical judgment.

Cough score is 0–2, 0: no choking cough, 1: Choking cough does not affect operation, 2: choking cough affects operation. The criteria for the Ramsay sedation score are 1–6, 1: Not quiet and irritable, 2: Quiet cooperation, 3: Sleepy, can follow instructions, 4: Sleep state, but can wake up, 5: Sleep state, response to strong stimuli, but lags in response, 6: Deep sleep state, the call is not to wake up. Score 2–4 are satisfactory with sedation and 5–6 have excessive sedation.

Outcome measures

The primary outcome measures were the cough score and the incidence and severity of hypoxemia. The secondary outcomes included recovery time; dosage of propofol; Ramsay score; arterial blood gas analysis before and after the operation; hemodynamic changes; the tolerance score for nasopharyngeal airway placement; satisfaction scores of the operator, anesthesiologist and patient; throat pain and epistaxis at 30 min after the end of the operation; throat pain; patients' scores on operation recall and willingness to receive treatment again at 24 h; and related adverse events such as post-operative pruritus, nausea and vomiting, bleeding, hemoptysis requiring invasive re-treatment, pneumothorax, etc.

Statistical analysis

All statistical analyses were performed using SPSS 26.0. Continuous variables are presented as the mean [standard deviation (SD)] or median [interquartile range, (IQR)]. The non-normally distributed data are presented as the median [IQR]. Categorical variables are presented as counts (%). Continuous variables were compared using the Mann-Whitney *U* test or *t*-test. EC95, EC50, the standard error and the

logarithm value of the 95% confidence interval (CI) of remifentanil were calculated by the formula of the sequential method (12). The sample size of the effective concentration titrated by the improved sequential method is not clearly defined. A sample size of 20–40 has been used in general studies (12). In the present study, the sample size of the effective concentration titrated by remifentanil was 30. The safety of 30 patients was also observed. Two-sided p-values <0.05 were considered significant.

Results

Patients

All 63 patients enrolled in the study; three patients were excluded because the operation time was more than 60 min, 60 patients were eligible for the data analysis, and none were discontinued due to safety concerns. The flow chart is shown in Figure 1. Demographic and operation-related data for all 60 patients are shown in Table 1.

Effective concentration of remifentanil

Figure 2 shows that the stress response of 30 patients with severe tracheal stenosis during fibreoptic bronchoscopy treatment was treated with remifentanil at different blood concentrations using the modified sequential method. The half effective effect-chamber concentration of remifentanil (EC50) was 2.243 ng/ml (95% CI, 2.061–2.446 ng/ml), and the EC95 was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml), as shown in Table 2.

Information related to surgery, hypoxemia and related adverse reactions

For 30 patients with EC95 TCI of remifentanil, hemodynamics were stable at each time point during the operation, as shown in Table 3. One case with remedy by 30 mg propofol was completed. The tolerance score for nasopharyngeal airway placement, Ramsay sedation score, cough score and satisfaction score are shown in Table 4. The

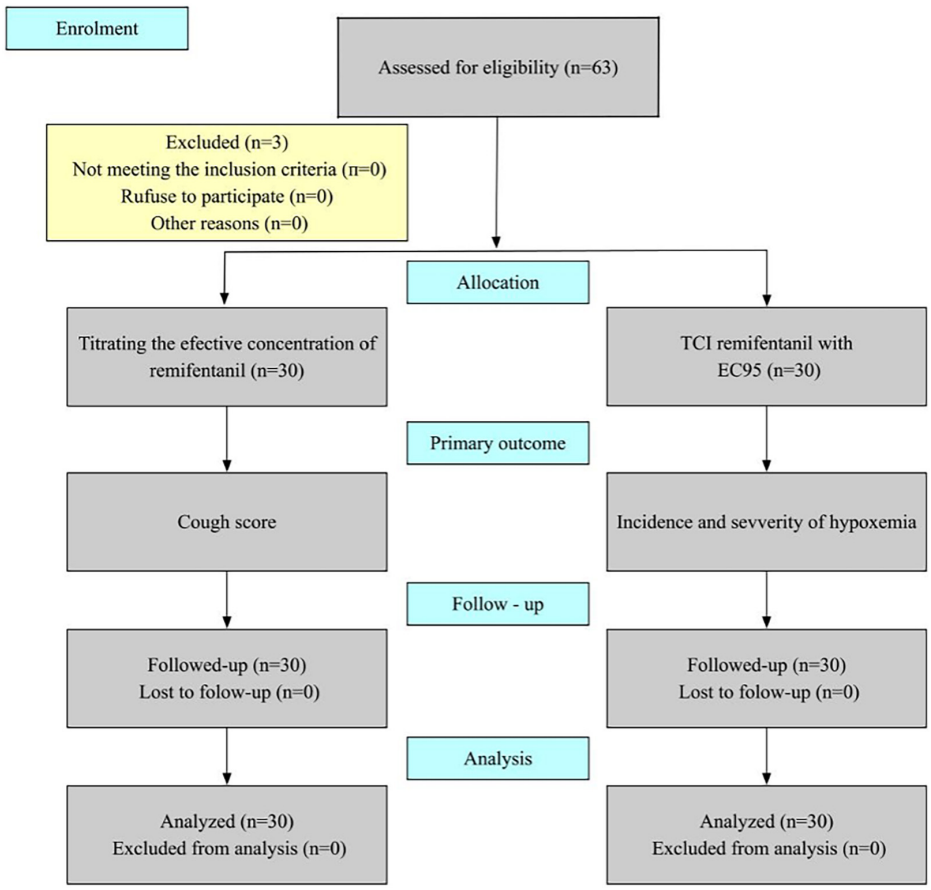

FIGURE 1
Consort flow diagram.

TABLE 1 Characteristics of patients in this study (n = 60).

Item	
Age, mean ± SD, years	48.6 ± 12.8
Male, *n* (%)	17 (56.7)
Height, mean ± SD, m	1.7 ± 0.1
Weight, mean ± SD, kg	64.8 ± 9.3
BMI, mean ± SD, kg/m^2	23.8 ± 2.6
ASA 1/2/3, *n* (%)	0(0)/42(70.0)/18(30.0)
Classification of airway stenosis	
2/3/4, *n* (%)	30(50)/24(40)/6(10)
Indications for bronchoscopy, *n* (%)	
Malignant tumor of trachea	30 (50.0)
Benign tumor of trachea	14 (23.3)
Stenosis after tracheotomy	6 (10.0)
Tracheomalacia	4 (6.7)
Other	6 (10.0)
Diagnostic interventions, *n* (%)	
Tumor removal	16 (26.7)
Tumor cauterization and cryopreservation	22 (36.7)
Stent placement	18 (30.0)
Balloon dilatation	4 (6.7)
Pre−bronchoscopic respiratory parameters	
SpO_2, median [IQR],%	96 [95–97]
RR, mean ± SD, per min	16 ± 2
PaO_2 [IQR], mmHg	82.0 [77.0–86.5]
$PaCO_2$ [IQR], mmHg	41.5 [40.3–43.7]
Pre−bronchoscopic hemodynamic parameters	
MAP, median, mmHg	96.5 ± 6.4
HR, mean ± SD, beat per min	89.2 ± 18.1

SpO_2, pulse oxygen saturation; IQR, interquartile range; RR, respiratory rate; SD, standard deviation; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; MAP, mean arterial pressure; HR, heart rate.

incidence of subclinical hypoxemia was 30%, the incidence of moderate hypoxemia was 20%, and the incidence of severe hypoxemia was 0%. Among all patients with oxygen saturation was less than 95%, 86.7% were restored to normal by awakening, one was restored to normal by mask-assisted ventilation, and another was restored to normal by laryngeal-mask mechanical ventilation (**Table 5**). The analysis of arterial blood gas before and after the operation is shown in **Figure 3**. Other sedation-related adverse reactions are shown in **Table 6**. There were cases of increased heart rate and blood pressure, none of which exceeded 20% of the baseline value. Adverse reactions related to oxygen delivery, including throat pain 30 min and 24 h after the operation, are shown in **Table 7**.

Discussion

Through the improved sequential method, we concluded that the EC95 for remifentanil inhibition of the stress response in fibreoptic bronchoscopy for patients with severe tracheal stenosis was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml) based on dexmedetomidine sedation and that the EC50 was 2.243 ng/ml (95% CI, 2.061–2.446 ng/ml). For all 30 patients, spontaneous breathing was retained during the diagnosis and treatment period, which improved the perioperative safety of severe patients and provided an effective and a new concept anesthesia scheme for patients with severe tracheal stenosis who were undergoing fibreoptic bronchoscopy.

With the development of fibreoptic bronchoscopy technology, it has been widely used in clinical practice, and more than 5,00,000 bronchoscopy procedures are performed in the United States every year (13). A large number of clinical studies have confirmed that the stress response cannot be effectively suppressed under only local anesthesia, which may lead to choking cough or laryngeal spasm resulting in a decrease in PaO_2, aggravating the patient's dyspnoea, interrupting the operation, and even causing serious life-threatening complications such as asphyxia, massive bleeding, malignant arrhythmia, and so on. Except for patients with obvious contraindications, the guidelines recommend routine sedation for all patients undergoing fibreoptic bronchoscopy (10, 14, 15). The application of sedative medicine during fibreoptic bronchoscopy can effectively improve the patient's tolerance, reduce the choking cough during the operation and increase the patient's willingness to revisit the diagnosis and treatment without significantly increasing the related complications (15–17). Compared with general patients, patients with severe stenosis are less tolerant to fibreoptic bronchoscopic intervention, which may improve airway obstruction. Therefore, it is a great challenge for anesthesiologists to provide anesthesia management for patients with severe tracheal stenosis through fibreoptic bronchoscopy, and there is currently no recognized standardized anesthesia management plan here or abroad (15, 18). There are unique challenges to anesthesiologists sharing the airway with the operator. The implementation of sedation and anesthesia reduces risk, improves the comfort of patients and operators and increases the continuity and success of the procedure. In 2009, a study in China showed that two out of 58 hospitals routinely used general anesthesia-assisted or controlled ventilation through laryngeal masks to complete such endoscopic diagnosis and treatment (19). However, anesthesia tolerated with the laryngeal mask may result in significant circulation inhibition and longer recovery time. In recent years, from the perspective of protecting the health and safety of medical personnel and patients and reducing costs, the number of stent placement for tracheal stenosis under X-ray fluoroscopy has gradually decreased. If the stent placement of airway stenosis (especially Y-shaped stent) is not positioned under X-ray, it is necessary to use the fiberoptic bronchoscope to accurately position the stent during the release process. In this case, when the laryngeal mask is used, the laryngeal mask space cannot

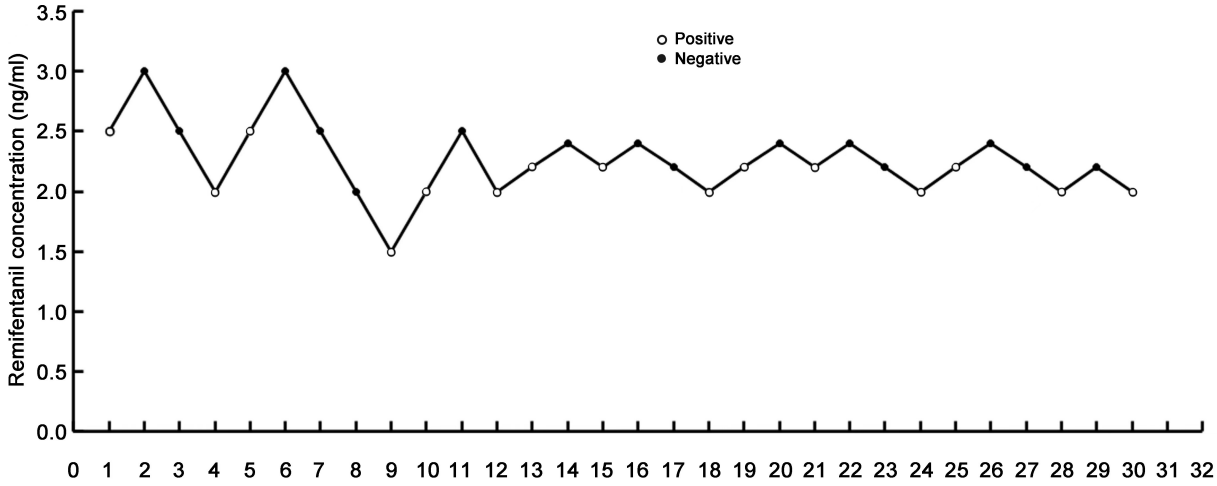

FIGURE 2
Stress response of patients to fiberoptic bronchoscopy.

accommodate the releaser and fiberoptic bronchoscope at the same time, and the arc shape of the laryngeal mask itself is not conducive to the operation of the endoscopist. Our experience shows that in this case, repeated airway operations can easily lead to laryngeal mask displacement. Laryngeal mask is a ventilation device on the glottis, when without compressed air and the ventilation effect is good, the airway is equivalent to a closed pure oxygen state after mechanical ventilation. However, the nasopharynx airway is placed in the nasopharynx, even if the anesthesia machine is connected to give oxygen, it only increases the local oxygen concentration in the nasopharynx, and the oxygen concentration in the airway is less than 100%. Because there is no compressed air in the respiratory endoscopy center of our hospital, laryngeal mask general anesthesia can only provide pure oxygenin. In this case, compared with nasopharynx airway, laryngeal mask ventilation has higher oxygen concentration in the airway, which is more likely to cause airway fire and damage during laser cauterization. It may even be necessary to suspend ventilation during operation. The main difference between laryngeal mask general anesthesia and MAC is whether to keep autonomous breathing. MAC can reduce the amount of anesthetic drugs, reduce medical expenses, and better meet the turnover of outpatient surgery patients. It has less impact on respiratory function and is more suitable for patients with respiratory dysfunction. However, the potential anesthetic risk may be higher and senior anesthesiologists are required to monitor during the whole process of operation. Of course, timely detection of problems and early intervention should reduce the risk and improve the safety. Compared with local and general anesthesia laryngeal mask, the MAC with autonomous breathing provided by the nasopharyngeal airway for oxygen has obvious advantages (19).

Sequential methods, also known as up-down methods or step-down methods, are simpler and more effective methods to study the effective concentration of drugs. The advantage of the sequential method is that it can make full use of the data provided by fewer cases and obtain results quickly

TABLE 2 Confidence interval of remifentanil effective concentration.

Confidence limit	95% Confidence limit		
Probability	**Estimate**	**Lower limit**	**Upper limit**
0.01	1.717	0.858	1.937
0.05	1.857	1.13	2.035
0.1	1.936	1.308	2.092
0.15	1.991	1.441	2.134
0.2	2.036	1.555	2.17
0.25	2.076	1.657	2.205
0.3	2.112	1.752	2.241
0.35	2.146	1.84	2.28
0.4	2.179	1.921	2.325
0.45	2.211	1.996	2.38
0.5	2.243	2.061	2.446
0.55	2.276	2.117	2.528
0.6	2.309	2.166	2.628
0.65	2.345	2.207	2.746
0.7	2.383	2.245	2.885
0.75	2.424	2.281	3.05
0.8	2.471	2.317	3.251
0.85	2.527	2.357	3.508
0.9	2.599	2.404	3.866
0.95	2.71	2.471	4.473
0.99	2.931	2.596	5.895

TABLE 3 Hemodynamic changes (HR, beats/min; MAP, mmHg; *n* = 30).

Item	T_0	T_1	T_2	T_3	T_4	T_5
HR	96.4 ± 18.7	80.8 ± 12.9	91.4 ± 17.3	85.3 ± 12.1	80.4 ± 11.1	78.1 ± 8.9
MAP	101.7 ± 10.0	89.9 ± 9.4	99.8 ± 12.2	93.1 ± 8.1	85.9 ± 6.1	85.4 ± 7.3

T_0, before procedure; T_1, procedure; T_2, 5 min after procedure; T_3, 10 min after procedure; T_4, 15 min after procedure; T_5, end of procedure.

TABLE 4 Procedure data, propofol dosage and satisfaction (*n* = 30).

Characteristic	
Procedure time, min	25.7 ± 8.1
Recovery time, min [IQR]	2 [1.0–2.3]
Sedation score [IQR]	3 [3–4]
Nasopharynx airway tolerance score [IQR]	2 [2–3]
Cough score [IQR]	1 [1–1]
SpO_2, median [IQR],%	99 [95–100]
RR, mean ± SD, per min	10 ± 2
Propofol dose, mg, *n* (%)	30, 1 (3.3)
Patient satisfaction score [IQR]	10 [10–10]
Bronchoscopist satisfaction score [IQR]	9 [9–10]
Anesthesiologist satisfaction score [IQR]	8 [8–8.5]
24-hour patient recall score for operation [IQR]	1 [0–1]
Patients' willingness to accept the operation again, yes, *n* (%)	28 (93.3)

IQR, interquartile range; SpO_2, pulse oxygen saturation; RR, respiratory rate; SD, standard deviation.

TABLE 5 Incidence of hypoxemia and need for airway assistance (*n* = 30).

Characteristic	
Respiratory depression, *n* (%)	15 (50.0)
Subclinical respiratory depression	9 (30.0)
Moderate hypoxemia	6 (20.0)
Severe hypoxemia	0 (0)
Need for airway assistance	15 (50.0)
Stimulation	13 (43.3)
Increasing oxygen delivery	0 (0)
Jaw thrust	0 (0)
Mask ventilation	1 (3.3)
Mechanical ventilation	1 (3.3)

and accurately, which can reduce the number of trial cases by 30 ∼ 40%. Remifentanil has a quick onset and rapid elimination, TCI makes its dose accurate and easy to adjust, and the inhibition of cardiovascular responses caused by stress can be quickly determined, which is suitable for sequential study (20, 21). EC50 refers to half of the subjects at a particular reaction dose and can be sensitive in reflecting changes in the drug concentration and effect. EC95 refers to the effective concentration for 95% of subjects with a specific reaction. The EC50 study concentration-response relationship of a drug is more sensitive and accurate than the EC95; however, the effectiveness of the EC95 is higher, and drug-related adverse reactions may be increased because of the higher drug concentration. In the second part of this study, the EC95 of remifentanil was used to evaluate patients' hypoxemia and other related adverse reactions, and its safety could be investigated better.

Our study showed that the incidence of oxygen saturation was less than 95% was 50% (15/30), that of subclinical hypoxemia was 30% (9/30), that of moderate hypoxemia was 20% (6/30), and that of severe hypoxemia was 0% (0/30) among 30 patients with TCI with EC95 of remifentanil. Respiratory depression can be manifested as the decrease of respiratory rate, the decrease of oxygen saturation, and the increase of end expiratory carbon dioxide. This study uses the decrease of oxygen saturation as the main observation index. During the research design, it is considered that the accuracy of oxygen saturation is high, the error is small, and the operation is simple. A total of 86.7% (13/15) of the patients with oxygen saturation was less than 95% returned to normal by wakening, one patient returned to normal by face-mask-assisted ventilation, and another patient returned to normal by laryngeal-mask mechanical ventilation. The patient with laryngeal-mask mechanical ventilation was 65 years old, weighed 46 kg, and had a height of 175 cm, a BMI of 15, hypertension, diabetes, and 75% airway stenosis. The Ramsay sedation score was five, the lowest SpO_2 was 85%, and SpO_2 became 100% by mask-assisted ventilation; however, breath was still not recovered. The operation was successfully completed through mechanical ventilation with the laryngeal mask, and the changes in MAP and HR did not exceed 10% of the baseline. The patient awakened 8 min after the operation, and no adverse reactions were found during the 24 h follow-up. This patient was analyzed as a frail patient with hypertension and diabetes accompanied by advanced age and low body weight. The EC95 was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml) for this patient, and the depth of anesthesia may have been too deep, excessive sedation, leading to moderate hypoxemia. In the study, subclinical hypoxemia refers to oxygen saturation greater than 90 and less than 95, and patients will not suffer from hypoxia. And Moderate hypoxemia means that the oxygen saturation is greater than or equal to 75, less than 90 s. In this study, the amount of dexmedetomidine and the target concentration of remifentanil are constant, and the anesthesia is too deep for some patients, which is also one of the main reasons why 20% of patients have moderate hypoxemia. The

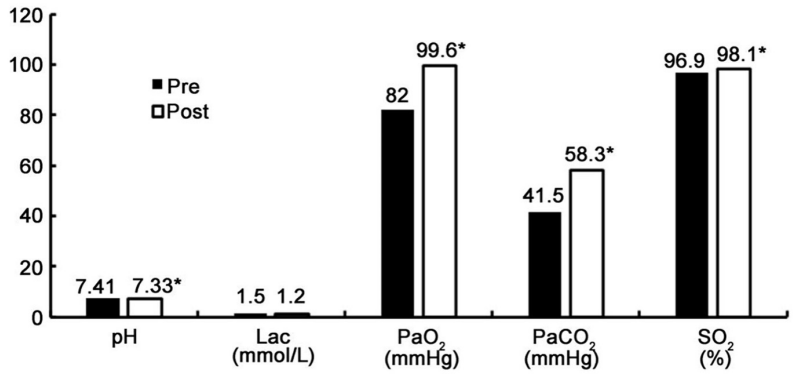

FIGURE 3
Results of arterial blood gas analysis before and after procedure. *$P < 0.05$.

TABLE 6 Other adverse events related to the sedation ($n = 30$).

Item	
Adverse even, *n* (%)	7 (23.3)
Minimal risk	0 (0)
Nausea/Vomiting	0 (0)
Muscle rigidity, myoclonus	0 (0)
Agitation during recovery	0 (0)
Prolonged recovery	0 (0)
Minor risk	7 (23.3)
Airway obstruction	0 (0)
Failed sedation	0 (0)
Allergic reaction without anaphylaxis	0 (0)
Bradycardia	0 (0)
Tachycardia	2 (6.7)
Hypotension	0 (0)
Hypertension	5 (16.7)
Sentinel risk	0 (0)
Cardiovascular collapse/shock	0 (0)
Cardiac arrest/absent pulse	0 (0)

anesthesia dosage can also be adjusted based on the EC50 of remifentanil. In the actual clinical operation, each patient is individualized. However, the dosages of dexmedetomidine and remifentanil in this study are the reference dosages of clinical anesthesia. In clinical practice, anesthesiologists need to adjust them in real time according to the reaction of patients to drugs and the operation steps.

In the study, the blood gas analysis value is obtained by a single arterial blood collection at two time points before anesthesia and at the end of the operation.

The results show that the $SpO_{2\%}$ median (IQR) before and after the operation was [96 (95–97) and 99 (95–100), $P < 0.05$], PaO_2 (mmHg) median (IQR) values were [82.0 (77.0–86.5) and 99.6 (85.0–145.2), $P < 0.05$]. The increase in SpO_2 and PaO_2 during the operation may have been related to the use of the nasopharyngeal airway (22) (No. 6/7, Medis, UK); oxygen was delivered by the anesthesia machine (6 L/min), and the APL valve was set to 30 cm HO_2. This special nasopharyngeal airway can be connected with an anesthesia machine to supply oxygen, providing a higher concentration and more effective oxygen therapy than nasal catheters. At the same time, changes in end-expiratory carbon dioxide and respiratory rate can be continuously monitored to detect respiratory depression as early as possible and even provide an early warning before the occurrence of decreased SpO_2 to reduce the risk of clinical hypoxemic events. In the future, relevant randomized controlled studies can be designed to obtain evidence-based medicine evidence. The $PaCO_2$ (mmHg) median (IQR) before and after the operation was [41.5 (40.3–43.7) and 58.3 (50.7–63.0), respectively, ($P < 0.05$)], the pH median (IQR) values were [7.41 (7.39–7.43) and 7.33 (7.28–7.36), $P < 0.05$], and the Lac (mmol/L) median (IQR) values were [1.50 (1.20–1.80) and 1.20 (1.00–1.80), $P > 0.05$]. Respiratory depression that occurred during the operation led to an increase in $PaCO_2$, but all of these values were <70 mmHg, which was within the range of permissible hypercapnia. The absolute level of $PaCO_2$ and the permissible degree of acidosis is debated, which is the concern of alveolar derecruitment and possible worsening of ventilation-perfusion mismatching (23). Permissive hypercapnia has not

TABLE 7 Adverse events related to oxygen delivery system ($n = 30$).

Adverse event	
30 min after procedure	5 (16.7)
Sore throat	5 (16.7)
Epistaxis	0 (0)
Dry mouth	0 (0)
24 h after procedure	2 (6.7)
Throat pain	2 (6.7)
Dry mouth	0 (0)

been widely implemented to near its physiologic limits ($PaCO_2$ up to 80 mmHg, arterial pH down to 7.20) (23). In current practice, mean maximum $PaCO_2$ and pH associated with permissive hypercapnia are around 67 mmHg and 7.2, respectively, (24). It was reported that hypercapnia can be well tolerated as long as tissue perfusion and oxygenation are preserved and there are no contraindications (25). But hypercapnia may cause cardiovascular and cerebrovascular problems and acid-base imbalance. The changes in pH and Lac were clinically within acceptable ranges, and the patients' circulation was stable. There was no special treatment in clinical practice. One patient was treated with propofol because performance of the operation was affected by choking cough; 30 mg of propofol was injected twice intravenously in order to complete the operation. The hemodynamics of all patients were stable at all time points during the operation, and no vasoactive drugs were used, indicating that this MAC can effectively inhibit such stress without affecting circulatory stability. The median tolerance score for nasopharyngeal airway placement was two, the median Ramsay sedation score was three, the median cough score was one, the median operator-physician satisfaction score was nine, the median anesthesiologist satisfaction score was eight, the median patient satisfaction score was 10, the median patient recall score for 24 h was one, and the willingness of patients to accept the procedure again was 93.3%. The results show that the MAC scheme of this study provides a comfortable process of diagnosis and treatment for patients and makes the operator more comfortable completing the operation. However, the satisfaction of anesthesiologists is not as high as that of operators and patients, which may be related to the continual focus of anesthesiologists on the patients' breathing status. Anesthesiologists have to spend more effort completing anesthesia-related tasks. It is worth noting that the MAC scheme in this study is secure under the anesthesia management of anesthesiologist with rich clinical experience. This MAC puts forward high requirements for anesthesiologists and brings a lot of benefits to patients and surgeons. In clinical work, there is no best anesthesia method, only the most appropriate anesthesia method. Other sedation-related adverse effects included an increasing heart rate and blood pressure, none of which exceeded 20% of baseline. Thirty minutes after the operation, five patients (16.7%) had laryngopharyngeal pain, with VAS < 3. The MAC technique of fibreoptic bronchoscopy is complicated, poses a high risk of respiratory depression and exacts a high demand from anesthesiologists. Studies have shown that 50% of bronchoscope-related adverse events are related to sedation or (and) anesthesia implementation, which is the main reason for the low rates of such surgical sedation and anesthesia procedures in China (26–28). In the process of MAC, sedation and inhibition of the airway response are mainly achieved by drugs. At present, there is no single drug that can perfectly achieve this purpose; consequently, the combined application of local anesthesia, sedatives and opioids is clinically selected for MAC. In the UK, benzodiazepines are reported to be the most commonly used drugs (63%), followed by opioids (14%) and benzodiazepines combined with opioids (12%). The latest Australian and New Zealand censuses showed 53% use of midazolam and fentanyl. In China, benzodiazepines and/or opioids for sedation were found to be used in 44% of 58 hospitals (28–30). Remifentanil can effectively inhibit choking cough, is also the mainstream clinical and ultra-short-acting opioid, is effectively and rapidly metabolized, and can better and more efficiently meet the demands of clinical operation. However, the literature has reported that chest wall rigidity and bradycardia often occur (31, 32). This study did not observe associated adverse events, which may have been related to the accurate quantitation of TCI. Minimal anesthetic drugs were used to inhibit stress and to reduce adverse reactions, while 5 min was set to reach the plasma target concentration. Dexmedetomidine (33) is a new sedative and analgesic drug that does not easily cause respiratory depression and has obvious sedative effects. It can cause arousal sedation or cooperative sedation, is similar to normal sleep, and can reduce the dosage of opioid analgesics and adverse reactions. Therefore, in this study, the combination of remifentanil and dexmedetomidine reduced the incidence of respiratory depression and other drug-related adverse reactions.

The shortcomings of this study are as follows: it was a prospective interventional study, not a randomized controlled study, and it did not perform comparisons with other MAC regimens. Unfortunately, our study did not carry out invasive arterial monitoring, and did not continuously monitor the changes of oxygen partial pressure and carbon dioxide. The MAC has advantages, but there is a risk of hypoxemia or hypercapnia. However, we believe that the risk will be reduced significantly and improve patient safety under close anesthesia management.

Conclusion

In summary, our study demonstrates that the MAC of remifentanil with spontaneous breathing provides a satisfactory sedative and analgesic effect for patients with severe tracheal stenosis during fibreoptic bronchoscopy. The EC95 of remifentanil for inhibiting the stress response of the operation was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml) and the EC50 was 2.243 ng/ml (95% CI, 2.061–2.446 ng/ml). The stress of the remaining patients was effectively suppressed, and the satisfaction of both the operator and the patient was high. Comfortable medical treatment of the patients was realized under the MAC. However, there may be a risk of hypoxemia or hypercapnia, anesthesiologists need to closely monitor the changes of patient's respiratory and deal with them in time. The study provided a possible choice for the anesthesia management of such high-risk special patients and explored personalized anesthesia management schemes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Tongji University Affiliated Shanghai Pulmonary Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YiZ was responsible for the actual development of the research, designed the work, obtained and analyzed the data, and wrote and revised the manuscript. WW, YuZ, and XL acquired and analyzed data and revised the manuscript. JL was general designer of the research, has made contributions to the concept and design of the work, confirmed the reply of all reviewers, reviewed and revised the manuscript, and confirmed the final version of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Fund of Shanghai Municipal Health Commission (Project No. 201940366) and the Fund of Science and Technology Commission of Shanghai Municipality (Project No. 19411967500).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Madan K, Mohan A, Agarwal R, Hadda V, Khilnani GC, Guleria R. A survey of flexible bronchoscopy practices in India: the Indian bronchoscopy survey (2017). *Lung India.* (2018) 35:98–107. doi: 10.4103/lungindia.lungindia_417_17

2. Respiratory Society of Chinese Medical Association. Expert consensus on diagnosis and treatment of benign central airway stenosis by bronchoscopic intervention. *Chin J Tuberculosis Respirat.* (2017) 40:408.

3. Respiratory and Tumor Interventional Diagnosis, Treatment Alliance of Beijing Health Promotion Association. Expert consensus on diagnosis and treatment of malignant central airway stenosis by bronchoscopy. *Chin J Pulmon Dis.* (2017) 10:647. doi: 10.1159/000497213

4. McGrath EE, Warriner D, Anderson P. The insertion of self expanding metal stents with flexible bronchoscopy under sedation for malignant tracheobronchial stenosis: a single-center retrospective analysis. *Arch Bronconeumol.* (2012) 48:43–8. doi: 10.1016/j.arbres.2011.09.008

5. Barnett AM, Jones R, Simpson G. A survey of bronchoscopy practice in australia and new zealand. *J Bronchol Int Pulmonol.* (2016) 23:22–8. doi: 10.1097/LBR.0000000000000251

6. Cracco C, Fartoukh M, Prodanovic H. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure. *Int Care Med.* (2013) 39:45–52. doi: 10.1007/s00134-012-2687-9

7. González Aguirre JE, Chavarría Martínez U, Rodríguez Mier D, Acosta Moreno M, Mercado Longoria R. Bronchoscope insertion route and patient comfort during flexible bronchoscopy. *Int J Tuberc Lung Dis.* (2015) 19:356–61. doi: 10.5588/ijtld.14.0632

8. Hautmann H, Hetzel J, Eberhardt R. Cross-sectional survey on bronchoscopy in germany–the current status of clinical practice. *Pneumologie.* (2016) 70:110–6. doi: 10.1055/s-0041-110288

9. José RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. *Eur Respir Rev.* (2013) 22:106–16. doi: 10.1183/09059180.00006412

10. José RJ, Shaefi S, Navani N. Anesthesia for bronchoscopy. *Curr Opin Anaesthesiol.* (2014) 27:453–7. doi: 10.1097/ACO.0000000000000087

11. Pathak V, Welsby I, Mahmood K, Wahidi M, MacIntyre N, Shofer S. Ventilation and anesthetic approaches for rigid bronchoscopy. *Ann Am Thorac Soc.* (2014) 11:628–34. doi: 10.1513/AnnalsATS.201309-302FR

12. Han JU, Cho S, Jeon WJ. The optimal effect-site concentration of remifentanil for lightwand tracheal intubation during propofol induction without muscle relaxation. *J Clin Anesth.* (2011) 23:379–83. doi: 10.1016/j.jclinane.2010.12.012

13. Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures: guidelines from the American college of chest physicians. *Chest.* (2003) 123:1693–717. doi: 10.1378/chest.123.5.1693

14. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S. British thoracic society guidelines on diagnostic flexible bronchoscopy. *Thorax.* (2001) 56:i1–21. doi: 10.1136/thx.56.suppl_1.i1

15. McCambridge AJ, Boesch RP, Mullon JJ. Sedation in bronchoscopy: a review. *Clin Chest Med.* (2018) 39:65–77. doi: 10.1016/j.ccm.2017.09.004

16. Maguire GP, Rubinfeld AR, Trembath PW, Pain MC. Patients prefer sedation for fibreoptic bronchoscopy. *Respirology.* (1998) 3:81–5. doi: 10.1111/j.1440-1843.1998.tb00101.x

17. Putinati S, Ballerin L, Corbetta L, Trevisani L, Potena A. Patient satisfaction with conscious sedation for bronchoscopy. *Chest.* (1999) 115:1437–40. doi: 10.1378/chest.115.5.1437

18. Medford AR, Bennett JA, Free CM, Agrawal S. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): applications in chest disease. *Respirology.* (2010) 15:71–9. doi: 10.1111/j.1440-1843.2009.01652.x

19. Cai Y, Li W, Chen K. Efficacy and safety of spontaneous ventilation technique using dexmedetomidine for rigid bronchoscopic airway foreign body removal in children. *Paediatr Anaesth.* (2013) 23:1048–53. doi: 10.1111/pan.12197

20. Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev.* (1991) 15:47–50. doi: 10.1016/s0149-7634(05)80090-9

21. Jin PH. *Medical statistical methods*. Shanghai: Shanghai Medical University Press (1993).

22. Müller M, Wehrmann T, Eckardt AJ. Prospective evaluation of the routine use of a nasopharyngeal airway (wendl tube) during endoscopic propofol-based sedation. *Digestion.* (2014) 89:247–52. doi: 10.1159/000360000

23. Asensio JA, Trunkey DD. Current therapy of trauma and surgical critical care E-book[M]. *Elsevier Health Sci.* (2008) 148:1017.

24. Roth JV. Is permissive hypercarbia pneumoprotective? *Anesthesiology.* (2015) 122:1179–1179. doi: 10.1097/ALN.0000000000000622

25. Garg SK. Permissive hypercapnia: is there any upper limit? *Indian J Crit Care Med.* (2014) 18:612–4. doi: 10.4103/0972-5229.140154

26. Goudra BG, Singh PM, Borle A, Farid N, Harris K. Anesthesia for advanced bronchoscopic procedures: state-of-the-art review. *Lung.* (2015) 193:453–65. doi: 10.1007/s00408-015-9733-7

27. Liu J, Deng XM. *Chinese anesthesiology guidelines and expert consensus*. Beijing: People's Medical Publishing House (2014).

28. Sarkiss M. Anesthesia for interventional bronchoscopic procedures. In: Díaz-Jimenez JP, Rodriguez AN editors. *Interventions in Pulmonary Medicine*. Cham: Springer International Publishing (2018). p. 67–81.

29. Hong KS, Choi EY, Park DA, Park J. Safety and efficacy of the moderate sedation during flexible bronchoscopic procedure: a systematic review and meta-analysis of randomized controlled trials. *Medicine.* (2015) 94:e1459. doi: 10.1097/MD.0000000000001459

30. Katsurada M, Izumo T. Anesthesia for bronchoscopy. In: Izumo T, Sasada S, Aso T, Nasu K, Arai Y editors. *Respiratory Endoscopy*. Singapore: Springer Singapore (2017). p. 53–8. doi: 10.1007/978-981-287-916-5_9

31. Goudra BG, Singh PM, Manjunath AK. Effectiveness of high dose remifentanil in preventing coughing and laryngospasm in non-paralyzed patients for advanced bronchoscopic procedures. *Ann Thorac Med.* (2014) 9:23–8. doi: 10.4103/1817-1737.124437

32. Lee H, Choe YH, Park S. Analgosedation during flexible fiberoptic bronchoscopy: comparing the clinical effectiveness and safety of remifentanil versus midazolam/propofol. *BMC Pulm Med.* (2019) 19:240. doi: 10.1186/s12890-019-1004-6

33. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Br J Anaesth.* (2015) 115:171–82. doi: 10.1093/bja/aev226

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 23 November 2022
DOI 10.3389/fsurg.2022.1049126

OPEN ACCESS

EDITED BY
Mohsen Ibrahim,
Sapienza University of Rome, Italy

REVIEWED BY
Jeremy Hornibrook,
University of Canterbury, New Zealand
Carmelina Cristina Zirafa,
University Hospital of Pisa, Italy

*CORRESPONDENCE
Sara Ricciardi
ricciardi.sara87@gmail.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 20 September 2022
ACCEPTED 31 October 2022
PUBLISHED 23 November 2022

CITATION
Cardillo G, Ricciardi S, Forcione AR, Carbone L, Carleo F, Di Martino M, Jaus MO, Perdichizzi S, Scarci M, Ricci A, Dello Iacono R, Lucantoni G and Galluccio G (2022) Post-intubation tracheal lacerations: Risk-stratification and treatment protocol according to morphological classification.
Front. Surg. 9:1049126.
doi: 10.3389/fsurg.2022.1049126

Post-intubation tracheal lacerations: Risk-stratification and treatment protocol according to morphological classification

Giuseppe Cardillo[1,2†], Sara Ricciardi[1,3*†], Anna Rita Forcione[1], Luigi Carbone[1], Francesco Carleo[1], Marco Di Martino[1], Massimo O. Jaus[1], Salvatore Perdichizzi[4], Marco Scarci[5], Alberto Ricci[6], Raffaele Dello Iacono[7], Gabriele Lucantoni[8] and Giovanni Galluccio[8]

[1]Unit of Thoracic Surgery, Azienda Ospedaliera San Camillo-Forlanini, Carlo Forlanini Hospital, Rome, Italy, [2]Unicamillus–Saint Camillus University of Health Sciences, Rome, Italy, [3]PhD Program, Alma Mater Studiorum, University of Bologna, Bologna, Italy, [4]Management Department, University of Bologna, Bologna, Italy, [5]Department of Cardiothoracic Surgery, Imperial College Healthcare NHS Trust, London, United Kingdom, [6]Unit of Pulmonology, Sapienza University of Rome, San Andrea Hospital, Rome, Italy, [7]Unit of Pulmonology and Thoracic Endoscopy, Azienda Ospedaliera San Camillo-Forlanini, Carlo Forlanini Hospital, Rome, Italy

Background: Post-intubation tracheal laceration (PITL) is a rare condition (0.005% of intubations). The treatment of choice has traditionally been surgical repair. Following our first report in 2010 of treatment protocol tailored to a risk-stratified morphological classification there is now clear evidence that conservative therapy represents the gold standard in the majority of patients. In this paper we aim to validate our risk-stratified treatment protocol through the largest ever reported series of patients.
Methods: This retrospective analysis is based on a prospectively collected series (2003–2020) of 62 patients with PITL, staged and treated according to our revised morphological classification.
Results: Fifty-five patients with Level I (#8), II (#36) and IIIA (#11) PITL were successfully treated conservatively. Six patients with Level IIIB injury and 1 patient with Level IV underwent a surgical repair of the trachea. No mortality was reported. Bronchoscopy confirmed complete healing in all patients by day 30. Statistical analysis showed age only to be a risk factor for PITL severity.
Conclusions: Our previously proposed risk-stratified morphological classification has been validated as the major tool for defining the type of treatment in PITL.

KEYWORDS

tracheal laceration, post-intubation, conservative treatment, morphological classification, surgery, fibrin glue

Introduction

Despite the large number of tracheal intubations performed every day, tracheal lacerations are extremely rare (0.005% of intubations), and generally involve the pars membranacea of the cervico-thoracic trachea in the midline (1).

The prevalence of PITL in elective intubations ranges from 1 in 20,000 to 75,000 patients (2–10) while in emergency procedures it is estimated to occur in up to 15% of cases (11). The report of PITL is higher (0.5%–1%) for double-lumen intubation (5, 10, 14–16). PITL may represent a life-threatening condition that requires prompt diagnosis, management, and treatment (11–14).

Risk factors for tracheal ruptures include multiple attempts at forced intubation, inexperience of the healthcare provider (e.g., anaesthesiologist) attempting the intubation, endotracheal tube introducers that protrude beyond the tip of the tube and inappropriate use of a stylet (17, 18). Patient-related factors that increase the risk for tracheal injury and rupture include congenital tracheal abnormalities, weakness of the pars membranacea of the trachea, chronic obstructive pulmonary disease and other inflammatory lesions of the tracheobronchial tree (19), advanced age and female gender (20–22). Symptoms of tracheal injury include soft tissue or mediastinal emphysema, pneumothorax, dyspnoea, and haemoptysis.

In the evaluation of treatment strategies for PITL several parameters should be considered such as presence of pneumothorax, stabilization of vital signs, respiratory status (either spontaneous or mechanical), bronchoscopy findings, and CT scan imaging.

Surgery has traditionally represented the cornerstone of PITL treatment, with most clinicians recommending surgical repair in the first instance of PITL in the hope that early surgical management prevents the potential lethal complications of PITL, mainly mediastinitis and tracheal stenosis. Conservative treatment was usually reserved for the minority of patients with small, haemodynamically stable tracheal lesions with a length of tracheal damage <3 cm (1, 2, 5, 7, 13), with the decision making depending mostly on the local expertise and no consensus or standardized treatment.

In 2010 we presented an original morphological classification for patients-risk-stratification in which the key element to guide surgeons in the choice of treatment of PITL (conservative vs. surgery) was the depth instead of the length of the tracheal injury (11).

The present study reports our overall series of 62 patients with PITL and represents an internal validation of our previously reported morphological classification in order to standardise the approach and develop clinical management protocols for tracheal lacerations (11). An external validation of our classification is also reported from the literature.

Materials and methods

This retrospective analysis is based on a prospectively collected series treated at Azienda Ospedaliera San Camillo Forlanini in Rome. All patients had provided informed consent prior to any procedures. Approval by the institution ethics committee was not required as dictated by local laws.

A total of 32 new patients of PITL were identified between December 2008 and January 2020. These cases were combined for internal validation with 30 cases that occurred from January 2003 to November 2008 and were reported in our previously published paper (11).

All patients with suspicious PITL underwent early bronchoscopy (within 48 h) to identify lesion site and extent, including the length and location of the tracheal tear, with careful assessment of the upper and lower lesion limit, lesion morphology, and depth of transmural involvement: depending on the depth of the tracheal wall involvement, PITL lesions were staged using the Cardillo's revised morphologic classification listed in **Table 1** and shown in **Figures 1**, **2**. The revised classification, compared to the previous, added a new stage, PITL Level IV**,** which represents an Extensive Loss of substance/fracture of tracheal rings.

All patients underwent Chest CT to detect pneumothorax, subcutaneous emphysema. pneumomediastinum, endotracheal tube displacement, and mediastinitis.

Patients with Level I, II or IIIA PITL underwent bronchoscopic application of 1 to 2 ml of fibrin sealant (Tisseel®, Baxter, Deerfield, MA, United States) onto the lesion, covering it with a complete layer. The fibrin sealant was applied through a catheter inserted in the operative channel of the bronchoscope with the endoscopic applicator provided by the manufacturer.

TABLE 1 Cardillo's revised morphologic classification of the tracheal injury.

Classification #	Morphologic description
Level I	Mucosal/Submucosal tracheal involvement without subcutaneous -mediastinal emphysema (partial thickness PITL)
Level II	Full-thickness tracheal lesion with subcutaneous or mediastinal emphysema without oesophageal injury or mediastinitis
Level IIIA	Full-thickness laceration of the tracheal wall with oesophageal or mediastinal soft-tissue hernia without oesophageal injury or mediastinitis
Level IIIB	Full-thickness laceration of the tracheal wall with oesophageal injury or mediastinitis
Level IV	Extensive Loss of substance/fracture of tracheal rings

Modified from: Cardillo G, et al. Eur J Cardio-thoracic Surg 2010; 37:581-587.

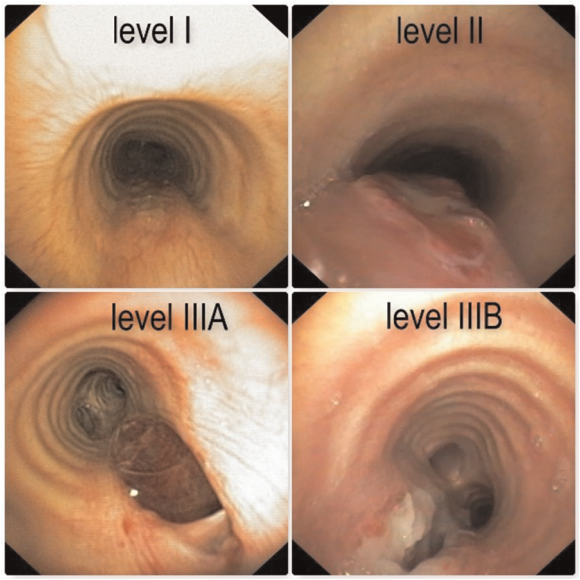

FIGURE 1
Photograph depictions of PITL level I, level II, level IIIA and level IIIB.

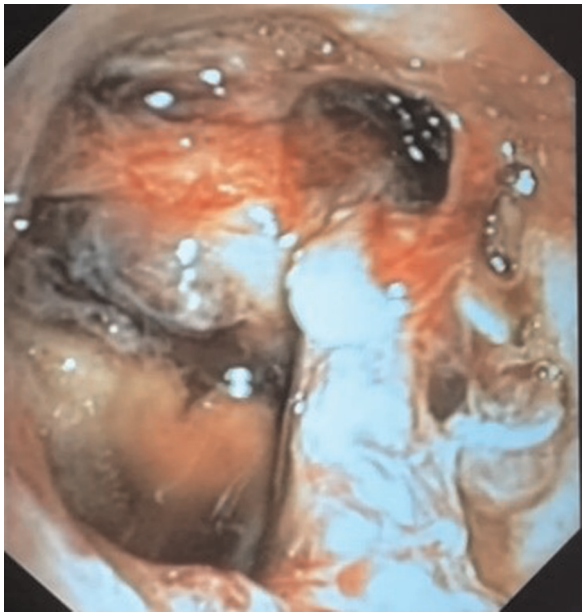

FIGURE 2
Photograph depictions of PITL level IV.

If possible, the procedure was performed with the patient on spontaneous ventilation under local anaesthesia with a flexible bronchoscope. After identification of tracheal laceration, the endoscopic applicator is introduced through the operative channel of flexible bronchoscope, with the distal tip close to the tracheal laceration, then a thin film of fibrin glue was instilled to cover the laceration. If necessary, a second layer of Tiseel was applied.

If the procedure was performed under mechanical ventilation, patients were extubated as soon as clinically indicated. Following endoscopic treatment, antibiotic therapy (as per hospital policy), cough-suppression medication, and total parenteral nutrition were provided to all patients for at least 7 days. Early assessment of bronchoscopic treatment is critical and is mainly based upon clinical signs (improvement of mediastinal/subcutaneous emphysema). On post-operative day 7 a bronchoscopy was routinely performed to confirm PITL healing: If no failure is observed, oral feeding can be initiated and discharge of the patient planned according to clinical course. Follow-up bronchoscopies at outpatient clinics were performed at approximately 28, 90, 180, and 270 days after the operation. Patients with Level IIIB and Level IV PITL underwent immediate surgical repair through thoracotomy, VATS or cervicothomy. Esophageal laceration was commonly repaired by direct running suture. Tracheal injury was repaired with running suture for membranous part, while interrupted single stiches were applied to the cartilaginous part. In case of extensive tissue damage (level IV laceration) tracheal resection of two rings and anastomosis was performed. In this case a muscle flap (sternocleidomastoid muscle) was interposed between trachea and esophagus.

Data analysis

Statistical analysis was performed using the Stata version 16.1 (STATA corporation, Texas, United States). Continuous variables were expressed in mean and standard deviation (SD) or median and range. Two-tailed Pearson's chi-square test was used for intergroup comparison of categorical variables while the Student *t*-test and Wilcoxon test were used for continuous variables. The boxplot analysis was used for studying the different behaviors of variable of interest in the diverse group. A regression analysis was performed to assess the determinant of PITL grade.

Results

In our overall series of 62 patients, 11 (17.8%) developed PITL following emergency intubation and 51 (82,2%) after intubation for elective surgery. The mean age of all cohort was 58.2 years (range 12–82).

The majority of PITL cases occurred in females (83.9%, 52/62) compared to males (16.1%, 10/62). According to the body mass index (BMI) the mean value of the entire cohort was 29.9 (range 21–43): 25 patients (40.3%) were overweight (BMI = 25–29.9) and 11 (14%) were obese (BMI > 30). The

TABLE 2 Patient characteristics, according to PITL level.

	Level I	Level II	Level IIIA	Level IIIB	Level IV
Cases	8 (12.9%)	36 (58%)	11 (17.8%)	6 (9.7%)	1 (1.6%)
F/M	7/1	32/4	9/2	4/2	0/1
Age (range)	56.7 (53–74)	55 (12–82)	65.2 (50–79)	63.5 (29–77)	62
BMI (kg/m^2)	26.2	25	28.1	26.3	36.6
BMI <24.9	3	16	4	3	0
BMI >25, < 29,9	3	18	3	1	0
BMI >30	2	2	4	2	1
Intubation: Elective/Emergency	7/1	29/7	11/0	4/2	0/1
Lumen Type: Single/double	4/4	26/10	6/5	3/3	1/0
Single lumen size	7.5 (#3), 8 (#1)	7.5 (#12), 8 (#13), 8.5 (#1)	7.5 (#4), 8 (#2)	7.5 (#1), 8 (#2)	8 (#1)
Double lumen size	35 (#2), 37 (#2), 39 (#1)	35 (#5), 37 (#4), 39 (#1)	35 (#2), 37 (#3)	35 (#1), 37 (#3)	0
Number of rings (range)	4.1 (3–6)	4.6 (2–10)	4.5 (3–8)	4 (3–6)	3
Length of tear [cm] (range)	2.9 (2–3.5)	2.9 (1–6)	2.8 (1.5–4.5)	2.1 (1.5–3.5)	2
Tracheal location (Upper/mid-lower/ lower)	1/6/1	7/20/9	1/9/1	0/5/1	0/1/0
Conservative approach (sealant)	8	36	11	0	0
Surgery	0	0	0	6	1
Hospital stay	10	10.6	11.5	17.6	40
Day of antibiotics	7.8	8	8.4	11.5	30
Complications	0	1	2	1	1
Atrial fibrillation		1 (PO day 5)	1 (PO day 7)	1 (PO day 5)	0
Renal failure		0	1 (PO day 4)	0	0
Prolonged intubation		0	0	0	1 (from PO day 0 to PO day 3)

PITL cases were staged as Level I ($n = 8$), Level II ($n = 36$), Level IIIA ($n = 11$), Level IIIB ($n = 6$), and Level IV ($n = 1$). (Table 2). Bronchoscopic repair with fibrin sealant (Tisseel, Baxter) was performed in all the 55 patients with Level I, II, and IIIA PITL. The 6 patients with Level III B PITL and the patient with Level IV, underwent primary tracheal repair through right posterolateral thoracotomy (5 patients), VATS assisted right anterior minithoracotomy (1), and midline cervicotomy (1).

No in hospital (30 day) mortality was reported. Morbidity included atrial fibrillation in 3 patients (1 II 2.7%, 1 IIIA 9%, 1 IIIB 16.6%), renal failure in one patient (1 IIIa 9%), and prolonged intubation in 1 (IIIB). Mean hospital stay was 11.8 (range 7–40) days. None of the 55 patients who received conservative treatment developed mediastinitis after application of fibrin sealant; on day 7 bronchoscopy was routinely performed and showed advanced healing process. Tracheal lesions fully healed within 30 days, without complications. Bronchoscopic evaluations performed 9 months follow-up did not show any tracheal abnormalities. Six of 7 patients who underwent surgical repair had an uneventful recovery with a mean hospital stay of 20.9 days (range 12–40). One patient (Level IV) had a prolonged postoperative intubation. Surgically treated patients were all re-evaluated with Chest-CT before discharged (day fifteen for IIIB, fifteen and thirty in IV).

The patients were then divided into two groups according to PITL grade: group 1 was composed by patients in the PITL stage I and II, and group 2 is formed by patients in the PITL stage IIIA, IIIB and IV.

TABLE 3 Descriptive statistics across PITL groups.

PITL Group	Age	Height	BMI
	Group 1		
Mean	55,73	162,61	25,87
SD	16,69	6,17	3,58
Min	12,00	152,00	20,30
Max	82,00	180,00	43,00
	Group 2		
Mean	64,59	162,06	27,46
SD	12,40	5,86	5,33
Min	29,00	149,00	21,00
Max	79,00	173,00	40,50
	Total		
Mean	58,20	162,46	26,32
SD	16,02	6,04	4,16
Min	12,00	149,00	20,30
Max	82,00	180,00	43,00

TABLE 4 Wilcoxon tests and two-sample *t*-tests on PITL groups (group 1 vs. group2).

	Wilcoxon test		*T*-test	
	Z_statistic	*P* (z)	T_statistics	*p*-value
BMI	−0.76	0.45	−1.13	0.27
Age	−1.92	0.05	−2.26	0.03
Height	−0.09	0.93	0.33	0.75

In Table 3, descriptive statistics for the two groups was presented. The mean age was 55.72 for group 1 and 64.59 for group 2. The mean value of height was not different between the two groups (162.61 cm. for group 1 and 162.06 cm. for group 2). Evaluating the gender in group 1 there were more females than men concerning group 2 (89% for group 1% and 76% for group 2). Finally, the BMI was higher for group 2 (27.46) concerning group 1 (25.87).

In Figure 3, showing the boxplot for BMI, a difference between the two groups was noticed: for group 1, the variance and the median were lower than group 2. Conversely in the boxplot for Height, showing in Figure 4, any difference between the two groups was seen. Finally, analyzing the boxplot for age (Figure 5), we found a significant difference across the two groups (in group 1, the median age of patients is lower than in group 2), and this is consistent with our finding in Table 3.

We implemented Wilcoxon tests (Wilcoxon (1945)) and two-sample *t*-tests to determine whether our variables of interest (BMI, age, and Height) were different across the two diverse PITL group. The null hypothesis for the Wilcoxon test (non-parametric test) was that both distributions were the same, vice-versa the two-sample *t*-test reports the *p*-value for a test for equality of means (Table 4).

In most cases, the statistics for the Wilcoxon tests and the *t*-tests were insignificant for both BMI and Height measures, suggesting that these measures were not different across the PITL groups. Notably, there was some evidence that there was a statistically significant difference in age across the diverse PITL group (both for Wilcoxon tests and *t*-test), suggesting that age was an important discriminating factor between the PITL groups.

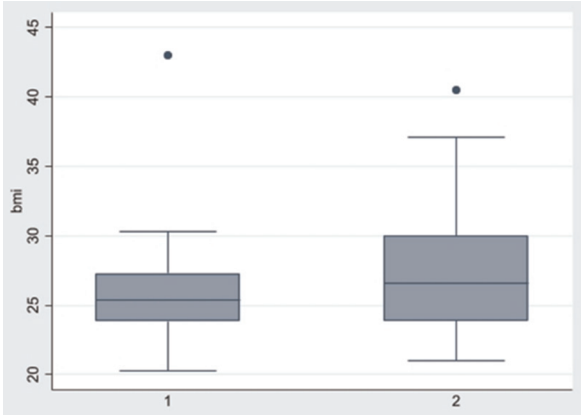

FIGURE 3
Boxplot BMI across groups.

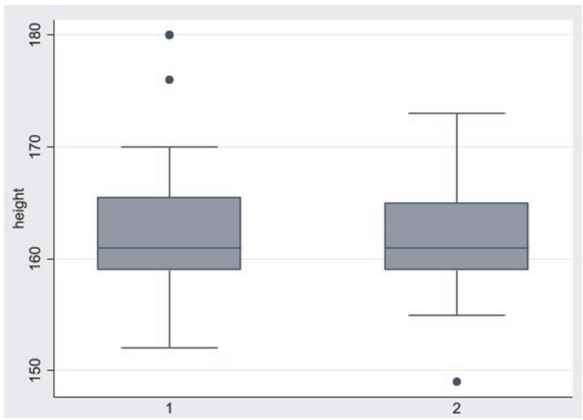

FIGURE 4
Boxplot height across groups.

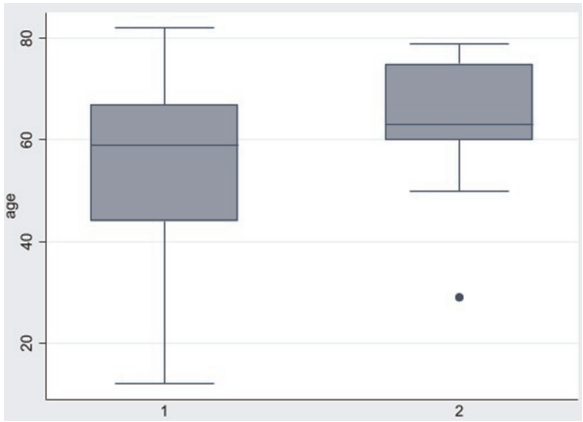

FIGURE 5
Boxplot age across groups.

Finally, we implemented a regression analysis to investigate which is the determinant to be in PITL group 1 or group 2. The empirical results were reported in Table 5. In column (1), we implemented an OLS regression, while in column (2), we implemented a LOGIT regression. The results suggest that an important determinant to be in group 2 was age. Older people were likely to be in group 2 (PITL level IIIA-IIIB-IV).

Discussion

A successful treatment of PITL requires early recognition with proper management according to a risk-stratified

TABLE 5 Regression analysis.

	OLS (1) PITL	Logit (2) PITL
Age	0.0059***	0.0369***
	−1.9677	−1.7006
Height	−0.0144	−0.0759
	(−1.1166)	(−1.0254)
Sex	−0.3511	−1.7158
	(−1.5389)	(−1.4896)
BMI	0.0136	0.0616
	−0.8416	−0.8181
Constant	2.2243	8.9379
	−0.9092	−0.6503
Observations	61	61
R-squared	0.125	

Robust *t*-statistics in parentheses.
*$p < 0.1$.
**$p < 0.05$.
***$p < 0.01$.

protocol which takes into account depth of tracheal involvement as reported in our modified classification (4, 8, 17). Bronchoscopy defines the exact size, site, and extent of the lesion; it can be also used to reposition the tube or to re-intubate the patient if necessary (17–19). The addition, a CT scan can also provide valuable information regarding the PITL and it is mandatory for the proper staging of PITL (**Figure 6**).

Initial anaesthesiologist approach should be focused on maintenance of cardio-pulmonary stability and assessment of current need for airway management in the non-intubated patient. Spontaneous ventilation should be continued in patients who are not in severe respiratory distress due to concerns for worsening of the injury with positive pressure ventilation or by pressure from an endotracheal tube or its cuff. Coughing should be strongly suppressed, and antibiotic treatment for prevention of mediastinitis should be started.

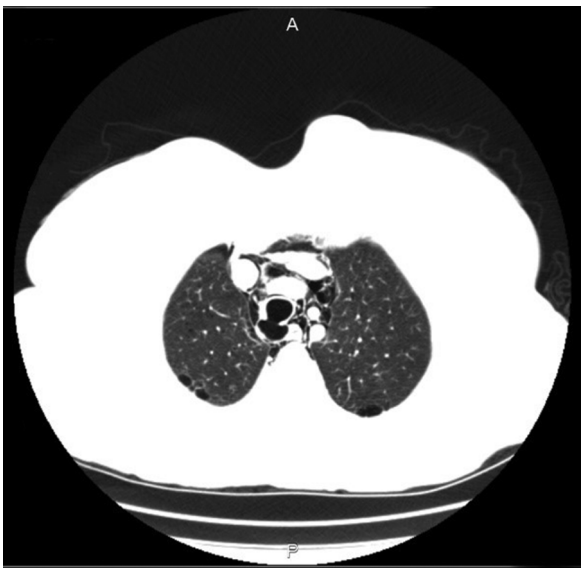

FIGURE 6
Computed tomography image of level IIIA PITL.

In a retrospective study of tracheobronchial injuries by Carretta and co-workers, 39 of 50 patients had iatrogenic tracheal injuries; of these, 30/39 patients (76.9%) were treated by open surgical repair while 9 were treated conservatively (23). A surgical approach by thoracotomy, cervicothomy. or VATS carries a high risk of complications, and should be used in selected higher-grade cases (2–9, 13–15, 19, 20, 24–26). Several conservative treatments have been proposed during the years, especially to manage patients unfit for surgery (27, 28). The use of tracheal stents has been described in patients with small tears (<2 cm in length): this approach requires stent explantation six weeks after placement as the risk for occurrence of granulation tissue rises after 3 months. Therefore, the use of tracheal stents seems not to be reliable: no clear indications, high costs and safety not yet been confirmed (2, 4, 6, 18, 21, 22, 29–33).

Most authors have increasingly been choosing and recommending the use of a conservative treatment approach to patients with superficial PITL, using lesion length as a criterion for treatment strategy (1, 4–9, 11–13, 33). However, the identification of PITL cases that would benefit from conservative treatment was not completely defined (1–20) until the publication, in 2010, of our morphological risk-stratified endoscopic classification. It was based on bronchoscopic and CT findings: the depth and not the length of the PITL (11) represents a powerful clinical tool for a risk-stratified therapeutic treatment as recently highlighted in the series by Herrmann (34) and in the review by Singh Grewal (35).

The role of fibrin glue infiltration (Tisseel®, Baxter Healthcare, Deerfield, MA, United States) to promote tissue sealing and regeneration of tracheal lacerations, has not yet been clearly understood (29). Fibrin glue is composed of one component which contains fibrinogen and coagulation factor XIII, and the other containing thrombin dissolved in calcium chloride. Thrombin cleaves fibrinogen, which results in formation of fibrin polymers. In the presence of calcium, thrombin catalyzes conversion of factor XIII to activated factor XIII (factor XIIIa). Factor XIIIa crosslinks the fibrin polymers into a stable, insoluble fibrin clot (36). We have successfully applied the fibrin sealant to all patients with Level I-IIIA PITL with outstanding results. Probably partial thickness PITL (i.e., Level I, which occurred in 8 cases of our series) may heal spontaneously (14, 2); anyway, since we do not have any control group, we suggest the same approach (3, 19, 20).

Level II PITL is by far the most common tracheal injury (36 out of 62 cases, equal to 58%): careful CT examination is needed

before the Level can be confirmed (absence of oesophageal injury or mediastinitis); a prompt and proper endoscopic management, as reported in the present series, is of paramount importance as we can avoid a surgical treatment to the majority of patients with PITL.

Level IIIA, characterized by oesophageal or mediastinal soft-tissue hernia, carries out an additional risk of oesophageal injury or mediastinitis. Conservative treatment can be safe unless there are signs of instability such as respiratory insufficiency, haemoptysis which require emergency surgery at any time. We suggest that these patients should be promptly referred to Units with high competence in thoracic surgery. Level IIIB and Level IV require emergency surgery with no delay.

The use of our modified staging classification reached up to now a 100% success rate for our approach.

An external validation of our morphological classification has been recently added by 2 authors who strictly independently followed our protocol: Herrmann from Germany reported a 97% success rate in a series of 64 patients (34) and Fiorelli from Italy who reported an 83% success rate in 6 pts (36).

The previously published results supplemented by these additional cases and our findings, validates this morphological classification approach to PITL treatment, which showed an overall impressive success rate of 99% (103/104).

Cornerstone of our treatment protocol is early bronchoscopy with treatment initiation within 48 h and close clinical evaluation in the post-operative period. If conservative management fails, surgery should be promptly provided.

Our PITL morphologic classification approach provides clinicians an evidence-based tool which gives the opportunity for treatment selection, offering conservative treatment in patients with stage Level I to IIIA, and surgery in advanced stages (Level IIIB, IV).

A key objective in the management of PITL is mediastinitis prevention. The involvement of oesophagus or the occurrence of a mediastinitis represent a caveat for PITL conservative therapy. In those without evidence of mediastinitis, endoscopic treatment in accordance with our strategies prevents the development of complications. In some instances, especially in stage Level III B and IV advanced life support with extracorporeal membrane oxygenation (ECMO) may be required as a bridge to recovery and/or definitive surgical intervention (34, 35).

The strength of our series is also the balance among the different stages, with most cases being in stage II (36/62; 58%).

The low number of patients surgically treated in our series (7/62; 11.3%); and the zero mortality represent the confirmation of the successful algorithm employed according to our staging system.

Some may question the timing of our follow-up bronchoscopy. In fact, the incidence of long-term tracheal stenosis, which is caused by a retraction phenomenon during recovery after management of PITL, is very low but necessitates a long-term follow-up (i.e., 9 months in our evaluation). We strongly believe that the inclusion of a 9-month bronchoscopy evaluation adds power to the strength of our findings.

A statistical analysis was performed to investigate if gender, BMI, Height and age had an influence on the severity of the PITL. Gender, which is an overall risk factor of developing a PITL (52 out of 62 patients were female) did not show any impact on the severity of PITL score. Height also did not have any influence on the severity of the PITL. BMI and Age showed a difference related to severity of disease in the Boxplot (**Figure 4** and **Figure 5**). Anyway, Wilcoxon tests, the *t*-tests and regression analysis showed advanced age only to be a risk factor: patients with more severe PITL (stage IIIa, IIIB and IV) were older that patients in stage I and II.

Conclusions

In summary all patients with suspected PITL require immediate (at least < 48 h) bronchoscopy and thoracic surgeon evaluation in order to assess the full extent of the injury, to grade the lesion, and to morphologically individualize the treatment strategy according to our morphological classification of PITL. (11, 34, 36).

Conservative bronchoscopic treatment is effective in patients with partial thickness PITL (level I) or full thickness PITL (level II) with no oesophageal or mediastinal soft-tissue hernia. The presence of oesophageal/mediastinal soft tissue hernia identifies a high-risk category (IIIA) which can be treated conservatively if an adequate respiratory status is achieved and only in highly experienced Centres because of the strong possibility of mediastinitis. Patients with oesophageal injury, mediastinitis (level IIIB) or with extensive loss of substance/fracture of tracheal rings (level IV) requires prompt surgical treatment. The application of fibrin glue on the tracheal laceration helps healing process, even if there are no clear data.

Our 62-patients case-series represent one of the largest experiences in the world literature on the management and outcome of PITL. Additional 42 cases reported from the literature have added external validation to our protocol. We believe that our treatment policy, based upon our proposed morphological classification, represents the gold standard in the treatment of post-intubation tracheal lacerations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conceptualization, GC, SR and GG; Methodology, GC, ARF, LC; Software, SP; Validation, MD, MOJ. Lucantoni and AR.; Formal Analysis, SP; Investigation, GC, SR, RD; Resources, GC, MS Data Curation, ARF, LC, FC; MOJ. Writing – Original Draft Preparation, GC, SR, Forcione. Writing – Review & Editing, SC, SR; Visualization, All authors; Supervision, GG, MS, AR; Project Administration, GC, SR; Funding Acquisition, GC, AR. All authors contributed to the article and approved the submitted version.

Acknowledgements

The authors acknowledge the assistance provided by Susan M. Garabedian-Ruffalo, PharmD of MedWrite, Inc. in the preparation of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Nobre de Jesus G, Freitas F, Fernandes SM, Alvarez A. Post-intubation tracheal laceration. *Intensive Care Med*. (2019) 45(4):521–2. doi: 10.1007/s00134-018-5450-z

2. Welter S, Krbek T, Halder R, Stamatis G. A new technique for complete intraluminal repair of iatrogenic posterior tracheal lacerations. *Interact Cardiovasc Thorac Surg*. (2011) 12(1):6–9. doi: 10.1510/icvts.2010.248641

3. Koletsis E, Prokakis C, Baltayiannis N, Apostolakis E, Chatzimichalis A, Dougenis D. Surgical decision making in tracheobronchial injuries on the basis of clinical evidences and the injury's Anatomical setting: a retrospective analysis. *Injury*. (2012) 43(9):1437–41. doi: 10.1016/j.injury.2010.08.038

4. Fong PA, Seder CW, Chmielewski GW, Welsh RJ. Nonoperative management of postintubation tracheal injuries. *Ann Thorac Surg*. (2010) 89(4):1265–6. doi: 10.1016/j.athoracsur.2009.07.093

5. Welter S, Jacobs J, Krbek T, Halder R, Stamatis G. A new endoscopic technique for intraluminal repair of posterior tracheal laceration. *Ann Thorac Surg*. (2010) 90(2):686–8. doi: 10.1016/j.athoracsur.2009.08.056

6. Leoncinii G, Iurilli L, Boni L, Blanco G, De Bellis P, Catrambone G. Treatment of iatrogenic and traumatic tracheal disruptions. *Monaldi Archives for Chest Disease=Archivio Monaldi per le Malattie del Torace*. (2008) 69(3):119–27. doi: 10.4081/monaldi.2008.389

7. Spaggiari L, Rusca M, Carbognani P, Solli P. Tracheobronchial laceration after double-lumen intubation for thoracic procedures. *Ann Thorac Surg*. (1998) 65(6):1837–9. doi: 10.1016/s0003-4975(98)00312-9

8. Leoncini G. Postintubation tracheal injuries: which criteria to guide non-surgical treatment? *Eur J Cardio-Thorac Surg*. (2011) 39(3):424–5. doi: 10.1016/j.ejcts.2010.05.041

9. Jougon J, Ballester M, Choukroun E, Dubrez J, Reboul G, Velly JF. Conservative treatment for postintubation tracheobronchial rupture. *Ann Thorac Surg*. (2000) 69(1):216–20. doi: 10.1016/s0003-4975(99)01129-7

10. Conti M, Pougeoise M, Wurtz A, Porte H, Fourrier F, Ramon P, et al. Management of postintubation tracheobronchial ruptures. *Chest*. (2006) 130(2):412–8. doi: 10.1378/chest.130.2.412

11. Cardillo G, Carbone L, Carleo F, Batzella S, Jacono RD, Lucantoni G, et al. Tracheal lacerations after endotracheal intubation: a proposed morphological classification to guide non-surgical treatment. *Eur J Cardio-Thorac Surg*. (2010) 37(3):581–7. doi: 10.1016/j.ejcts.2009.07.034

12. Wagner DL, Gammage GW, Wong ML. Tracheal rupture following the insertion of a disposable double-lumen endotracheal tube. *Anesthesiol*. (1985) 63(6):698–700. doi: 10.1097/00000542-198512000-00026

13. Satyadas T, Nasir N, Erel E, Mudan SS. Iatrogenic tracheal rupture: a novel approach to repair and a review of the literature. *J Trauma*. (2003) 54(2):369–71. doi: 10.1097/01.TA.0000031940.95165.FE

14. Panagiotopoulos N, Patrini D, Barnard M, Koletsis E, Dougenis D, Lawrence D. Conservative versus surgical management of iatrogenic tracheal rupture. Medical principles and practice: international journal of the Kuwait university. *Health Sci Centre*. (2017) 26(3):218–20. doi: 10.1159/000455859

15. Leinung S, Möbius C, Hofmann HS, Ott R, Rüffert H, Schuster E, et al. Iatrogenic tracheobronchial ruptures - treatment and outcomes. *Interact Cardiovasc Thorac Surg*. (2006) 5(3):303–6. doi: 10.1510/icvts.2005.117242

16. Maxeiner H. Weichteilverletzungen an kehlkopf bel notfallmaessigner intubation. *Anaesth Intensivmed*. (1988) 29:42–9.

17. Gabor S, Renner H, Pinter H, Sankin O, Maier A, Tomaselli F, et al. Indications for surgery in tracheobronchial ruptures. *Eur J Cardio-Thorac Surg*. (2001) 20(2):399–404. doi: 10.1016/s1010-7940(01)00798-9

18. Miñambres E, Burón J, Ballesteros MA, Llorca J, Muñoz P, González-Castro A. Tracheal rupture after endotracheal intubation: a literature systematic review. *Eur J Cardio-Thorac Surg*. (2009) 35(6):1056–62. doi: 10.1016/j.ejcts.2009.01.053

19. Conti M, Fournier C, Hysi I, Ramon PP, Wurtz A. Conservative management of postintubation tracheal membrane ruptures. *Intensive Care Med*. (2010) 36(9):1622–3. doi: 10.1007/s00134-010-1906-5

20. Lampl L. Tracheobronchial injuries. Conservative treatment. *Interact Cardiovasc Thorac Surg*. (2004) 3(2):401–5. doi: 10.1016/j.icvts.2004.02.016

21. Gómez-Caro Andrés A, Moradiellos Díez FJ, Ausín Herrero P, Díaz-Hellín Gude V, Larrú Cabrero E, de Miguel Porch E, et al. Successful conservative management in iatrogenic tracheobronchial injury. *Ann Thorac Surg*. (2005) 79(6):1872–8. doi: 10.1016/j.athoracsur.2004.10.006

22. Sippel M, Putensen C, Hirner A, Wolff M. Tracheal rupture after endotracheal intubation: experience with management in 13 cases. *Thorac Cardiovasc Surg*. (2006) 54(1):51–6. doi: 10.1055/s-2005-865917

23. Carretta A, Melloni G, Bandiera A, Negri G, Voci C, Zannini P. Conservative and surgical treatment of acute posttraumatic tracheobronchial injuries. *World J Surg*. (2011) 35(11):2568–74. doi: 10.1007/s00268-011-1227-z

24. Hashem B, Smith JK, Davis WB. A 63-year-old woman with subcutaneous emphysema following endotracheal intubation. *Chest*. (2005) 128(1):434–8. doi: 10.1378/chest.128.1.434

25. Jones TS, Sullivan A, Damle S, Weyant MJ, Mitchell JD, Weitzel NS, et al. Assessment and management of post-intubation airway injuries. *Semin Cardiothorac Vasc Anesth*. (2017) 21(1):99–104. doi: 10.1177/1089253216647488

26. Martínez-Hernández NJ, Sánchez-García F, Váquez-Sánchez A, Galbis-Caravajal JM. Video-Assisted thoracic surgical repair of the airway. *Ann Thorac Surg*. (2019) 108(1):e45–6. doi: 10.1016/j.athoracsur.2018.10.070

27. Chen EH, Logman ZM, Glass PS, Bilfinger TV. A case of tracheal injury after emergent endotracheal intubation: a review of the literature and causalities. *Anesth Analg*. (2001) 93:5. doi: 10.1097/00000539-200111000-00047

28. Medina CR, Camargo J, Felicetti JC, Machuca TN, Gomes B, Melo IA. Post-intubation tracheal injury: report of three cases and literature review. *Jornal Bras Pneumol*. (2009) 35(8):809–13. doi: 10.1590/s1806-37132009000800014

29. Portes KP, Duprat A, Lancellotti CL, Silva L, Souza FC. Influence of sealant fibrin on the wound healing of the pigs vocal folds. *Braz J Otorhinolaryngol*. (2012) 78(1):51–6. doi: 10.1590/s1808-86942012000100008

30. Hussein E, Pathak V, Shepherd RW, Shojaee S. Bronchoscopic management of iatrogenic tracheal laceration using polyurethane-covered nitinol tracheal stents. *J Trauma Acute Care Surg*. (2016) 81(5):979–83. doi: 10.1097/TA.0000000000001233

31. Lee BE, Korst RJ. Successful treatment of an iatrogenic tracheal laceration with a temporary polyurethane-coated nitinol stent. *Ann Thorac Surg*. (2016) 102(1):e11–2. doi: 10.1016/j.athoracsur.2015.12.030

32. Marchese R, Mercadante S, Paglino G, Agozzino C, Villari P, Di Giacomo G. Tracheal stent to repair tracheal laceration after a double-lumen intubation. *Ann Thorac Surg*. (2012) 94(3):1001–3. doi: 10.1016/j.athoracsur.2011.12.080

33. Schneider T, Storz K, Dienemann H, Hoffmann H. Management of iatrogenic tracheobronchial injuries: a retrospective analysis of 29 cases. *Ann Thorac Surg*. (2007) 83(6):1960–4. doi: 10.1016/j.athoracsur.2007.01.042

34. Herrmann D, Volmerig J, Al-Turki A, Braun M, Herrmann A, Ewig S, et al. Does less surgical trauma result in better outcome in management of iatrogenic tracheobronchial laceration? *J Thorac Dis*. (2019) 11(11):4772–81. doi: 10.21037/jtd.2019.10.22

35. Grewal HS, Dangayach NS, Ahmad U, Ghosh S, Gildea T, Mehta AC. Treatment of tracheobronchial injuries: a contemporary review. *Chest*. (2019) 155(3):595–604. doi: 10.1016/j.chest.2018.07.018

36. Fiorelli A, Cascone R, Di Natale D, Pierdiluca M, Mastromarino R, Natale G, et al. Endoscopic treatment with fibrin glue of post-intubation tracheal laceration. *J Vis Surg*. (2017) 3:102. doi: 10.21037/jovs.2017.06.12

frontiers | Frontiers in Surgery

TYPE Mini Review
PUBLISHED 20 January 2023
DOI 10.3389/fsurg.2022.1126486

OPEN ACCESS

EDITED BY
Federico Raveglia,
ASST-Monza, Italy

REVIEWED BY
Riccardo Orlandi,
University of Milan, Italy
Francesca Colonese,
San Gerardo Hospital, Italy

*CORRESPONDENCE
Savvas Lampridis
savvas.lampridis@nhs.net

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 17 December 2022
ACCEPTED 31 December 2022
PUBLISHED 20 January 2023

CITATION
Lampridis S and Scarci M (2023) Perioperative systemic therapies for non-small-cell lung cancer: Recent advances and future perspectives.
Front. Surg. 9:1126486.
doi: 10.3389/fsurg.2022.1126486

Perioperative systemic therapies for non-small-cell lung cancer: Recent advances and future perspectives

Savvas Lampridis* and Marco Scarci

Department of Cardiothoracic Surgery, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

The mainstay of treatment for early-stage non-small-cell lung cancer (NSCLC) is surgical resection. Traditionally, chemotherapy has been used perioperatively in locally extensive disease to improve the oncologic outcomes of surgery, with a 5-year absolute survival benefit of approximately 5%. In recent years, immunotherapy and molecular targeted therapy have shown excellent results in the treatment of locoregionally advanced and metastatic NSCLC, replacing chemotherapy as first-line treatment in certain cases. Consequently, researchers have been increasingly investigating the use of immunotherapy or targeted therapy in combination with surgery for the treatment of early-stage disease. This growing research interest has resulted in several published and ongoing studies of various size and design. In this mini review, we provide a succinct and up-to-date overview of recently published, phase 3 randomized clinical trials on adjuvant and neoadjuvant immunotherapy or targeted therapy for NSCLC. We subsequently discuss some important unresolved clinical issues, including the optimal duration of treatment, scheduling with respect to surgery, and potential combinations of different systemic therapies. Finally, we reference large, randomized, phase 3 studies that are currently in progress and may give answers to those and other clinical questions.

KEYWORDS

adjuvant, immunotherapy, lung cancer, molecular targeted therapy, neoadjuvant, perioperative, surgery

Introduction

The standard of care for early-stage non-small-cell lung cancer (NSCLC) is surgical resection (1). Patients with stage I NSCLC who decline surgery have an estimated 5-year overall survival of as low as 11%, compared to 60%–80% in those with surgically resected disease of the same stage (2). However, patients who undergo surgery remain at substantial risk for recurrence even after complete resection of their disease. Indeed, it is estimated that 30%–75% of the patients with NSCLC who undergo surgery with curative intent develop recurrence, and they eventually die of their disease after 8–14 months (3). It therefore becomes evident that systemic anticancer therapies can be a valuable adjunct in the effort to improve the oncologic outcomes conferred by surgery.

Traditionally, chemotherapy has been the most important perioperative systemic treatment for NSCLC. The development of platinum-based combinations and the completion of randomized clinical trials assessing the activity of such regimens led to the use of chemotherapy in both the adjuvant and neoadjuvant setting. The Lung Adjuvant Cisplatin Evaluation, a pooled analysis of patient data from the five largest trials of cisplatin-based chemotherapy for completely resected stage I to III NSCLC, indicated that adjuvant chemotherapy can yield a 5-year absolute survival benefit of 5.4% (4). Similarly, a meta-analysis of individual participant data from 15 randomized controlled trials assessing neoadjuvant chemotherapy for stage IB to IIIA NSCLC showed an absolute survival improvement of 5% at 5 years, from 40% to 45% (5). Although these benefits of perioperative

chemotherapy were statistically significant, there was an urgent need for enhanced treatment strategies to further improve the survival of those patients.

During the past decade, the discovery of predictive biomarkers has created new opportunities in the treatment of NSCLC. After the successful application of immune checkpoint inhibitors and molecular targeted therapies in the treatment of locoregionally advanced and metastatic NSCLC, these treatment modalities were inevitably trialed in early-stage disease in combination with surgery. As a result, there has been a recent surge of studies of various size and design in this field. The aim of this mini review is to provide a concise and up-to-date overview of recently published, phase 3 randomized clinical trials on adjuvant and neoadjuvant immunotherapy or targeted therapy for NSCLC, discuss important aspects of their application in routine practice, and identify areas for future research.

Adjuvant immunotherapy for NSCLC

Following its successful clinical application in locoregionally advanced and metastatic NSCLC, immunotherapy has attracted growing interest for the treatment of early-stage disease. The IMpower010 trial was the first phase 3 randomized study to show significant improvement in disease-free survival with immunotherapy following adjuvant chemotherapy in patients with resected, early-stage NSCLC (6). Among 882 patients with stage II to IIIA NSCLC [as per the 7th edition of the American Joint Committee on Cancer (AJCC) staging system] who had undergone complete resection and received up to 4 cycles of adjuvant cisplatin-based chemotherapy, those randomly assigned to 16 cycles of atezolizumab experienced improvements in disease-free survival relative to best supportive care (at a median follow-up of 33 months, median disease-free survival was 42 vs. 35 months; hazard ratio, 0.79; 95% confidence interval [CI], 0.64–0.96; $P = 0.020$). A greater magnitude of benefit was observed among the 476 patients with tumors expressing programmed death-ligand 1 (PD-L1) in at least 1% of neoplastic cells (not evaluable vs. 35 months; hazard ratio, 0.66; 95% CI, 0.50–0.88; $P = 0.004$). Three-year disease-free survival rates in the overall group were 56% for atezolizumab and 49% for best supportive care, while among those with PD-L1-positive disease, the respective rates were 60% vs. 48%. Overall survival data were immature, but hazard ratio for overall survival at this early timepoint was 0.99 (95% CI, 0.73–1.33) among all patients with stage II to IIIA disease and 0.77 (95% CI, 0.51–1.17) in the subgroup of patients with PD-L1-positive tumors. The toxicity profile was consistent with that previously reported with atezolizumab monotherapy, with grade 3 or 4 adverse events occurring in 11% and grade 5 in 1% of patients, respectively. It is worth mentioning that subset analyses did not show clear benefits for atezolizumab in patients who were never-smokers, those with epidermal growth factor (EGFR)- or anaplastic lymphoma kinase (ALK)-mutated tumors, and in those with tumor expression of PD-L1 in less than 50% of neoplastic cells, although these were not powered analyses. Based on the findings of this trial, adjuvant atezolizumab is recommended in patients with completely resected, PD-L1-positive, stage II to IIIA NSCLC who received previous adjuvant platinum-doublet chemotherapy (7).

At the second prespecified interim analysis of the PEARLS/KEYNOTE-091 trial, an international phase 3 randomized study, adjuvant pembrolizumab significantly extended disease-free survival after resection of early-stage NSCLC and adjuvant chemotherapy, when indicated according to national and local guidelines (8). Among 1,177 patients with completely resected, PD-L1-positive, stage IB to IIIA NSCLC (as per the 7th edition of the AJCC staging system), adjuvant pembrolizumab improved disease-free survival compared to placebo (54 vs. 42 months; hazard ratio, 0.76; 95% CI, 0.63–0.91; $P = 0.001$), with a nonsignificant trend towards improvement in those with tumor expression of PD-L1 of 50% or more (median disease-free survival not reached in either arm; hazard ratio, 0.82; 95% CI, 0.57–1.18; $P = 0.140$). The significance boundary for overall survival in the intention-to-treat population was not crossed (18-month rate of 91.7% vs. 91.3%, respectively), but the results were immature. Grade 3 or greater adverse events occurred in 34% vs. 26% of the patients receiving pembrolizumab and placebo, respectively, without new safety signals detected. Regulatory approval prior to routine use of pembrolizumab in the adjuvant setting is awaited.

Neoadjuvant immunotherapy for NSCLC

Similar to the adjuvant setting, immunotherapy has also been recently investigated as neoadjuvant treatment for resectable NSCLC. At the first prespecified interim analysis of the CheckMate 816 trial, an international phase 3 randomized study, among 358 patients with stage IB to IIIA NSCLC (as per the 7th edition of the AJCC staging system) and no known sensitizing EGFR mutations or ALK translocations, the addition of nivolumab to 3 cycles of neoadjuvant platinum-doublet chemotherapy significantly improved event-free survival, with a 37% reduction in the risk of disease progression, recurrence, or death, as compared to chemotherapy alone (hazard ratio, 0.63; 95% CI, 0.45–0.87; $P = 0.005$) (9). Furthermore, nivolumab improved pathological complete response rates (24.0% vs. 2.2%; odds ratio, 13.9; 99% CI, 3.5–55.8; $P < 0.001$), without decreasing the percentage of patients who underwent surgery (83.2% vs. 75.4%) or increasing the rate of grade 3 or 4 adverse events (33.5% vs. 36.9%). Although the hazard ratio for death did not cross the boundary for statistical significance, 74% of patients were still alive at the time of this analysis. Finally, treatment-related safety was consistent with that in previous reports. Based on the results of the CheckMate 816 trial, neoadjuvant nivolumab should be considered in combination with neoadjuvant platinum-doublet chemotherapy in patients with resectable NSCLC that measures 4 cm or more in greatest dimension or has regional lymph-node metastasis (7).

Adjuvant molecular targeted therapy for NSCLC

The introduction of tyrosine kinase inhibitors in the treatment of EGFR-mutated NSCLC significantly improved the survival time of patients with locoregionally advanced and metastatic disease, and it

has shown great potential in those who undergo surgical resection of early-stage NSCLC. The ADAURA trial was an international, randomized, phase 3 study assessing the role of osimertinib, a third-generation EGFR tyrosine kinase inhibitor, in completely resected, EGFR-mutated, stage IB to IIIA NSCLC (as per the 7th edition of the AJCC staging system) of non-squamous-cell histology, with or without administration of standard adjuvant chemotherapy (10). Among 682 patients, those assigned to receive osimertinib for 3 years demonstrated significantly improved 2-year disease-free survival rates compared to placebo (89% vs. 52%; hazard ratio for disease recurrence or death, 0.20; 99% CI, 0.14–0.30; $P < 0.001$). At 2 years, 98% of the patients in the osimertinib group and 85% of those in the placebo group were alive without central nervous system (CNS)-related disease (hazard ratio, 0.18; 95% CI, 0.10–0.33). The use of adjuvant osimertinib led also to a significantly reduced risk of disease recurrence or death by 83% in the subgroup of patients with stage II to IIIA NSCLC (hazard ratio, 0.17; 99.1% CI, 0.11–0.26; $P < 0.001$). The effect on overall survival remains unknown, since such data were still immature at the time of the analysis. Results of the ADAURA trial led to recommendation of adjuvant osimertinib in patients with completely resected, EGFR-mutated, stage IB to IIIA NSCLC who received previous adjuvant platinum-based chemotherapy (7).

Improvements in disease-free survival were also recently observed in 2 randomized, phase 3 studies of adjuvant gefinitib, a first-generation EGFR tyrosine kinase inhibitor, although of lesser magnitude (11, 12). In the Chinese ADJUVANT/CTONG1104 trial, adjuvant treatment with gefitinib significantly improved disease-free survival compared to chemotherapy with cisplatin and vinorelbine in patients with completely resected, EGFR-mutated, stage II to IIIA NSCLC (28.7 vs. 18.0 months; hazard ratio, 0.60; 95% CI, 0.42–0.87; $P = 0.005$) (11). Nevertheless, analysis of mature data failed to demonstrate a similar effect on overall survival. At a median follow-up of 80 months, 5-year overall survival rates with gefitinib and chemotherapy were 53.2% and 51.2%, respectively ($P = 0.784$). In the IMPACT/WJOG6410l trial, patients with completely resected, EGFR-mutated, stage II to III NSCLC who received adjuvant gefitinib experienced longer disease-free survival compared to those who received chemotherapy with cisplatin and vinorelbine (35.9 vs. 25.1 months) (12); however, the difference was not statistically significant. Interestingly, an exploratory subset analysis revealed that patients 70 years old in the gefitinib group survived longer than their counterparts in the chemotherapy group (hazard ratio, 0.31; 95% CI, 0.10–0.98; $P = 0.046$).

Icotinib, another first-generation EGFR tyrosine kinase inhibitor, was also recently assessed against platinum-based doublet chemotherapy as adjuvant treatment for completely resected, EGFR-mutated, stage II to IIIA NSCLC (as per the 7th edition of the AJCC staging system) in a Chinese, multicenter, phase 3 randomized trial (EVIDENCE) (13). At a median follow-up of 24.9 months, the median disease-free survival was significantly longer in the icotinib group compared to the chemotherapy group (47.0 vs. 22.1 months; hazard ratio, 0.36; 95% CI, 0.24–0.55; $P < 0.001$). The hazard ratio for overall survival was 0.91 (95% CI, 0.42–1.94) in the full analysis set, but overall survival data were immature. Treatment-related, serious adverse events occurred in only 1% of the patients in the icotinib group vs. 14% of those in the chemotherapy group.

Discussion

The landscape of NSCLC treatment has changed dramatically since the advent of immunotherapy and molecular targeted therapy. In recent years, immunotherapy has shown better efficacy and lower toxicity than chemotherapy in the treatment of PD-L1-positive, metastatic NSCLC (14). Consequently, various antibodies inhibiting programmed death 1 and PD-L1 have been investigated in combination with surgery for early-stage disease. Two recent randomized, phase 3 studies confirmed longer disease-free survival with chemotherapy and immunotherapy compared to chemotherapy alone for resected, stage II to IIIA NSCLC (6, 15). In both trials, immunotherapy was administered after completion of adjuvant chemotherapy. A logical question that follows concerns the significance of the timing of immunotherapy relative to chemotherapy, as concurrent administration could be hypothesized to result in improved efficacy, but potentially increased toxicity. The answer to this question may be given by the ALCHEMIST Chemo-IO trial, an ongoing, phase 3 randomized study investigating the integration of immunotherapy to adjuvant chemotherapy for resected, stage II-IIIB NSCLC (as per the 8th edition of the AJCC staging system) (16). Recruited patients are being randomized to adjuvant platinum-based chemotherapy alone, vs. sequential chemotherapy followed by pembrolizumab, vs. concurrent chemotherapy and pembrolizumab.

Whether immunotherapy is more beneficial when administered prior to or following surgery is undetermined, and trials directly comparing the two approaches are challenging to design and conduct. Historical studies of neoadjuvant chemotherapy were underpowered, as these closed when more rapidly accruing trials of adjuvant chemotherapy demonstrated survival advantage. Nevertheless, immunotherapy may be more suitable as neoadjuvant treatment than chemotherapy, since the preoperative tumor bulk with higher levels of endogenous tumor antigen may result in presentation to, and thus priming of, more tumor-specific T lymphocytes circulating systemically (17). This systemic response continues to exert antitumor effects on the remaining neoplastic cells after surgical resection of the primary tumor, thereby potentially preventing disease recurrence (18). Another advantage of preoperative immunotherapy, as opposed to adjuvant treatment, is the assessment of tumor response in the resected specimen. Pathological response following neoadjuvant therapy in resectable NSCLC can predict survival, thus representing a prognostic factor that can inform further management strategies (19). Another significant benefit of integrating neoadjuvant immunotherapy to chemotherapy may be the radiologic downstaging of the disease, without resulting in a higher incidence or greater severity of adverse events than chemotherapy alone, and without increasing surgery-related adverse events or impeding the feasibility of surgery (9, 20). Furthermore, the addition of immunotherapy to neoadjuvant chemotherapy has been associated with more favorable surgical outcomes as compared with chemotherapy alone, with numerically shorter operating times, fewer surgery cancellations

TABLE 1 Current phase 3 randomized clinical trials of immunotherapy as adjuvant and neoadjuvant treatment for non-small-cell lung cancer.

Trial identifier (name)	NSCLC stage	Study arms	Primary endpoint
NCT02273375	IB–IIIA	Adjuvant durvalumab vs. adjuvant placebo; patients may have received prior adjuvant platinum-based chemotherapy	DFS
NCT02595944 (ALVIN)	IB–IIIA	Adjuvant nivolumab (13 cycles) following adjuvant chemotherapy vs. observation following adjuvant chemotherapy	DFS, OS
NCT03425643 (KEYNOTE-671)	II–IIIB	Neoadjuvant pembrolizumab (4 cycles) and cisplatin plus gemcitabine or pemetrexed, followed by adjuvant pembrolizumab (13 cycles) vs. neoadjuvant placebo, and cisplatin plus gemcitabine or pemetrexed, followed by adjuvant placebo	EFS, OS
NCT03456063 (IMpower030)	II–IIIB	Neoadjuvant atezolizumab (4 cycles) and platinum-based chemotherapy, followed by adjuvant atezolizumab (4 cycles) vs. neoadjuvant placebo and platinum-based chemotherapy, followed by best supportive care after surgery	EFS
NCT03800134 (AEGEAN)	II–IIIB	Neoadjuvant durvalumab and platinum-based chemotherapy vs. neoadjuvant placebo and platinum-based chemotherapy	pCR, EFS
NCT04025879	II–IIIB	Neoadjuvant nivolumab and platinum-doublet chemotherapy, followed by adjuvant nivolumab vs. neoadjuvant placebo and platinum-doublet chemotherapy, followed by adjuvant placebo	EFS
NCT04267848 (ALCHEMIST Chemo-IO)	II–IIIB	Adjuvant pembrolizumab and platinum-doublet chemotherapy (4 cycles), followed by pembrolizumab (12 or 13 cycles) vs. adjuvant platinum-doublet chemotherapy (4 cycles), followed by pembrolizumab (16 or 17 cycles) vs. adjuvant platinum-doublet chemotherapy (4 cycles), followed by observation	DFS
NCT04379635	II–IIIA	Neoadjuvant tislelizumab and cisplatin or carboplatin plus paclitaxel or pemetrexed, followed by adjuvant tislelizumab vs. neoadjuvant placebo and cisplatin or carboplatin plus paclitaxel or pemetrexed, followed by adjuvant placebo	MPR, EFS
NCT04385368 (MERMAID-1)	II–III	Adjuvant durvalumab and platinum-based chemotherapy vs. adjuvant placebo and platinum-based chemotherapy	DFS
NCT04564157 (NADIM-ADJUVANT)	IB–IIIA	Adjuvant nivolumab and carboplatin plus paclitaxel (4 cycles), followed by nivolumab (6 cycles) vs. carboplatin plus paclitaxel (4 cycles), followed by observation	DFS
NCT04642469 (MERMAID-2)	II–III	Adjuvant durvalumab vs. adjuvant placebo	DFS

DFS, disease-free survival; EFS, event-free survival; MPR, major pathological response; NSCLC, non-small-cell lung cancer; OS, overall survival; pCR, pathological complete response.

(including for disease progression), greater use of minimally invasive techniques, and fewer cases of pneumonectomy (9).

Despite the benefits of immunotherapy in the neoadjuvant setting, certain drawbacks and risks have also been noted. First, the risk of early disease progression during neoadjuvant treatment, rendering the tumor nonresectable, remains a concern. In a pilot study evaluating neoadjuvant nivolumab in resectable NSCLC, radiological reassessment with computed tomography prior to surgery did not correlate with pathological response (21). The optimal method of monitoring disease progression during or response to neoadjuvant treatment is uncertain. Second, although the toxicity of neoadjuvant immunotherapy is acceptable in results reported to date, the fact that the host immune system may be more functional in early (as compared to late) cancer stages carries the theoretical risk of marked immune-related adverse events developing concurrently with enhanced immune-mediated tumor regression (22). Finally, surgical complications as a result of neoadjuvant immunotherapy may still be a concern. Even though surgical morbidity and rates of conversion from a minimally invasive approach to open thoracotomy due to neoadjuvant immunotherapy have been reported as acceptable in multiple studies (23–25), there have also been reports of tumor-associated inflammation and fibrosis that can potentially compromise surgical plans (26).

Many other questions regarding the perioperative administration of immunotherapy for NSCLC remain unanswered, including the optimal duration of treatment, scheduling with respect to surgery, and the requirement for consolidation therapies. Ongoing and future trials will hopefully provide useful insights into these issues. **Table 1** summarizes the main features of current phase 3 randomized trials investigating immunotherapy as adjuvant and neoadjuvant treatment for NSCLC.

In a fashion similar to immunotherapy, molecular targeted therapy has recently occupied a prominent place in the treatment of resected NSCLC. Despite the promising results of adjuvant tyrosine kinase inhibitors, however, certain clinical questions remain unanswered. For instance, multidisciplinary tumor boards may be called to decide between adjuvant chemotherapy followed by osimertinib, as investigated in the ADAURA trial (10), or adjuvant tyrosine kinase inhibitor alone, as studied in the ADJUVANT/CTONG1104 trial (11) and the EVIDENCE trial (13). It should be argued that adjuvant cisplatin-based chemotherapy confers definite overall survival benefit and remains recommended for resected, stage II to IIIA NSCLC in the recently updated clinical practice guidelines by the American Society of Clinical Oncology (27). On the other hand, improvements in overall survival with tyrosine kinase inhibitors in the adjuvant setting has not been demonstrated thus far. Studies investigating adjuvant

TABLE 2 Current phase 3 randomized clinical trials of tyrosine kinase inhibitors as adjuvant and neoadjuvant treatment for non-small-cell lung cancer.

Trial identifier (name)	Molecular target	NSCLC stage	Treatment strategy	Study arms	Duration of TKI	Primary endpoint
NCT01996098 (ICTAN)	EGFR	II–IIIA	Adjuvant	Icotinib for 6 months following chemotherapy vs. icotinib for 12 months following chemotherapy vs. chemotherapy	6 or 12 months	DFS
NCT02125240 (ICWIP)	EGFR	II–IIIA	Adjuvant	Icotinib vs. placebo	NA	DFS
NCT02193282 (ALCHEMIST-EGFR)	EGFR	IB–IIIA	Adjuvant	Erlotinib vs. placebo vs. observation	2 years	OS
NCT02201992 (ALCHEMIST-ALK)	ALK	IB–IIIA	Adjuvant	Crizotinib vs. observation	2 years	OS
NCT03381066	EGFR	II–IIIB	Adjuvant	Gefitinib and cisplatin plus pemetrexed (4 cycles) vs. cisplatin plus vinorelbine (4 cycles)	1 year	DFS
NCT03456076 (ALINA)	ALK	IB–IIIA	Adjuvant	Alectinib vs. platinum-based chemotherapy	2 years	DFS
NCT04351555 (NeoADAURA)	EGFR	II–IIIB	Neoadjuvant	Osimertinib vs. osimertinib and cisplatin or carboplatin plus pemetrexed (3 cycles) vs. placebo and cisplatin or carboplatin plus pemetrexed (3 cycles)	9 weeks	MPR
NCT04687241	EGFR	II–IIIB	Adjuvant	Almonertinib vs. placebo	NA	DFS
NCT04762459 (APEX)	EGFR	II–IIIA	Adjuvant	Almonertinib vs. almonertinib and cisplatin plus pemetrexed vs. cisplatin plus pemetrexed	3 years	DFS
NCT04853342 (FORWARD)	EGFR	II–IIIA	Adjuvant	Furmonertinib vs. placebo	NA	DFS

ALK, anaplastic lymphoma kinase; DFS, disease-free survival; EGFR, epidermal growth factor receptor; MPR, major pathological response; NA, not available; NSCLC, non-small-cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

targeted therapy have not been powered to detect statistically significant differences in overall survival, or data on overall survival from such studies are still immature. Because its impact on overall survival is thus far unknown, patients may reasonably choose not to receive adjuvant targeted therapy.

Another question that arises from the adjuvant administration of tyrosine kinase inhibitors for NSCLC is the duration of treatment. The treatment time with osimertinib was 3 years in the ADAURA trial (10), while treatment duration was 2 years in the ADJUVANT/CTONG1104 trial (11) and in the EVAN trial, a phase 2 randomized study evaluating erlotinib vs. vinorelbine and cisplatin as adjuvant therapy in Chinese patients with EGFR-mutated, stage IIIA NSCLC (as per the 7th edition of the AJCC staging system) (28). Notably, a *post hoc* analysis of the ADJUVANT/CTONG1104 trial reported a unique spatiotemporal treatment failure pattern with adjuvant gefitinib, with cancer recurrence increasing at a steady rate 12 months following surgery and a first peak of extracranial metastases occurring 24–36 months postoperatively (29). The optimal duration of adjuvant targeted therapy remains unclear and needs additional investigation. Until then, a reasonable approach would be the administration of targeted therapy for durations used in the respective trials, with consideration also of potential toxicities of the specific tyrosine kinase inhibitor.

Neoadjuvant targeted therapies have not attracted nearly as much attention to date as have adjuvant treatments (30). The EMERGING/CTONG1103 trial has been the largest published study investigating neoadjuvant treatment with a tyrosine kinase inhibitor (31). This was a Chinese, multicenter, phase 2, randomized controlled trial comparing erlotinib with chemotherapy (cisplatin plus gemcitabine) in patients with resectable, EGFR-mutated, stage IIIA (N2) NSCLC. Improvements in the primary end point of objective response rate observed with erlotinib were not significant (54.1% vs. 34.3%; odds ratio, 2.26; 95% CI, 0.87–5.84; $P = 0.092$); nevertheless, median progression-free survival was significantly longer with erlotinib than chemotherapy (21.5 vs. 11.4 months; hazard ratio, 0.39; 95% CI, 0.23–0.67; $P < 0.001$). This advantage in progression-free survival, however, did not translate to an overall survival benefit (32). At the final analysis, after a median follow-up of 62.5 months, the median overall survival was 42.2 months in the erlotinib group and 36.9 months in the chemotherapy group (hazard ratio, 0.83; 95% CI, 0.47–1.47, $P = 0.513$). The 3- and 5-year overall survival rates were 58.6% and 40.8% with erlotinib, as compared to 55.9% and 27.6% with chemotherapy, respectively ($P = 0.819$ and $P = 0.252$ for 3- and 5-year overall survival, respectively). More randomized trials are underway, but only the NeoADAURA is a phase 3 study. This trial will evaluate neoadjuvant osimertinib with or without chemotherapy vs. chemotherapy alone in patients with resectable, EGFR-mutated, stage II-IIIB NSCLC, with major pathological response as the primary end point (33).

The relative effectiveness of different tyrosine kinase inhibitors also remains unexplored. For example, osimertinib demonstrates excellent penetrance to the CNS and has been associated with an

82% reduction in the risk of CNS disease recurrence or death in the ADAURA trial (10). In EGFR-mutated, advanced NSCLC, osimertinib showed longer progression-free survival than gefitinib or erlotinib (18.9 vs. 10.2 months; hazard ratio, 0.46; 95% CI, 0.37–0.57; $P < 0.001$) (34). Icotinib has also a lower CNS penetrance rate than osimertinib, thereby raising concerns of potential CNS recurrences (35). Future studies that will directly compare different tyrosine kinase inhibitors in the adjuvant and neoadjuvant setting will help determine which agent is more suitable for various subgroups of patients.

These and other questions may find answers in ongoing and future trials of perioperative tyrosine kinase inhibitors for NSCLC. It should be noted that some of these studies investigate targeted therapy against oncogenic driver alterations other than EGFR mutations, including ALK and ROS oncogene 1 rearrangements. **Table 2** details the main characteristics of current phase 3 randomized trials of adjuvant or neoadjuvant therapy with tyrosine kinase inhibitors.

In the past few years only, there has been a prosperous development of clinical trials investigating immunotherapies and molecular targeted therapies for NSCLC as adjuvant and neoadjuvant treatments. Strong evidence from phase 3 randomized studies have provided clinicians with new therapeutic options that can improve oncologic outcomes. In clinical practice, however, many questions remain unanswered and require further exploration. It is expected that current and future studies will optimize the integration of immunotherapy and targeted therapy to the perioperative patient pathway to maximize oncologic benefits and minimize treatment-related toxicities. This impending innovation represents an opportunity to improve the long-term outcomes of surgery in patients with NSCLC and ultimately change the prognosis of early-stage, potentially curable disease.

Author contributions

SL conceptualized the review and drafted the manuscript. MS revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet*. (2021) 398:535–54. doi: 10.1016/S0140-6736(21)00312-3

2. Raz DJ, Zell JA, Ou S-HI, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest*. (2007) 132:193–9. doi: 10.1378/chest.06-3096

3. Sekihara K, Hishida T, Yoshida J, Oki T, Omori T, Katsumata S, et al. Long-term survival outcome after postoperative recurrence of non-small-cell lung cancer: who is "cured" from postoperative recurrence? *Eur J Cardiothorac Surg*. (2017) 52:522–8. doi: 10.1093/ejcts/ezx127

4. Pignon J-P, Tribodet H, Scagliotti GV, Douillard J-Y, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. *J Clin Oncol*. (2008) 26:3552–9. doi: 10.1200/JCO.2007.13.9030

5. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. (2014) 383:1561–71. doi: 10.1016/S0140-6736(13)62159-5

6. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. (2021) 398:1344–57. doi: 10.1016/S0140-6736(21)02098-5

7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology - non-small cell lung cancer version 6.2022 (2022). Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed December 2, 2022).

8. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. (2022) 23:1274–86. doi: 10.1016/S1470-2045(22)00518-6

9. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. (2022) 386:1973–85. doi: 10.1056/NEJMoa2202170

10. Wu Y-L, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. (2020) 383:1711–23. doi: 10.1056/NEJMoa2027071

11. Zhong W-Z, Wang Q, Mao W-M, Xu S-T, Wu L, Wei Y-C, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC: final overall survival analysis of CTONG1104 phase III trial. *J Clin Oncol*. (2021) 39:713–22. doi: 10.1200/JCO.20.01820

12. Tada H, Mitsudomi T, Misumi T, Sugio K, Tsuboi M, Okamoto I, et al. Randomized phase III study of gefitinib versus cisplatin plus vinorelbine for patients with resected stage II-IIIA non-small-cell lung cancer with EGFR mutation (IMPACT). *J Clin Oncol*. (2022) 40:231–41. doi: 10.1200/JCO.21.01729

13. He J, Su C, Liang W, Xu S, Wu L, Fu X, et al. Icotinib versus chemotherapy as adjuvant treatment for stage II-IIIA EGFR-mutant non-small-cell lung cancer (EVIDENCE): a randomised, open-label, phase 3 trial. *Lancet Respir Med*. (2021) 9:1021–9. doi: 10.1016/S2213-2600(21)00134-X

14. Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. *N Engl J Med*. (2017) 377:849–61. doi: 10.1056/NEJMra1703413

15. Paz-Ares L, O'Brien MER, Mauer M, Dafni U, Oselin K, Havel L, et al. VP3-2022: pembrolizumab (pembro) versus placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. *Ann Oncol*. (2022) 33:451–3. doi: 10.1016/j.annonc.2022.02.224

16. Sands JM, Mandrekar SJ, Kozono D, Oxnard GR, Hillman SL, Wigle DA, et al. Integration of immunotherapy into adjuvant therapy for resected non-small-cell lung cancer: ALCHEMIST chemo-IO (ACCIO). *Immunotherapy*. (2021) 13:727–34. doi: 10.2217/IMT-2021-0019

17. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science*. (2020) 367:eaax0182. doi: 10.1126/science.aax0182

18. Krishnamoorthy M, Lenehan JG, Maleki Vareki S. Neoadjuvant immunotherapy for high-risk, resectable malignancies: scientific rationale and clinical challenges. *J Natl Cancer Inst*. (2021) 113:823–32. doi: 10.1093/JNCI/DJAA216

19. Pataer A, Kalhor N, Correa AM, Raso MG, Erasmus JJ, Kim ES, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. *J Thorac Oncol*. (2012) 7:825–32. doi: 10.1097/JTO.0b013e318247504a

20. Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. (2020) 21:1413–22. doi: 10.1016/S1470-2045(20)30453-8

21. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*. (2018) 378:1976. doi: 10.1056/NEJMOA1716078

22. Ahern E, Solomon BJ, Hui R, Pavlakis N, O'Byrne K, Hughes BGM. Neoadjuvant immunotherapy for non-small cell lung cancer: right drugs, right patient, right time? *J Immunother Cancer*. (2021) 9:e002248. doi: 10.1136/jitc-2020-002248

23. Yang C-FJ, McSherry F, Mayne NR, Wang X, Berry MF, Tong B, et al. Surgical outcomes after neoadjuvant chemotherapy and ipilimumab for non-small cell lung cancer. *Ann Thorac Surg*. (2018) 105:924–9. doi: 10.1016/j.athoracsur.2017.09.030

24. Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. (2019) 158:269–76. doi: 10.1016/j.jtcvs.2018.11.124

25. Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. (2020) 21:786–95. doi: 10.1016/S1470-2045(20)30140-6

26. Bott MJ, Cools-Lartigue J, Tan KS, Dycoco J, Bains MS, Downey RJ, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. *Ann Thorac Surg*. (2018) 106:178–83. doi: 10.1016/j.athoracsur.2018.02.030

27. Pisters K, Kris MG, Gaspar LE, Ismaila N. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA NSCLC guideline expert panel. Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO guideline rapid recommendation update. *J Clin Oncol*. (2022) 40:1127–9. doi: 10.1200/JCO.22.00051

28. Yue D, Xu S, Wang Q, Li X, Shen Y, Zhao H, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. *Lancet Respir Med*. (2018) 6:863–73. doi: 10.1016/S2213-2600(18)30277-7

29. Xu S-T, Xi J-J, Zhong W-Z, Mao W-M, Wu L, Shen Y, et al. The unique spatial-temporal treatment failure patterns of adjuvant gefitinib therapy: a post hoc analysis of the ADJUVANT trial (CTONG 1104). *J Thorac Oncol*. (2019) 14:503–12. doi: 10.1016/j.jtho.2018.11.020

30. Muthusamy B, Patil PD, Pennell NA. Perioperative systemic therapy for resectable non-small cell lung cancer. *J Natl Compr Canc Netw*. (2022) 20:953–61. doi: 10.6004/jnccn.2022.7021

31. Zhong W-Z, Chen K-N, Chen C, Gu C-D, Wang J, Yang X-N, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer (EMERGING-CTONG 1103): a randomized phase II study. *J Clin Oncol*. (2019) 37:2235–45. doi: 10.1200/JCO.19.00075

32. Wu Y-L, Zhong W, Chen K-N, Chen C, Yang F, Yang X-N, et al. CTONG1103: final overall survival analysis of the randomized phase 2 trial of erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non–small cell lung cancer. *J Clin Oncol*. (2021) 39:8502. doi: 10.1200/JCO.2021.39.15_suppl.8502

33. Tsuboi M, Weder W, Escriu C, Blakely C, He J, Dacic S, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: neoADAURA. *Future Oncol*. (2021) 17:4045–55. doi: 10.2217/fon-2021-0549

34. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. (2018) 378:113–25. doi: 10.1056/NEJMoa1713137

35. Zhou L, He J, Xiong W, Liu Y, Xiang J, Yu Q, et al. Impact of whole brain radiation therapy on CSF penetration ability of icotinib in EGFR-mutated non-small cell lung cancer patients with brain metastases: results of phase I dose-escalation study. *Lung Cancer*. (2016) 96:93–100. doi: 10.1016/j.lungcan.2016.04.003

frontiers | Frontiers in Surgery

TYPE Case Report
PUBLISHED 08 February 2023
DOI 10.3389/fsurg.2023.1120404

OPEN ACCESS

EDITED BY
Ugo Cioffi,
University of Milan, Italy

REVIEWED BY
Ahmed G. Elkhouly,
Tanta University, Egypt
Michael Peer,
Tel Aviv Sourasky Medical Center, Israel

*CORRESPONDENCE
Simone Tombelli
✉ simone.tombelli@unifi.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 09 December 2022
ACCEPTED 17 January 2023
PUBLISHED 08 February 2023

CITATION
Tombelli S, Viggiano D, Gatteschi L, Voltolini L and Gonfiotti A (2023) Video-assisted transcervical-transtracheal repair of posterior wall laceration of thoracic trachea: A new approach. Case Report.
Front. Surg. 10:1120404.
doi: 10.3389/fsurg.2023.1120404

Video-assisted transcervical-transtracheal repair of posterior wall laceration of thoracic trachea: A new approach. Case Report

Simone Tombelli*, Domenico Viggiano, Lavinia Gatteschi, Luca Voltolini and Alessandro Gonfiotti

Division of Thoracic Surgery, Careggi University Hospital, Florence, Italy

Iatrogenic tracheal lacerations are a rare but potentially fatal event. In selected acute cases, surgery plays a key role. Treatment can be conservative, for lacerations of less than 3 cm; surgical or endoscopic, depending on the size and location of the lesion and fan efficiency. There is no clear indication of the use of any of these approaches and the decision is therefore linked to local expertise. We present an emblematic clinical case of a 79 years old female patient undergoing polytrauma as a result of a road accident, without neurological damage, which required intubation and subsequent tracheotomy due to a significant limitation to ventilation. Imaging has shown the tracheal laceration involving the anterior wall and the pars membranacea up to the origin of the right main bronchus.A percutaneous tracheotomy was permormed without any improvement of the respiratory dynamic. Therefore, the patient underwent a surgical repair of the tracheal laceration with a hybrid mini-cervicotomic/endoscopic approach. This less invasive approach successfully repaired the extensive loss of substance.

KEYWORDS

tracheal laceration, cervicotomy, hybrid approach, case report, thoracoscopy (VATS)

Introduction

The trachea is an unequal median organ that, following the larynx, ends in the thorax bifurcating in the main right and left bronchus. In its course it makes contact with multiple structures such as the esophagus, thyroid, major arterial and venous vessels of the mediastinal region and neck, nerve structures such as the recurrent laryngeal nerves and the vagus nerve and, posteriorly, with the vertebra and spinal cord (1).

It is therefore clear why the majority of patients who suffer tracheal injuries can exhale before arrival in emergency facilities, given the proximity of all these vital structures. The true incidence of trachea bronchial injuries (TBI) is still unknown since 30%–80% of these trauma victims still die at the scene of the accident (2). Currently, the incidence of TBI among trauma patients with chest and neck injuries is between 0.5% and 2%. Major causes of tracheal injury include trauma (contusive and penetrating) and iatrogenic injury. Considering endotracheal intubations, which represent one of the leading iatrogenic causes, iatrogenic trachea lesions occur once every 20,000–75,000 elective intubations and increase up to 15% for intubations performed in emergency (2). Tracheal lacerations differ depending on the involvement of the cervical region or thoracic region, the impairment of the anterior wall or the pars membranacea, and if the tracheal wall is involved partially or at full thickness.

For all the reasons listed above, early detection is one of the most important factors to reduce morbidity and mortality related to this injury. Proper airway management is vital (3). Despite the high mortality and morbidity of this kind of injuries there is still not a unanimous expert consensus on the most proper treatment to apply and every center relies on its expertise. In this article we would like to depict an extremely severe case of tracheal laceration and our innovative method to repair it.

Case description

We present a clinical case of a 79-year-old patient subjected to polytrauma following a car accident, without obvious neurological damage, which required intubation at the scene of the accident performed by the emergency service personnel.

The patient was taken to the emergency room of the Careggi University Hospital and was then admitted to the intensive care unit (ICU) where, due to an increasing and significant limitation to ventilation the patient was sedated and muscle relaxers were used. Eventually a percutaneous bed-side tracheotomy had to be performed in order to achieve a proper ventilation management with no immediate periprocedural complications. Nevertheless, during the ICU stay there was a progressive difficulty in mechanical ventilation with evidence of air leakage from the ventilation circuit. Chest x-ray did show neither pneumothorax nor subcutaneous emphysema, therefore a direct thoracic computed tomography (CT) scan was performed and it revealed a tracheal tear extending from about 5 cm from the glottis up to the carena, involving the origin of the right main bronchus. A fibrobronchoscopy was taken and confirmed the extent of the laceration and showed the esophagus bulging through the mediastinum into the trachea. Considering the wide loss of substance, and the likely iatrogenic nature of the lesion, a conservative approach was impossible to carry out and the multidisciplinary decision was to perform a surgical procedure. Since there was no pneumothorax we opted for a cervical approach.

The patient was taken to the operating room where mini-cervicotomic surgical access comprehending the previous transcutaneous tracheotomy allowed us to reach the thyroid plane with subsequent isolation and section of the isthmus. The anterior wall of the trachea was damaged as well as the posterior one. There were broken down fractures with loss of substance of cricoid cartilage and the first four tracheal rings, determining the opening of the airway from the base of the larynx up to the upper third of the trachea. In order to verify and manage the whole length of the laceration we decided to use a 5 mm 30° degrees thoracoscope inserted through the cervicotomic access. It magnified and showed us the known lesion of the pars membranacea, 5 cm from the glottis up to the carena and involving the origin of the right main bronchus. The tear was confirmed to be at full thickness with bulging of the esophagus and large virtual space between the anterior esophageal wall and trachea, resulting in a false lumen produced by the tracheostomic cannula (**Figure 1**). The pars membranacea in the posterior right portion was retracted with multiple lacerations and consequent loss of substance.

Transtracheal repair was carried out with video-assisted technique in intermittent apneic ventilation after partial anterior

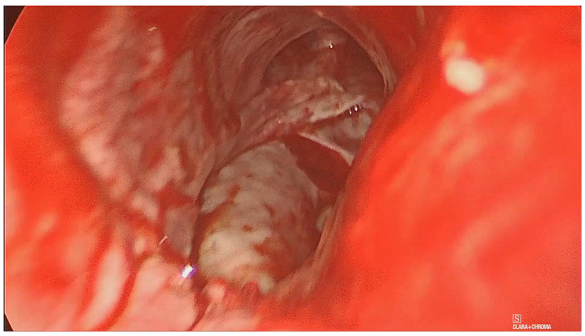

FIGURE 1
Lesion of the pars membranacea extending from 5 cm from the glottis up to carena, including the origin of the main right bronchus. Bulging of the anterior esophageal wall is visible through the loss of trachea substance.

opening of the remaining pars cartilaginea. The pars membranacea was repaired with continuous suturing in 3-0 absorbable monofilament Polydiossanone while the anterior tracheal wall was sutured with single 2-0 Polyglactin braided absorbable stitches using cervicotomic access (**Figure 2**). Thanks to the scope we managed to repair the whole posterior wall laceration through the cervicotomy, with no need of entering the chest.

The posterior wall was successfully repaired but there still was an important alteration of the tracheal anatomy. At the end, the loss of substance due to the fractures of tracheal rings and the cricoid forced us to pack a, tracheotomy in order to protect the airway. Proper functioning of the mechanic ventilation and no air leakage were detected. Operation time was 180 min. This surgical approach let a quick visualization of the lesion, amplifying the images. The only use of the cervical access has also allowed us to avoid the sternotomic or thoracotomic access with advantages in terms of trauma and operation time.

Discussion

When a conservative approach is not feasible, the standard surgical approach should be the cervicotomy in the case it was

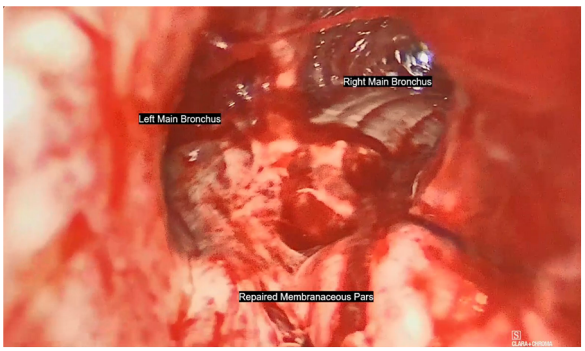

FIGURE 2
The pars membranacea was repaired with continuous suturing in 3-0 absorbable monofilament Polydiossanone while the anterior tracheal wall was sutured with single 2-0 Polyglactin braided absorbable stitches using cervicotomic access.

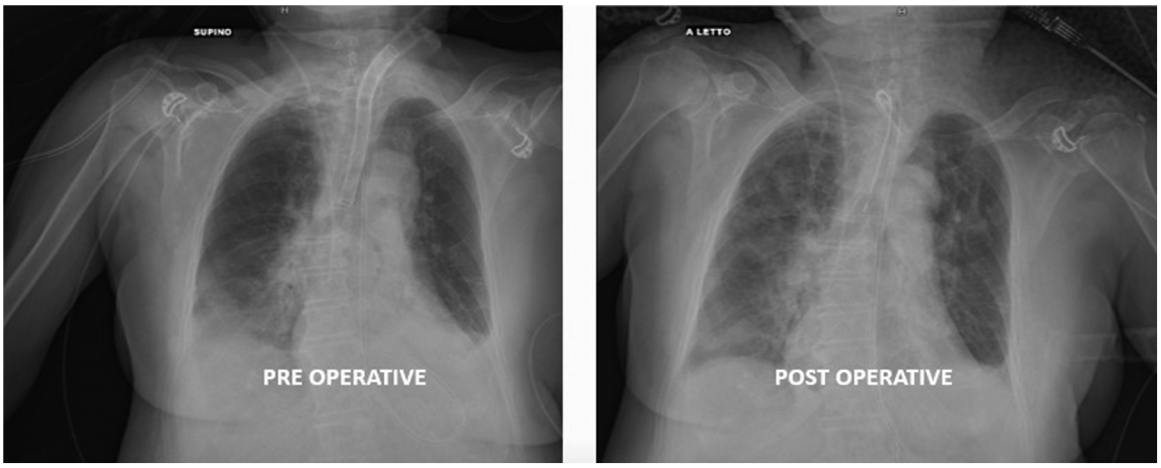

FIGURE 3
An adequate tracheal caliber and the presence of the new tracheostomic cannula can be appreciated at the post-operative x-ray. The mechanical ventilation system showed no air losses in the circuit at the end of surgery.

injured the 2/3 superior trachea and the larynx, as first described by Angelillo-Mackinlay (4), or the thoracotomy if the trauma involves the 1/3 inferior trachea. For tracheal lesions occurred to the carena or involving the origin of the main bronchi the approach in anterolateral thoracotomy or right posterolateral thoracotomy can be used. If the lesion distally affects the left main bronchus, this could be addressed through a left posterior thoracotomy if necessary. When increased exposure of the hemithorax or mediastinum is required, such as in the case of a suspected intrapericardial injury, a median partial sternotomy or clamshell incision could be used, even though this does not provide better access to the trachea (5).

As described by Grillo and colleagues (6) tracheal dissection around the lesion must be performed meticulously and closed along the trachea to minimize the risk for laryngeal nerve injury. Tracheal wall should be sutured with running suture in absorbable monofilament (7).

Our hybrid surgical approach allowed us to repair the posterior laceration with a running suture in 3-0 absorbable monofilament Polydiossanone under visual control using the endoscopic camera while the anterior tracheal wall was sutured with single 2-0 Polyglactin braided absorbable stitches entirely using the cervicotomic access under direct vision while maintaining an adequate caliber of the airway (**Figure 3**). In addition, the association of endoscopy with traditional surgery has favored a less invasive approach, compared with the techniques described above, as proposed by Mussi et al. (8). Unfortunately, the patient died four days after the surgery due to unforeseen complications related to organ damage reported as a result of the trauma, unrelated to airway problems.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LV, AG, DV and ST contributed to the acquisition, analysis and interpretation of data. ST and LG wrote the manuscript. LG and DV revising it critically for important content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1120404/full#supplementary-material.

References

1. Netter FH. *Atlas of human anatomy*. Philadelphia, PA: Saunders/Elsevier (2011).

2. Prokakis C, Koletsis EN, Dedeilias P, Fligou F, Filos K, Dougenis D. Airway trauma: a review on epidemiology, mechanisms of injury, diagnosis and treatment. *J Cardiothorac Surg*. (2014) 30:9–117. doi: 10.1186/1749-8090-9-117

3. Farley LS, Schlicksup KE. *Tracheal injury*. Treasure Island (FL): StatPearls Publishing (2022). PMID: 31613457

4. Angelillo-Mackinlay T. Transcervical repair of distal membranous. *Ann Thrac Surg*. (1995) 59(2):531–2. doi: 10.1016/0003-4975(94)00882-8

5. Rossbach MM, Johnson SB, Gomez MA, Sako EY, Miller OL, Calhoon JH. Management of major tracheobronchial injuries. *Ann Thorac Surg*. (1998) 65 (1):186–2. doi: 10.1016/0003-4975(94)00882-8

6. Grillo HC, Zannini P, Michelassi F. Complications of tracheal reconstruction: incidence, treatment, and prevention. *J Thorac Cardiovac Surg*. (1986) 91(3):322–8. doi: 10.1016/S0022-5223(19)36046-5

7. Welter S. Repair of tracheobronchial. *Thorac Surg Clin*. (2014) 24(1):41–50. doi: 10.1016/j.thorsurg.2013.10.006

8. Mussi A, Ambrogi MC, Ribechini A, Lucchi M, Menoni F, Angeletti CA. Acute major airway injuries: clinical features and management. *Eur J Cardiothorac Surg*. (2001) 20(1):46–51. doi: 10.1016/S1010-7940(01)00702-3

frontiers | Frontiers in Surgery

TYPE Perspective
PUBLISHED 13 February 2023
DOI 10.3389/fsurg.2023.1118477

OPEN ACCESS

EDITED BY
Alex Volinsky,
University of South Florida, United States

REVIEWED BY
Dania Nachira,
Agostino Gemelli University Polyclinic (IRCCS), Italy

*CORRESPONDENCE
Riccardo Orlandi
riccardo.orlandi@unimi.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 07 December 2022
ACCEPTED 24 January 2023
PUBLISHED 13 February 2023

CITATION
Orlandi R, Raveglia F, Calderoni M, Cassina EM, Cioffi U, Guttadauro A, Libretti L, Pirondini E, Rimessi A, Tuoro A and Passera E (2023) Management of COVID-19 related tracheal stenosis: The state of art.
Front. Surg. 10:1118477.
doi: 10.3389/fsurg.2023.1118477

Management of COVID-19 related tracheal stenosis: The state of art

Riccardo Orlandi[1]*, Federico Raveglia[2], Matteo Calderoni[2], Enrico Mario Cassina[2], Ugo Cioffi[3], Angelo Guttadauro[4], Lidia Libretti[2], Emanuele Pirondini[2], Arianna Rimessi[2], Antonio Tuoro[2] and Eliseo Passera[2]

[1]Department of Thoracic Surgery, University of Milan, Milan, Italy, [2]Department of Thoracic Surgery, San Gerardo Hospital, ASST Monza, Monza, Italy, [3]Department of Surgery, University of Milan, Milan, Italy, [4]Department of Medicine and Surgery, School of Medicine and Surgery, Università degli Studi di Milano Bicocca, Monza, Italy

Tracheal stenosis (TS) is a debilitating disease promoted by pathologic narrowing of the trachea. The acute respiratory distress syndrome caused by COVID-19 has been demonstrated to trigger enhanced inflammatory response and to require prolonged invasive mechanical ventilation as well as high frequency of re-intubation or emergency intubation, thus increasing the rate and complexity of TS. The standard-of-care of COVID-19-related tracheal complications has yet to be established and this is a matter of concern. This review aims at collecting latest evidence on this disease, providing an exhaustive overview on its distinctive features and open issues, and investigating different diagnostic and therapeutic strategies to handle COVID-19-induced TS, focusing on endoscopic versus open surgical approach. The former encompasses bronchoscopic procedures: electrocautery or laser-assisted incisions, ballooning dilation, submucosal steroid injection, endoluminal stenting. The latter consists of tracheal resection with end-to-end anastomosis. As a rule, traditionally, the endoscopic management is restricted to short, low-grade, and simple TS, whereas the open techniques are employed in long, high-grade, and complex TS. However, the critical conditions or extreme comorbidities of several COVID-19 patients, as well as the marked inflammation in tracheal mucosa, have led some authors to apply endoscopic management also in complex TS, recording acceptable results. Although severe COVID-19 seems to be an issue of the past, its long-term complications are still unknown and considering the increased rate and complexity of TS in these patients, we strongly believe that it is worth to focus on it, attempting to find the best management strategy for COVID-19-related TS.

KEYWORDS

tracheal stenosis, thoracic surgery, endoscopic thoracic surgery, COVID-19, tracheal procedures

Introduction

Tracheal stenosis (TS) is an invalidating disease characterized by emphasized tissue fibrotic reaction leading to pathologic narrowing of the trachea (1). Traditionally, iatrogenic intubation injury, prolonged intubation or tracheostomy are the most frequent causes of TS (2). Other causes include local radiotherapy, inflammatory or autoimmune diseases, idiopathic, and neoplastic diseases. Coronavirus Disease 2019 (COVID-19) has been reported to be strictly related to TS. Indeed, longer times of invasive ventilation and differed tracheostomy to promote prone position as well as higher rates of iatrogenic intubation injuries have resulted in significant rise in rate and complexity of TS in patients with severe COVID-19 (3).

Abbreviations and Acronyms
TS, tracheal stenosis; COVID-19, coronavirus disease 2019; ICU, intensive care unit; CSA, cross sectional area.

Experiences on COVID-19-related TS are still limited and there is lack of publications in literature on this topic: its best management has not been yet clearly established. Therefore, we performed a review to provide a brief but exhaustive overview on this relatively new disease, focusing on its distinctive features and open issues.

Epidemiology

Rate of TS following endotracheal intubation is estimated from 10% to 22%, but only 1%–2% of cases will complain severe dyspnea (4, 5), with reported incidence of 4.9 cases per million per year (6). During the pandemic, almost half of COVID-19 patients in ICU required invasive mechanical ventilation, with mean duration of 17 days and high rate of reintubation (7). The exact number of intubated COVID-19 patients developing TS is unknown, but its incidence is reported to widely range from 3.3% (8) to 40% (9, 10). The raw incidence of TS seems to be higher in COVID-19 patients than in pre-COVID-19 era (11), and the medical community has been alerted to the possibility of an unprecedented surge in TS (12), despite the limited number of cases in literature does not allow to draw definitive conclusions in this regard. The mean age ranges from 50 (13–15) to 60 (8, 11, 16) years old, and males seem to be more prone to develop this disease, with approximately prevalence of 60%–70% (8, 11, 13, 14, 16, 17).

Risk factors

Risk factors could be divided into patient-related versus mechanical. The formers include patient's comorbidities, poor health conditions, history of diabetes, lower levels of PaO_2/FiO_2 and increased hypoxia (10), obesity, severe inflammation as well as microbial dysregulation of the airways (11, 16), COVID-19-related laryngitis and laryngeal edema (14), disrupted laryngotracheal microcirculation due to prothrombotic and antifibrinolytic state, high viral replication in the tracheal epithelium (11) leading to viral tracheitis (18). Instead, the latters consist of iatrogenic lesions during intubation due to poor visibility and chaotic situations, cuff overinflation to avoid aerosol sprays, prolonged intubation, high rate of reintubation, prone position ventilation with movement of the tube, delayed tracheostomy to allow prone position and viral clearance (11), vasopressor use (8), high-dose corticosteroid resulting in mucosal atrophy and altered healing, impaired nursing service due to workload of pandemics.

Pathophysiology

TS is a pathological narrowing of the trachea, typically occurring in the upper half, at the cuff or, less frequently, at the stomal site, because of mispositioning of tracheostomy or high placement of endotracheal tube. The extension is variable. In 1965 Cooper and Grillo (19) explained the reason, by performing tracheal autoptic evaluation on 30 patients who died during invasive ventilation. The macro and microscopic examination revealed a pattern of damage to the tracheal wall at the cuff site: mucosal hemorrhage or ulceration, necrosis and dissolution of adjacent cartilaginous rings, up to scarring fibrosis. Pathophysiologic basis of this phenomenon must be searched in pressure of the cuff. Cuff pressure of endotracheal tube above the capillary perfusion pressure of tracheal mucosa ranging from 20 to 30 mmHg leads to mucosal ischemia, which, if prolonged, results in submucosal damages (20). Ongoing compression causes injury to cartilaginous rings, which are usually fed by diffusion from mucosa and sub-mucosa. Once full epithelium's depth is interested by ischemic injury, healing can no longer rely on epithelium regeneration, but it requires collagen deposition, leading to scarring (21). On the other hand, the examination of tracheal wall at the stomal site revealed granulation tissue along the stoma and the loss of support of anterior cartilaginous arch because of too large stoma or enlargement by leverage of endotracheal tube (19). Ultimately, whatever the origin, TS is mediated by pathologic deposition of collagen in the upper airway, which is triggered by fibroblasts: several cytokines have been reported to promote the profibrotic myofibroblast phenotype observed in TS (22), such as interleukin IL-1, IL-6, IL-13, fibroblast growth factor (FGF), tumor necrosis factor α (TNF-α) and transforming growth factor β (TGF-β). All these cytokines have been demonstrated to be elicited by COVID-19 (23). Recently, some Authors (11, 15) have described microscopic findings of tracheal samples in COVID-19 patients affected by TS, highlighting patchy coagulative necrosis of the epithelium, granulation tissue, extensive presence of lymphocytes, multinucleated giant cells, non-fistulized abscesses leading to cartilage lysis, as well as thrombotic vessels and lymphocytic microvasculitis. Interestingly, cells with viral cytopathic involvement have been identified (11), and viral particles in tracheal epithelial cells have been detected (24), which could support the pathogenetic role of viral tracheitis theorized by Ershadi and colleagues (18). Moreover, Roncati and colleagues (25) have recently reported, by immunohistochemistry, a high density of IgG4-secreting plasma cells on fibrotic tissue from resected tracheal samples in patients affected by COVID-19-related TS. According to Stratakos and colleagues (16), severe COVID-19 could trigger massive Th2 response, which has already been demonstrated to mediate development of TS (22), by inducing localized IgG4 overproduction with resulting fibrosis and scarring in the upper airway.

Manifestations

Symptoms can widely vary depending on site and extension of airway stenosis (8): occlusive TS localized within 2–3 cm from vocal cords will occur during the hospitalization with difficulties in extubating the patient or weaning tracheostomy; whereas progressive TS localized beyond 3 cm from vocal cords will show up with progressive shortness of breath after discharging. Manifestations will also depend on the degree of obstruction, which in turn influences airflow rate and pressure changes (8, 17): mild stenosis (<50%) will be broadly asymptomatic since the pressure at the stenosis is comparable to that at the glottic plane; moderate stenosis (51%–70%) will result in fluctuating symptoms, based on significant pressure drop manifesting under exertion or

other contexts requiring higher airflow rate; severe stenosis (>71%) will produce symptoms even at rest, due to massive pressure drop. The typical presentation consists of dyspnea, wheezing and stridor on physical examination occurring after several days from extubating (8, 9, 14). Symptoms may include dysphonia and communication difficulties (22), hoarseness, dry cough, and swallowing problems (12). Symptoms can occur immediately after extubating or they can be delayed up to 6 months or even within a few years from ventilation weaning (26). TS at the stomal site could be more subtle and less rapidly progressive, leading to functional impairment up to years or even decades later (8). COVID-19-related TS has more severe clinical presentations than other TS because of more complex stenotic airway segments (11) and delayed diagnosis, since symptoms of TS could be initially misdiagnosed as post-COVID-19 respiratory symptoms (16, 17). Whatever the symptoms, without proper management, TS can lead to life-threatening situations due to impaired respiratory function (22).

Diagnosis

Clinically, TS are divided into simple (or web-like) and complex stenosis: the formers are less than 1 cm long circumferential stenosis, without any cartilage involvement; the latters are more than 1 cm long articulated and mixed stenosis, with involvement of cartilage (17). TS could potentially affect each segment of the trachea. The majority of COVID-19-related TS is complex (8, 13, 16), with higher incidence of associated tracheomalacia, vocal cord paralysis and tracheoesophageal fistula (13), and localized in the upper third segment (8, 13, 14, 17). The stenotic segment is highly variable in extension, but it is most reported as around 2 cm long (8, 11, 13, 16). The most critical factor in TS is assessing tracheal width in the stenotic segment, which is graded according to Cotton-Myer Classification System, based on endoscopic tracheal evaluation (27): I, cross sectional area (CSA) obstruction <50%; II, CSA obstruction 51%–70%; III, CSA obstruction 71%–99%; IV complete obstruction without detectable lumen. Most patients with COVID-19-related TS are graded III (8, 13, 14). Appropriate diagnostic investigations are mandatory to properly classify the TS and to subsequently tailor the best treatment option for each patient: an accurate physical examination, a thorough radiologic assessment and an extensive endoscopic evaluation are the pillars of an adequate preoperative workup (12). The use of laryngoscopy or flexible bronchoscopy is of utmost importance, enabling to gather several dynamic details on vocal mobility, swallowing function, local inflammation, localization, extent and degree of TS, presence of airway lesions, malacic or scar tissue. Endoscopy is the gold standard and should always be performed. CT scan (more rarely MRI) of the trachea can be highly relevant and complementary, mainly in case of complete TS obstruction, providing the possibility to measure extent and narrowing of TS, or in case of suspected laryngo-tracheal framework alteration. In case of apparent TS, a thorough airway evaluation under general anesthesia should be considered. Pulmonary functions should be multidisciplinary assessed, through routine lung function tests, differentiating TS from other respiratory diseases (12).

Treatment

The optimal management of TS is still a matter of debate, irrespective of the disease which led to invasive ventilation, and clear guidelines on the best treatment option are still demanded, even more so in COVID-19-related TS. **Table 1** gathers main case-series studies available in literature on this topic. Currently, treatment of this disease must be personalized, based on patient's clinical conditions and morbidities, and on anatomic characteristics of the stenotic segment. An early specialistic referral and thorough clinical, radiologic, and endoscopic evaluation are mandatory to plan the best therapeutic management. Main treatment options are endoscopic versus surgical procedures. As a rule, endoscopic approach is recommended as first-line definitive treatment in shorter than 2 cm, low-graded intrinsic and well localized TS, or in heavily comorbid patients on poor general conditions, otherwise it is suggested as bridge therapy for definitive surgery. On the other hand, surgery is recommended in longer than 2 cm, high-graded, complex TS, extended to different segments or associated with malacia, altered laryngo-tracheal framework, as well as in case of unsuccessful multiple endoscopic attempts (12). Another available therapeutic option is the tracheostomy, which should be reserved to selected cases. Indeed, the right planning of the treatment procedure would avoid a tracheostomy or redo-tracheostomy with further tracheal damages; anyway, if needed, tracheostomy should be performed into the stenotic or affected segment not to injury healthy tracheal segments (12), through either open or percutaneous techniques, since they have shown to have comparable results in terms of perioperative mortality and morbidity rates in general population (34), and there are no current evidences on the preferable approach to adopt in COVID-19 patients (35). Eventually, treatment options for COVID-19-related TS are like those adopted for any-causes TS (31).

Conservative treatment

Conservative procedures consist of rigid bronchoscopy with tracheal dilation by ballooning or mucosal resection through electrocautery, cryoablation or laser, resection of granulation tissue, stenting, intralesional mucosal steroid injection (12). The best endoscopic technique, which could be variably combined, depends on experience of the center and on type of TS. Onorati and colleagues (15) favor endoscopic treatment in COVID-19-related TS, mainly in case of persistent local inflammation of the trachea, reporting encouraging results through bronchoscopic procedures (balloon dilation, stenting, and resection of granuloma) on 8 patients, with 75% success and 25% complication rates. Ayten and colleagues (8) showed 100% success rate in patients affected by simple TS undergoing 1–3 bronchoscopy dilation procedures; they suggest applying endoscopic procedures as first-line therapy in web-like TS smaller than 1 cm and without malacia. Mattioli and colleagues (3) suggest to avoide surgery as primary choice in COVID-19 patients, because of their heavy comorbidities and debilitated conditions, proposing to use balloon dilation procedures with intralesional corticosteroid injection, even in case of complex

10.3389/fsurg.2023.1118477

TABLE 1 Main studies reporting the management of COVID-19-related tracheal stenosis.

References	N[a] of patients	Type of TS	MC grade	Lenght	Treatment	Technique	Complications	Outcomes
Palacios (13)	63	NA	IV 1 III 56 II 3 I 3	3.5	Endoscopic 0	-	-	-
					Surgical 63	Tracheal resection/ anastomosis 59 T-tube placement 1 Tracheostomy 3	Infection 18 Dehiscence 4 T-tube obstruction 7 Restenosis 6 Bleeding 2 Pneumonia 2	73% success
Stratakos (16)	23	Simple 2 Complex 21	III 23	2.85 ± 0.9	Endoscopic 15	Dilation/ablation 3 Dilation/ ablation + stenting 12	Pneumothorax 1 Restenosis 7 Stent migration 1	87% success
					Surgical 8	Tracheal resection/ anastomosis	Restenosis 2	80% success
Piazza (14)	14	NA	III 14	NA	Endoscopic 0	-	-	-
					Surgical 8	Tracheal resection/ anastomosis 8	Restenosis 2	80% success
Piazza (14)	14	NA	III 14	NA	Endoscopic 0	-	-	-
					Surgical 14[b]	Tracheal resection/ anastomosis 14	Subcutaneous emphysema 1	93% success
Tintinago (11)	12	Complex 12	II 8 I 4	3.5	Endoscopic 0	-	-	-
					Surgical 11[a]	Tracheal resection/ anastomosis 11	Restenosis 1	83% success
Topolnitskiy (28)	11	Simple 5 Complex 6	I 1 II 3 III 6 IV 1	3.4 ± 1.1	Endoscopic 1	Stenting 1	Stent migration 1	0% success
					Surgical 10	Tracheal resection/ anastomosis 4 Laryngotracheoplasty 6	Partial dehiscence 1 Synechiae 1	90% success
Onorati (15)	9	NA	NA	NA	Endoscopic 8	Dilation/ablation 4 Dilation + stenting 2 Conservative 2	Restenosis 2	75% success
					Surgical 1[b]	Tracheal resection/ anastomosis 1	None	100% success
Ayten (8)	7	Simple 3 Complex 4	III 4 II 2 I 1	1.81 ± 0.8	Endoscopic 3	Dilation 3	None	100% success
					Surgical 4[b]	Tracheal resection/ anastomosis 4	None	100% success
Beyoglu (17)	7	NA	III 5 II 2	2.03 ± 0.3	Endoscopic 0	-	-	-
					Surgical 7[b]	Tracheal resection/ anastomosis 7	Infection 2 Pneumonia 2 Arrhytmia 1 Anastomotic granulation 1	100% success
Vasudevan (29)	4	NA	NA	NA	Endoscopic 4	Dilation/ablation 2 Conservative 2	Restenosis 3	25% success
					Surgical 0	-	-	-
Tapias (30)	4	NA	NA	2.75	Endoscopic 0	-	-	-
					Surgical 4	Tracheal resection/ anastomosis 4	None	100% success
Alturk (31)	2	NA	III 1 II 1	2.7	Endoscopic 0	-	-	-
					Surgical 2[b]	Tracheal resection/ anastomosis 2	None	100% success
Gervasio (9)	2	NA	III 1 II 1	NA	Endoscopic 1	Conservative 1	None	100% success
					Surgical 1	Tracheal resection/ anastomosis 1	None	100% success
Miwa (32)	2	Simple 2	III 2	NA	Endoscopic 0	-	-	-
					Surgical 2	Tracheostomy 2	None	100% success

(*continued*)

TABLE 1 Continued

References	N[a] of patients	Type of TS	MC grade	Lenght	Treatment	Technique	Complications	Outcomes
Menna (33)	1	Complex 1	III 1	NA	Endoscopic 0	-	-	-
					Surgical 1[b]	Total tracheal replacement 1[c]	Pneumonia 1	100% success

NA, not available information; TS, tracheal stenosis; MC, Myer-Cotton.
[a]1 patient died before the procedure.
[b]After endoscopic dilation bridge.
[c]Cryopreserved aortic allograft.

TS, particularly in "young and thin" stenosis, allowing to heal some patients, or at least to buy time delaying surgery to gain better clinical conditions. Indeed, according to authors supporting conservative treatments, surgical procedures should be reserved to selected fit patients without significative comorbidities (3). Stratakos and colleagues (16) reported 88% success rate after endoscopic dilation and silicon stenting in 15 patients, with 60% complication rate mainly related to stent obstruction due to mucous accumulation and pseudomembranous. Tracheal resection and anastomosis are contraindicated in TS longer than 5–6 cm (8, 14, 31), because of the marked increase in anastomotic complications, and in such contexts, endoscopy could be considered with salvage intent before performing definitive tracheostomy or Montgomery T-tube placement. Since patients could relapse after endoscopic management, it is advisable to strictly follow-up them: they are thought to require an overage of 3.5 review flexible bronchoscopy procedures within the first 6 months (16). Medical therapy with antibiotics and intravenous steroid injection can be considered as ancillary: some authors (9, 15) reported clinical improvement and successful discharge of patients without further need for invasive procedures.

Surgical treatment

Surgical approaches include right thoracotomy, cervicotomy, cervical collar T-incision with or without manubrium split, median sternotomy, depending on experience of the center and localization of the stenotic segment. Whatever the chosen approach, the tracheal stenotic segment must be released, the damaged rings are removed, then end-to-end anastomosis is performed with 3–0 monofilament sutures by continuous as well as interrupted sutures (36). Traditionally, tracheal resection with end-to-end anastomosis is considered the gold standard treatment in TS (11), even if there are no specific guidelines. Several authors (8, 11–14, 17, 31) believe that surgical treatment is the standard of care also in COVID-19-related TS, especially in complex and articulated stenosis with cartilaginous involvement. In these cases, some authors (8, 13) consider endoscopic procedures even contraindicated, since the high rate of recurrence and the potential increase of the injured segment could decrease the chance of successful surgery. Others (11, 14, 31) rather suggest performing bronchoscopic dilation preoperatively in symptomatic patients as a bridge to definitive surgery, also in reiterated sessions. Concerning the timing of surgery, prevailing indication is to repair TS as early as possible, after the patient has tested negative for SARS-CoV-2 and as soon as he has recovered from the hospitalization (11, 17), if local inflammation is off and chronic steroid course can be discontinued to avoid anastomotic healing complications (15). Beyoglu and colleagues (17) propose to consider the time elapsed between the dilating procedure and the recurrence of symptoms to choose the right timing for surgical procedure: surgery should be planned if the time span between two consecutive sessions is less than 2 weeks. Different studies have reported complication rate of 15%–45% after tracheal resection and anastomosis for any-causes TS (37). Regarding COVID-19-related TS, complication rates range from less than 15% (8, 14) to over 40% (13, 17), whereas the reported success rate is around 80% (11, 13, 16), with 30-day mortality rate of 0%. In case of TS recurrence after surgery, which is reported to occur in 10%–20% of patients (13, 14, 16), dilating rigid bronchoscopy and eventually stenting is indicated as second-line treatments; in case of further failure definitive tracheostomy or Montgomery T-tube placement must be considered.

Prevention

To prevent COVID-19-related TS, the most critical element is to carefully manage mechanical risk factors listed above, especially choosing the appropriate endotracheal tube for each patient and strictly monitoring cuff pressure (17). The quality of care in COVID-19 has significantly improved since start of the pandemic, and this should slow down the presumed increase in TS rate. Anyway, an early diagnosis is of utmost importance, and therefore each patient with medical history of COVID-19-related invasive ventilation should be clinically, radiologically, and eventually endoscopically followed up to early detect any signs of TS (10, 12), suspecting TS in case of breathing distress after mechanical ventilation weaning (31). Topical or systemic use of steroids, as well as antibiotics and anti-inflammatory drugs, together with early endoscopic dilation and local debridement, could avoid progression to major TS (12).

Conclusion

COVID-19-related TS may become a relevant pathology within the next few years: it has distinctive features which differentiate it from other-causes TS, and it is worth to hold attention on its development. An early diagnosis is fundamental, and it is based on

clinical, radiological, and endoscopic investigations. Patients diagnosed with COVID-19-related TS should be referred to experienced tertiary centers. Treatment should be personalized and tailored on each patient, through multidisciplinary discussion. Therapeutic options consist of endoscopic or surgical procedures, which could provide high success and low complication rates when performed on selected patient in right timing.

Author contributions

RO, FR, and ElP contributed to conception and design of the study. RO and ElP wrote the first draft of the manuscript. RO, FR, ElP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Grillo HC. The management of tracheal stenosis following assisted respiration. *J Thorac Cardiovasc Surg*. (1969) 57(1):52–71. doi: 10.1016/S0022-5223(19)42762-1

2. Cooper JD, Grillo HC. The evolution of tracheal injury due to ventilatory assistance through cuffed tubes: a pathologic study. *Ann Surg*. (1969) 169(3):334–48. doi: 10.1097/00000658-196903000-00007

3. Mattioli F, Marchioni A, Andreani A, Cappiello G, Fermi M, Presutti L. Post-intubation tracheal stenosis in COVID-19 patients. *Eur Arch Otorhinolaryngol*. (2021) 278(3):847–8. doi: 10.1007/s00405-020-06394-w

4. Goldenberg D, Ari EG, Golz A, Danino J, Netzer A, Joachims HZ. Tracheotomy complications: a retrospective study of 1130 cases. *Otolaryngol Head Neck Surg*. (2000) 123(4):495–500. doi: 10.1067/mhn.2000.105714

5. Li M, Yiu Y, Merrill T, Yildiz V, deSilva B, Matrka L. Risk factors for posttracheostomy tracheal stenosis. *Otolaryngol Head Neck Surg*. (2018) 159 (4):698–704. doi: 10.1177/0194599818794456

6. Nouraei SA, Ma E, Patel A, Howard DJ, Sandhu GS. Estimating the population incidence of adult post-intubation laryngotracheal stenosis. *Clin Otolaryngol*. (2007) 32 (5):411–2. doi: 10.1111/j.1749-4486.2007.01484.x

7. Möhlenkamp S, Thiele H. Ventilation of COVID-19 patients in intensive care units. *Herz*. (2020) 45(4):329–31. doi: 10.1007/s00059-020-04923-1

8. Ayten O, Iscanli IGE, Canoglu K, Ozdemir C, Saylan B, Caliskan T, et al. Tracheal stenosis after prolonged intubation due to COVID-19. *J Cardiothorac Vasc Anesth*. (2022) 36(8 Pt B):2948–53. doi: 10.1053/j.jvca.2022.02.009

9. Gervasio CF, Averono G, Robiolio L, Bertoletti M, Colageo U, De Col L, et al. Tracheal stenosis after tracheostomy for mechanical ventilation in COVID-19 pneumonia: a report of 2 cases from northern Italy. *Am J Case Rep*. (2020) 21: e926731. doi: 10.12659/AJCR.926731

10. Fiacchini G, Tricò D, Ribechini A, Forfori F, Brogi E, Lucchi M, et al. Evaluation of the incidence and potential mechanisms of tracheal complications in patients with COVID-19. *JAMA Otolaryngol Head Neck Surg*. (2021) 147(1):70–6. doi: 10.1001/jamaoto.2020.4148

11. Tintinago LF, Victoria W, Escobar Stein J, Gonzales LF, Fernandez MI, Candelo E. Laryngotracheal stenoses post-acute respiratory distress syndrome due to COVID-19: clinical presentation, histopathological findings and management. A series of 12 cases. *Indian J Otolaryngol Head Neck Surg*. (2022) 74(Suppl 2):3262–7. doi: 10.1007/s12070-022-03076-3

12. Piazza C, Filauro M, Dikkers FG, Nouraei SAR, Sandu K, Sittel C, et al. Long-term intubation and high rate of tracheostomy in COVID-19 patients might determine an unprecedented increase of airway stenoses: a call to action from the European laryngological society. *Eur Arch Otorhinolaryngol*. (2021) 278(1):1–7. doi: 10.1007/s00405-020-06112-6

13. Palacios JM, Bellido DA, Valdivia FB, Ampuero PA, Figueroa CF, Medina C, et al. Tracheal stenosis as a complication of prolonged intubation in coronavirus disease 2019 (COVID-19) patients: a Peruvian cohort. *J Thorac Dis*. (2022) 14(4):995–1008. doi: 10.21037/jtd-21-1721

14. Piazza C, Lancini D, Filauro M, Sampieri C, Bosio P, Zigliani G, et al. Post-COVID-19 airway stenosis treated by tracheal resection and anastomosis: a bicentric experience. *Acta Otorhinolaryngol Ital*. (2022) 42(2):99–105. doi: 10.14639/0392-100X-N1952

15. Onorati I, Bonnet N, Radu DM, Freynet O, Guiraudet P, Kambouchner M, et al. Case report: laryngotracheal post-intubation/tracheostomy stenosis in COVID-19 patients. *Front Surg*. (2022) 9:874077. doi: 10.3389/fsurg.2022.874077

16. Stratakos G, Anagnostopoulos N, Alsaggaf R, Koukaki E, Bakiri K, Emmanouil P, et al. COVID-19 patients presenting with post-intubation upper airway complications: a parallel epidemic? *J Clin Med*. (2022) 11(6):1719. doi: 10.3390/jcm11061719

17. Beyoglu MA, Sahin MF, Turkkan S, Yazicioglu A, Yekeler E. Complex post-intubation tracheal stenosis in COVID-19 patients. *Indian J Surg*. (2022) 84(4):805–13. doi: 10.1007/s12262-022-03498-x

18. Ershadi R, Rafieian S, Sarbazzadeh J, Vahedi M. Tracheal stenosis following mild-to-moderate COVID-19 infection without history of tracheal intubation: a case report. *Gen Thorac Cardiovasc Surg*. (2022) 70(3):303–7. doi: 10.1007/s11748-021-01747-6

19. Cooper JD. Tracheal injuries complicating prolonged intubation and tracheostomy. *Thorac Surg Clin*. (2018) 28(2):139–44. doi: 10.1016/j.thorsurg.2018.01.001

20. Sultan P, Carvalho B, Rose BO, Cregg R. Endotracheal tube cuff pressure monitoring: a review of the evidence. *J Perioper Pract*. (2011) 21(11):379–86. doi: 10.1177/175045891102101103

21. Delaere P, De Leyn P. Surgical anatomy of the trachea and techniques of resection and reconstruction. In: 3rdJ LoCicero, RH Feins 3rd, YL Colson, G Rocco, editors. *Shields' general thoracic surgery*, 8th ed. Philadelphia: Wolters Kluwer (2019). p. 1782–811.

22. Davis RJ, Hillel AT. Inflammatory pathways in the pathogenesis of iatrogenic laryngotracheal stenosis: what do we know? *Transl Cancer Res*. (2020) 9(3):2108–16. doi: 10.21037/tcr.2020.01.21

23. Hasanvand A. COVID-19 and the role of cytokines in this disease. *Inflammopharmacology*. (2022) 30(3):789–98. doi: 10.1007/s10787-022-00992-2

24. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington state: a case series. *Lancet*. (2020) 396(10247):320–32. doi: 10.1016/S0140-6736(20)31305-2

25. Roncati L, Bergonzini G, Lusenti B, Nasillo V, Paolini A, Zanelli G, et al. High density of IgG4-secreting plasma cells in the fibrotic tissue from a surgically resected tracheal ring impaired by complex subglottic stenosis post-tracheostomy as immune expression of a Th2 response due to severe COVID-19. *Ann Hematol*. (2021) 100 (10):2659–60. doi: 10.1007/s00277-020-04231-y

26. Stoelben E, Koryllos A, Beckers F, Ludwig C. Benign stenosis of the trachea. *Thorac Surg Clin*. (2014) 24(1):59–65. doi: 10.1016/j.thorsurg.2013.09.001

27. Myer CM 3rd, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. *Ann Otol Rhinol Laryngol*. (1994) 103(4 Pt 1):319–23. doi: 10.1177/000348949410300410

28. Topolnitskiy E, Chekalkin T, Marchenko E, Volinsky A. Treatment of post-resuscitation cicatricial tracheal stenosis after suffering severe COVID-19 associated pneumonia: a report of 11 cases. *Respir Med Case Rep*. (2022) 40:101768. doi: 10.1016/j.rmcr.2022.101768

29. Vasudevan A, Achu R, Perry A, Yarrington C, Norris M, Tracy L, et al. Impact of pregnancy on airway complications after intubation for COVID-19 infection: a case series. *Am J Otolaryngol*. (2022) 43(5):103522. doi: 10.1016/j.amjoto.2022.103522

30. Tapias LF, Lanuti M, Wright CD, Hron TA, Ly A, Mathisen DJ, et al. COVID-19-related post-intubation tracheal stenosis: early experience with surgical treatment. *Ann Surg*. (2022) 275(1):e271–3. doi: 10.1097/SLA.0000000000004884

31. Alturk A, Bara A, Darwish B. Post-intubation tracheal stenosis after severe COVID-19 infection: a report of two cases. *Ann Med Surg*. (2021) 67:102468. doi: 10.1016/j.amsu.2021.102468

32. Miwa M, Nakajima M, Kaszynski R H, Hamada S, Nakano T, Shirokawa M, et al. Two cases of post-intubation laryngotracheal stenosis occurring after severe COVID-19. *Intern Med*. (2021) 60(3):473–7. doi: 10.2169/internalmedicine.6105-20

33. Menna C, Andreetti C, Ibrahim M, Ciccone AM, D'Andrilli A, Maurizi G, et al. Successful total tracheal replacement by cryopreserved aortic allograft in a patient post-COVID-19 infection. *Chest*. (2021) 160(6):e613–7. doi: 10.1016/j.chest.2021.08.037

34. Johnson-Obaseki S, Veljkovic A, Javidnia H. Complication rates of open surgical versus percutaneous tracheostomy in critically ill patients. *Laryngoscope*. (2016) 126 (11):2459–67. doi: 10.1002/lary.26019

35. David AP, Russell MD, El-Sayed IH, Russell MS. Tracheostomy guidelines developed at a large academic medical center during the COVID-19 pandemic. *Head Neck*. (2020) 42(6):1291–6. doi: 10.1002/hed.26191

36. Delaere P, De Leyn P. Surgical anatomy of the trachea and techniques of resection and reconstruction. In: 3rdJ LoCicero, RH Feins 3rd, YL Colson, G Rocco, editors. *Shields' general thoracic surgery*, 8th ed. Philadelphia: Wolters Kluwer (2019). p. 1782–811.

37. Siciliani A, Rendina EA, Ibrahim M. State of the art in tracheal surgery: a brief literature review. *Multidiscip Respir Med*. (2018) 13:34. doi: 10.1186/s40248-018-0147-2

frontiers | Frontiers in Surgery

TYPE Perspective
PUBLISHED 13 February 2023
DOI 10.3389/fsurg.2023.1125997

OPEN ACCESS

EDITED BY
Marco Anile,
Sapienza University of Rome, Italy

REVIEWED BY
Duilio Divisi,
University of L'Aquila, Italy

*CORRESPONDENCE
Eliseo Passera
✉ eliseo.passera@gmail.com
Riccardo Orlandi
✉ riccardo.orlandi@unimi.it

The manuscript was presented at the XXI SIET National Meeting on Friday 30th September 2022, in Rome, Italy.

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 16 December 2022
ACCEPTED 19 January 2023
PUBLISHED 13 February 2023

CITATION
Passera E, Orlandi R, Calderoni M, Cassina EM, Cioffi U, Guttadauro A, Libretti L, Pirondini E, Rimessi A, Tuoro A and Raveglia F (2023) Post-intubation iatrogenic tracheobronchial injuries: The state of art.
Front. Surg. 10:1125997.
doi: 10.3389/fsurg.2023.1125997

Post-intubation iatrogenic tracheobronchial injuries: The state of art

Eliseo Passera[1]*, Riccardo Orlandi[2]*, Matteo Calderoni[1], Enrico Mario Cassina[1], Ugo Cioffi[3], Angelo Guttadauro[4], Lidia Libretti[1], Emanuele Pirondini[1], Arianna Rimessi[1], Antonio Tuoro[1] and Federico Raveglia[1]

[1]Department of Thoracic Surgery, San Gerardo Hospital, ASST Monza, Monza, Italy, [2]Department of Thoracic Surgery, University of Milan, Milan, Italy, [3]Department of Surgery, University of Milan, Milan, Italy, [4]Department of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy

Iatrogenic tracheobronchial injury (ITI) is an infrequent but potentially life-threatening disease, with significant morbidity and mortality rates. Its incidence is presumably underestimated since several cases are underrecognized and underreported. Causes of ITI include endotracheal intubation (EI) or percutaneous tracheostomy (PT). Most frequent clinical manifestations are subcutaneous emphysema, pneumomediastinum and unilateral or bilateral pneumothorax, even if occasionally ITI can occur without significant symptoms. Diagnosis mainly relies on clinical suspicion and CT scan, although flexible bronchoscopy remains the gold standard, allowing to identify location and size of the injury. EI and PT related ITIs more commonly consist of longitudinal tear involving the pars membranacea. Based on the depth of tracheal wall injury, Cardillo and colleagues proposed a morphologic classification of ITIs, attempting to standardize their management. Nevertheless, in literature there are no unambiguous guidelines on the best therapeutic modality: management and its timing remain controversial. Historically, surgical repair was considered the gold standard, mainly in high-grade lesions (IIIa-IIIb), carrying high morbi-mortality rates, but currently the development of promising endoscopic techniques through rigid bronchoscopy and stenting could allow for bridge treatment, delaying surgical approach after improving general conditions of the patient, or even for definitive repair, ensuring lower morbi-mortality rates especially in high-risk surgical candidates. Our perspective review will cover all the above issues, aiming at providing an updated and clear diagnostic-therapeutic pathway protocol, which could be applied in case of unexpected ITI.

KEYWORDS

iatrogenic tracheal injury, tracheal surgery, thoracic surgery, endoscopy, tracheobronchial laceration

Introduction

Iatrogenic tracheobronchial injury (ITI) can be defined as any lesion occurring in the airway due to invasive medical or surgical procedure. Main causes are orotracheal intubation and tracheostomy, defining the post-intubation ITIs, and this review will focus on them (1, 2). Other causes include thoracic and neck surgeries but discussing them is beyond the aims of the present review. Globally, post-intubation ITI is considered rare (2), thanks to advancements in medical devices and development of innovative less-invasive procedures; nonetheless its consequences could be awful (3). The recent SARS-CoV-2 pandemic has well raised the issue since the high rate of emergency intubation and close radiological imaging monitoring have brought out several ITI cases (3–5). However, experiences in this field are

limited just by the rarity of this condition, and literature is still lacking updated definitive indications on its identification and management. Therefore, the following perspective review aims at discussing the main aspect of post-intubation ITIs, eventually proposing an updated diagnostic-therapeutic algorithm, appliable in case of unexpected ITI.

Epidemiology

The real incidence of ITIs is unknown, but it is estimated to be 0.005% for all endotracheal (ET) intubation, up to 0.5% for double-lumen tube procedures, and 1% for tracheostomy (6, 7). These rates are likely underestimated, due to several cases are underrecognized or even underreported. Surely, emergency procedures increase the risk for accidental injury; in such settings, the incidence is reported to be up to 15% (2, 8).

Risk factors

Predisposing factors can be divided into patient-related and procedure-related. The formers are largely unmodifiable and consist of advanced age, female gender, obesity, chronic use of inhaled or systemic steroids, local inflammation and all those conditions leading to tissue malacia (3, 7, 9–11); furthermore, anatomic variations or alterations, such as tracheal diverticula or neoplasms, neck or mediastinal masses dislocating the trachea, marked cervical lordosis or scoliosis, fall into this category (7). The latters include multiple attempts or limited experience in intubation, misuse of a stylet or rigid-guide, as well as incorrect choice of tube or cannula size, double-lumen tube, mishandling of cuff pressure or leverage of the tube (2). Emergency procedures can enhance each of the described risk factors, explaining the higher prevalence of ITIs in emergency settings (12).

Pathophysiology

Usually, post-intubation ITIs are caused by friction of the endotracheal tube against the pars membranacea of the tracheal wall, at the midline along the posterior membrane or at the cartilaginous-membrane junction, whereas cartilaginous rings and ligaments offer relative protection from injury to the anterior wall (13). Typically, the injury consists of longitudinal tear at the tracheal middle third, which may spread to the lower third or even to the main bronchi: the length is highly variable (14). The depth of the laceration is similarly variable, but it is critical to be assessed. Indeed, based on depth of the lesion, in 2010 Cardillo and colleagues (8) proposed a morphological classification for patients-risk-stratification, aiming at standardizing treatments. According to that classification, post-intubation ITIs were categorized as follows: I, partial-thickness lesion (limited to mucose or submucose) without mediastinal or subcutaneous emphysema; II, full-thickness lesion with mediastinal or subcutaneous emphysema, but without esophageal or mediastinal soft-tissue involvement; IIIA, full-thickness lesion with esophageal or mediastinal soft-tissue herniation, but without esophageal injury or mediastinitis; IIIB, full-thickness lesion with esophageal injury or mediastinitis. Recently this classification has been revised, adding level IV lesions, characterized by extensive loss of substance or fracture of tracheal rings (8, 15, 16).

Clinical features

Usual clinical presentation consists of facial and upper-trunk subcutaneous emphysema together with cough, occurring within a variable interval of time from ET intubation, generally up to 3 days (14, 17). Dyspnoea can variably occur, from breathing discomfort up to real acute respiratory failure, depending on severity of the lesion and association of unilateral or bilateral pneumothorax (2). ITI may also have asymptomatic course, especially in case of partial-thickness lacerations (14, 17, 18). In mechanical ventilated patients, ITIs can have either subtle development (17), with delayed occurrence in case the cuff overcomes or covers the lesion as well as with ventilatory leaks needing for over-cuffing the tube, or catastrophic presentation (2, 14), with rapid-onset massive pneumomediastinum, tension pneumothorax and difficult ventilation, mainly depending on extent of the tear. Based on mediastinal involvement degree and extent of pneumomediastinum, pneumopericardium, angina or even hypovolemic or cardiogenic shock may occur (4). Haemoptysis or pneumoperitoneum are seldom reported in literature (2, 18, 19).

Diagnosis

Nowadays, several ITIs are likely misdiagnosed, leading to delayed workup and late treatment, with detrimental effects on patients' outcome (2). To overcome this issue, it is recommended keeping high suspicion in case of suggestive symptoms in patients under mechanical ventilation or with medical history of recent intubation. To define and characterize the suspected lesion, radiologic imaging and endoscopic visualization are two complementary pillars of the diagnostic workup (20). Imaging can be obtained either through chest x-ray or CT-scan. The former allows to promptly rule out pneumothorax, large pneumomediastinum, pneumoperitoneum or subcutaneous emphysema, and it can be very useful in emergency settings to shrink differential diagnosis (21). The latter allows to detect the same findings as x-ray does, with greater sensitivity and accuracy (20–22).

Furthermore, contrast-enhanced CT scan may directly reveal tracheal laceration, approximately defining its site and extent, assessing alterations or deformities of the tracheal wall and cartilaginous rings, as well as identifying collateral damages to mediastinal organs or mediastinitis (12, 23). Typically, a tracheal tear may be highlighted as follows: discontinuity in the tracheal wall, localized pneumomediastinum, overdistension or herniation of the cuff, or tube displacement (24); in case of laceration expanding towards a main bronchus, the fallen lung sign could be noted (25). Another crucial role of the CT scan is to provide a

non-invasive evaluation of the tube location and cuff inflation (22). Eventually, double-contrast-enhanced CT scan may even reveal oesophageal injury with mediastinal contrast spreading (23, 26, 27). Despite the valuable information that can be gained through CT, endoscopy remains the gold standard in properly characterizing the tracheal tear and it is mandatory to perform it as soon as possible. Flexible bronchoscopy allows to dynamically evaluate location, length, and depth of the lesion, ruling out involvement of mediastinal soft-tissue or oesophagus and correctly classifying the injury. In mechanical ventilated patients, basic bronchoscopic assessment may fail identifying the lesion, which could be hidden by the cuff or the tube itself; therefore, in such setting, it is recommended to perform a thorough evaluation with cuff deflation and tube manipulation. It is worth underlining that a correct ITI management cannot be planned without performing both CT-scan and bronchoscopy (21, 26).

Management

ITIs are burdened by significant morbidity and mortality rates (28), which impose an early and efficacious treatment. Nowadays, therapeutic options for management of post-intubation ITIs are the following: conservative, endoscopic, and surgical treatments (27, 28). Currently, definitive indications on best treatment option are still demanded. However, it is broadly recommended to personalize treatment case-by-case, depending on characteristics of the laceration, patient's clinical features, general conditions, and comorbidities, as well as experience of the centre. Main experiences on the management of this disease are reported in **Table 1**. Traditionally, surgical repair has long been considered the gold standard, praised to be the only procedure preventing mediastinitis or further tracheal scarring stenosis (30, 38). Nevertheless, due to technical difficulties and non-negligible complications rate affecting surgery, there has recently been a shift towards conservative or less-invasive management of ITIs, which has been allowed by development of innovative materials and spread of minimally invasive procedures (27, 30, 39, 40).. Eventually, multidisciplinary assessment is recommended to choose the best treatment option for each patient, invariably depending on his clinical and respiratory conditions.

Conservative treatment

Conservative approach is widely suggested in asymptomatic patients with small partial-thickness laceration (level I), hemodynamical and respiratory stability, without mediastinal involvement (8, 17). However, indications to conservative management are now spreading to larger (up to 9 cm) or even deeper (up to level IIIA) tears (30, 41). Conservative options consist of observation, intubation, tracheostomy, fibrin glue application. Whatever the chosen conservative technique, strictly follow-up of patients is of paramount importance to early detect any clinical worsening.

- Observation is based on rest, antitussive drugs, and broad-spectrum antibiotics. This management may be adopted in case of small (< 2 cm) level I tears in asymptomatic or pauci-symptomatic patients (40).
- Intubation allows to overcome the injured segment, by placing the cuff distally in healthy tissue, ensuring ventilation support (22, 27). This management may be adopted in case of level I-IIIa tears in patients needing for ventilation. Anyway, ventilator setting should provide protective ventilation, by minimizing airway pressures. If the length of the lesion does not allow to place the cuff distally, after considering a double-lumen tube, and the respiratory failure is not otherwise manageable, ECMO support is worth to be accounted (42).
- Tracheostomy (40, 43) is considered a fallback option, due to significant side effects, but may be indicated in long level I–II tears, since it decreases endotracheal pressure ensuring progressive healing of the injury.
- Glue application is an innovative procedure proposed by Cardillo and colleagues (8); it consists of instillation of fibrin sealant to directly cover the tear through flexible bronchoscopy. It is generally appliable in level I–IIIA tears. Recently, the same authors (16) have presented an updated series of 55 patients treated by glue application, showing 100% success rate, when the procedure is performed in experienced centres on fit patients.

Endoscopic treatment

Several cases of patients with endoscopically managed ITIs have been reported in literature with encouraging results (40, 41). In the recent past, this option was reserved to poor surgical candidates (12), deemed unfit for surgery, due to comorbidities. The reported satisfactory results have prompted some physicians to spread the indications for this technique (2, 27, 40). Nowadays, endoscopic treatment may be suggested for treating level IIIA or even selected IIIB lesions instead of surgical approach, in patients with worsening clinical conditions, such as expanding pneumomediastinum/subcutaneous emphysema, high risk for mediastinitis, if without signs of actual mediastinitis, or prolonged mechanical ventilation without short-term perspective of weaning (40, 41, 43–45). The technique consists of rigid bronchoscopy and temporary placement of covered metallic or silicone stent over the laceration, allowing for granulation tissue to close the defect. It is suggested to keep the stent in position from 4 to 8 weeks, then it can be removed (46). This procedure is inherited by lung transplantation field, where it is applied in case of post-transplant tracheobronchial dehiscence (44). Complications reported in literature include stent migration, tracheal stenosis, mucus plugging and local infections (44, 47, 48). If benefits overcome these risks, stenting could be a valid surrogate of surgery, allowing for bridge treatment and delaying surgical approach after improving general conditions of the patient, or even for definitive repair, ensuring lower morbi-mortality rates especially in high-risk surgical candidates (34, 49, 50). The placement of nitinol-coated self-expandable metallic stents (n-SEMS) seems to be particularly interesting (33, 41, 43, 45) since it could apparently fit better in the airway than silicone ones, decreasing the risk of migration, while preserving the tracheal segment from air leakage.

TABLE 1 Significant studies focusing on management of post-intubation iatrogenic tracheal injuries.

Reference	No of patients	Cause	Site	Lenght	Cardillo grade	Management	Type of treatment	Success rate
Conti et al. (13)	30	Elective intubation 16	Posterior membrane 30	4.5 ± 1.5	NA	Conservative 28	Observation 15	86%
							Intubation 13	
		Emergency intubation 14			—	Endoscopic 0	—	—
					NA	Surgical 2	Posterolateral thoracotomy 2	0%
Cardillo et al. (8)	30	Elective intubation 22	NA	3.2 ± 1.1	I 3	Conservative 29	Glue application 29	100%
					II 24			
					IIIA 2			
		Emergency intubation 8			—	Endoscopic 0	—	—
					IIIB 1	Surgical 1	Posterolateral thoracotomy 1	100%
Schneider et al. (1)	29	Elective intubation 6	NA	4	NA	Conservative 11	Observation 3	100%
		Emergency intubation 10					Intubation 8	
		Tracheostomy 10			—	Endoscopic 0	—	—
		Other 3			NA	Surgical 18	Transtracheal 7	100%
							Posterolateral thoracotomy 11	
Gomez-Caro Andrés et al. (29)	18	Elective intubation 14	Posterior membrane 17	2.83 ± 1.02	NA	Conservative 17	NA	82%
		Emergency intubation 1	Carina 1		—	Endoscopic 0	—	—
		Tracheostomy 3			NA	Surgical 1	Cervicotomy 1	0%
Sippel et al. (30)	13	Elective intubation 4	Posterior membrane 9	4.4 ± 2.9	NA	Conservative 2	Intubation 2	100%
		Emergency intubation 8			—	Endoscopic 0	—	—
		Tracheostomy 1	Membranous-cartilaginous 4		NA	Surgical 11	Lateral thoracotomy 11	73%
Cardillo et al. (16)	62[a]	Elective intubation 51	NA	2.54	I 8	Conservative 55	Glue application 55	100%
		Emergency intubation 11			II 36			
					IIIA 11			
					—	Endoscopic 0	—	—
					IIIB 6	Surgical 7	Posterolateral thoracotomy 5	100%
					IV 1		VATS 1	
							Cervicotomy 1	
Herrmann et al. (31)	64	Elective intubation 19	NA	4	I 2	Conservative 21	Observation 2	100%
		Emergency intubation 17			II 14		Glue application 19	

(*continued*)

10.3389/fsurg.2023.1125997

TABLE 1 Continued

Reference	No of patients	Cause	Site	Lenght	Cardillo grade	Management	Type of treatment	Success rate
		Tracheostomy 26			IIIA 5			
		Other 2			—	Endoscopic 0	—	—
					IIIA 23	Surgical 43	Transcervical 29	77%
					IIIB 20		Lateral thoracotomy 14	
Fiorelli et al. (32)	6	Elective intubation 6	NA	3.5	II 3	Conservative 6	Glue application 6	83%
					IIIA 3			
					—	Endoscopic 0	—	—
					—	Surgical 0	—	—
Tazi-Mezalek et al. (33)]	35	Elective intubation 19	Posterior membrane 20	3.74 ± 1.76	NA	Conservative 24	Observation 7	96%
		Tracheostomy 16	Membranous-cartilaginous 14				Intubation 17	
			Anterior wall 1		NA (IIIB 1)	Endoscopic 8	Silicon Y stenting 7	62%
							Oesophageal stenting 1	
					IIIB 3	Surgical 3	NA	0%
Hussein et al. (34)	4	Emergency intubation 3	Posterior membrane 4	5.62	—	Conservative 0	—	—
		Tracheostomy 1			IIIA 4	Endoscopic 4	Nitinol stenting 4	100%
					—	Surgical 0	—	—
Carretta et al. (35)	36	Elective intubation 23	NA	3.5 ± 1	NA	Conservative 16	Observation[b]	94%
		Emergency intubation 7					Tracheostomy[b]	
		Tracheostomy 6			—	Endoscopic 0	—	—
					NA	Surgical 20	Lateral thoracotomy[b]	90%
							Cervicotomy[b] Transtracheal[b]	
da Silva Costa et al. (36)	2	Emergency intubation 2	NA	5.5	NA	Conservative 0	—	—
					NA	Endoscopic 0	—	—
					NA	Surgical 2	Combined VATS/transtracheal	100%
Welter et al. (37)	17	NA	NA	NA	NA	Conservative 0	—	—
					NA	Endoscopic 0	—	—
					NA	Surgical 18	Endotracheal 18	94%

(*continued*)

10.3389/fsurg.2023.1125997

10.3389/fsurg.2023.1125997

TABLE 1 Continued

Reference	No of patients	Cause		Site	Lenght	Cardillo grade		Management	Type of treatment	Success rate
San Gerardo Hospital[c]	14	Elective intubation 6		Posterior membrane 8	3.14 ± 1.09	II 4		Conservative 4	Intubation 4	100%
		Emergency intubation 4				IIIA 9		Endoscopic 10	Nitinol stenting 10	100%
		Tracheostomy 4		Membranous-cartilaginous 6		IIIB 1		Surgical 0	—	—

NA, not available data.
[a]30 patients from previous publication were included.
[b]Type of treatment is specified, whereas number of patients treated by a specific approach cannot be derived.
[c]Authors' personal experience.

Authors' personal experience

In the last three years, 14 patients with post-intubation ITIs were referred to the Department of Thoracic Surgery of our tertiary centre (San Gerardo Hospital, Monza, Italy). The injury was due to endotracheal tube mispositioning in 10 patients and emergency tracheotomy in 4 patients. It was along the tracheal posterior membrane in 8 cases (57%) and at the tracheal membrane-cartilaginous junction in the remaining patients. 4 lacerations were classified as level II, 9 as IIIA, 1 as IIIB. Upon multidisciplinary discussion, we have successfully treated all the patients, through conservative or endoscopic treatment, depending on patients' clinical and respiratory conditions, according to the in-hospital protocol reported in **Figure 1**: 4 patients (level II) were conservatively treated, 10 patients (9 IIIA and 1 IIIB) were endoscopically managed. The conservative treatment consisted of endotracheal tube proper positioning and observation. On the other hand, the endoscopic treatment consisted of n-SEMS placement through rigid bronchoscopy, within 72 h from detection of ITIs; 30-day morbidity and mortality rates were null, and the stent was removed 4–6 weeks later without complications. All the injuries were completely healed at 1-month, without any relapse at 6-month follow-up. We were prompted to endoscopically handle patients with level III injuries, instead of adopting a conservative strategy, because of their respiratory conditions: all the patients were still ventilatory-dependent, due to primary lung failure, without a perspective of weaning in short time. In such setting, we strongly believe that a conservative treatment could be hardly feasible.

Surgical treatment

Surgery is recommended for highly symptomatic patients with large level IIIA, especially in case of ineffective mechanical ventilation, or level IIIB lacerations, mainly when involving vascular structures or esophagus, as well as for level IV tears, or any lesion occurring with mediastinitis (22, 35, 38). Most authors agree that fit patients with rapidly worsening clinical conditions, despite previous conservative or endoscopic treatment, should undergo surgery, preferably within 48–72 h from the original event, to mitigate morbidity and mortality rates (2, 35, 50). Different surgical approaches are described in literature (2, 12): open, video-assisted thoracoscopy surgery (VATS), and endotracheal. The decision to perform one rather than others approach relies on the site and extent of injury, the emergency or elective setting, the experience of the center. Open techniques consist of posterolateral right thoracotomy (28), which was traditionally the approach of choice for emergency procedures and for middle or lower thirds tracheal injuries, and cervicotomy, as introduced by Angelillo-Mackinlay (51) in case of upper third lesions, possibly associated with sternal split if middle third is involved. VATS techniques include right thoracoscopy, as well as video-assisted transcervical-transtracheal approach, which was proposed by da Silva Costa and colleagues (36) introducing an endoscopic needle holder and a 0-degree camera though the tracheal incision. Either in open or

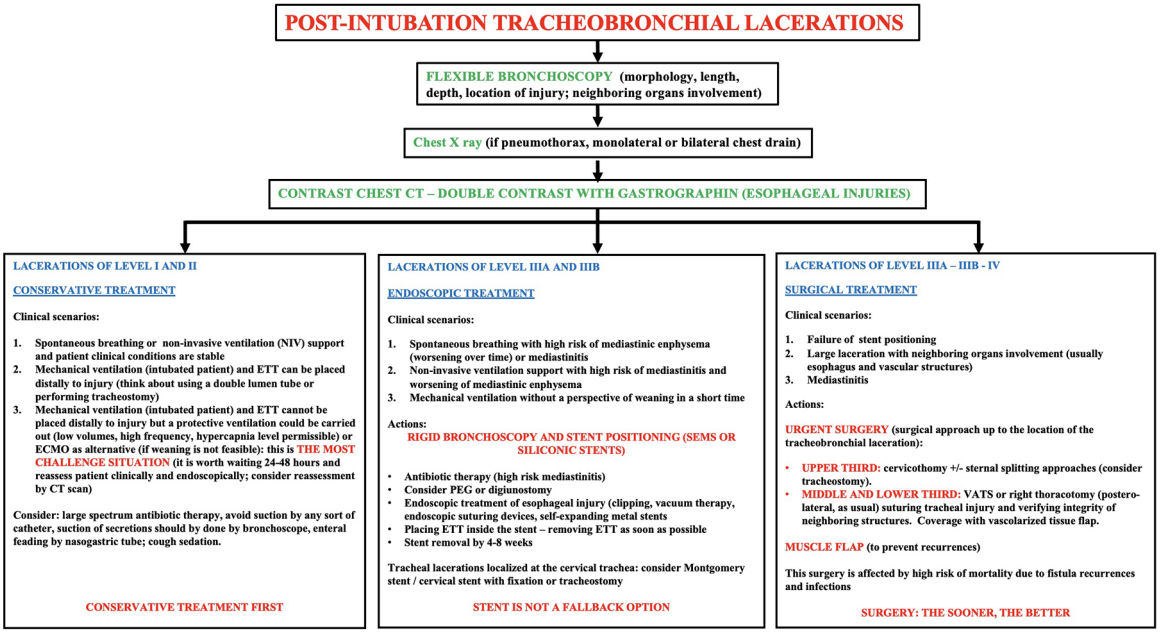

FIGURE 1
Diagnostic-therapeutic algorithm proposal for management of post-intubation tracheobronchial injuries.

VATS approach, continuous running or interrupted sutures are used, based on surgeons' choice. To prevent recurrences or fistulas, mainly in case of mediastinal inflammation or infection, pedicled muscle flaps are placed over the suture line (50). Another promising technique is the endotracheal repair, firstly described in 2011 by Welter and colleagues (37). It is performed using an endoscopic needle holder through rigid tracheoscopy, leading to a totally intraluminal repair, with lower surgical trauma and postoperative pain (37).

Conclusions

Post-intubation ITIs are rare complications of intubation or tracheostomy, nevertheless they are clinically significant due to their high morbidity and mortality rates. Keeping high clinical suspicion is of utmost importance, and patients with suggestive symptoms should early undergo thorough diagnostic workup, through radiologic and endoscopic assessment to detect and characterize the suspected injury. The management of post-intubation ITIs is still a matter of debate and definitive guidelines are still lacking. Procedural and instrumental innovation, as well as medical development, have likely revolutionized traditional management of post-intubation ITIs, broadening the use of conservative treatment and introducing the opportunity of endoscopic approach, with interesting success and reasonable complication rates. In such setting, endoscopic stenting may be a viable alternative to surgery and no more a fallback option, limiting surgical management to advanced stages or in case of failure of other treatments. On the other hand, surgery has become less and less invasive, leading to lower morbidity and mortality rates than in the past. Patients' general clinical and respiratory conditions must be considered in the management pathway. Anyway, multidisciplinary evaluation and personalized treatment of each patient at experienced centres are strongly recommended.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RO, FR, and EP contributed to conception and design of the study. RO and EP wrote the first draft of the manuscript. RO, FR, EP, MC wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Schneider T, Volz K, Dienemann H, Hoffmann H. Incidence and treatment modalities of tracheobronchial injuries in Germany. *Interact Cardiovasc Thorac Surg*. (2009) 8(5):571–6. doi: 10.1510/icvts.2008.196790

2. Miñambres E, Burón J, Ballesteros MA, Llorca J, Muñoz P, González-Castro A. Tracheal rupture after endotracheal intubation: a literature systematic review. *Eur J Cardiothorac Surg*. (2009) 35(6):1056–62. doi: 10.1016/j.ejcts.2009.01.053

3. Fiacchini G, Tricò D, Ribechini A, Forfori F, Brogi E, Lucchi M, et al. Evaluation of the incidence and potential mechanisms of tracheal complications in patients with COVID-19. *JAMA Otolaryngol Head Neck Surg*. (2021) 147(1):70. doi: 10.1001/jamaoto.2020.4148

4. Prokakis C, Koletsis EN, Dedeilias P, Fligou F, Filos K, Dougenis D. Airway trauma: a review on epidemiology, mechanisms of injury, diagnosis and treatment. *J Cardiothorac Surg*. (2014) 9:117. doi: 10.1186/1749-8090-9-117

5. Massard G, Rougé C, Dabbagh A, Kessler R, Hentz JG, Roeslin N, et al. Tracheobronchial lacerations after intubation and tracheostomy. *Ann Thorac Surg*. (1996) 61(5):1483–7. doi: 10.1016/0003-4975(96)00083-5

6. Trottier SJ, Hazard PB, Sakabu SA, Levine JH, Troop BR, Thompson JA, et al. Posterior tracheal wall perforation during percutaneous dilational tracheostomy: an investigation into its mechanism and prevention. *Chest*. (1999) 115(5):1383–9. doi: 10.1378/chest.115.5.1383

7. Misak VB, Beraković AP, Vukusić I, Kogler J, Pazanin L, Ozegović SO. Postintubation tracheal injuries–case series and literature review. *Acta Clin Croat*. (2012) 51(3):467–71. PMID: 23330416

8. Cardillo G, Carbone L, Carleo F, Batzella S, Jacono Rd, Lucantoni G, et al. Tracheal lacerations after endotracheal intubation: a proposed morphological classification to guide non-surgical treatment. *Eur J Cardiothorac Surg*. (2010) 37(3):581–7. doi: 10.1016/j.ejcts.2009.07.034

9. Jougon J, Ballester M, Choukroun E, Dubrez J, Reboul G, Velly JF. Conservative treatment for postintubation tracheobronchial rupture. *Ann Thorac Surg*. (2000) 69(1):216–20. doi: 10.1016/S0003-4975(99)01129-7

10. Singh P, Wojnar M, Malhotra A. Iatrogenic tracheal laceration in the setting of chronic steroids. *J Clin Anesth*. (2017) 37:38–42. doi: 10.1016/j.jclinane.2016.10.043

11. Farzanegan R, Alijanipour P, Akbarshahi H, Abbasidezfouli A, Pejhan S, Daneshvar A, et al. Major airways trauma, management and long term results. *Ann Thorac Cardiovasc Surg*. (2011) 17(6):544–51. doi: 10.5761/atcs.oa.11.01679

12. Grewal HS, Dangayach NS, Ahmad U, Ghosh S, Gildea T, Mehta AC. Treatment of tracheobronchial injuries: a contemporary review. *Chest*. (2019) 155(3):595–604. doi: 10.1016/j.chest.2018.07.018

13. Conti M, Fournier C, Hysi I, Ramon PP, Wurtz A. Conservative management of postintubation tracheal membrane ruptures. *Intensive Care Med*. (2010) 36(9):1622–3. doi: 10.1007/s00134-010-1906-5

14. Boutros J, Marquette CH, Ichai C, Leroy S, Benzaquen J. Multidisciplinary management of tracheobronchial injury. *Eur Respir Rev*. (2022) 31(163):210126. doi: 10.1183/16000617.0126-2021

15. Marty-Ané CH, Picard E, Jonquet O, Mary H. Membranous tracheal rupture after endotracheal intubation. *Ann Thorac Surg*. (1995) 60(5):1367–71. doi: 10.1016/0003-4975(95)00643-Y

16. Cardillo G, Ricciardi S, Forcione AR, Carbone L, Carleo F, di Martino M, et al. Post-intubation tracheal lacerations: risk-stratification and treatment protocol according to morphological classification. *Front Surg*. (2022) 9:1049126. doi: 10.3389/fsurg.2022.1049126

17. Mussi A, Ambrogi MC, Ribechini A, Lucchi M, Menoni F, Angeletti CA. Acute major airway injuries: clinical features and management. *Eur J Cardiothorac Surg*. (2001) 20(1):46–51. discussion 51-2. doi: 10.1016/S1010-7940(01)00702-3

18. Koletsis E, Prokakis C, Baltayiannis N, Apostolakis E, Chatzimichalis A, Dougenis D. Surgical decision making in tracheobronchial injuries on the basis of clinical evidences and the injury's anatomical setting: a retrospective analysis. *Injury*. (2012) 43(9):1437–41. doi: 10.1016/j.injury.2010.08.038

19. Barnhart GR, Brooks JW, Kellum JM. Pneumoperitoneum resulting from tracheal rupture following blunt chest trauma. The journal of trauma: injury. *Infect Crit Care*. (1986) 26(5):486–8. doi: 10.1097/00005373-198605000-00015

20. Chen JD, Shanmuganathan K, Mirvis SE, Killeen KL, Dutton RP. Using CT to diagnose tracheal rupture. *AJR Am J Roentgenol*. (2001) 176(5):1273–80. doi: 10.2214/ajr.176.5.1761273

21. Palas J, Matos AP, Mascarenhas V, Herédia V, Ramalho M. Multidetector computer tomography: evaluation of blunt chest trauma in adults. *Radiol Res Pract*. (2014) 2014:864369. doi: 10.1155/2014/864369

22. Deja M, Menk M, Heidenhain C, Spies CD, Heymann A, Weidemann H, et al. Strategies for diagnosis and treatment of iatrogenic tracheal ruptures. *Minerva Anestesiol*. (2011) 77(12):1155–66.

23. Exarhos DN, Malagari K, Tsatalou EG, Benakis SV, Peppas C, Kotanidou A, et al. Acute mediastinitis: spectrum of computed tomography findings. *Eur Radiol*. (2005) 15(8):1569–74. doi: 10.1007/s00330-004-2538-3

24. Scaglione M, Romano S, Pinto A, Sparano A, Scialpi M, Rotondo A. Acute tracheobronchial injuries: impact of imaging on diagnosis and management implications. *Eur J Radiol*. (2006) 59(3):336–43. doi: 10.1016/j.ejrad.2006.04.026

25. Tack D, Defrance P, Delcour C, Gevenois PA. The CT fallen-lung sign. *Eur Radiol*. (2000) 10(5):719–21. doi: 10.1007/s003300050992

26. Gray ND, Miller K, Brath L, Shepherd W. Tracheal ring herniation. *J Bronchology Interv Pulmonol*. (2010) 17(1):54–5. doi: 10.1097/LBR.0b013e3181c7fe9c

27. Ross HM, Grant FJ, Wilson RS, Burt ME. Nonoperative management of tracheal laceration during endotracheal intubation. *Ann Thorac Surg*. (1997) 63(1):240–2. doi: 10.1016/S0003-4975(96)01077-6

28. Grillo HC. Surgical treatment of postintubation tracheal injuries. *J Thorac Cardiovasc Surg*. (1979) 78(6):860–75. doi: 10.1016/S0022-5223(19)38030-4

29. Gómez-Caro Andrés A, Moradiellos Díez FJ, Ausín Herrero P, Díaz-Hellín Gude V, Larrú Cabrero E, de Miguel Porch E, et al. Successful conservative management in iatrogenic tracheobronchial injury. *Ann Thorac Surg*. (2005) 79(6):1872–8. doi: 10.1016/j.athoracsur.2004.10.006

30. Sippel M, Putensen C, Hirner A, Wolff M. Tracheal rupture after endotracheal intubation: experience with management in 13 cases. *Thorac Cardiovasc Surg*. (2006) 54(1):51–6. doi: 10.1055/s-2005-865917

31. Herrmann D, Volmerig J, Al-Turki A, Braun M, Herrmann A, Ewig S, et al. Does less surgical trauma result in better outcome in management of iatrogenic tracheobronchial laceration? *J Thorac Dis*. (2019) 11(11):4772–81. doi: 10.21037/jtd.2019.10.22

32. Fiorelli A, Cascone R, di Natale D, Pierdiluca M, Mastromarino R, Natale G, et al. Endoscopic treatment with fibrin glue of post-intubation tracheal laceration. *J Vis Surg*. (2017) 3:102. doi: 10.21037/jovs.2017.06.12

33. Tazi-Mezalek R, Musani AI, Laroumagne S, Astoul PJ, D'Journo XB, Thomas PA, et al. Airway stenting in the management of iatrogenic tracheal injuries: 10-year experience. *Respirology*. (2016) 21(8):1452–8. doi: 10.1111/resp.12853

34. Hussein E, Pathak V, Shepherd RW, Shojaee S. Bronchoscopic management of iatrogenic tracheal laceration using polyurethane-covered nitinol tracheal stents. *J Trauma Acute Care Surg*. (2016) 81(5):979–83. doi: 10.1097/TA.0000000000001233

35. Carretta A, Melloni G, Bandiera A, Negri G, Voci C, Zannini P. Conservative and surgical treatment of acute posttraumatic tracheobronchial injuries. *World J Surg*. (2011) 35(11):2568–74. doi: 10.1007/s00268-011-1227-z

36. da Silva Costa A, Juliano Perfeito JA, Succi JE, Villaça Leão LE, Rymkiewicz E, da Matta CAS, et al. A video-assisted endotracheal suture technique for correction of distal tracheal laceration after intubation. *Ann Thorac Surg*. (2012) 93(6):2073–5. doi: 10.1016/j.athoracsur.2011.11.018

37. Welter S, Krbek T, Halder R, Stamatis G. A new technique for complete intraluminal repair of iatrogenic posterior tracheal lacerations. *Interact Cardiovasc Thorac Surg*. (2011) 12(1):6–9. doi: 10.1510/icvts.2010.248641

38. Mussi A, Ambrogi MC, Menconi G, Ribechini A, Angeletti CA. Surgical approaches to membranous tracheal wall lacerations. *J Thorac Cardiovasc Surg*. (2000) 120(1):115–8. doi: 10.1067/mtc.2000.107122

39. Borasio P, Ardissone F, Chiampo G. Post-intubation tracheal rupture. A report on ten cases. *Eur J Cardiothorac Surg*. (1997) 12(1):98–100. doi: 10.1016/S1010-7940(97)00111-5

40. Marquette CH, Bocquillon N, Roumilhac D, Nevière R, Mathieu D, Ramon P. Conservative treatment of tracheal rupture. *J Thorac Cardiovasc Surg*. (1999) 117(2):399–401. doi: 10.1016/S0022-5223(99)70443-5

41. Yamamoto S, Endo S, Endo T, Mitsuda S. Successful silicon stent for life-threatening tracheal wall laceration. *Ann Thorac Cardiovasc Surg*. (2013) 19(1):49–51. doi: 10.5761/atcs.cr.11.01768

42. Son BS, Cho WH, Kim CW, Cho HM, Kim SH, Lee SK, et al. Conservative extracorporeal membrane oxygenation treatment in a tracheal injury: a case report. *J Cardiothorac Surg*. (2015) 10:48. doi: 10.1186/s13019-015-0252-7

43. Conti M, Pougeoise M, Wurtz A, Porte H, Fourrier F, Ramon P, et al. Management of postintubation tracheobronchial ruptures. *Chest*. (2006) 130(2):412–8. doi: 10.1378/chest.130.2.412

44. Fruchter O, Raviv Y, Fox BD, Kramer MR. Removal of metallic tracheobronchial stents in lung transplantation with flexible bronchoscopy. *J Cardiothorac Surg*. (2010) 5:72. doi: 10.1186/1749-8090-5-72

45. Mughal MM, Gildea TR, Murthy S, Pettersson G, DeCamp M, Mehta AC. Short-term deployment of self-expanding metallic stents facilitates healing of bronchial dehiscence. *Am J Respir Crit Care Med*. (2005) 172(6):768–71. doi: 10.1164/rccm.200410-1388OC

46. Murthy SC, Gildea TR, Mehta AC. Removal of self-expandable metallic stents: is it possible? *Semin Respir Crit Care Med*. (2004) 25(4):381–5. doi: 10.1055/s-2004-832711

47. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: ischemia, dehiscence, and stenosis. *Proc Am Thorac Soc*. (2009) 6 (1):79–93. doi: 10.1513/pats.200808-094GO

48. Bottero S, Meucci D, Trozzi M, Carotti A. Dehiscence of bronchial anastomosis after lung transplantation: a successful unconventional treatment. *Ann Thorac Surg*. (2018) 106(2):e81–3. doi: 10.1016/j.athoracsur.2018.02.058

49. Marchese R, Mercadante S, Paglino G, Agozzino C. Villari P, di giacomo G. Tracheal stent to repair tracheal laceration after a double-lumen intubation. *Ann Thorac Surg*. (2012) 94(3):1001–3. doi: 10.1016/j.athoracsur.2011.12.080

50. Gabor S, Renner H, Pinter H, Sankin O, Maier A, Tomaselli F, et al. Indications for surgery in tracheobronchial ruptures. *Eur J Cardiothorac Surg*. (2001) 20(2):399–404. doi: 10.1016/S1010-7940(01)00798-9

51. Angelillo-Mackinlay T. Transcervical repair of distal membranous tracheal laceration. *Ann Thorac Surg*. (1995) 59(2):531–2. doi: 10.1016/0003-4975(94)00882-8

frontiers | Frontiers in Surgery

TYPE Systematic Review
PUBLISHED 14 February 2023
DOI 10.3389/fsurg.2023.1039615

OPEN ACCESS

EDITED BY
Filippo Lococo,
Agostino Gemelli University Polyclinic (IRCCS), Italy

REVIEWED BY
Bruno Lorenzi,
Broomfield Hospital, United Kingdom
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

*CORRESPONDENCE
Liangshuang Jiang
jls18980070581@163.com

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 08 September 2022
ACCEPTED 10 January 2023
PUBLISHED 14 February 2023

CITATION
Gong S, Rao X, Yuan Y, Yao X, Li G, Wang N, Li D and Jiang L (2023) Clinical-pathological features and perioperative outcomes of mediastinoscopy vs. thoracoscopy esophagectomy in esophageal cancer: A meta-analysis.
Front. Surg. 10:1039615.
doi: 10.3389/fsurg.2023.1039615

Clinical-pathological features and perioperative outcomes of mediastinoscopy vs. thoracoscopy esophagectomy in esophageal cancer: A meta-analysis

Sheng Gong[1], Xin Rao[1], Ye Yuan[1], Xiaojun Yao[1], Gang Li[1], Ning Wang[2], Dan Li[1] and Liangshuang Jiang[1]*

[1]Department of Thoracic Surgery, The Public Health Clinical Center of Chengdu, Chengdu, China, [2]Department of Public Health, Chengdu Medicine College, Chengdu, China

Objective: To compare the clinicopathological features and perioperative outcomes of video-assisted mediastinoscopy esophagectomy (VAME) compared to video-assisted thoracoscopy esophagectomy (VATE) in esophageal cancer.
Methods: We comprehensively searched online databases (PubMed, Embase, Web of Science and Wiley online library) to find available studies exploring the clinicopathological features and perioperative outcomes between VAME and VATE in esophageal cancer. Relative risk (RR) with 95% confidence interval (CI) and standardized mean difference (SMD) with 95% CI were used to evaluate the perioperative outcomes and clinicopathological features.
Results: A total of seven observational studies and one randomized controlled trial involving 733 patients were considered eligible for this meta-analysis, of which 350 patients underwent VAME in contrast to 383 patients underwent VATE. Patients in the VAME group had more pulmonary comorbidities (RR = 2.18, 95% CI 1.37–3.46, $P = 0.001$). The pooled results showed that VAME shortened the operation time (SMD = –1.53, 95% CI –2.308––0.76, $P = 0.000$), and retrieved less total lymph nodes (SMD = –0.70, 95% CI –0.90––0.50, $P = 0.000$). No differences were observed in other clinicopathological features, postoperative complications or mortality.
Conclusions: This meta-analysis revealed that patients in the VAME group had more pulmonary disease before surgery. The VAME approach significantly shortened the operation time and retrieved less total lymph nodes and did not increase intra- or postoperative complications.

KEYWORDS
esophageal cancer, mediastinoscopy, thoracoscopy, esophagectomy, perioperative outcomes

Introduction

Esophageal cancer is the eighth most frequently diagnosed cancer worldwide accounting for millions of deaths each year due to its poor prognosis especially in Asian countries (1, 2). Surgery plays a substantial role in treating esophageal cancer, with the rapid development of neoadjuvant and adjuvant therapies (3, 4). During the past few decades, minimally invasive surgery has gained steady progress in the field of esophagectomy, and minimally invasive esophagectomy could achieve equal or better oncologic outcomes (5, 6). Minimally invasive esophagectomy has become the chief choice in many institutions.

Traditional minimally invasive esophagectomy releases the esophagus through the thoracic cavity, known as video-assisted thoracoscopy esophagectomy (VATE) (7). In this operation, unilateral pulmonary ventilation cessation or carbon dioxide artificial pneumothorax is

imperative to make adequate space for operation, which inevitably narrow the surgical indications, particularly for elderly patients or those with poor cardiopulmonary function. The novel minimally invasive esophagectomy, video-assisted mediastinoscopy esophagectomy (VAME), in which the thoracic segment of the esophagus is released through the posterior mediastinum under direct vision with the assistance of mediastinoscopy, without interrupting the breath and oxygenation during the operation, hopefully reducing trauma and gives operation chance for those who could not put up with oxygenation reduction, particularly for those with poor cardiopulmonary function (8, 9).

Since the introduction of VAME, surgeons focused on this field have attempted to apply this technology to appropriate patients. Case series and cohort studies have been reported, while the perioperative results were not consistent or even opposed in certain outcomes (10–25), such as operation time, lymph node retrieval or postoperative complications. Considering that only a limited number of studies with small sample size have been conducted to compare the superior and inferior of VAME and VATE, it is reasonable to perform a meta-analysis to pool the results from published studies to provide relatively valid evidence and conclusions.

Materials and methods

Literature search and selection

A systematic and comprehensive literature search of the online databases PubMed, Embase (*via* OVID), Web of Science and Wiley online library was performed to identify potential studies published before November 23, 2021 that explored the perioperative outcomes as well as clinicopathological features in esophageal cancer patients who received VAME compared to those received VATE. References of the included studies were manually reviewed to identify additional potential available studies. Key words and related variants were used in the search, including esophageal cancer, esophageal neoplasm, video-assisted, mediastinoscopy, thoracoscope, etc. The searching strategy was included as supplementary material. We evaluated all searched results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (5) guidelines.

Study inclusion/exclusion criteria

Studies satisfying the following criteria were considered eligible for this meta-analysis.

Inclusion criteria: randomized controlled trials (RCTs) or observational studies that investigated the clinical effectiveness of VAME compared with VATE; one or more interest outcomes were reported: operation time, retrieved lymph nodes, intraoperative blood loss, postoperative complications, mortality, duration of postoperative hospitalization; only studies reported in English were included.

Exclusion criteria: studies without interested parameters including noncomparative studies, reviews, abstracts, case or series reports, new technical studies and letters, robot-assisted surgery was also considered ineligible.

Definition of VAME

The patient was placed in the supine position with bilateral lung ventilation. An incision was made through the left neck, and the cervical surgery team performed upper and middle esophageal mobilization with the video-assisted mediastinoscope *via* the left cervical approach. The cervical esophagus should be exposed carefully to preserve the recurrent laryngeal nerve. Care must be taken to avoid any damage to the membrane of trachea and main bronchus when dividing the area of the tracheal bifurcation. The abdominal surgery team performed the lower esophageal and gastric dissection *via* a transabdominal approach either simultaneously or subsequently.

Data extraction and quality assessment

Data were extracted independently by two investigators, and conflicts were adjudicated by team discussion. The following outcomes were used to compare the two surgical methods: operation time, lymph nodes retrieved, intraoperative blood loss, postoperative complications, mortality, and duration of postoperative hospitalization. Available clinicopathological features were also compared.

The Cochrane handbook risk of bias (RoB2—2019) was used to assess the risk of bias in RCTs. Newcastle-Ottawa Scale (NOS) was employed to assess the quality level of non-randomized studies (26). The NOS contains three items: patient selection, comparability of the study groups and assessment of outcome. A high-quality study was defined as a study with quality scores ≥7 (**Table 1**). Any disagreement was resolved *via* team discussion.

Statistical analysis

The relative ratio (RR) and standardized mean difference (SMD) with 95% CIs were calculated for categorical data and continuous data respectively. We used the Cochran chi-square test and I^2 to examine the heterogeneity among studies. Statistical heterogeneity among studies was defined as an I^2 statistic greater than 50%. A fixed-effects model was preferred to a random-effects model when there was no statistically significant heterogeneity. We planned to perform and examine a funnel plot, as well as Begg's test and Egger's test to explore possible publication biases (27). However, we would not produce any funnel plots if the number of researches included was less than 10. Statistical significance was taken as 2-sided ($P < 0.05$). Theanalysis was conducted with STATA 14.0 software (Stata Corporation, College Station, TX).

Results

Study selection

Records were screened from previously mentioned online databases. A manual search and inspection of the reference lists identified no additional relevant studies. After exclusion of

TABLE 1 Basic characteristics of included studies.

Authors	Publishing year	Country	Study period	Sample size (VAME/ VATE)	Age (years) (MAE/ TAE)	TNM stage	Pathology			NOS	Study design
							ESCC	EAC	Other		
Koide N et al	2011	Japan	1997–2009	17/37	Mean:66.3 ± 12.9/ 65.3 ± 8.9	I/II or more	49	0	5	8	ROS
Feng MX et al	2011	China	2000–2009	27/27	Median:58.6 (37–79)/61.1 (46–76)	0-IV	54	0	0	8	Pair-matched case–control study
Nomura T et al	2016	Japan	2001–2005	20/15	Mean:64/65	NA	NR			6	ROS
Wang QY et al	2014	China	2005–2010	109/58	Median:62 (54–78)/62 (55–72)	T1	167	0	0	5	ROS
Jin YX et al	2018	China	2016–2017	19/30	Mean:62.50 ± 8.46/59.74 ± 7.92	I–IIIB	48	1	0	6	ROS
Guo L et al	2020	China	Jun 2015 -Jan2019	28/48	Mean: 66.71 ± 8.10/ 63.69 ± 6.03	0 -IIIc -	76	0	0	7	Retrospective case-control study
Liu W et al	2020	China	Jan 2018 to Dec 2019	30/68	Mean: 58.03 ± 8.79/56.97 ± 8.88	cT1-N0-1M0	98	0	0	8	ROS
Shi KF et al	2021	China	NA	100/100	66.3 ± 6.7/ 66.3 ± 6.1	I–III	200	0	0	NA	RCT

VAME, video-assisted mediastinoscopy esophagectomy; VATE, video-assisted thoracoscopic esophagectomy; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; NOS, Newcastle-Ottawa Scale; NR, not reported; ROS, retrospective observational study; RCT, randomized controlled trial.

duplications, a total of 185 studies remained. Then 166 records were immediately excluded by screening the titles and abstracts. We read the full text of the remaining 19 studies carefully, and 8 studies meeting our criteria were finally considered eligible in this meta-analysis (18–25). The flow chart of the literature evaluation process in our meta-analysis is presented in **Figure 1**.

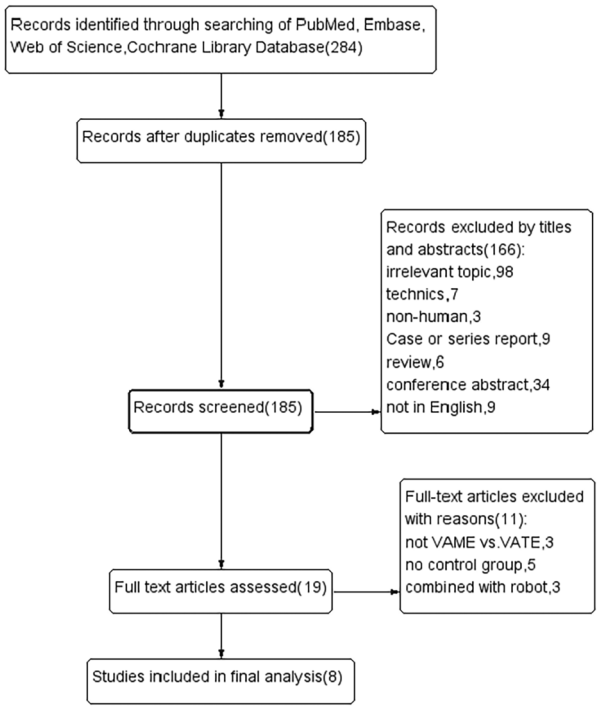

FIGURE 1
Flow diagram of selecting studies.

Baseline characteristics of the included studies

Six of eight studies were conducted in China and another two were conducted in Japan. Seven studies were retrospective observational studies, of which one was a pair-matched case-control study, and the other one was a RCT. Data from a total of 733 patients were recorded, of which 350 patients underwent VAME in contrast to 383 patients underwent VATE. Patients in the VATE group received thoraco-laparoscopic three-incision esophagectomy, namely, the McKeown esophagectomy, while patients in the VAME group received mediastinoscopy combined laparoscopy or laparotomy esophagectomy. The main data extracted from the included studies are presented in **Table 1**.

Quality assessment

Quality assessment results of the observational studies were depicted in **Table 1** and the summary figure of the RCT was depicted in **Figure 2**. Four out of the seven observational studies were ranked with medium quality (18, 20, 22, 24), while the other three were ranked with high quality (19, 21, 25) (**Table 1**). The RCT arose some concerns regarding the risk of bias (23).

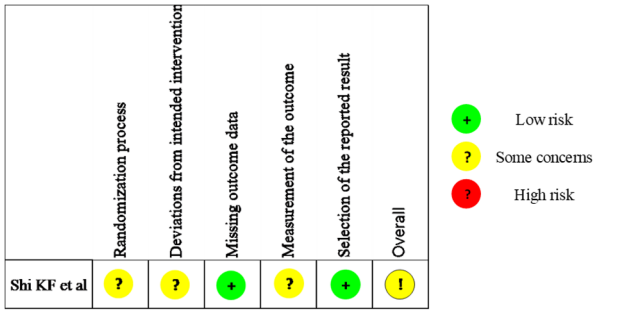

FIGURE 2
Risk of bias assessment of the included randomized controlled trial.

Clinical-pathological features

Clinical parameters, including age, sex, comorbidities and pathology parameters including pathological type, tumor stage and tumor location were obtained. The pooled results revealed no significant difference in age (fixed effect: SMD = 0.00, 95% CI −0.18–0.19, $P = 0.966$; $I^2 = 13.2\%$) or sex (fixed effect: RR = 1.03, 95% CI 0.94–1.13, $P = 0.546$; $I^2 = 0\%$) in the VAME group compared to the VATE group. Patients in the VAME group had more pulmonary disease (fixed effect: RR = 2.18, 95% CI 1.37–3.46, $P = 0.001$; $I^2 = 0\%$), but not other comorbidities including hypertension (fixed effect: RR = 1.13, 95% CI 0.59–2.18, $P = 0.716$; $I^2 = 0\%$), diabetes (fixed effect: RR = 1.20, 95% CI 0.60–2.40, $P = 0.612$; $I^2 = 0\%$) and cardiac disease (fixed effect: RR = 2.00, 95% CI 0.88–4.56, $P = 0.098$; $I^2 = 0\%$) (Figure 3, Table 2).

No differences were observed in pathological type (fixed effect: RR = 1.04, 95% CI 0.94–1.14, $P = 0.432$; $I^2 = 16.1\%$) in the VAME group compared with the VATE group. The pooled results indicated no difference regarding tumor stage in the VAME group (fixed effect: RR = 0.98, 95% CI 0.88–1.10, $P = 0.7204$; $I^2 = 0\%$) or tumor location (fixed effect: RR = 0.88, 95% CI 0.59–1.30, $P = 0.513$; $I^2 = 0\%$) compared to the VATE group (Figure 4, Table 2).

Intraoperative outcomes

We retrieved intraoperative data including operation time, intraoperative blood loss and total lymph nodes retrieved. Meta-analysis results indicated a shorter operation time (random effect: SMD = −1.53, 95% CI −2.308–−0.76, $P = 0.000$; $I^2 = 92.9\%$) and less total lymph nodes (fixed effect: SMD = −0.70, 95% CI −0.90–−0.50, $P = 0.000$; $I^2 = 20.4\%$) in the VAME group, but no difference in intraoperative blood loss (random effect: SMD = −0.37, 95% CI −1.03–0.29, $P = 0.275$; $I^2 = 92.3\%$) compared to the VATE group (Figure 5, Table 3).

Postoperative outcomes

Short-term postoperative outcomes for analysis included length of postoperative hospital stay and specific complications such as laryngeal recurrent nerve injury, anastomotic leak, postoperative pneumonia, chylothorax, arrhythmia and mortality. Meta-analysis indicated no difference in the duration of postoperative hospital stay in the VAME group compared with the VATE group (random effect: SMD = −0.21, 95% CI −0.72–0.31, $P = 0.434$; $I^2 = 76.1\%$). No differences were observed regarding postoperative complications including anastomotic leakage(fixed effect: RR = 1.02, 95% CI 0.69–1.516, $P = 0.404$; $I^2 = 0\%$), postoperative pulmonary complications (random effect: RR = 0.80, 95% CI 0.34–1.86, $P = 0.050$; $I^2 = 62.0\%$), pneumonia(random effect: RR = 0.54, 95% CI 0.15–1.90, $P = 0.335$; $I^2 = 82.5\%$) or laryngeal recurrent nerve injury rate (random effect: RR = 2.24 95% CI 0.93–5.39, $P = 0.071$; $I^2 = 51.5\%$), chylothorax (fixed effect: RR = 0.34, 95% CI 0.11–1.02, $P = 0.055$; $I^2 = 0\%$), arrhythmia(fixed effect: RR = 0.72, 95% CI 0.35–1.46, $P = 0.360$;

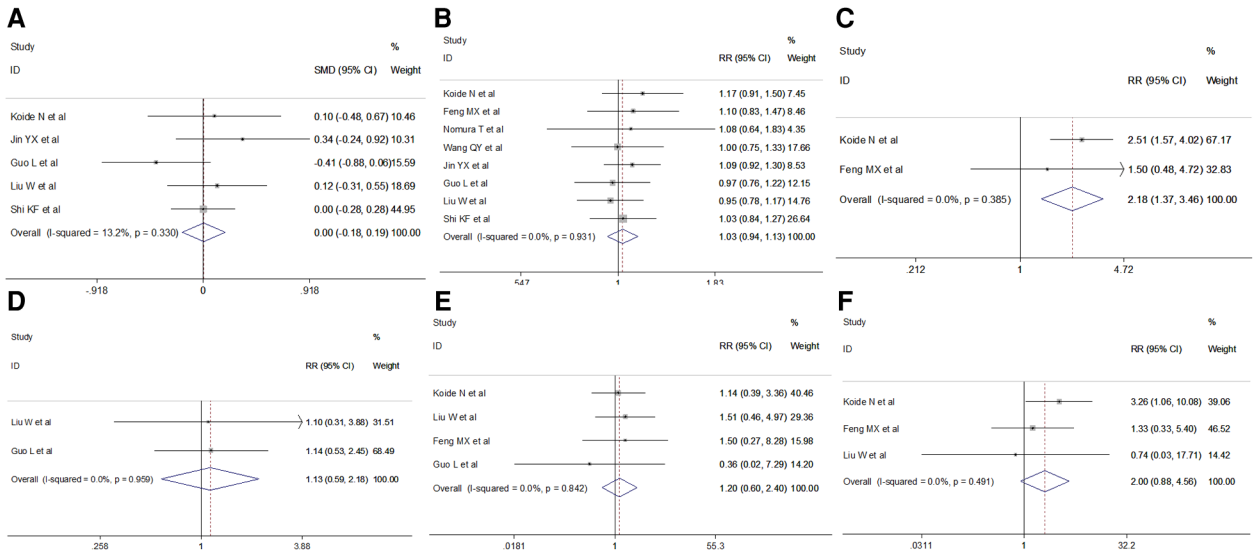

FIGURE 3
Meta-analysis of clinical features: (A) Age; (B) Gender; (C) Pulmonary disease; (D) Hypertension; (E) Diabetes; (F) Cardiac disease.

TABLE 2 Meta-analysis of clinical-pathological features.

Analysis item	No. of studies	Effects model	RR/SWD (95% CI)	Significance	Heterogeneity test		
					Chi^2	I^2	*P*
Age	5	Fixed	SMD = 0.00, 95% CI −0. 18–0.19	$P = 0.966$	4.61	13.2	0.330
Sex	8	Fixed	RR = 1.03, 95% CI 0.94–1.13	$P = 0.546$	2.45	0	0.931
Hypertension	2	Fixed	RR = 1.13, 95% CI 0.59–2.18	$P = 0.716$	0	0	0.959
Pulmonary disease	2	Fixed	RR = 2.18, 95% CI 1.37–3.46	$P = 0.001$	0.76	0	0.385
Diabetes	4	Fixed	RR = 1.20, 95% CI 0.60–2.40	$P = 0.612$	0.83	0	0.842
Cardiac disease	3	Fixed	RR = 2.00, 95% CI 0.88–4.56	$P = 0.098$	1.42	0	0.491
Tumor length	3	Fixed	SMD = −0.02, 95% CI −0.45–0.40	$P = 0.917$	0.01	0	0.749
Pathology (ESCC vs others)	4	Fixed	RR = 1.04, 95% CI 0.94–1.14	$P = 0.432$	3.57	16.1	0.311
Overall stage (II–IV vs 0–I)	6	Fixed	RR = 0.98, 95% CI 0.88–1.10	$P = 0.720$	1.01	0	0.908
Tumor location (cervical/upper thoracia vs middle thoracic/ lower thoracic/ abdominal esophagus)	5	Fixed	RR = 0.88, 95% CI 0.59–1.30	$P = 0.513$	1.30	0	0.861

RR, relative risk; SMD, standardized mean difference; CI, confidence interval; ESCC, esophageal squamous cell carcinoma.

$I^2 = 0\%$) and mortality(fixed effect: RR = 0.75, 95% CI 0.16–3.58, $P = 0.722$; $I^2 = 0\%$) in the VAME group compared with the VATE group (Figure 6, Table 3).

Sensitivity analysis and publication bias

We did not perform sensitivity analysis and funnel plots because the number of included researches was less than 10.

Discussion

As a newly developed surgical method, VAME has drawn a great body of attention since its first description in early 1990 (28). VAME overcomes the defects of visual field defects of blunt and blind operations in traditional transhiatal esophagectomy and enables surgeons to dissect the esophagus under direct vision though mediastinoscopy (29). Meanwhile, it adapts to patients in weak physical conditions, such as those combined with cardiopulmonary disease or aging patients to reduce postoperative complications (30). Previous reports have declared that this new approach has clinical advantages over the VATE approach. Considering that only a scarce number of studies with relatively limited sample sizes have been published, the evidence is patchy and the conclusion unclear. Therefore, we conducted this meta-analysis to comprehensively determine the strengths and weaknesses of VAME compared to VATE in esophageal cancer and try to provide solid evidence. To our knowledge, this is the first comprehensive meta-analysis on this topic.

In our meta-analysis, we included a total of eight studies, of which 350 esophageal cancer patients underwent VAME and 383

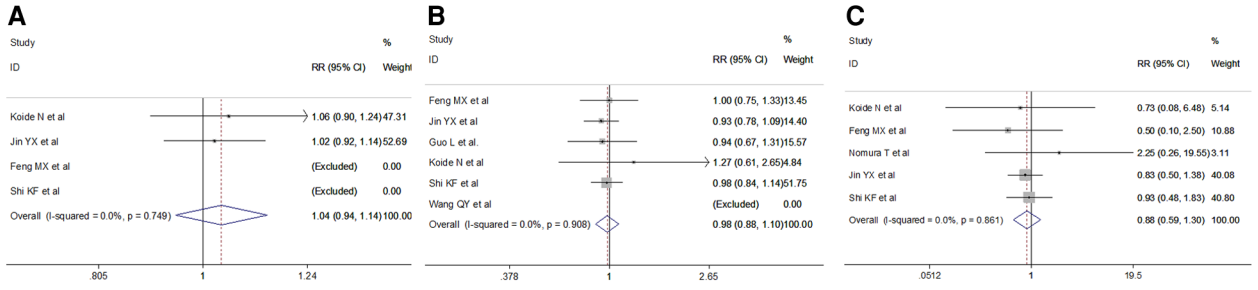

FIGURE 4
Meta-analysis of pathological features: (A) Pathology; (B) Stage; (C) Tumor location.

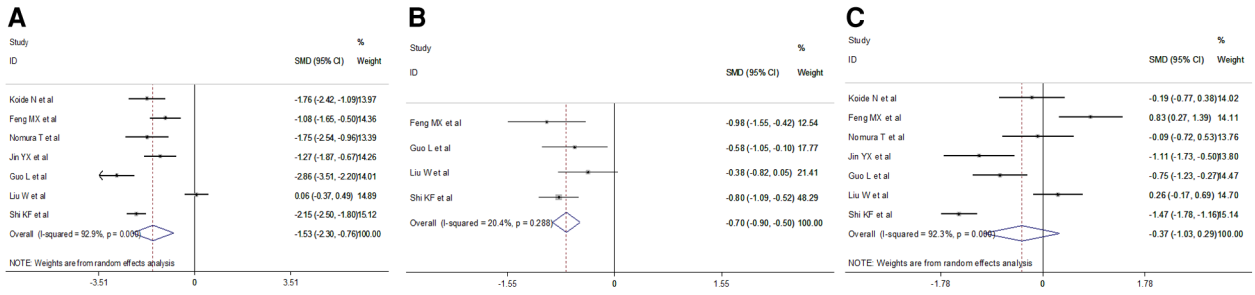

FIGURE 5
Meta-analysis of intraoperative outcomes: (A) Operation time; (B) Total lymph node retrieved; (C) Intraoperative blood loss.

patients underwent VATE. This meta-analysis revealed that the VAME approach significantly shortened the operation time. Since surgery could be conducted more smoothly without having to change patients' positions in the VAME approach and could also be conducted by two teams simultaneously, while the thoracic segment of esophagus has to be loosened in a lateral position and the neck and abdominal approach could only be conducted in a supine position in the VATE approach. In order to reduce the heterogeneity, we did not included studies which compared robot-assisted transmediastinal esophagectomy with VATE for the much difference between robot-assisted and video-assisted surgery.

However, the VAME group retrieved less total lymph nodes than the VATE group. Lower thoracic mediastinal and abdominal lymph node dissection during the VAME approach were possible and not different compared to the VATE approach. Owing to the limited space and vision in the mediastinum, lymph node dissection in the middle mediastinum especially around the tracheal bifurcation was much more difficult. This revealed the defect of a less radical option for thoracic esophageal cancer due to view limitations and insufficient mediastinal lymphadenectomy compared with VATE (30). Lymph node metastasis along the recurrent laryngeal nerve is common in esophageal cancer and its dissection is of significance to improve long-term outcomes (31). Hence, some surgeons have suggested that VAME is suitable for patients without obvious enlargement of mediastinal lymph nodes. For patients with early-stage esophageal cancer, VAME can achieve parallel therapeutic effects.

Regarding postoperative complications, no difference was observed in common complications after esophagectomy. The VAME approach may resulted in relatively high recurrent laryngeal nerve injury rate or hoarse in the surgeons' early learning period. As summarized by Jin YX and colleagues (22), manipulation close to the esophagus and compression or stretching of adjacent tissues by instruments lead to lesion and edema of nerve tissues in the VAME approach. Furthermore, the overexposing laryngeal nerve affects the local blood supply to nerves and resulted in a high incidence of hoarseness. But after pooling the results, no significant difference was observed in the rate of recurrent laryngeal nerve injury rate. This may be owing to the proficiency of the surgeons after the initial learning period.

Pleural integration was usually retained in VAME surgery, which improved lung function compared to the VATE approach and

TABLE 3 Meta-analysis of perioperative outcomes.

Analysis item	No. of studies	Effects model	RR/SWD (95% CI)	Significance	Heterogeneity test		
					Chi^2	I^2	*P*
Operation time	7	Random	SMD = −1.53, 95% CI −2.30–−0.78	*P* = 0.000	84	92.9	0.000
Intraoperative hemorrhage	7	Random	SMD = −0.37, 95% CI −1.03–0.29	*P* = 0.275	77.65	92.3	0.000
Number of lymph nodes retrieved	4	Fixed	SMD = −0.70, 95% CI −0.90–−0.50	*P* = 0.000	3.77	20.4	0.288
Postoperative hospital stay	4`	Random	SMD = −0.21, 95% CI −0.72–0.31	*P* = 0.434	12.57	76.1	0.006
Morbidity							
Laryngeal recurrent nerve damage	7	Random	RR = 2.24 95% CI 0.93–5.39	*P* = 0.071	12.36	51.5	0.054
Anastomotic leakage	7	Fixed	RR = 1.02, 95% CI 0.69–1.51	*P* = 0.927	2.57	0	0.861
Pulmonary complications	3	Random	RR = 0.80, 95% CI 0.34–1.86	*P* = 0.349	5.26	62.0	0.072
Pneumonia	5	Random	RR = 0.54, 95% CI 0.15–1.90	*P* = 0.335	22.92	82.5	0.000
Chylothorax	7	Fixed	RR = 0.34, 95% CI 0.11–1.02	*P* = 0.055	0.39	0	0.996
Arrhythmia	3	Fixed	RR = 1.17, 95% CI 0.38–3.64	*P* = 0.783	0.36	0	0.635
Mortality	6	Fixed	RR = 0.75, 95% CI 0.16–3.58	*P* = 0.722	1.52	0	0.468

RR, relative risk; SMD, standardized mean difference; CI, confidence interval.

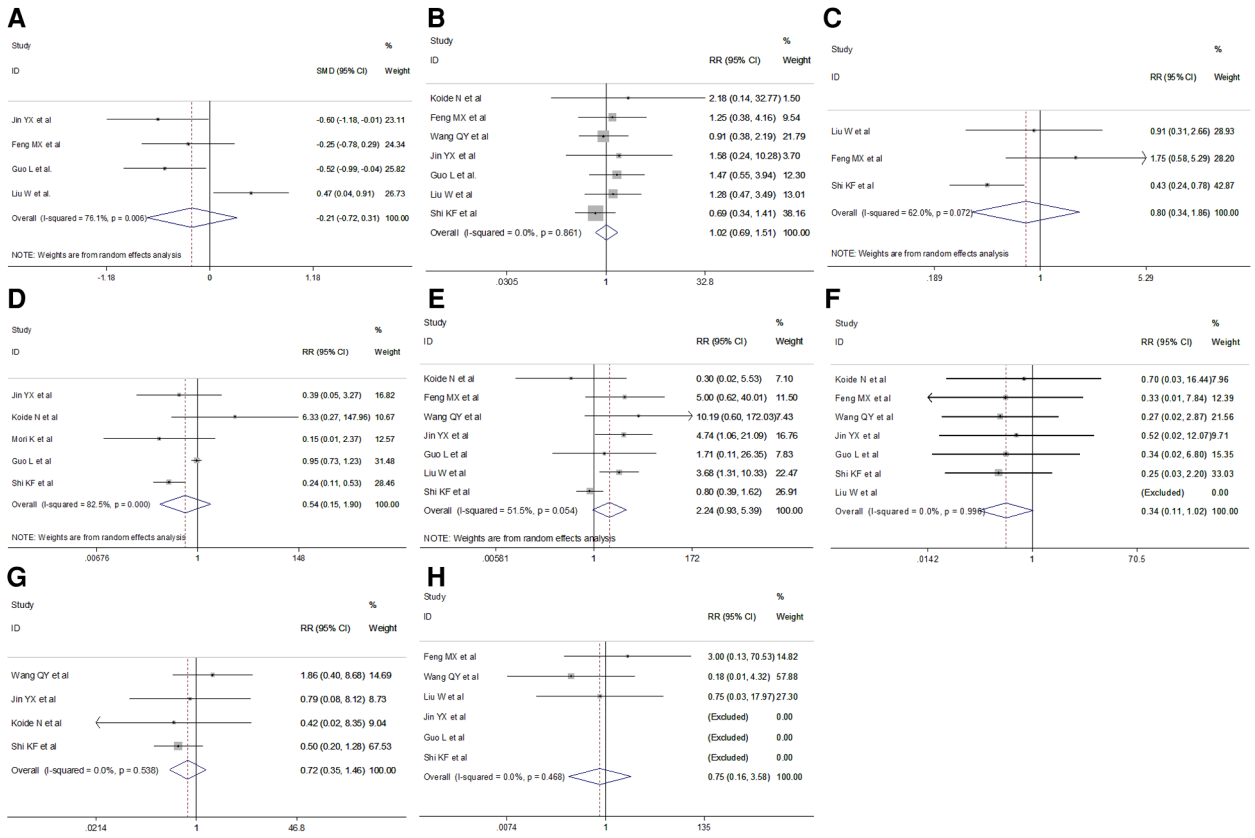

FIGURE 6
Meta-analysis of postoperative outcomes: (A) Postoperative hospital stay; (B) Anastomotic leakage; (C) Respiratory complications; (D) Postoperative pneumonia; (E) Laryngeal recurrent nerve injury; (F) Chylothorax; (G) Arrhythmia; (H) Mortality.

reduced the influence on the lung and heart. On the other hand, patients underwent VAME may experience less chest pain after surgery, which makes it possible for patients to expectorate and exercise effectively in the early postoperative period. However, the pooled results revealed no difference of postoperative pulmonary complications and pneumonia between the two groups. As Feng MX et al. has noted (21), pulmonary complications were a kind of major problem after esophagectomy, and preserving the function of respiratory muscles and less pain resulting from a smaller incision could be beneficial in preventing pulmonary complications but the high rate of recurrent laryngeal nerves injury would exert adverse effects on patients receiving VAME. The two opposite effects could partly explain why no difference was observed in postoperative pulmonary complications between groups.

VAME alters the traditional surgical approach, and transthoracic operation is avoided, which is believed to play a significant role in reducing chest injury and maintaining the integrity of the thoracic cavity. Patients with poor cardiopulmonary functions unsuitable for thoracic surgery could now stand for trans-mediastinal surgery, because one-lung ventilation is omitted (30). From the traditional impression, patients who undergo VAME may have poor pulmonary function and be older. From our meta-analysis, no significant difference in age was observed in the VAME group compared with the VATE group ($P = 0.955$), the results of which were consistent with each single study. Two studies reported preoperative pulmonary function, and forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity were not different between groups partly because of the difference in the study disign (19, 21).

Several limitations existed in our meta-analysis. First of all, as a complex operation, outcomes of which were significant association with the surgeon's techniques, clinical heterogeneities among the studies could also affect the validity of our result, and the operation type in the VATE group was also different which inevitably increased the clinical heterogeneity. Moreover, as a new technology, this approach has not been widely applied, and only a limited number of studies with small sample sizes could be obtained for analysis, which reduced the statistical power. Furthermore, there were much difference with regard to study design and outcomes definitions populations, so the internal heterogeneity was a big obstacle to interpret the results. Last but not least, esophageal cancer treatment has changed dramatically over the time period, particularly with respect to the standardized use of induction therapy for locally advance disease, therefore confounding factors are almost certainly present.

Conclusion

In this meta-analysis, we compared the short-term outcomes and clinical pathological features in esophageal cancer patients receiving VAME to those receiving VATE. The results revealed that the

VAME approach could significantly shorten operation time, but retrieved less lymph nodes. Intro- and postoperative complications were not different between the two groups. Further prospective studies with larger sample sizes are needed to confirm and update our results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contribution

LJ and SG conceived and designed the study; SG, XR, YY and XY collected and analyzed the data; GL, NW, DL wrote the initial manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. (2015) 65:87–108. doi: 10.3322/caac.21262

2. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the linxian general population trial cohort in China. *Int J Cancer*. (2005) 113:456–63. doi: 10.1002/ijc.20616

3. Chan KKW, Saluja R, Delos Santos K, Lien K, Shah K, Cramarossa G, et al. Neoadjuvant treatments for locally advanced, resectable esophageal cancer: a network meta-analysis. *Int J Cancer*. (2018) 143:430–7. doi: 10.1002/ijc.31312

4. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. *Lancet Oncol*. (2007) 8:545–53. doi: 10.1016/S1470-2045(07)70172-9

5. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. *Ann Surg*. (2012) 256:95–103. doi: 10.1097/SLA.0b013e3182590603

6. Tonutti M, Elson DS, Yang GZ, Darzi AW, Sodergren MH. The role of technology in minimally invasive surgery: state of the art, recent developments and future directions. *Postgrad Med J*. (2017) 93:159–67. doi: 10.1136/postgradmedj-2016-134311

7. Li B, Xiang J, Zhang Y, Li H, Zhang J, Sun Y, et al. Comparison of Ivor-Lewis vs Sweet esophagectomy for esophageal squamous cell carcinoma: a randomized clinical trial. *JAMA Surg*. (2015) 150:292–8. doi: 10.1001/jamasurg.2014.2877

8. Wu B, Xue L, Qiu M, Zheng X, Zhong L, Qin X, et al. Video-assisted mediastinoscopic transhiatal esophagectomy combined with laparoscopy for esophageal cancer. *J Cardiothorac Surg*. (2010) 5:132. doi: 10.1186/1749-8090-5-132

9. Navarro-Ripoll R, Cordova H, Rodriguez-D'Jesus A, Boada M, Rodriguez de Miguel C, Beltran M, et al. Cardiorespiratory impact of transesophageal endoscopic mediastinoscopy compared with cervical mediastinoscopy: a randomized experimental study. *Surg Innov*. (2014) 21:487–95. doi: 10.1177/1553350613517943

10. Yin Q, Liu H, Song Y, Zhou S, Yang G, Wang W, et al. Clinical application and observation of single-port inflatable mediastinoscopy combined with laparoscopy for radical esophagectomy in esophageal squamous cell carcinoma. *J Cardiothorac Surg*. (2020) 15:125. doi: 10.1186/s13019-020-01168-1

11. Okumura H, Uchikado Y, Matsumoto M, Omoto I, Sasaki K, Kita Y, et al. Clinical significance of mediastinoscope-assisted transhiatal esophagectomy in patients with esophageal cancer. *Langenbeck's Arch. Surg*. (2015) 400:699–706. doi: 10.1007/s00423-015-1330-y

12. Yamagata Y, Saito K, Hirano K, Oya M. Long-term outcomes and safety of radical transmediastinal esophagectomy with preoperative docetaxel, cisplatin, and 5-fluorouracil combination chemotherapy for locally advanced squamous cell carcinoma of the thoracic esophagus. *World J Surg Oncol*. (2020) 18:252. doi: 10.1186/s12957-020-02023-2

13. Wang QY, Li JP, Zhang L, Jiang NQ, Wang ZL, Zhang XY. Mediastinoscopic esophagectomy for patients with early esophageal cancer. *J Thorac Dis*. (2015) 7:1235–40. doi: 10.3978/j.issn.2072-1439.2015.07.20

14. Wang J, Jiang NQ, Jiang B, Wang ZL, Zhang XY. Mediastinoscopy-assisted oesophagectomy in T1 oesophageal cancer patients with serious comorbidities: a 5-year long-term follow-up. *Interact Cardiovasc Thorac Surg*. (2015) 20:477–81. doi: 10.1093/icvts/ivu433

15. Yoshimura S, Mori K, Ri M, Aikou S, Yagi K, Yamagata Y, et al. Comparison of short-term outcomes between transthoracic and robot-assisted transmediastinal radical surgery for esophageal cancer: a prospective study. *BMC Cancer*. (2021) 21:338. doi: 10.1186/s12885-021-08075-1

16. Sugawara K, Yoshimura S, Yagi K, Nishida M, Aikou S, Yamagata Y, et al. Long-term health-related quality of life following robot-assisted radical transmediastinal esophagectomy. *Surg Endosc Other Interv Tech*. (2020) 34:1602–11. doi: 10.1007/s00464-019-06923-7

17. Yoshimura S, Mori K, Yamagata Y, Aikou S, Yagi K, Nishida M, et al. Quality of life after robot-assisted transmediastinal radical surgery for esophageal cancer. *Surg Endosc Other Interv Tech*. (2018) 32:2249–54. doi: 10.1007/s00464-017-5918-x

18. Guo L, Zhao Q, Wang K, Zhao D, Ye X, Li T. A case-control study on the therapeutic effect of mediastinoscope-assisted and thoracoscope-assisted esophagectomy. *Surg Innov*. (2021) 28:316–22. doi: 10.1177/1553350620958265

19. Koide N, Takeuchi D, Suzuki A, Miyagawa S. Mediastinoscopy-assisted esophagectomy for esophageal cancer in patients with serious comorbidities. *Surg Today*. (2012) 42:127–34. doi: 10.1007/s00595-011-0042-3

20. Nomura T, Matsutani T, Hagiwara N, Fujita I, Nakamura Y, Makino H, et al. Mediastinoscopy-assisted transhiatal esophagectomy for esophageal cancer: a single-institutional cohort study. *Surg Laparosc Endosc Percutan Tech*. (2016) 26:E153–6. doi: 10.1097/SLE.0000000000000348

21. Feng MX, Wang H, Zhang Y, Tan LJ, Xu ZL, Qun W. Minimally invasive esophagectomy for esophageal squamous cell carcinoma: a case-control study of thoracoscope versus mediastinoscope assistance. *Surg Endosc Other Interv Tech* (2012) 26:1573–8. doi: 10.1007/s00464-011-2073-7

22. Jin Y, Lu X, Xue L, Zhao X. Retrospective comparison of two minimally invasive esophagectomy in the treatment of esophageal cancer: pneumatic mediastinoscopy versus thoracoscopy. *J Laparoendosc Adv Surg Tech* (2019) 29:638–42. doi: 10.1089/lap.2018.0512

23. Shi K, Qian R, Zhang X, Jin Z, Lin T, Lang B, et al. Video-assisted mediastinoscopic and laparoscopic transhiatal esophagectomy for esophageal cancer. *Surg Endosc Other Interv Tech*. (2021) 36:7–4214. doi: 10.1007/s00464-021-08754-x

24. Wang QY, Tan LJ, Feng MX, Zhang XY, Zhang L, Jiang NQ, et al. Video-assisted mediastinoscopic resection compared with video-assisted thoracoscopic surgery in patients with esophageal cancer. *J Thorac Dis*. (2014) 6:663–7. doi: 10.3978/j.issn.2072-1439.2014.06.29

25. Liu W, Guo X, Zhao H, Yu X, Wang C, Du L, et al. Mediastinoscopy-assisted transhiatal esophagectomy versus thoraco-laparoscopic esophagectomy for esophageal cancer: a single-center initial experience. *J Thorac Dis*. (2020) 12:4908–14. doi: 10.21037/jtd-20-1328

26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

28. Buess G, Becker HD. Minimally invasive surgery in tumors of the esophagus. *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir*. (1990):1355–60.

29. Bumm R, Hölscher AH, Feussner H, Tachibana M, Bartels H, Siewert JR. Endodissection of the thoracic esophagus. Technique and clinical results in transhiatal esophagectomy. *Ann Surg*. (1993) 218:97–104. doi: 10.1097/00000658-199307000-00015

30. Mimatsu K, Oida T, Kawasaki A, Aramaki O, Kuboi Y, Kanou H, et al. Mediastinoscopy-assisted esophagectomy is useful technique for poor surgical-risk patients with thoracic esophageal cancer. *Surg Laparosc Endosc Percutan Tech*. (2009) 19:e17–20. doi: 10.1097/SLE.0b013e31818aa5cc

31. Tsurumaru M, Kajiyama Y, Udagawa H, Akiyama H. Outcomes of extended lymph node dissection for squamous cell carcinoma of the thoracic esophagus. *Ann. Cardiothorac. Surg.* (2001) 7:325–9.

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 17 February 2023
DOI 10.3389/fsurg.2023.1120414

OPEN ACCESS

EDITED BY
Ugo Cioffi,
University of Milan, Italy

REVIEWED BY
Gianluca Perroni,
San Raffaele Hospital (IRCCS), Italy
Giuseppe Mangiameli,
Humanitas University, Italy

*CORRESPONDENCE
Alessandro Gonfiotti
✉ a.gonfiotti@unifi.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 09 December 2022
ACCEPTED 16 January 2023
PUBLISHED 17 February 2023

CITATION
Mugnaini G, Viggiano D, Fontanari P, Forzini R, Voltolini L and Gonfiotti A (2023) Awake uniportal VATS sublobar lung resections in high-comorbidity patients: Single-center early post-operative outcomes.
Front. Surg. 10:1120414.
doi: 10.3389/fsurg.2023.1120414

Awake uniportal VATS sublobar lung resections in high-comorbidity patients: Single-center early post-operative outcomes

Giovanni Mugnaini[1], Domenico Viggiano[1], Paolo Fontanari[2], Rossella Forzini[2], Luca Voltolini[1,3] and Alessandro Gonfiotti[1,3]*

[1]Thoracic Surgery Unit, Careggi University Hospital, Florence, Italy, [2]Department of Anhestesiology and Reanimation, Careggi University Hospital, Florence, Italy, [3]Department of Experimental and Clinical Medicine, University of Florence, Italy

Introduction: Awake minimally invasive Uniportal Video Assisted Thoracic Surgery (U-VATS) represents the last challenge in thoracic surgery that could change the future scenario for high comorbidity patients with early-stage non-small cell lung cancer (NSCLC). We report a single center preliminary experience of awake thoracoscopic uni-portal anatomic and non-anatomic sub-lobar resections in this setting.
Methods: We retrospectively analyzed data collected on a prospective database of patients undergoing U-VATS awake sub-lobar lung resections for NSCLC between September 2021 and September 2022. Inclusion criteria were clinical stage I disease; contraindication to standard lobectomy due to high respiratory function impairment; general anesthesia considered at high risk based on the American Society of Anesthesiologist score and on the Charlson Comorbidity Index. All patients underwent a standardized awake non-intubated anesthesia protocol approved by our institutional board.
Results: They were $n = 10$ patients: $n = 8$ wedge resections; $n = 2$ segmentectomies. We had $n = 1$ (10%) conversion to standard general anesthesia and $n = 1$ laryngeal mask support but maintaining spontaneous breathing. $N = 5$ patients (50%) needed an Intensive Care Unit recovery (mean time = 17.20 h). Mean chest tube duration and Hospital stay were 2.0 and 3.5 days respectively. We did not register 30- days postoperative mortality.
Conclusion: Awake thoracic surgery is a feasible technique, and it could be performed also in high comorbidities' patients without a high rate of complications and allows to operate patients that so far were considered borderline for surgery.

KEYWORDS

awake thoracic surgery, non-intubated thoracic surgery, spontaneous breathing, uniportal video assisted thoracic surgery, minimally invasive thoracic surgery, sublobar lung resections

Introduction

Surgical interventions in spontaneous breathing patients, without mechanical ventilation and general anesthesia, have spread over the last two decades. Non-Intubated thoracic surgery (NITS) defined also as awake or tubeless thoracic surgery, and more specifically, non-intubated video-assisted thoracic surgery (NIVATS) have been increasingly adopted in

Abbreviations
NITS, non-intubated thoracic surgery; NIVATS, non-intubated video-assisted thoracic surgery; U-VATS, uniportal video-assisted thoracic surgery; LVRS, lung volume reduction surgery; NSCLC, non-small cell lung cancer; HPV, hypoxic pulmonary vasoconstriction; COPD, chronic obstructive pulmonary disease; PFTs, pulmonary function tests; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing capacity of carbon monoxide; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

thoracic surgery, also for complex lung resection, and it could potentially become the least minimally invasive procedure for lung resections.

General anesthesia with one-lung ventilation was mandatory for thoracic surgery until Pompeo et al. (1) had demonstrated the feasibility of lung resection in spontaneous breathing patients, first for wedge resection and lung volume reduction surgery (LVRS) (2–4) and then also for major resection (5). Nowadays, awake thoracic surgery has become a feasible surgical option that can also include patients with NSCLC or lung metastases who cannot undergo general anesthesia due to their high comorbidity.

The aim of this study is to show early postoperative outcomes of the awake lung resection in high comorbidity patients operated in our center in the last year and to demonstrate the feasibility of this technique also in this high-risk category.

Materials and methods

We retrospectively analyzed data collected on a prospective database of patients undergoing U-VATS awake anatomic and non-anatomic sub-lobar lung resections for NSCLC in our center between September 2021 and September 2022. Inclusion criteria were: clinical stage I disease; contraindication to standard lobectomy due to high respiratory function impairment; general anesthesia considered at high risk based on the American Society of Anesthesiologist score (ASA score) and on the Charlson Comorbidity Index. The preoperative evaluation to consider a patient feasible for awake thoracic surgery is based on the latest literature exclusion criteria (6). All patients underwent conventional pre-operative examinations, including cardiological assessment and pulmonary function tests (PFTs), contrast enhanced thoracic and abdominal computed tomography scan (CT), brain CT scan and positron emission tomography-CT (PET-CT) scan. We performed an uniportal VATS resection, with a surgical access at the level of the anterior axillary line in the IV or in the V intercostal space, depending on the position of the lung lesion. The lesions were transected with endoscopic staplers. In the two segmental resections we performed an individual dissection of the pulmonary artery(ies), bronchus, and vein(s) and all these structures were transected with endoscopic staplers or by ligation and the use of energy devices. Every patient left the surgical theatre with a chest tube. The in-hospital post-operative evaluation consisted in monitoring a possible air leak and the 24 h amount of pleural liquid drained, as well as in executing a chest radiograph in post-operative day 1 and day 3 (unless patients were discharged before). All patients were referred to respiratory physiotherapy service from post-operative day 1 to the discharge. Preoperative characteristics were resumed in Table 1. We reported mean and median values of age, ASA score and CCI. Mean preoperative value of FEV1%, FVC% and DLCO% were 77.30%, 83.60% and 87.60% respectively.

A written consent for the procedure was obtained from all patients.

Anesthesiologic protocol for awake thoracic surgery

In collaboration with the anesthesiologist of our center (SOD Anestesia e Rianimazione, AOUC), for awake lung resection we developed a protocol that could lead to a safe surgical intervention and that could protect patients from severe hypoxia and hypercapnia, avoiding making them feel pain during surgical resections and reducing the cough reflex, allowing surgeons to operate and manipulate the lung in a safer way. We never performed the block of the vagus nerve. Airway nebulization of lidocaine and atomization of the lung and of the ilum failed in controlling the cough reflex in only one patient (10%). Table 2 shows protocol steps.

Results

Our database reported that 10 patients underwent U-VATS awake resections between September 2021 and September 2022; $n = 8$ (80%) wedge resections (two of the RUL, three of the RLL, one of the LUL and two of the LLL) and $n = 2$ (20%) segmentectomies (one lingulectomy and one S6 left segmentectomy) were performed. Table 3 shows our results. We reported mean and median values. Among wedge resections, $n = 1$ patient (12.5%) required conversion to general anesthesia with orotracheal intubation due to difficulty controlled parenchymal bleeding and $n = 4$ patients (50%) required post-operative ICU monitoring due to their comorbidity. The mean time in ICU (hours) for the $n = 4$ four wedge resections who needed it was 17.50 h. There were no post-operative major complications, no prolonged air leak, and no infection and only the patient who needed conversion to general anesthesia needed a prolonged O2 support in the post-operative period. In the wedge resection group, the mean and the median time of maintenance of the chest tube were respectively 2.0 and 1.8 days and the mean and the median length of the hospitalization were 2.9 and 2.5 respectively.

The S6 left segmentectomy was a high comorbidity patient with a definitive tracheostomy due to a previous squamous carcinoma of the larynx, treated with neoadjuvant RT and CHT and then with a partial laryngectomy. He had a lesion of the left S6 suspected of NSCLC (and then confirmed by the pathological post-operative analysis, Figure 1), and we chose to perform a S6 segmentectomy to have good resection margin (Figure 2, Supplementary Video S1). This patient had no intraoperative complication but needed a post-operative monitoring in ICU (16 h) because of his comorbidities. He maintained the chest tube for 2 days. His hospitalization (8 days) was prolonged because of sputum retention due to the presence of the tracheostomy, and he underwent two post-op disobstructive bronchoscopies. The lingulectomy needed a laryngeal mask during the operation because of an uncontrolled cough reflex that did not allow a safe resection. The laryngeal mask enabled the anesthesiologist to control the cough reflex, the airway and the sO2 keeping the patient breathing spontaneously, without the use of muscle relaxants. The positioning of the parenchymal stapler required a controlled apnea (<1 min). He had no post operative complications and maintained the chest tube for two days. Among all patients who needed an ICU monitoring ($n = 5$, 50%), the mean time of ICU was of 17.20 h. The global mean time of ICU

10.3389/fsurg.2023.1120414

TABLE 1 Patients' preoperative characteristics. ASA: American Society of Anesthesiologists Classification; CCI: Charlson Comorbidity Index; COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; FEV1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity for Carbon Monoxide; WR: Wedge Resection.

Patient's Preoperative Characteristics	
Sex	
Male	6
Female	4
Age	
Mean	68.60
Median	69.50
Smoke history	
Current	5
Former	3
Never	2
ASA	
WR 1	2
WR 2	3
WR 3	2
WR 4	2
WR 5	1
WR 6	1
WR 7	2
WR 8	2
S6 segm.	3
Lingulectomy	2
ASA (mean)	2.0
CCI	
WR 1	1
WR 2	3
WR 3	2
WR 4	2
WR 5	2
WR 6	1
WR 7	2
WR 8	2
S6 segm.	3
Lingulectomy	2
CCI (mean)	2.0
Comorbidities	
COPD	4
Cardiopathy	4
Arteriopathy	4
DM (I or II)	5
Others	6
FEV1% pre	
Mean	77.30
Median	80.50
FVC% pre	
Mean	83.60
Median	86.50
DLCO% pre	
Mean	87.60
Median	88.00

(*continued*)

TABLE 1 Continued

was 8.6 h. The global mean value of length of hospitalization and maintenance of the chest tube were respectively 3.5 and 2.0 days (Table 3). We did not register 30-days post-operative mortality.

Discussion

Spontaneous ventilation vs. general anesthesia

General anesthesia with one lung ventilation was considered necessary for lung resections, mainly because the surgeon can

TABLE 2 Careggi university hospital anesthesiology protocol for awake lung resections. VM: VentiMask.

Anesthesiology protocol for Awake Thoracic Surgery
Premedication before starting sedation (15 min before):
• Atropine 0.01 mg/Kg e.v. • Dihydrocodeine 15 gtt per os
Sedation:
• VM with reservoir (6–10 L/min O2) to maintain SpO2 > 92% • Propofol 1–2 mg/Kg/h • Remifentanil 0.03–0.07 mcg/kg/min
Ultrasound guided paravertebral blockade: ESP (Erector Spinal Block) with ropivacaine 0.5%, 20–30 ml
In supine position, at least 30 min before surgery:
• Airway nebulization with lidocaine 2% (5 ml on high flow O2 with aerosol kit
Advanced patient monitoring with BIS™ (Bispectral Index)
Surgical incision infiltration with lidocaine 2%
Just before the surgical resection:
• Lidocaine (2%) atomization on the lung surface and on the hilum
Place a Laryngeal Mask if needed due to severe hypoxia and/or Hypercapnia

10.3389/fsurg.2023.1120414

TABLE 3 Early post-operative outcomes. ICU: Intensive Care Unit; WR: Wedge Resection.

	Length of stay	Chest tube duration (days)	Post-op ICU (hours)	Intra-op Complications	Post-op complications	30-days mortality
WR 1	2	1.8	20	None	None	–
WR 2	4	2	0	None	None	–
WR 3	2	1.6	0	none	None	–
WR 4	5	2.7	15	Conversion to general anesthesia due to bleeding	Prolonged O2 support needed	–
WR 5	3	0.8	0	None	None	–
WR 6	3	3	0	None	None	–
WR 7	2	1.8	17	None	None	–
WR 8	2	1.2	**18**	None	None	–
Mean	**2.9**	**2.0**	**8.8 (17.50)**			
Median	**2.5**	**1.8**	**7.5 (17.50)**			
Left S6 segmentectomy	8	2	16	None	Sputum retention	–
lingulectomy	4	2	0	Laryngeal mask needed (with spontaneous breath) due to uncontrolled cough reflex	none	–
Mean	3.5	**2.0**	**8.6 (17.20)**			
Median	3	**2**	**7.5 (17.00)**			

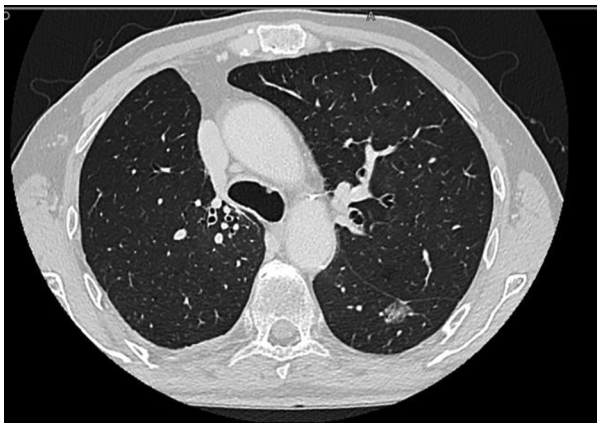

FIGURE 1
Pre-operative CT-scan of the left S6 segmentectomy showing the lesion.

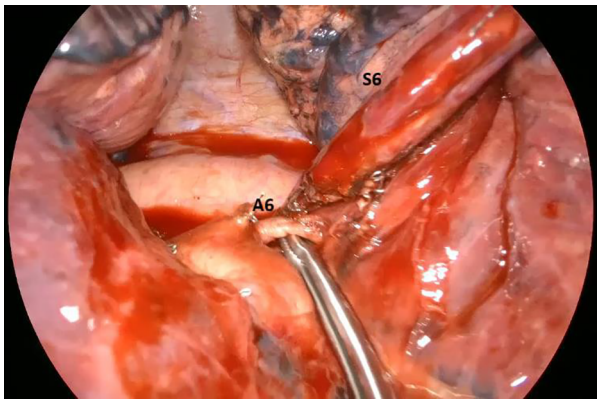

FIGURE 2
Intra-operative image showing the artery (A6) for the apical segment of the left lower lobe (S6).

operate with non-ventilated lung and no breathing expansion. However, it has been demonstrated that general anesthesia and mechanical ventilation have a large series of potential side effects that could influence patients' post operative morbidity and mortality, their length of the hospital stay and post-operative quality of life. Indeed, mechanical ventilation could lead to a lung damage because of an airway pressure-induced injury, atelectasis in the non-ventilated lung, the release of pro-inflammatory mediators (7–10). General anesthesia, use of muscle relaxant and use of opioids could cause a prolonged hospital stay and an augmented risk of mortality and morbidity and post operative cognitive dysfunction (11–13). In addition, orotracheal and bronchial intubation have potential, not insignificant, complications such as post-op throat pain or laryngeal and/or tracheal injuries (14).

Surgical pneumothorax in non-intubated thoracic surgery requires the anesthesiologist to manage the paradoxical ventilation and the risk of hypoxemia, due to a potential increase of the right-left intrapulmonary shunt. Hypoxic pulmonary vasoconstriction, a defense mechanism which is activated by the hypoxic alveoli, is more efficient during NITS, since we do not use some anesthetic drugs, like volatile anesthetics that can inhibit the protective vasomotor response of HPV (15). Furthermore, the anesthesiologist must avoid severe hypercapnia and acidosis during the awake thoracic surgery. Patients with a background of severe COPD or neuromuscular diseases have a higher risk for developing intraoperative hypercapnia. However, transient perioperative permissive hypercapnia has been well described (16).

Cough reflex, triggered by lung manipulation, could be the surgeon's 'enemy' during NITS: in the last years several techniques were developed to reduce this reflex: inhalation of aerosolized lidocaine, application of a spray of lidocaine on the lung surface, a stellate ganglion block or a vagus nerve block placed intrathoracically were all feasible techniques (16).

Thoracic surgery in non-intubated patients was already known in the 1920s, when Jacobeaus began to use thoracoscopy in patients with a suspected tuberculosis or other intrathoracic diseases to make diagnosis and to perform cauterization of adhesions in awake patients (17). After all, mechanical ventilation was not introduced before the 1960s and patients' survival after a thoracotomy in spontaneous ventilation was extremely low. At the end of the '50s, high number cases studies have been published reporting awake anesthesia techniques for major lung resections that have subsequently inspired current techniques (18, 19). With the introduction of the mechanical ventilation in early 1960s and mainly with the introduction of the double lumen tube, the one lung ventilation with a controlled general anesthesia became the gold standard for thoracic surgery. At the beginning of the XXI century, thoracic surgeons started to question themselves about the feasibility of lung resections avoiding general anesthesia. The first study was undertaken by Pompeo et al., who published a small randomization of 60 patients who underwent a wedge resection in general anesthesia (control group) or without it, with sole thoracic epidural anesthesia (awake group) and providing oxygen *via* a face mask. They demonstrated that the awake group had a significant reduced hospital stay, a greater anesthesia satisfaction score and a significantly lower post-operative ΔPaO2 (1). Since then, there has been a growing interest in this technique: only three years later, in 2007, Al-Abdullatief et al. published an observational study showing the possibility to perform awake anesthesia also in some cases of major thoracic resection, emphasizing above all the importance of avoiding muscle relaxants during thymectomies in patients with myasthenia gravis (20). In 2012, Chen et Al. published an important work showing a 3-years' experience of non-intubated lung resection with 285 cases, of which 159 (55.8%) patients for primary lung cancer. They reported only fourteen (4.9%) conversion to tracheal intubation and no perioperative mortality (21). First applied for wedge resection, lung biopsies, metastasectomies (22) and lung volume reduction surgery (23, 24), the awake technique had a high development in the last years and recent studies reported the use of awake anesthesia for major lung resection (5) and even during thoracotomy (25), without significant differences in terms of survival and post-operative mortality, but with a faster recovery after surgery and a low rate of conversion to general anesthesia (0%–3%) (26). Awake lung biopsies still play a leading role in diagnosis of interstitial lung disease although the increasing diffusion of cryobiopsy, that still have a lower diagnostic yield compared to surgery (27).

In this study we reported a single center' preliminary experience and early post-operative outcomes of awake U-VATS sublobar lung resection performed between September 2021 and September 2022. We performed $n = 8$ wedge resections and $n = 2$ segmentectomies (one lingulectomy and one S6 left segmentectomy) for NSCLC, without post-operative major complications. Only $n = 5$ (50%) patients needed an ICU post-operative monitoring with a mean time of 17.20 h. We reported length of stay and chest tube duration values higher than other results in literature (26), mainly because we selected high comorbidities' patients for our awake lung resections. Indeed, this kind of patients would have been difficult to enroll for lung surgery under general anesthesia, due to the higher risk of post-operative complications, morbidity, and mortality.

This study has several limits: first, it is a single-center retrospective analysis of a small cohort of high-selected patients. Reporting early post operative outcomes, we cannot include overall and event-free survival in our results. We are carrying out a larger follow-up of these patients and updated results may be published in the future.

Conclusions

This work confirms what has been reported in literature and given our results (although relating to a limited number of cases) we can assume that awake U-VATS sub-lobar surgery is a feasible technique and a viable option to the well-known VATS under general anesthesia and could represent an innovative strategy in high comorbidities NSCLC patients traditionally considered at high risk for anatomical resections under general anesthesia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

GM, AG, RF, PF: conception, design, and writing; GM, DV: data research and collection; AG, LV, PF: final approval of the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1120414/full#supplementary-material.

References

1. Pompeo E, Mineo D, Rogliani P, Sabato AF, Mineo TC. Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules. *Ann Thorac Surg*. (2004) 78(5):1761–8. doi: 10.1016/j.athoracsur.2004.05.083

2. Pompeo E, Rogliani P, Palombi L, Orlandi A, Cristino B, Dauri M. Awake thoracic surgery research group (ATSRG). the complex care of severe emphysema: role of awake lung volume reduction surgery. *Ann Transl Med*. (2015) 3(8):108. doi: 10.3978/j.issn.2305-5839.2015.04.17

3. Pompeo E, Rogliani P, Tacconi F, Dauri M, Saltini C, Novelli G, et al. Awake thoracic surgery research group. Randomized comparison of awake nonresectional versus nonawake resectional lung volume reduction surgery. *J Thorac Cardiovasc Surg*. (2012 Jan) 143(1):47–54.54.e1. doi: 10.1016/j.jtcvs.2011.09.050

4. Pompeo E, Tacconi F, Mineo TC. Comparative results of non-resectional lung volume reduction performed by awake or non-awake anesthesia. *Eur J Cardiothorac Surg*. (2011) 39(4):e51–8. doi: 10.1016/j.ejcts.2010.11.071

5. Gonzalez-Rivas D, Fernandez R, de la Torre M, Rodriguez JL, Fontan L, Molina F. Single-port thoracoscopic lobectomy in a nonintubated patient: the least invasive procedure for major lung resection? *Interact Cardiovasc Thorac Surg*. (2014) 19 (4):552–5. doi: 10.1093/icvts/ivu209

6. Gonzalez-Rivas D, Bonome C, Fieira E, Aymerich H, Fernandez R, Delgado M, et al. Non-intubated video-assisted thoracoscopic lung resections: the future of thoracic surgery? *Eur J Cardiothorac Surg*. (2016) 49(3):721–31. doi: 10.1093/ejcts/ezv136

7. Della Rocca G, Coccia C. Acute lung injury in thoracic surgery. *Curr Opin Anaesthesiol*. (2013) 26:40–6. doi: 10.1097/ACO.0b013e32835c4ea2

8. Schilling T, Kozian A, Huth C, Buhling F, Kretzschmar M, Welte T, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. *Anesth Analg*. (2005) 101:957–6. doi: 10.1213/01.ane.0000172112.02902.77

9. Gothard J. Lung injury after thoracic surgery and one-lung ventilation. *Curr Opin Anaesthesiol*. (2006) 19:5–10. doi: 10.1097/01.aco.0000192783.40021.c1

10. Munoz JF, Ibanez V, Real MI, Gonzalez O, Munoz P, German MJ, et al. High-frequency jet ventilation in thoracic surgery. *Rev Esp Anestesiol Reanim*. (1998) 45:353–4. PMID: 9847648.

11. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, et al. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology*. (2012) 116:1195–203. doi: 10.1097/ALN.0b013e31825683dc

12. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS, et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. *Anesth Analg*. (2013) 117:133–41. doi: 10.1213/ANE.0b013e3182742e75

13. Hausman MS Jr, Jewell ES, Engoren M. Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease: does avoiding general anesthesia reduce the risk of postoperative complications? *Anesth Analg*. (2015) 120:1405–12. doi: 10.1213/ANE.0000000000000574

14. Fitzmaurice BG, Brodsky JB. Airway rupture from double-lumen tubes. *J Cardiothorac Vasc Anesth*. (1999) 13:322–9. doi: 10.1016/S1053-0770(99)90273-2

15. David P, Pompeo E, Fabbi E, Dauri M. Surgical pneumothorax under spontaneous ventilation-effect on oxygenation and ventilation. *Ann Transl Med*. (2015) 3(8):106. doi: 10.3978/j.issn.2305-5839.2015.03.53

16. Kiss G, Castillo M. Nonintubated anesthesia in thoracic surgery: general issues. *Ann Transl Med*. (2015) 3(8):110. doi: 10.3978/j.issn.2305-5839.2015.04.21

17. Jacobaeus HC. The cauterization of adhesions in artificial pneumothorax treatment of pulmonary tuberculosis under thoracoscopic control. *Proc R Soc Med*. (1923) 16:45–62. PMID: 19982912; PMCID: PMC2103718.

18. Vischnevski AA. Local anesthesia in thoracic surgery: lungs, heart and esophagus. *Minerva Anestesiol*. (1954) 20:432–5. PMID: 14355684.

19. Ossipov BK. Local anesthesia in thoracic surgery: 20 years experience with 3265 cases. *Anesth Analg*. (1960) 39:327–32. doi: 10.1213/00000539-196007000-00012

20. Al-Abdullatief M, Wahood A, Al-Shirawi N, Arabi Y, Wahba M, Al-Jumah M, et al. Awake anaesthesia for major thoracic surgical procedures: an observational study. *Eur J Cardiothorac Surg*. (2007) 32(2):346–50. doi: 10.1016/j.ejcts.2007.04.029

21. Chen KC, Cheng YJ, Hung MH, Tseng YD, Chen JS. Nonintubated thoracoscopic lung resection: a 3-year experience with 285 cases in a single institution. *J Thorac Dis*. (2012) 4(4):347–51. doi: 10.3978/j.issn.2072-1439.2012.08.07

22. Pompeo E, Mineo TC. Awake pulmonary metastasectomy. *J Thorac Cardiovasc Surg*. (2007) 133(4):960–6. doi: 10.1016/j.jtcvs.2006.09.078

23. Mineo TC, Pompeo E, Mineo D, Tacconi F, Marino M, Sabato AF. Awake nonresectional lung volume reduction surgery. *Ann Surg*. (2006) 243(1):131–6. doi: 10.1097/01.sla.0000182917.39534.2c

24. Pompeo E, Elkhouly A, Rogliani P, Dauri M, Peer M, Sergiacomi G, et al. Quasilobar minimalist lung volume reduction surgery. *Eur J Cardiothorac Surg*. (2021) 60(3):598–606. doi: 10.1093/ejcts/ezab174

25. Furák J, Szabó Z, Tánczos T, Paszt A, Rieth A, Németh T, et al. Conversion method to manage surgical difficulties in non-intubated uniportal video-assisted thoracic surgery for major lung resection: simple thoracotomy without intubation. *J Thorac Dis*. (2020) 12 (5):2061–9. doi: 10.21037/jtd-19-3830

26. Szabo Z, Fabo C, Oszlanyi A, Hawchar F, Géczi T, Lantos J, et al. Anesthetic (r) evolution from the conventional concept to the minimally invasive techniques in thoracic surgery-narrative review. *J Thorac Dis*. (2022) 14(8):3045–60. doi: 10.21037/jtd-22-80

27. Korevaar DA, Colella S, Fally M, Camuset J, Colby TV, Hagmeyer L, et al. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases [published online ahead of print, 2022 jun 16]. *Eur Respir J*. (2022) 60:2200425. doi: 10.1183/13993003.00425-2022

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 27 February 2023
DOI 10.3389/fsurg.2023.1103101

OPEN ACCESS

EDITED BY
Marco Scarci,
Hammersmith Hospital, United Kingdom

REVIEWED BY
Zhuangzhuang Cong,
Nanjing University, China
Jing-Sheng Cai,
Peking University People's Hospital, China

*CORRESPONDENCE
Dania Nachira
✉ danynac@libero.it
Venanzio Porziella
✉ venanzio.porziella@policlinicogemelli.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 19 November 2022
ACCEPTED 08 February 2023
PUBLISHED 27 February 2023

CITATION
Nachira D, Congedo MT, Calabrese G, Tabacco D, Petracca Ciavarella L, Meacci E, Vita ML, Punzo G, Lococo F, Raveglia F, Chiappetta M, Porziella V, Guttadauro A, Cioffi U and Margaritora S (2023) Uniportal-VATS vs. open McKeown esophagectomy: Surgical and long-term oncological outcomes. Front. Surg. 10:1103101. doi: 10.3389/fsurg.2023.1103101

Uniportal-VATS vs. open McKeown esophagectomy: Surgical and long-term oncological outcomes

Dania Nachira[1]*, Maria Teresa Congedo[1], Giuseppe Calabrese[1], Diomira Tabacco[1], Leonardo Petracca Ciavarella[1], Elisa Meacci[1], Maria Letizia Vita[1], Giovanni Punzo[2], Filippo Lococo[1], Federico Raveglia[3], Marco Chiappetta[1], Venanzio Porziella[1]*, Angelo Guttadauro[4], Ugo Cioffi[5] and Stefano Margaritora[1]

[1]Department of General Thoracic Surgery, Fondazione Policlinico Universitario "A. Gemelli", IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, [2]Department of Anesthesiology and Intensive Care Medicine, Fondazione Policlinico Universitario "A. Gemelli", IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, [3]Department of Thoracic Surgery, ASST Monza, San Gerardo Hospital, Monza, Italy, [4]Department of Medicine and Surgery- School of Medicine and Surgery, Università Degli Studi di Milano Bicocca, Milan, Italy, [5]Doctorate Professor, University of Milan, Milan, Italy

Background: Till now there are very few reports about surgical results of Uniportal-VATS esophagectomy and no one about long-term outcomes. This study is the first comparing surgical and oncological outcomes of Uniportal-VATS with open McKeown esophagectomy, with the largest reported series and longest oncological follow-up.

Methods: The prospectively collected clinical, surgical and oncological data of 75 patients, undergone McKeown esophagectomy at our Thoracic Surgery Department, from January 2012 to August 2022, were retrospectively analyzed. Nineteen patients underwent esophagectomy by thoracotomy and reconstruction according to McKeown technique while 56 by Uniportal-VATS approach. Gastric tubulization was performed totally laparoscopic or through a mini-laparatomic access and cervical anastomosis was made according to Orringer's technique.

Results: The mean operative thoracic time was similar in both accesses (102.34 ± 15.21 min in Uniportal-VATS vs. 115.56 ± 23.12 min in open, *p*: 0.646), with a comparable number of mediastinal nodes retrieved (Uniportal-VATS:13.40 ± 8.12 vs. open:15.00 ± 6.86, *p*: 0.275). No case needed conversion from VATS to open. The learning curve in Uniportal-VATS was completed after 34 cases, while the Mastery was reached after 40. Both approaches were comparable in terms of minor post-operative complications (like pneumonia, lung atelectasis, anemization, atrial fibrillation, anastomotic-leak, left vocal cord palsy, chylothorax), while the number of re-operation for major complications (bleeding or mediastinitis) was higher in open group (21.0% vs. 3.6%, *p*: 0.04). Both techniques were also effective in terms of surgical radicality and local recurrence but VATS approach allowed a significantly lower chest tube length (11.89 ± 9.55 vs. 25.82 ± 24.37 days, *p*: 0.003) and post-operative stay (15.63 ± 11.69 vs. 25.53 ± 23.33, *p*: 0.018). The 30-day mortality for complications related to surgery was higher in open group (*p*: 0.002). The 2-, 5- and 8-year survival of the whole series was 72%, 50% and 33%, respectively. Combined 2- and 5-year OS in Uniportal-VATS group was 76% and 47% vs. 62% and 62% in open group, respectively (Log-rank, *p*: 0.286; Breslow-Wilcoxon: *p*: 0.036). No difference in DFS was recorded between the two approaches (5 year-DFS in Uniportal-VATS: 86% vs. 72%, *p*: 0.298). At multivariate analysis, only pathological stage independently affected OS (*p*: 0.02), not the surgical approach (*p*: 0.276).

Conclusions: Uniportal-VATS seems to be a safe, feasible and effective technique for performing McKeown esophagectomy, with equivalent surgical and long-term oncological results to standard thoracotomy, but with a faster and unharmed recovery, and a quite short learning curve.

KEYWORDS

uniportal-VATS, mckeown esophagectomy, esophageal cancer, disease-Free survival, oncological outcomes, CUSUM, learning curve

1. Introduction

Esophagectomy still represents the crucial therapeutic choice of resectable esophageal cancers in multimodal treatments. Open esophagectomy, being a high invasive surgery with 2 or 3 access fields involved, it is burdened by a high post-operative mortality, with about 50% of patients at risk for developing post-operative respiratory complications and long hospital stay (1).

In the last 20 years, minimally invasive esophagectomy (MIE) has been proven to be superior to open esophagectomy (OE) in surgical and short-term results, reducing morbidity, however the oncological outcomes are still controversial and required further verification by randomized trials (2).

In this scenario and in the field of MIE, the role of Uniportal-Video assisted Thoracic Surgery (VATS) esophagectomy is even more debated and right now very limited reports (mainly cases series with short-term results or surgical technique papers) are available to can address this point (3, 4).

The main reason of lack of study on long-term outcomes in Uniportal-VATS esophagectomy are ascribable to the fact that it is considered a surgical demanding technique, with a quite longer learning curve, that requires not only a large experience in esophageal surgery and posterior mediastinum manipulation but also good surgical skills in single-access approach and dexterity in hand-eye coordination (5, 6).

Based on our long experience in esophageal surgery and Uniportal-VATS field, in this paper we reported the surgical and long-term oncological outcomes of Uniportal-VATS approach compared with thoracotomy for performing McKeown esophagectomy.

2. Materials and methods

The prospectively collected clinical, surgical and oncological data of consecutive 75 patients, undergone McKeown esophagectomy at our Thoracic Surgery Department, from January 2012 to August 2022, were retrospectively analyzed. All patients had a diagnosis of upper, middle or lower esophageal cancer.

Among these, 19 underwent esophagectomy by thoracotomy (the performed approach at our center from January 2012 to November 2016) and reconstruction according to McKeown technique while 56 patients underwent Uniportal-VATS approach (December 2016 – August 2022), that has become the preferred approach at our center for major and minor thoracic procedures, since June 2016. All patients undergone other esophageal reconstructions (as Ivor-Lewis esophagectomy open or VATS) along the study period were excluded to reduce selection biases related to different surgical procedures.

The diagnostic and preoperative evaluations included: esophagogastroduodenoscopy (EGD) for diagnosis and endoscopic ultrasound (EUS) to evaluate T-stage and nodal involvement, Total-body computed tomography (CT) and PET-CT for disease stage, pulmonary function test, cardiac tests and blood analyses.

While indication to neoadjuvant and/or surgical treatment of esophageal cancer may vary according to TNM stage and local institutions, at our center each case was discussed in a dedicated tumor board (involving oncologists, radiotherapists, thoracic and general surgeons) and, in agreement with recent guide-lines (7), patients with a IIB–IIIB stage (8th Edition of American Joint Committee on Cancer (AJCC) TNM staging system (8) underwent preoperative inductive radio/chemotherapy.

Post-induction re-evaluation and staging was done by PET-CT and EUS when necessary.

All patients signed an informed consent before surgery for the treatment of their clinical data.

2.1. Surgical technique

According to McKeown technique, radical esophagectomy and reconstruction include 3 surgical times: thoracic, abdominal and cervical one.

The main steps of each time (Uniportal-VATS thoracic approach, abdominal and cervical approaches) were already described in a previous paper (9) on the technique by our group.

According to our experience, a particular importance must be given to the position of patient on the operative table and to the use of operative table itself, during Uniportal-VATS.

Indeed, the patient lies on his left side, with the bed flexed down of 30–45° at the level of his V intercostal space. After blocking and ensuring the patient on the bed by a vacuum matrass, the bed is tilted about 45° toward patient's ventral side (where surgeons stand during the operation) and 30° in anti-Trendelenburg's position. These precautions, together with the location of the 4 cm Uniportal-VATS incision (on V intercostal space but more posterior than for lung surgery, on the anterior margin of latissimus dorsi, that is spared), give the possibility to have more space for the simultaneous use of several instruments through a small incision, and to better expose and dissect the

posterior mediastinum, the esophagus itself and all mediastinal nodal stations.

On the contrary, in open thoracic approach, a lateral muscle sparing thoracotomy is performed at V intercostal spaces. The steps of esophageal dissection and mobilization are the same as in VATS surgery. In both groups, the thoracic duct was not always closed or clipped routinely during the study time.

A careful lymphadenectomy was performed in both approaches, removing all fatty tissue and nodes along esophagus, aorta, thoracic duct, pulmonary ligament, sub-carinal and upper para-tracheal space and Barety's space. In open approach, elettrocautery and clips were used to coagulate and seal lymphatic vessel, in VATS surgery the same energy device used for esophageal dissection was employed.

At the end of open esophagectomy, 2 chest tubes (28 Fr) were left in place through the VII (anterior apical drain) and VIII (posterior basal drain) intercostal spaces, instead of one (through the same incision) as in Uniportal-VATS approach.

The abdominal time was carried out open or laparoscopic, according to the period when the operation was performed at our center.

In each patient, a jejunostomy tube was placed at the end of surgery for early enteral nutrition.

2.2. Intra- and peri-operative management

Surgery was carried out in general anesthesia, with single-lung ventilation. For analgesic purpose, all patients underwent intercostal nerve blockade (in the incision space, one space above and 2–3 spaces below) by 5% ropivacaine (3–5 cc per space) under direct view by surgeon, at the end of thoracic time. An elastomeric pump was also used for intravenous administration of Tramadol (12.5 mg/h in VATS group) and Morphine (1 mg/h in open group) for 24 h. Patients were extubated immediately after surgery or the day after, in the intensive care unit, according to anesthesiological decision, based on patient's clinical condition and length of surgery.

All patients received post-operative intravenous antibiotics (second-generation cephalosporin, metronidazole and fluconazole).

Since the first post-operative day, the early mobilization of the patient was stimulated to enhance the recovery. Meanwhile, a progressive implementation of enteral nutrition was achieved by jejunostomy to obtain the correct metabolic intake according to the dedicated team of nutritionists.

An x-ray esophagogram was performed on V-VI post-operative day for evaluating transit of swallow and excluding cervical anastomotic leak, before restarting oral intake. The cervical drainage and last chest tube were removed after starting re-alimentation per os in absence of clinic-radiological complications.

2.3. Oncological follow-up

Patients were followed-up by a dedicated team of oncologists every 3 months for the first 2 years, then every 6 months in the following 3 years, and then annually from the 5th year. The radiological examinations used were neck and chest CT scan and complete abdomen ultrasound. Other specific blood markers or endoscopic evaluations were required by oncologist according to the case.

2.4. Statistical analysis

Continuous variables were expressed as mean and standard deviation, while categorical variables as absolute numbers and percentages (%). Kolmogorov–Smirnov test was used to evaluate normal distribution of data. Continuous variables were compared by independent sample Student's *t*-test if normal distributed or by Mann–Whitney *U*-test if not normal. Categorical variables were compared by Chi-squared test.

Overall survival (OS) was defined as time elapsed from surgery to death; disease-free survival (DFS) as time between surgery and first recurrence of disease in any site.

Survival and disease-free analyses were performed by Kaplan-Meier method; differences in survivals were evaluated by Log-Rank test or Breslow-Wilcoxon where indicated. Univariate analysis with a Cox proportional hazard model was conducted to evaluate prognostic factors. All covariates with $p < 0.15$ at univariate analysis were selected for Multivariate Cox regression analysis to assess factors independently affecting survival.

The CUSUM technique of the operative time was used to define the completion of our learning curve (CLC) in Uniportal-VATS esophagectomy.

The CUSUM series was defined as follows: $\sum(Xi-X0)$, where Xi was an individual measurement [operative time of each case (ni)] and ×0 was a predetermined reference level, here set as the mean operative time of all cases. The CUSUM series was plotted against the consecutive procedures to calculate the point of downward inflection on the graph or cut-off value [the number of surgical procedures (ni) to overcome the LC, at which the highest value of $\sum(Xi-X0)$ was reached].

Furthermore, a two-sided Bernoulli CUSUM chart was plotted to define the point of "mastery" of Uniportal-VATS esophagectomy, defined as the point where the operative time became consistent with the mean, without further significant changes in terms of mean operative time.

A p-value < 0.05 was considered statistically significant.

Statistical analysis was performed using IBM SPSS Statistics for Macintosh (version 25.0, IBM Corp, Armonk, NY, United States).

3. Results

The 56 patients operated on by Uniportal-VATS approach and the 19 patients by open technique were completely comparable in terms of main clinic-pathological characteristics, **Table 1**. In particular, no statistical difference was found in age, comorbidities, cancer histology, stage and neo-adjuvant and adjuvant therapies. The mean age in Uniportal-VATS group was 63.38 ± 10.17 years, while in open group was 63.95 ± 12.15

TABLE 1 Comparison of clinico-pathological characteristics of patients in 2 groups.

Variables	Uniportal-VATS Esophagectomy (#56 pts)	Open Esophagectomy (#19 pts)	*p*
Gender (male)	44 (78.6%)	12 (63.2%)	0.182
Age (years)	63.38 ± 10.17	63.95 ± 12.15	0.841
Smoking habitus	10 (17.9%)	5 (26.3%)	0.426
COPD	12 (21.4%)	4 (21.1%)	0.972
Diabetes mellitus II	6 (10.7%)	5 (26.3%)	0.097
Hypertension	13 (23.2%)	5 (26.3%)	0.784
Cardiovascular diseases	12 (21.4%)	5 (26.3%)	0.660
Histology			
Adenocarcinoma	40 (71.4%)	11 (57.9%)	0.274
Squamous cell	16 (28.6%)	8 (42.1%)	
Tumor extension (cm)	3.50 ± 2.42	4.02 ± 2.00	0.645
Tumor location			
Upper esophagus	4 (7.1%)	2 (10.5%)	0.593
Middle esophagus	31 (55.4%)	13 (68.4%)	
Distal esophagus	21 (37.5%)	4 (21.1%)	
Pathological stage:			
Complete response	2 (3.6%)	1 (5.3%)	0.734
I	20 (35.7%)	4 (21.1%)	
II	14 (25.0%)	6 (31.6%)	
III	15 (26.8%)	7 (36.7%)	
IVA (N2)	5 (8.9%)	1 (5.3%)	
Neoadjuvant therapy	33 (58.9%)	6 (31.6%)	0.079
Neoadjuvant chemotherapy	26 (46.4%)	4 (21.1%)	0.476
Neoadjuvant radiotherapy	32 (57.1%)	5 (26.3%)	0.539
Adjuvant therapy	20 (35.7%)	7 (36.8%)	0.808

TABLE 2 Comparison of surgical and short-term outcomes.

Variables	Uniportal-VATS Esophagectomy (#56 pts)	Open Esophagectomy (#19 pts)	*p*
Thoracic time (min)	102.34 ± 15.21	115.56 ± 23.12	0.646
Conversion	0	/	/
Number of thoracic nodes retrieved	13.40 ± 8.12	15.00 ± 6.86	0.275
Re-operation	2 (3.6%)	4 (21.0%)	**0.04**
Post-operative minor complications:			
Lung Atelectasis	3 (5.3%)	3 (5.4%)	0.148
Atrial fibrillation	7 (13.0%)	3 (5.4%)	0.716
Anemization	4 (7.1%)	1 (5.3%)	0.482
Pneumonia	7 (13.0%)	4 (21.1%)	0.363
Anastomotic leak	4 (7.1%)	4 (21.1%)	0.095
Chylothorax	3 (5.5%)	2 (10.5%)	0.435
Left vocal cord palsy	3 (5.3%)	1 (5.2%)	0.987
Myocardial infarction	0	1 (5.2%)	0.084
Chest drain (or last drain) removal (days)	11.89 ± 9.55	25.82 ± 24.37	**0.003**
Post-operative stay (days)	15.63 ± 11.69	25.53 ± 23.33	**0.018**
R + status	1 (1.8%)	0	0.655
Local recurrence	5 (8.9%)	2 (10.5%)	0.854
Thirty-day mortality	0	3 (15.7%)	**0.002**
Death of disease	15 (26.8%)	2 (10.5%)	0.135

(*p*: 0.841). The main histology was adenocarcinoma in both groups (40 (71.4%) in Uniportal-VATS vs. 11 (57.9%) in open, *p*: 0.274). Thirty-three (58.9%) patients underwent neoadjuvant therapy in Uniportal-Vats group vs. 6 (31.6%) in open, *p*: 0.079; in particular, radiotherapy was the concurrent treatment in 57.1% of patients operated by Uniportal-VATS approach vs. 26.3% of open surgery, *p*: 0.539.

No case needed conversion in Uniportal-VATS group. The mean operative thoracic time was similar in both accesses (102.34 ± 15.21 min in Uniportal-VATS vs. 115.56 ± 23.12 min in open, *p*: 0.646), Table 2. In our experience, the learning curve of Uniportal-VATS esophagectomy was completed after 34 cases (CLC point in Figure 1A), while the mastery was reached after 40 cases (Figure 1B). All Uniportal-VATS esophagectomies were performed by the same operators (S.M., D.N.) during the study time.

A comparable number of mediastinal nodes was retrieved in Uniportal-VATS (13.40 ± 8.12) and open group (15.00 ± 6.86), *p*: 0.275, Table 2. Both approaches were also comparable in terms of minor post-operative complications (like pneumonia, lung atelectasis, anemization, atrial fibrillation, anastomotic-leak, left vocal cord palsy, chylothorax, Table 2), while the number of re-operation for major complications (bleeding or mediastinitis) or chylothorax was higher in open group (21.0% vs. 3.6%, *p*: 0.04). The 4 re-operations (21%) in open group were due to persistent chylothorax (in 2 cases) that required the surgical closure of thoracic duct, bleeding (in 1 case) or mediastinitis consequent to anastomotic leak (1 case), that needed a surgical toilette.

Both techniques were also effective in terms of surgical radicality and local recurrence (Table 2) but VATS approach allowed a significantly lower chest tube length (11.89 ± 9.55 vs. 25.82 ± 24.37 days, *p*: 0.003) and post-operative stay (15.63 ± 11.69 vs. 25.53 ± 23.33, *p*: 0.018). The 30-day mortality for complications related to surgery (pneumonia or mediastinitis) was higher in open group (3 patients (15.7%) vs. 0, *p*: 0.002). The recorded level of pain on I post-operative day in Uniportal-VATS group was 1.89 ± 1.60 vs. 4.68 ± 2.91 in open group, *p*: << 0.001.

The median FUP period was 35 months in the Uniportal-VATS series, while 52 months in the open one (median FUP of the whole series: 42 months). Twenty-one (28%) patients were lost at FUP, 8 (42%) from open group.

The 2-, 5- and 8-year survival of the whole series was 72%, 50% and 33%, respectively, Figure 2.

Combined 2- and 5-year OS in Uniportal- VATS group was 76% and 47% vs. 62% and 62% in open group, respectively (Log-rank test, *p*: 0.286, Figure 3). The results of Kaplan-Meier survival estimator model can be explained by the high number of events (deaths) recorded in open group during 60-days after surgery (4 events out of 7), while only 2 deaths for disease occurred during FUP period (with 8 patients lost). Therefore, the survival curves were also compared by Breslow-Wilcoxon test for having a more reliable analysis that took into account the events of the first period (*p*: 0.036).

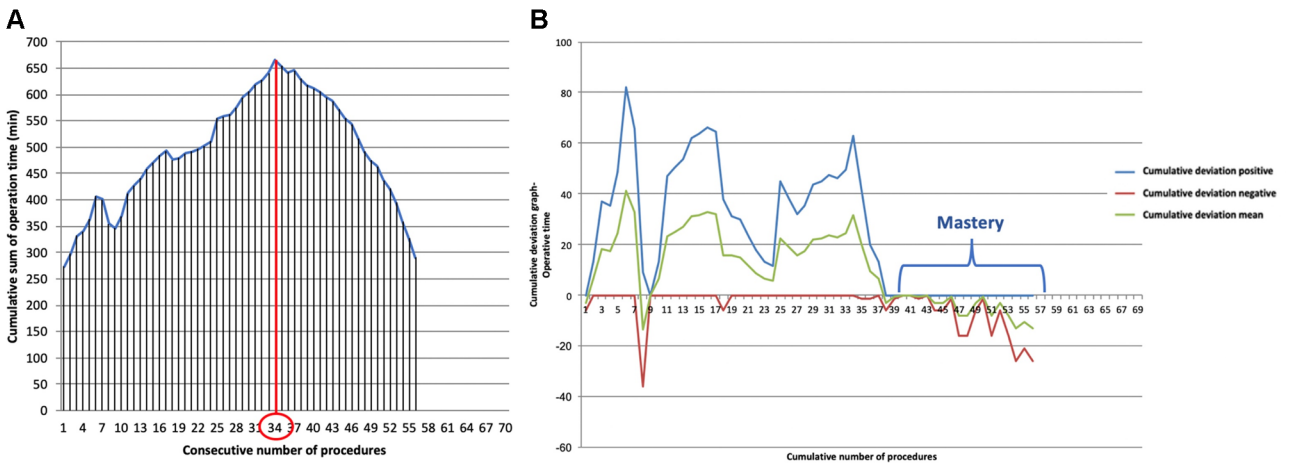

FIGURE 1
(**A**). Cumulative sum (CUSUM) plot for the overall surgical time; the red circle is the CLC cut-off value on the plot of CUSUM analysis. CLC, completion of learning curve. (**B**). Bernoulli cumulative deviation curves for CUSUM.

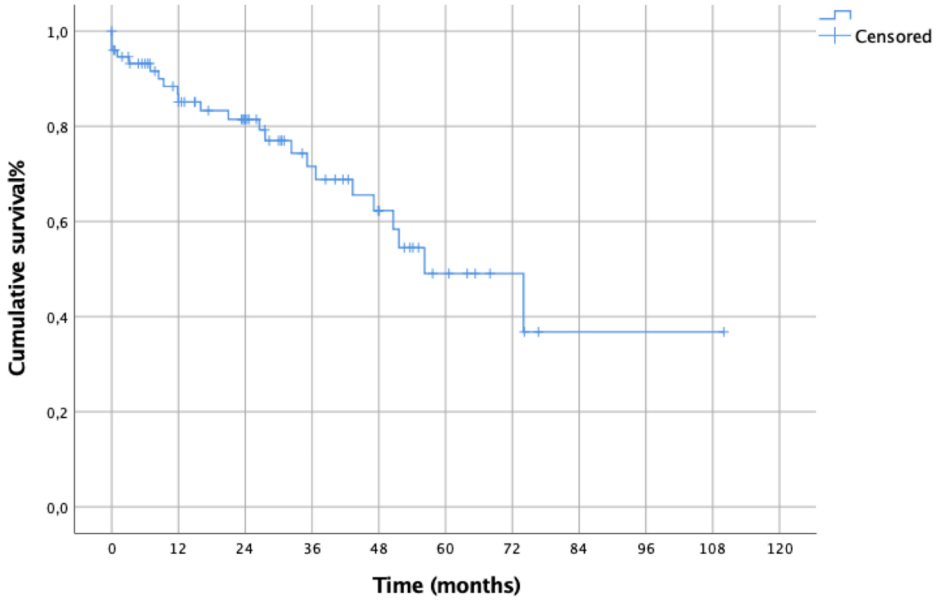

FIGURE 2
Overall survival of the whole population.

No difference in OS was also recorded evaluating the survival per surgical approach in pathological stage I (*p*: 0.424) and II (*p*: 0.329), respectively. On the contrary, in stage III, the 5-year OS in Uniportal-VATS group was statistically superior than in open group (58% vs. 29%, *p*: 0.040). This was related to the fact that 6 out of 7 deaths in open group occurred among stage III patients, in particular the 4 patients died during first 60-days after surgery for complications.

No difference was recorded in DFS between the two approaches in general (5 year-DFS in Uniportal-VATS: 86% vs. 72%, *p*: 0.298, Figure 4) and per pathological stage II (*p*: 0.633) and III (*p*: 0.512), while in stage I the 5-year DFS in Uniportal-VATS was 100% vs. 60% in open, *p*: 0.019.

Both in Uniportal-VATS group (*p*: 0.029, Figure 5) and open group (*p*: 0.006) the pathological stage significantly affected OS.

At multivariate Cox regression analysis, to assess factors independently affecting survival in the whole series, only pathological stage (stage I vs. other stages) confirmed its role (HR [95% CI]: 0.127 [0.022–0.723], *p*: 0.02), not the surgical approach (Uniportal-VATS vs. open: HR [95% CI]: 0.588 [0.226–1.529], *p*: 0.276).

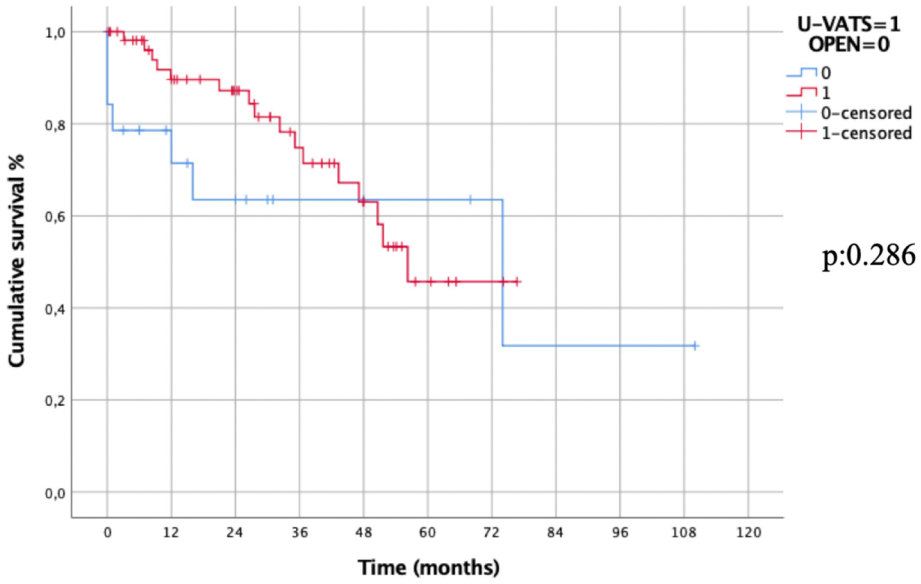

FIGURE 3
Overall survival in uniportal-VATS vs. open groups.

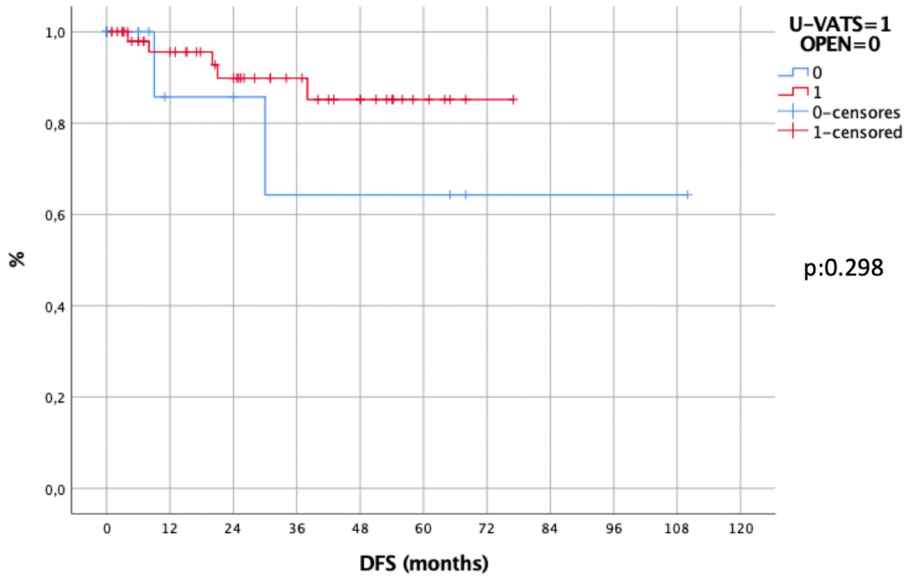

FIGURE 4
Disease-free survival in uniportal-VATS vs. open group.

4. Discussion

Till now, only small retrospective studies, mainly technical, have been published about Uniportal-VATS esophagectomy.

Therefore, it is of crucial importance having evidences about safety, surgical and oncological effectiveness of Uniportal-VATS approach compared to standard open technique or other MIEs.

After our preliminary series of 12 procedures (all McKeown) reported in 2018 (9), other authors confirmed the feasibility and efficacy of Uniportal-VATS approach for esophagectomy (3, 10).

The main used criteria for evaluating surgical and short-term outcomes of esophageal surgery are: duration of surgery, R0-resection, number of thoracic nodes removed and rate of anastomotic leak (3).

Batirel (3), in his preliminary series on 18 Uniportal-VATS esophagectomy (16 Ivor-Lewis and 2 McKeown), reported a mean number 23 ± 8 lymph nodes, with a mean VATS time of 82 ± 22 min. Three patients developed a leak (2 in the thorax and

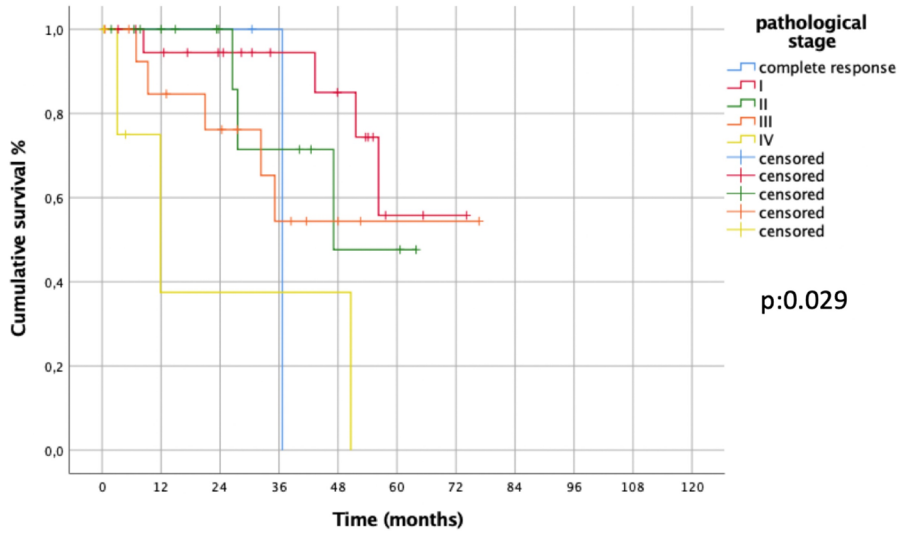

FIGURE 5
Overall survival in uniportal-VATS group per pathological stage.

1 in the neck). Similar results were reported on an updated series of 40 patients by the same group (VATS time: 90–100 min, lymph node yield: 20–25) (3). To date, the largest published series (10) on Uniportal-VATS (prone position) McKeown esophagectomy involved 44 cases, with a reported mean thoracic time of 163 ± 16 min and 24 (range: 14–36) nodes resected. All patients had a R0-resection; the mean hospital stay was 11.8 days (range:7–22), with 2 major complications descried and mortality null at 2-month FUP.

The only report comparing Uniportal-VATS esophagectomy short-term outcomes with a propensity-matched control group (multiportal MIE) was published by Lee (11) in 2017. Forty-eight patients undergone Uniportal-VATS (22 McKeown) for esophageal cancer were compared with 48 multiportal MIE patients. The authors concluded that both techniques were comparable in terms of duration of surgery, bleeding, total thoracic nodes retrieved and surgical complications (as anastomotic leak).

Only the pain-score one week after surgery was significantly lower in the Uniportal-VATS group ($p < 0.05$).

Our retrospective series of 56 McKeown esophagectomies is the largest reported with Uniportal-VATS approach and the first with a control group (open), from a single center prospectively recorded data. Moreover, in our study all patients underwent the same esophageal reconstruction (McKeown), excluding all Ivor-Lewis procedures (the other available comparison studies (11, 12) evaluated together McKeown and Ivor-Lewis esophagectomies) in order to reduce any bias related to different esophageal reconstruction (as anastomotic leaks) in comparing open and Uniportal-VATS approaches.

Furthermore, while all the previous papers dealt with only short-term outcomes, we also compared long-term oncological outcomes, with a median FUP period of 42 months.

According to our findings, Uniportal-VATS approach seemed comparable to standard open approach for McKeown esophagectomy in terms of thoracic surgical time (102.34 ± 15.21 vs. 115.56 ± 23.12 min, p: 0.646), nodes retrieved (13.40 ± 8.12 vs. 15.00 ± 6.86, p: 0.275), R + status (1 (1.8%) vs. 0, p: 0.655) and surgical complications, like anastomotic leak (4 (7.1%) vs. 4 (21.1%), p: 0.095), **Table 2**.

A superiority of Uniportal-VATS approach was recorded for a significantly lower re-operation rate (p: 0.004), chest drain duration (p: 0.003), in-hospital stay (p: 0.018), pain on I post-operative day ($p << 0.001$) and 30-day mortality (p: 0.002). Fifty percent of re-operations in open group was due to persistent chylothorax (in cases where surgical duct was not closed at time of esophagectomy), that was surgically treated after failure of conservative treatment (by exclusive parenteral nutrition for at least 7–10 days). Two cases of chylothorax were solved by conservative treatment only. Chylothorax, together with anastomotic leak (where one chest drain was kept in place precautionary till leak resolution) and the higher average of pleural effusion after thoracotomy explained the longer chest drain duration in open group.

In our Uniportal-VATS series, 58.9% of patients underwent neoadjuvant therapy and 57.1% concomitant radiotherapy, therefore this aspect did not discourage indication to minimally-invasive approach or cause conversion to open surgery.

Furthermore, in the hands of experienced Uniportal-VATS surgeons and high-volume centers in esophageal surgery, as in our series, Uniportal-VATS esophagectomy seems to have a quite short learning curve, with only 34 cases necessary to reach CLC and 40 cases for mastery.

Oncological outcomes, as 5-year OS (Log-rank test, p: 0.286; Breslow- Wilcoxon test, p: 0.036.) and DFS (p: 0.298) of patients undergone Uniportal-VATS esophagectomy were not inferior to those of standard treatment (open surgery), and the only factor independently affecting survival in our series was pathological stage (p: 0.02) not surgical access (p: 0.276).

Our results were in line with those reported by the TIME Trial (12), the only prospective randomized study comparing 56 open esophagectomies (McKeown and Ivor-Lewis) with 59 multiportal

MIE, in terms of surgical and long-term oncological outcomes (12, 13). Indeed, Uniportal-VATS, as MIE in Time Trial, was superior to open surgery for in-hospital stay and post-operative pain, but comparable with open surgery for complications, nodal yeld and radicality, with similar long-term OS and DFS. This suggests that Uniportal-VATS approach allows comparable esophageal dissection as MIE and open surgery, without compromising long-term oncological outcomes, even after neoadjuvant chemoradiation, but with better post-operative recovery than thoracotomy.

From a purely technical point of view, we agree with Wang and colleagues (10) in performing the 4 cm Uniportal-VATS incision in the V intercostal space but more posteriorly than in lung surgery (14), between posterior and middle axillary line. But we believe that it is not necessary to put the patient in prone position (10) for easily and safely dissecting the posterior mediastinum. As Batirel (3), we strongly emphasize the importance of using surgical table as an instrument in this technique, for improving mediastinum exposure. In fact, tilting the patient on his ventral side of 30–45°, with 30–45° of anti-Trendelenburg position, we have no difficult at all in dissecting the esophagus, performing radical lymphadenectomy and managing several instruments through the same incision, without fencing. In our experience, we always used the V intercostal space, so we cannot support with our data the improvement reported by Batirel (3) by performing the incision in VI intercostal space.

The present study has several limitations. As single center, retrospective, non-randomized study, it is affected by several selection biases: the sample size is not large, and the control group is small (although both groups were statistically comparable for main clinic-pathological variables, as in **Table 1**), enrollment of patients in the 2 groups is time-depending (due to change in surgical approach –open vs. Uniportal-VATS- occurred at our center in 2016), and some survival data are lacking with 28% of patients lost at FUP (42% of which from open group).

However, to the best of our knowledge, this report is the first comparing surgical and oncological outcomes of only Uniportal-VATS and open McKeown esophagectomy (without involving other esophageal reconstruction techniques as Ivor-Lewis), with the largest Uniportal-VATS series reported in literature and longest oncological FUP (Median FUP: 42 months vs. 22 months of TIME Trial (13).

According to our results, Uniportal-VATS seems to be a safe, feasible and effective technique for performing McKeown esophagectomy, with equivalent surgical and long-term oncological results as the standard thoracotomy, but with a faster and unharmed recovery and a quite short learning curve.

Further prospective randomized trials with open and other minimally-invasive approaches are claimed to confirm the effectiveness of Uniportal-VATS in esophageal surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was evaluated by the Institutional Review Board (IRB) of Catholic University of Sacred Hearth and, as this was a retrospective review for service evaluation (within an audit approved by our Surgical Department) and there was no modification in patients' care (no prospective randomized study), we did not need the final ethical approval of our IRB. All patients signed an informed consent before the operation for the anonymous treatment of their clinical data.

Author contributions

DN, MTC, VP: study design, manuscript writing, and critical revision of the manuscript. GC, DT, EM, LPC, MLV, GP, MC, FL, FR, AG, UC: data collection and manuscript writing. DN: statistical analysis. SM: supervision. All authors contributed to the article and approved the submitted version.

Acknowledgments

Ministero della Salute – Ricerca Corrente 2023 (Ministry of Health – Current Research 2023).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med*. (2002) 347(21):1662–9. doi: 10.1056/NEJMoa022343

2. Zheng Y, Li Y, Liu X, Sun H, Shen S, Ba Y, et al. Minimally invasive versus open McKeown for patients with esophageal cancer: a retrospective study. *Ann Surg Oncol*. (2021) 28(11):6329–36. doi: 10.1245/s10434-021-10105-y

3. Batirel H. Uniportal VATS approach in esophageal cancer - how to do it update. *Front Surg*. (2022) 9:844796. doi: 10.3389/fsurg.2022.844796

4. Dmitrii S, Pavel K. Uniportal video-assisted thoracic surgery esophagectomy. *Thorac Surg Clin*. (2017) 27(4):407–15. doi: 10.1016/j.thorsurg.2017.06.009

5. Lerut T. Uniportal video-assisted thoracoscopic surgery in esophageal diseases: an introduction. *J Vis Surg*. (2017) 3:182. doi: 10.21037/jovs.2017.11.04

6. Batirel HF. Uniportal video-assisted thoracic surgery for esophageal cancer. *J Vis Surg*. (2017) 3:156. doi: 10.21037/jovs.2017.09.14

7. Berry MF. Esophageal cancer: staging system and guidelines for staging and treatment. *J Thorac Dis*. (2014) 6(Suppl 3):S289–97. doi: 10.3978/j.issn.2072-1439.2014.03.11

8. Rice TW, Patil DT, Blackstone EH. 8th Edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg*. (2017) 6(2):119–30. doi: 10.21037/acs.2017.03.14

9. Nachira D, Meacci E, Mastromarino MG, Pogliani L, Zanfrini E, Iaffaldano A, et al. Initial experience with uniportal video-assisted thoracic surgery esophagectomy. *J Thorac Dis*. (2018) 10(Suppl 31):S3686–95. doi: 10.21037/jtd.2018.04.17

10. Wang Q, Ping W, Cai Y, Fu S, Fu X, Zhang N. Modified McKeown procedure with uniportal thoracoscope for upper or middle esophageal cancer: initial experience and preliminary results. *J Thorac Dis*. (2019) 11(11):4501–6. doi: 10.21037/jtd.2019.11.07

11. Lee JM, Chen SC, Yang SM, Tseng YF, Yang PW, Huang PM. Comparison of single- and multi-incision minimally invasive esophagectomy (MIE) for treating esophageal cancer: a propensity-matched study. *Surg Endosc*. (2017) 31(7):2925–31. doi: 10.1007/s00464-016-5308-9

12. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet*. (2012) 379(9829):1887–92. doi: 10.1016/S0140-6736(12)60516-9

13. Straatman J, van der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial. *Ann Surg*. (2017) 266(2):232–6. doi: 10.1097/SLA.0000000000002171

14. Ismail M, Nachira D. Devising the guidelines: the concept of uniportal video-assisted thoracic surgery—instrumentation and operatory room staff. *J Thorac Dis*. (2019) 11(Suppl 16):S2079–85. doi: 10.21037/jtd.2019.08.69

frontiers | Frontiers in Surgery

TYPE Perspective
PUBLISHED 09 March 2023
DOI 10.3389/fsurg.2023.1129803

OPEN ACCESS

EDITED BY
Federico Raveglia,
Thoracic Surgery, ASST-Monza, Italy

REVIEWED BY
Eliseo Passera,
Azienda Socio Sanitaria Territoriale (ASST) di Monza, Italy
Michele Mondoni,
University of Milan, Italy

*CORRESPONDENCE
Serena Conforti
✉ serena.conforti@ospedaleniguarda.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 22 December 2022
ACCEPTED 01 February 2023
PUBLISHED 09 March 2023

CITATION
Conforti S, Licchetta G, Reda M, Astaneh A, Pogliani L, Fieschi S, Rinaldo A and Torre M (2023) Management of COVID-19-related post-intubation tracheal stenosis.
Front. Surg. 10:1129803.
doi: 10.3389/fsurg.2023.1129803

Management of COVID-19-related post-intubation tracheal stenosis

Serena Conforti*, Gloria Licchetta, Marco Reda, Arash Astaneh, Luca Pogliani, Stefano Fieschi, Alessandro Rinaldo and Massimo Torre

Department of Thoracic Surgery, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

Introduction: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has affected Italy since the beginning of 2020. Endotracheal intubation, prolonged mechanical ventilation, and tracheostomy are frequently required in patients with severe COVID-19. Tracheal stenosis is a potentially severe condition that can occur as a complication after intubation. The aim of this study was to evaluate the utility and safety of endoscopic and surgical techniques in the treatment of tracheal stenosis related to COVID-19.
Materials and Methods: Between June 2020 and May 2022, consecutive patients with tracheal stenosis who were admitted to our surgical department were considered eligible for participation in the study.
Results: A total of 13 patients were included in the study. They consisted of nine women (69%) and four men (31%) with a median age of 57.2 years. We included seven patients with post-tracheostomy tracheal stenosis. Bronchoscopy was performed to identify the type, location, and severity of the stenosis. All patients underwent bronchoscopic dilation and surveillance bronchoscopy at 7 and 30 days after the procedure. We repeated endoscopic treatment in eight patients. Three patients underwent tracheal resection anastomosis. Final follow-up bronchoscopy demonstrated no residual stenosis.
Conclusions: The incidence of and risk factors associated with tracheal stenosis in critically ill patients with COVID-19 are currently unknown. Our experience confirms the efficacy and safety of endoscopic management followed by surgical procedures in cases of relapsed tracheal stenosis.

KEYWORDS

COVID-19, tracheal stenosis, endoscopic treatment, tracheal surgery, balloon dilatation

Introduction

Over the last few years, the world has been hit by pandemic waves of a new coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has caused >90 million infections (1). From January 2020, the World Health Organization (WHO) considered this disease to be a public health emergency (2). This infection has a wide variety of clinical presentations, ranging from asymptomatic to severe cases of acute respiratory distress syndrome (ARDS) (3). Prior to the pandemic, up to 9% of patients requiring invasive ventilation experienced tracheal stenosis (6). During the COVID-19 era, this rate increased. Up to 90% of patients admitted to an intensive care unit (ICU) undergo intubation and invasive mechanical ventilation, often requiring tracheostomy (4). COVID-19 patients have a median ventilation duration of 17 days and a high frequency of reintubation (5). As reported in the literature (6), prolonged mechanical intubation

may lead to mucosal damage and inflammation, the development of granulation tissue, and the subsequent formation of cicatricial stenotic tissue (7, 8). In addition, prone position, overinflation of the tube cuff, and use of a larger endotracheal tube can contribute to the risk of stenosis (9).

Tracheal stenosis (TS) is usually the result of scar formation with associated morbidity depending on the location, extent, and thickness of the tissue. Tracheal stenosis can occur anywhere from the level of the endobronchial tube up to the glottic and subglottic area, particularly at the site where the tube cuff comes into contact with the tracheal mucosa and at the tracheal stoma site after the tracheostomy procedure is performed (10, 11). Multiple other factors create a predisposition to tracheal stenosis, such as a high tracheostomy site, traumatic intubation, infections, chronic inflammatory diseases, obesity, advanced age, excessive corticosteroid use, and autoimmune diseases. The symptoms are variable and depend on the site and grade of the stenosis (12). In terms of diagnosis, computerized tomography is used more often than magnetic resonance imaging and correlates well with endoscopic findings (13). However, bronchoscopy is the gold standard for diagnosis. This is performed to identify the type, location, and severity of the stenosis (11, 13) (**Figure 1A**). As regards management, we consider endoscopic and surgical approaches. Through endoscopic balloon dilation and intra-lesional corticosteroid injection, it is possible to guarantee a significant improvement in airway patency, avoiding tracheostomy. Endoscopic management does not preclude open surgical procedures, when necessary. The aim of this study was to evaluate the utility and safety of endoscopic and surgical techniques in the management of tracheal stenosis related to COVID-19.

Methods

A retrospective, single-center series of cases was collected in an Italian training hospital. The need for informed consent from individual patients was waived owing to the retrospective nature of the study. All patients admitted between 1 June 2020 and 31 May 2022, inclusive of these dates, were screened for eligibility. The inclusion criterion was a laboratory-confirmed history of

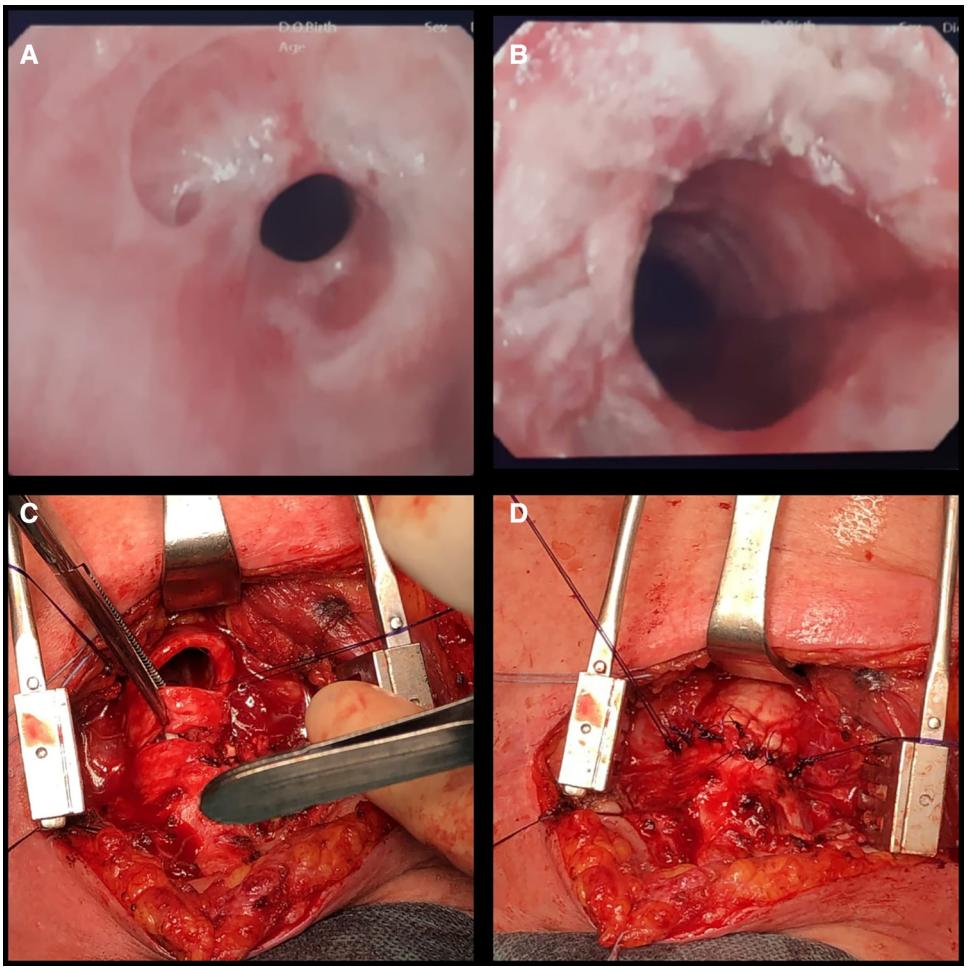

FIGURE 1
(A) Tracheal stenosis (Myer–Cotton grade II); bronchoscopic examination. (B) Endoscopic result after balloon dilation. (C) Surgical resection of the trachea. (D) Suture of the anterior tracheal wall.

SARS-CoV-2 infection (i.e., positive result of real-time reverse transcriptase-polymerase chain reaction assay of nasal and pharyngeal swabs). The exclusion criteria were: age < 18 years; admission for causes other than respiratory failure; malignant or benign tracheal neoplasm; and idiopathic TS or other iatrogenic cases of tracheal stenosis. Clinical data were extracted from the patient data management system and a unique database was created. For every included patient, we recorded demographic and anthropometric data, comorbidities, and medical history. Information regarding airway management (i.e., performance of a tracheostomy, extubation, or decannulation) was acquired daily until ICU discharge. Data concerning treatments included the number and type of endoscopic therapeutic procedures. Finally, data concerning endoscopic and/or surgical outcomes and clinical follow-up duration were collected.

Results

Between June 2020 and May 2022, 13 consecutive patients were admitted to our department for tracheal stenosis after COVID-19 infection. They consisted of nine women (69%) and four men (31%), with an age range of 45–72 years (median age: 57.2 years). Table 1 summarizes the baseline characteristics of the patients at ICU admission. Twelve patients (92.3%) had at least one comorbidity; specifically, eight (61.5%) presented with obesity (body mass index > 30 kg/m^2), four (30.7%) with hypertension, five (38.4%) with diabetes mellitus, four (30.7%) with cigarette smoking and chronic obstructive pulmonary disease, and three (23%) with use of corticosteroids in autoimmune disease. Data regarding respiratory maintenance during COVID-19 consisted of duration of ICU hospitalization, time of intubation, presence and type of tracheostomy, and any subsequent reintubation. These data indicated that the median ICU and hospital stay lasted 20 (9–29) days and 28 (15–47) days, respectively. The mean intubation time was 18 days. Tracheostomy was performed in seven patients: this was surgically performed in three cases (42.8%) and by a percutaneous technique in four cases (57.1%). Symptoms of stenosis appeared between 3 and 9 weeks following ICU admission. These symptoms were inspiratory stridor, dyspnoea, persistent dry cough, wheezing, and recurrent attacks of respiratory obstruction caused by mucus; two patients (15.3%) also presented with hemoptysis. Symptoms usually occur when the tracheal diameter is reduced to 8 mm, and stridor occurs when it is less than 5 mm (12). Initially, we used awake flexible bronchoscopic examination to assess vocal fold mobility, to exclude potential airway anomalies, and to evaluate the stenosis and its main characteristics: length, location, and extent of obstruction. Tracheal stenosis can be divided into simple and complex stenosis. When the length of the stenosis segment is >1 cm, and it is accompanied by cartilage involvement, malaise, and inflammation, the stenosis is considered complex; in contrast, a stenosis segment with a length of <1 cm, with involvement limited to the mucosa and with the absence of malaise and cartilage loss, denotes "simple stenosis" (14, 15). The Myer–Cotton system of grading classifies stenosis severity on the basis of the diameter of the remaining airway in correlation with the diameter of tracheal tubes, ranging from Stage I classification for cases of less than 70% obstruction to Stage IV classification if there is 100% obstruction (16). In this study, seven patients (53.8%) presented with Stage II stenosis and six (46.2%) with Stage III. As regards the site of the stenosis, eight cases (61.5%) were located in the subglottic area and five (38.5%) in the mid-tracheal area. The diagnosis was confirmed via neck and chest CT scan with 3D reconstruction of the airways.

Endoscopic procedure

All patients underwent rigid bronchoscopy in the operating room. Patients maintained spontaneous ventilation during the

TABLE 1 Summary of data from 13 patients with tracheal stenosis COVID-19 related.

Data from 13 patients with tracheal stenosis									
Patient									
N°	Age	Sex	Comorbidities	Grade of stenosis	ICU stay (days)	Hospital stay (days)	Tracheostomy	Treatment	Outcome
1	49	F	Smoker, steroid	II	10	15	N	Endo	Full recovery
2	53	M	DM	III	24	31	Y	Endo (2)	Full recovery
3	72	M	DM, HTN, obesity	II	20	22	N	Endo	Full recovery
4	45	F	DM	III	23	28	Y	Endo (2)	Full recovery
5	53	M	HTN, obesity	II	22	26	Y	Endo (4)	Full recovery
6	52	F	Smoker, obesity	II	17	25	N	Endo	Full recovery
7	68	M	HTN, obesity	II	19	27	N	Endo (2)	Full recovery
8	55	F	Smoker, steroid	III	25	47	Y	Endo (4) + Surg	Full recovery
9	59	F	DM, obesity	III	23	31	Y	Endo (4) + Surg	Full recovery
10	62	F	Steroid	II	9	16	N	Endo	Full recovery
11	71	F	AMI, HTN, obesity	II	18	26	Y	Endo	Full recovery
12	48	F	Obesity	III	21	24	N	Endo (2) + Surg	Full recovery
13	57	F	Smoker, DM, obesity	III	29	46	Y	Endo (2)	Full recovery

M, male; F, female; DM, diabetes mellitus; HTN, hypertension; AMI, acute myocardial infarction.

entire procedure with anesthetic assistance. This treatment was facilitated by continuous propofol infusion, which enables various levels of sedation while maintaining a minimum level of discomfort. In our practice, we do not use devices such as jet ventilation or poncho; deep sedation with spontaneous breathing is therefore considered appropriate. The intervention was performed using instruments (flexible bronchoscope, dilation catheter, etc.) passed through the rigid endoscope. In cases of web-like stenosis, we applied radial incision with a pre-cut needle (Needle Knife Papillotome, 4 mm, Cook Medical). Balloon dilation (15–16.5–18 mm/3–4.5–7 ATM × 55 mm; Micro-Tech Endoscopy, Nanjing, Co. Ltd.) was introduced into the airway under direct visualization at the site of the stenosis. A stylet was used to facilitate atraumatic access across narrow stenosis. The balloon was inflated to a predetermined pressure corresponding to the desired diameter, applying controlled radial pressure to the stricture. Balloon dilation offers many advantages over the use of alternative dilatation instruments. The most important of these is that, if the balloon is placed correctly, it exerts a radial expansible force in the stenotic area and distributes this force over the entire circumference of the stenosis, avoiding rupture at any point. A diameter of 15 mm can be achieved with a pressure of 4.5 atm, and a diameter of 18 mm with 7 atm (at a length of 5.5 cm). We agreed on the three-stage technique for the sessions included in this study, in which inflation would be carried out three times, with each inflation lasting 40–60 s, according to the patient's oxygen reserves and saturation during inflation. At the end of the session, we removed the catheter to allow ventilation and to control the result of dilation (**Figure 1B**). In our specialist center with a highly trained and experienced team, we recorded a negligible number of complications (dental or vocal cord trauma, hemorrhage, pneumothorax) across all such procedures conducted.

Surgical treatment

In our institution, all patients undergoing surgical treatment ($n = 3$; 23% of the total) were treated with an anterior tracheal approach. All were positioned supine with an inflatable bag behind their shoulders and cervical extension. The incision was a classic cervical low collar incision. Initial dissection permitted us to move the upper flap to the level of the cricoid cartilage. Inferiorly, the cutaneous and platysmal flaps were raised to the sternal notch. The midline was identified and section was performed at the midline from the cricoid cartilage to the interclavicular ligament. Ligature and section of the thyroid isthmus was performed in every patient. At this time, dissection of the anterior face of the trachea was possible; this was carried out from the larynx to the carina in the anterior-lateral plane, and not in the posterior-lateral plane, to avoid injuries to the circulatory system. In every patient, a flexible endotracheal tube with its connectors and sterile anesthesia tubing was retained at the level of the incision, and the proximal anesthesia tubes were passed to the anesthesiologist. After retraction of the oro-tracheal tube and direct endoscopic control, to confirm the level of stenosis, circumferential resection of the trachea was performed (**Figure 1C**). Two points of PDS 3/0 were positioned at the posterior angles of the distal trachea as traction points to allow better distal dissection. In all patients, simple tracheal surgery was performed with end-to-end resection anastomosis, with posterior running suture of the membranous wall (PDS 4/0) and simple suture of the anterior wall (PDS 3/0) (**Figure 1D**). At the end of the surgery, two drains were left in the neck and the anterior mediastinum. All patients were immediately extubated in the operating room. In general, patients with comorbidities and poor performance status may not be eligible for surgery (17). Mortality rates of up to 5% can be seen after end-to-end anastomosis (17,18), along with complications such as restenosis, suture granuloma formation, infections, and hemorrhage (18–20). Surgical management is often definitive, but patient selection and preparation are essential for surgical success.

In the present study, no severe complications occurred during the interventional endoscopic procedures; specifically, no procedure-related deaths or immediate major complications (i.e., pneumothorax or massive bleeding) occurred, and the outcomes were uneventful in all patients. Patients reported subjective symptomatic relief immediately after the procedure, and they were able to perform normal activities and maintain normal speech. All patients underwent endoscopic treatment through rigid bronchoscopy. Stenosis recurred in eight patients (61.5%) in the period from 15 to 30 days after the first dilation procedure. All of these patients underwent a new rigid endoscopic procedure (second dilation). In two of these cases (25% of the eight patients), multiple endoscopic procedures were performed (once per month, for a total of four procedures). Three patients (two of these, 23% of the total) underwent surgical treatment as a result of multiple and/or severe recurrences. In one patient, we observed neck subcutaneous emphysema that resolved spontaneously within 72 h. The mean hospitalization time was 10.6 days (8–17). Surveillance bronchoscopy was performed at 7 and 30 days after the procedure. Final follow-up bronchoscopy demonstrated no residual stenosis and adequate respiratory space after both endoscopic and surgical treatment.

Discussion

The treatment of iatrogenic tracheal stenosis is controversial because the role and efficacy of surgical techniques vs. endoscopic procedures depend on the experience of the staff working in a given center and on the referral pattern (20). A multidisciplinary team should plan definitive management. The characteristics of patients with this condition may make them high-risk surgical candidates; thus, endoscopic intervention is often preferable. However, all patients should be considered for surgery. Some authors have reported obtaining different results from the endoscopic procedure as an initial approach. The anatomical and functional characteristics of the laryngotracheal structure present particular difficulties. Lesions that involve the infraglottic larynx as well as the upper trachea are much more difficult to repair surgically. In our patients, we found that the

tracheal cartilage healed poorly and only a limited segment of the trachea could be removed and re-anastomosis accomplished. Surgical procedures include anterior and posterior cricoid splits, mucosal and cutaneous grafts, and free grafts of cartilage and hyoid. Tracheal resection is now a well-established technique that is performed in the presence of specific indications. According to the literature, the success rate of this procedure varies from 71% to 97% (21). Complications of tracheal surgery include restenosis, dehiscence, fistula formation, and development of granulations at the suture line. Reported rates of complications are low, but this rate increases with multiple resections at increasingly high levels (22). Tracheal stenosis is evaluated on the basis of the distance from the stenotic region to the vocal cords, the length of the stenotic region, and the distance from the distal part of the stenotic region to the carina. Currently, tracheal resection is indicated in cases of high-grade mature stenosis (grades III and IV) with cranio-caudal extension >1 cm (but <5.5 cm) and/or laryngotracheal framework impairment, or in cases of a lack of response to multiple endoscopic procedures (13). Generally, patients with low-grade stenosis that is intrinsic, short (< 1 cm), and limited to a single subsite in the airway may benefit from endoscopic treatments such as radial incision or balloon dilation, alone or in combination (23). Endoscopic treatment offers minimal morbidity with good functional outcomes; however, stenosis can recur and repeated dilations may be required. This treatment is well tolerated even by heavily comorbid patients and, if adequately performed, does not cause additional injury. In contrast, indications for stent placement in cases of benign disease are controversial because of the better long-term prognosis and reported complications of stent use. In our practice, we do not use a metallic or silicone stent in benign TS. Galluccio et al. have confirmed that endoscopic procedures are a valid option in certain select cases of both simple and complex stenosis (success rate: 96% and 69%, respectively) (15). Stratakos et al. have also published analogous results (24).

In the present study, all patients were followed up for at least 12 months and achieved good clinical treatment results. Evaluation showed that after tracheal stenosis was resolved, their endoscopic condition was stable, with good mid- and long-term effects. These results suggest that the endoscopic technique is feasible, safe, and without complications. Proper selection of strategy is necessary to break the vicious cycle of "injury/recovery/stenosis/reinjury." In cases of relapsed stenosis, the surgical procedures were definitive; no other follow-up endoscopic treatment was required.

The SARS-CoV-2 pandemic signified an unexpected challenge in terms of both the large number of patients who required ICU treatment with ventilator support and the later effects of this treatment, which included a non-negligible percentage of post-intubation TS. The increase in the use of invasive ventilation during the COVID-19 pandemic led to an overall increase in the number and severity of cases of airway damage. In Italy, the number of people with complications also increased, particularly because in northern Italy, especially in Lombardia, a large number of infections occurred during the first pandemic wave (8). Several laryngological works (25, 29) and a recent paper from the European Laryngological Society show a rise in iatrogenic sequelae (27). The incidence of and risk factors associated with tracheal stenosis in critically ill patients with COVID-19 are currently unknown, but the latter may include female sex, obesity, diabetes mellitus, cardiovascular disease, tracheostomy, prolonged intubation (including high ventilator pressure and high tube cuff pressure), and hyperinflammatory state (26). Furthermore, the need for frequent pronation cycles has been found to increase the incidence of TS. In our experience, we have recorded no differences between surgical and percutaneous tracheostomy techniques, which is in accordance with the literature (28). In post-COVID-19 patients, we expected an increased incidence of TS and have recommended that patients presenting symptoms within 6 months after ICU discharge receive a targeted evaluation aimed at ruling out the possibility of iatrogenic stenosis (29). The major limitation of our work is the small number of patients treated so far, which does not allow for a comparison with cases of non-COVID-19 TS. However, we can still confirm that endoscopic treatment is effective in patients falling into the category included in this study and can also be used as a bridge to the surgical approach.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Author contributions

SC, GL, MR, AA, and LP conceptualized the study design. GL, LP, SF, and AR collected data. SC, GL, and AA wrote the manuscript. CS and MT reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering. 2020 (cited 2020 Jul 2). Available at: https://coronavirus.jhu.edu/map.html.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395 (10223):497–506. doi: 10.1016/S0140-6736(20)30183

3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CH, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Eng J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032

4. Phua H, Weng L, Ling L, Egi M, Lim CM, Divatia J, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med*. (2020) 8:506–17. doi: 10.1016/S2213-2600(20)30161-2

5. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID 19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. (2020) 180:1345–55. doi: 10.1001/jamainternmed.2020.3539

6. Nouraei S, Ma E, Patel A, Howard D, Sandhu G. Estimating the population incidence of adult post-intubation laryngotracheal stenosis. *Clin Otolaryngol*. (2007) 32:411–2. doi: 10.1111/j.1749-4486.2007.01484.x

7. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. (2020) 395:1763–70. Available at: http://dx.doi.org/10.1016/S0140-6736(20)31189-2. doi: 10.1016/S0140-6736(20)31189-2

8. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. (2020) 323:1574–81. doi: 10.1001/jama.2020.5394

9. Cooper JD, Grillo HC. The evolution of tracheal injury due to ventilatory assistance through cuffed tubes. *Ann Surg*. (1969) 169:334–48. doi: 10.1097/00000658-196903000-00007

10. Wright CD, Li S, Geller AD, Lanuti M, Gaissert HA, Muniappan A, et al. Postintubation tracheal stenosis: management and results 1993 to 2017. *Ann Thorac Surg*. (2019) 108:1471–7. doi: 10.1016/j.athoracsur.2019.05.050

11. Poetker DM, Ettema SL, Blumin J, Toohill RJ, Merati AL. Association of airway abnormalities and risk factors in 37 subglottic stenosis patients. *Otolaryngol Head Neck Surg*. (2006) 135(3):434–7. doi: 10.1016/j.otohns.2006.04.013

12. Geffin B, Grillo HC, Cooper JD, Pontoppidan H. Stenosis following tracheostomy for respiratory care. *JAMA*. (1971) 216:1984–8. doi: 10.1001/jama.1971.03180380042009

13. Hadi U, Hamdan AL. Diagnosis and management of tracheal stenosis. *J Med Liban*. (2004) 52(3):131–5.

14. Monnier P, Dikkers FG, Eckel H, Sittel C, Piazza C, Campos G, et al. Preoperative assessment and classification of benign laryngotracheal stenosis: a consensus paper of the European Laryngological Society. *Eur Arch Otorhinolaryngol*. (2015) 272:2885–96. doi: 10.1007/s00405-015-3635-4

15. Galluccio G, Lucantoni G, Battistoni P, Paone G, Batzella S, Lucifora V, et al. Interventional endoscopy in the management of benign tracheal stenoses: definitive treatment at long-term follow-up. *Eur J Cardiothorac Surg*. (2009) 35:429–33. discussion 933-4. doi: 10.1016/j.ejcts.2008.10.041

16. Myer CM 3rd, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. *Ann Otol Rhinol Laryngol*. (1994) 103:319–23. doi: 10.1177/000348949410300410

17. Brichet A, Verkindre C, Dupont J, Carlier ML, Darras J, Wurtz A, et al. Multidisciplinary approach to management of postintubation tracheal stenosis. *Eur Respir J*. (1999) 13(4):888–93. doi: 10.1034/j.1399-3003.1999.13d32.x

18. Wright CD, Grillo HC, Wain JC, Wong DR, Donahue DM, Gaissert HA, et al. Anastomotic complications after tracheal resection: prognostic factors and management. *J Thorac Cardiovasc Surg*. (2004) 128(5):731–9. doi: 10.1016/j.jtcvs.2004.07.005

19. Fernandez RB, Moran AM, Vidal MJ, Barro JCV, Garcia AS. Resection with end-to end anastomosis for post-intubation tracheal stenosis. *Acta Otorrinolaryngol Esp*. (2007) 58:16–9. doi: 10.1016/S0001-6519(07)74870-7

20. Grillo HC, Donahue DM, Mathisen DJ, Wright CD. Postintubation tracheal stenosis. Treatment and results. *J Thorac Cardiovasc Surg*. (1995) 109(3):486–92. doi: 10.1016/S0022-5223(95)70279-2

21. Grillo HC, Ponn RB. Management of nonneoplastic diseases of the trachea. In: TW Shields, IIIJ LoCicero III, editors. *General thoracic surgery vol 1*. Philadelphia: Lippincott Williams and Wilkins (2000). p. 885–97.

22. Lanuti M, Mathisen DJ. Management of complications of tracheal surgery. *Chest Surg Clin N Am*. (2003) 13(2):385–97. doi: 10.1016/S1052-3359(03)00007-3

23. Kocdor P, Siegel ER, Suen JY, Richter G, Tuluna Y, Ugur OE. Comorbidities and factors associated with endoscopic surgical outcomes in adult laryngotracheal stenosis. *Eur Arch Otorhinolaryngol*. (2016) 273:419–24. doi: 10.1007/s00405-015-3750-2

24. Stratakos G, Anagnostopoulos N, Alsaggaf R, Koukaki E, Bakiri K, Emmanouil P, et al. COVID-19 Patients presenting with post-intubation upper airway complications: a parallel epidemic? *J Clinic Med*. (2022) 11:1719. doi: 10.3390/jcm11061719

25. Fiz I, Monnier P, Koelmel JC, Di Dio D, Missale F, Piazza C, et al. Multicentric study applying the European laryngological society classification of benign laryngotracheal stenosis in adults treated by tracheal or cricotracheal resection and anastomosis. *Laryngoscope*. (2020) 130:1640–5. doi: 10.1002/lary.28274

26. Felix L, Tavares TL, Almeida VPB, Tiago RSL. Incidence of laryngotracheal lesions after orotracheal intubation in coronavirus disease patients. *Laryngoscope*. (2021) 132:1075–81. doi: 10.1002/lary.29862

27. Piazza C, Filauro M, Dikkers FG, Nouraei SA, Sandu K, Sittel C, et al. Long term intubation and high rate of tracheostomy in COVID-19 patients might determine an unprecedented increase of airway stenoses: a call to action from the European laryngological society. *Eur Arch Oto Rhino Laryngol*. (2021) 278:1–7. doi: 10.1007/s00405-020-06112-6

28. Long SM, Feit N, Chern A, Cooley V, Hill SS, Rajwani K, et al. Percutaneous and open tracheostomy in patients with COVID-19: the Weill Cornell experience in New York City. *Laryngoscope*. (2021) 131:E2849–56. doi: 10.1002/lary.29669

29. Piazza C, Lancini D, Filauro M, Peretti G, Sampieri C, Bosio P, et al. Post-COVID-19 airway stenosis treated by tracheal resection and anastomosis: a bicentric experience. *ACTA Othorinolaryngol Italica*. (2022) 42:99–105. doi: 10.14639/0392-100X-N1952

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 15 March 2023
DOI 10.3389/fsurg.2023.1127627

OPEN ACCESS

EDITED BY
Federico Raveglia,
ASST-Monza, Italy

REVIEWED BY
Andrea De Vico,
Azienda Usl Teramo, Italy
Filippo Lococo,
Agostino Gemelli University Polyclinic (IRCCS), Italy

*CORRESPONDENCE
Giovanni Mattioni
g.mattioni@outlook.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 19 December 2022
ACCEPTED 20 February 2023
PUBLISHED 15 March 2023

CITATION
Palleschi A, Mattioni G, Mendogni P and Tosi D (2023) A real-world experience of transition to robotic-assisted thoracic surgery (RATS) for lung resections.
Front. Surg. 10:1127627.
doi: 10.3389/fsurg.2023.1127627

A real-world experience of transition to robotic-assisted thoracic surgery (RATS) for lung resections

Alessandro Palleschi[1], Giovanni Mattioni[1,2]*, Paolo Mendogni[1] and Davide Tosi[1]

[1]Thoracic Surgery and Lung Transplantation Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]School of Thoracic Surgery, University of Milan, Milan, Italy

Objective: We report our experience of transition to robotic-assisted thoracic surgery (RATS) for lung resections with the da Vinci Xi surgical system, exposing short-term results.
Materials and methods: This is a single-center, retrospective analysis of RATS lung resections performed between April 2021 and September 2022 during our new robotic program. The surgical approach evolved over time, starting from a four-arm approach with four incisions. Alternative RATS approaches were subsequently evaluated, such as uniportal and biportal.
Results: During a 17-month period, 29 lung resections were performed. Of them, 16 were lobectomies, 7 were segmentectomies, and 6 were wedge resections. The most common indication for anatomical lung resection was non-small cell lung cancer. A uniportal approach was used for two simple segmentectomies and a biportal RATS was performed in five lobectomies and two segmentectomies. A mean number of 8.1 lymph nodes and a mean of 2.6 N2 and 1.9 N1 stations were resected during surgery, and no nodal upstaging was observed. Negative resection margins were 100%. There were two (7%) conversions, one to open surgery and one to video-assisted thoracic surgery (VATS). Eight (28%) patients experienced complications with no 30-day mortality.
Discussion: High-ergonomic and high-quality views were immediately observed. After some procedures, we abandoned uniportal RATS because of the possibility of arm collisions and the necessity of a VATS-skilled surgeon at the operating table.
Conclusion: RATS for lung resections was safe and effective, and from the surgeon's standpoint, several practical advantages over VATS were observed. Further analysis on outcomes will help better understand the value of this technology.

KEYWORDS
robotic-assisted thoracic surgery, RATS, biportal, uniportal, lung cancer, brief report

1. Introduction

The application of robotic surgical systems in thoracic surgery is still rapidly increasing. Robotic-assisted thoracic surgery (RATS) is believed to offer specific advantages: enhanced and 3D view, instruments articulation, higher ergonomics, and movement filtering. The transition to RATS in lung resections has been suggested to differ when starting from a precedent open surgery experience rather than starting from video-assisted thoracic surgery (VATS). The approach used (e.g., uniportal, biportal) may also have a significance. In April 2021, our thoracic surgery department started a RATS program,

using the da Vinci Xi surgical system (Intuitive Surgical, California, United States). Both pulmonary and mediastinal procedures were performed. Previously, lung resections were routinely performed with a uniportal VATS approach. In this brief report, we expose our real-world experience of transition to RATS for lung resections, along with obstacles and challenges met.

2. Materials and methods

A single-center, retrospective analysis was conducted. Data from patients who underwent RATS lung resections with the da Vinci Xi from April 2021 to September 2022 in our institution (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy) were retrieved. All patients provided informed consent prior to surgery, and the study was approved by the ethical review board of our institution (approval no. 3.11/2022-273). A dedicated weekly session was established for the RATS program. Initially, mediastinal and simple lung procedures were performed, in order to get familiar with the robotic system. The selected anatomical lung resections were lobectomies and simple segmentectomies. Pneumonectomies, bilobectomies, and sleeve lobectomies were excluded, as well as lung resections after neoadjuvant treatment. The previous diagnostic and therapeutic pathway for non-small cell lung cancer (NSCLC) was not changed by the RATS program. Prior to surgery, all patients affected by a diagnosed or suspected NSCLC received a contrast-enhanced computed tomography (CT) scan of the thorax and a total body fluorodeoxyglucose positron emission tomography (FDG-PET) scan. If a pathological diagnosis was not available, a frozen section analysis on a wedge resection was performed prior to an eventual anatomical resection. During segmentectomies, an N1 lymph node was resected for intraoperative frozen section analysis, and if positive, a lobectomy would have been performed. The intersegmental plane was identified using indocyanine green venous injection after arterial stapling. Preoperative functional tests (mainly respiratory) were performed in accordance with international guidelines (1, 2).

2.1. RATS approaches

In the early phase of the program, the robotic-assisted (RA) approach with four arms described by Veronesi et al. was employed. The anterior mini-thoracotomy, typically in the fourth intercostal space, was used for both a robotic arm and the space for the assistant activity. A soft tissue retractor (Alexis®) was positioned here. Additionally, three robotic ports were positioned along the seventh and eighth intercostal space, with the camera located in the midaxillary line port (3, 4). Subsequently, alternative RATS approaches were applied. The three-arm biportal approach consisted in a mini-thoracotomy, usually performed in the sixth to seventh intercostal space, on the anterior axillary line, and an additional robotic port positioned in the sixth to seventh intercostal space, on the posterior axillary line. The camera port, an arm port, and the space for the assistant activity were located in the mini-thoracotomy, and the other arm port was positioned in the second access. The three-arm uniportal approach was based on a 5-cm mini-thoracotomy in the sixth intercostal space, on the midaxillary line, from which both the robotic arms and the assistant could work. Finally, after this experience, a triportal approach was attempted, with a mini-thoracotomy in the fourth-fifth intercostal space, on the anterior axillary line, to accommodate both the arm port and the assistant. The camera port was positioned in the seventh to eighth intercostal space, midaxillary line, and the arm port in the seventh to eighth intercostal space. The patient position was always the same, in the lateral decubitus. A schematic representation of approaches can be found in Figures 1, 2. Manual staplers were used by the assistant. No CO_2 was insufflated and a 30° camera was used.

3. Results

During a 17-month period of RATS program, 29 lung resections were performed with the da Vinci Xi robotic surgical system. Of them, 16 were lobectomies, 7 were segmentectomies, and 6 were wedge resections. All procedures were performed by two surgeons (DT and AP). The most common indication for anatomical lung resection was NSCLC. Only one hamartoma was treated with segmentectomy due to its position, impeding a wedge resection. Mean age of patients was 64 (±12) years, and 20 (69%) were female. Twelve (41%) were never smokers, whereas 11 (38%) were former smokers and 6 (21%) were active smokers. Twenty-three (79%) had at least one polymorbidity (e.g., systemic arterial hypertension, diabetes), and 10 (34%) at least two. Concerning preoperative respiratory function, mean % predicted (%p) forced expiratory volume 1 s (FEV1) was 103% (±0.21), mean %p forced vital capacity (FVC) was 109% (±0.18), and mean %p diffusing capacity of the lungs for carbon monoxide (DLCO) was 77% (±0.16). Details concerning disease and procedure characteristics and perioperative outcomes are reported in Table 1. Mean operative time was 238 min (median 232) for lobectomy, 230 min (median 212) for segmentectomy, and 98 min (median 99) for wedge. Even if a formal statistical analysis was not conducted (given the small number of procedures), a difference in operative times between the different approaches of lobectomy was noted. In particular, the biportal lobectomies carried an additional mean of 101 min than multiport lobectomies. There were two conversions (7%). One was a planned RATS segmentectomy for a cT1cN0 stage NSCLC that was converted to VATS lobectomy for technical reasons. The other one was a RATS lobectomy in a cT3N1 stage NSCLC that was converted to open surgery due to bleeding from a pulmonary artery branch. Regarding lymphadenectomy, we found that a mean number of 8.1 lymph nodes were retrieved during surgery. A mean number of 2.6 N2 and 1.9 N1 stations were resected. No nodal upstaging was observed. Negative resection margins were obtained in all cases (100%). The mean postoperative length of stay was 6.8 days for lobectomy, 7.2 for segmentectomy, and 3 for wedge resection. Mean chest tube duration was 5.3 days for lobectomy, 5.7 for segmentectomy, and

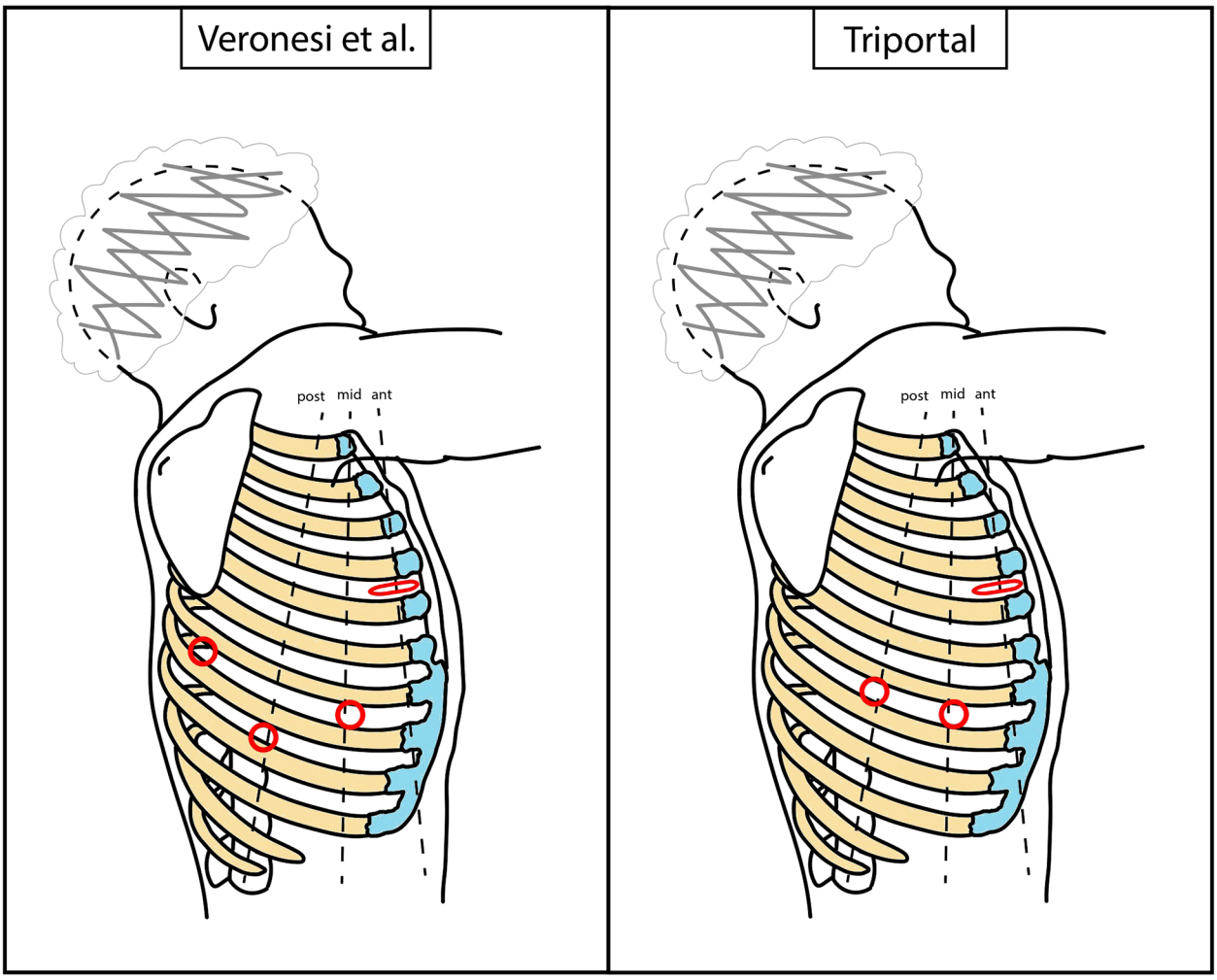

FIGURE 1
Schematic representation of RATS accesses positioning. Dimensions and distances are not to scale, but only indicative. Red circle, robotic port; red flattened circle, mini-thoracotomy (valid as assistant access too). RATS, robotic-assisted thoracic surgery.

1.8 for wedge resection. Globally, eight (28%) patients experienced complications. Of these, six were grade I and three were grade II [Clavien–Dindo classification (5)]. Further details are available in Table 2. No 30-day readmission in hospital nor 30-day death were recorded.

The first lobectomy was performed after 8 procedures with a standard four-arm approach, whereas the first segmentectomy after 21 cases and with a uniportal approach. Overall, four uniportal (two segmentectomies and two uniportal pleurodesis with wedge resection), and eight biportal (five lobectomies, two segmentectomies, and one pleurodesis with wedge resection) procedures were performed. The first uniportal operation was a pleurodesis and wedge resection, whereas the first biportal procedure was a simple segmentectomy.

4. Discussion

Our study represents a real-world report of a thoracic surgery unit transitioning to RATS for lung resections. During a transition to a new technique or approach, it is legit to question if it will achieve better results. Four major objectives should be pursued: higher, or at least equal, safety, reduced time, lower costs, and increased results. In this case, increased results concerns both surgical and oncological outcomes. However, all these four may not be always obtained simultaneously. In the case of lung resections, the transition to RATS can happen either from open surgery or VATS. Differences between these two transitions are thought to exist. It has been suggested that transition from open surgery to RATS is easier than from open surgery to VATS (4). The hypothesized reason is the similarity of surgical steps in lung resections between open and RATS. However, it is also common to believe that an experienced VATS surgeon has less difficulties in approaching RATS than an open surgeon. This idea could be supported by the similarity of RATS to VATS because of the reduced to absent tactile feedback and the visualization of the thoracic cavity through the screen (6). Results from single-surgeon experiences of transition to RATS suggest similar performances between RATS and VATS.

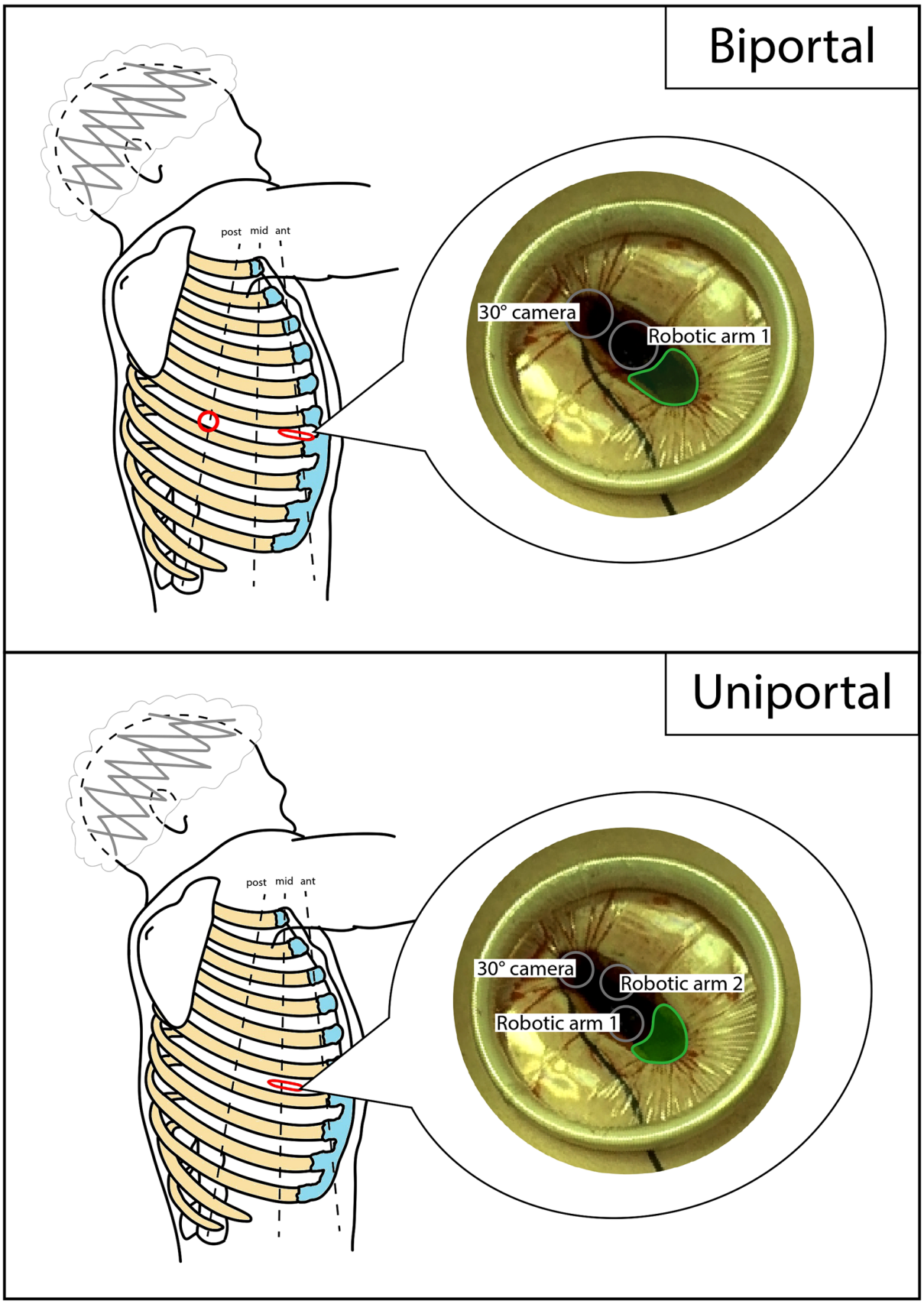

FIGURE 2
Schematic representation of biportal and uniportal RATS accesses positioning. Dimensions and distances are not to scale, but only indicative. Red circle, robotic port; red flattened circle, mini-thoracotomy (valid as assistant access too); gray circle, robotic trocar; green area, assistant area/access. RATS, robotic-assisted thoracic surgery.

TABLE 1 Surgical details of patients that underwent RATS lung resections.

Variable	Value
Histotype[a]	
Adenocarcinoma	20 (87%)
Squamocellular carcinoma	1 (4%)
Large cell anaplastic carcinoma	1 (4%)
Hamartoma	1 (4%)
pTNM stage 8th ed. ($n = 22$)[a]	
0 (is)	1
IA1	3
IA2	6
IA3	2
IB	4
IIA	1
IIB	3
IIIA	2
Tumor location[a]	
Right upper lobe	10
Right inferior lobe	4
Left upper lobe	2
Left S6 segment	3
Left S1–S3 segments	2
Right S1–S2 segments	1
Right S3 segment	1
Conversions[a]	
RATS to open surgery	1
RATS to VATS	1
Lymphadenectomy[a]	
Mean no. of resected lymph nodes	8.1
Mean no. of resected lymph node stations	
N1	1.9
N2	2.6
Nodal upstaging	0%
Negative resection margins	100%
Mean operative time (min)[b]	
Lobectomy	238
Segmentectomy	230
Postoperative complications	
Grade I	6
Grade II	3
Mortality	0%
Mean hospital length of stay (days)	
Lobectomy	6.8
Segmentectomy	7.2
Wedge resection	3
Mean chest tube duration (days)	
Lobectomy	5.3
Segmentectomy	5.7
Wedge resection	1.8

RATS, robotic-assisted thoracic surgery.
[a]Concerns only RATS anatomical lung resections.
[b]Concerns only RATS anatomical lung resections without conversion.

TABLE 2 Early postoperative complications details.

Cases ($n = 8$ pts)	Grade I	Grade II
2° lobectomy	Dyspnea	
4° segmentectomy	PAL, subcutaneous emphysema	PAL (blood patch)
5° segmentectomy		Pneumonia (antibiotics)
8° lobectomy		
10° lobectomy	PAL	
11° lobectomy	TIA	
7° segmentectomy	PAL, subcutaneous emphysema	
15° lobectomy	PAL, subcutaneous emphysema	Anemia (transfusion)

pts, patients; PAL, prolonged air leak; TIA, transient ischemic attack.

Initially, RATS operative times are longer probably due to docking time and familiarization with instruments (7, 8).

At the beginning of our RATS experience, we had some concerns on performing multiple accesses for a robotic lung resection, rather than a single one as in uniportal VATS. However, after some operations, we acquired confidence with the multiport approach. Some practical advantages over VATS were immediately observed after the first procedures. First of all, the high ergonomics resulted in a less tiring and more comfortable surgery for the console operator. In addition, the quality of the view was significantly higher, thanks to the enhanced quality of the video, the 3D vision, and the stability of the camera. This somehow helped compensating the absence of haptic feedback, especially during dissection of hilar elements. As a consequence, we expected that RATS would result in a higher number of resected lymph nodes than VATS. Nevertheless, even if a formal analysis and comparison were not made, the results did not favor this hypothesis. We are still in an early phase and more cases are needed to make our results more robust. In our experience, staplers were used by the assistant, thus reducing the independence of the console operator. However, we believe autonomy was higher compared to VATS, given that all the instruments, camera included, were easily controlled by the operating surgeon.

Our previous uniportal VATS experience eventually led our team to experiment alternative RATS approaches, with the objective of reducing the incisions. Therefore, both biportal and uniportal RATS approaches were performed. The time required for setting the robotic arms, and for adjusting them during the operation to avoid collision, inevitably determined longer operative times. Collisions were significantly higher with the uniportal approach, and as reported in recent papers, it required the presence of a uniportal VATS-skilled surgeon at the operating table (9). Collisions between instruments are potentially harmful for the patient, and the assistant's help revealed to be important during several steps. Given these issues, we decided to abandon the uniportal approach for major lung resections. In addition, it should be kept in mind that to date this type of technique is not approved by the manufacturer, so medical–legal issues could also arise in case of major complications. We believe that in the future, once the technology for the uniportal approach is developed, this may be a viable option under conditions of greater patient safety.

At present, our preferred approach for RATS lung resections is the triportal one. In general, a certain degree of freedom of choice on the number and location of the incisions is accepted, based on surgeon's preference and case characteristics. No superior study between one approach and another has yet been published. Still,

one interesting issue is multiple nerve damage as a possible cause of more pain. Some authors believe this may cause more pain compared to approaches that are performed accessing only one or two intercostal spaces (10–12). In our experience, multiport VATS was thought to be more painful than uniportal VATS (13). During our RATS program we did not systematically collect quality data concerning postoperative pain; thus, we were not able to make any comparison or analysis. From a theoretical standpoint, damaging only one intercostal nerve rather than more than one, when positioning multiple ports, would logically result in less pain. However, to date, a reliable systematic analysis and comparison is still not available and is likely to be particularly complex given the number of factors involved in postoperative pain. On the other hand, our experience taught us that practical advantages of accessing the thorax through different intercostal spaces are ensuring more possible directions for instruments and a wider triangulation.

In our experience, we preferred not to use CO_2 insufflation. We considered that the benefit of CO_2 in lung resections was not worth the need for dedicated devices (e.g., Alnote-Lapsingle©), given the presence of the mini-thoracotomy. We believed it would be probably simpler to use CO_2 with a robotic portal (RP) approach (3). Of course, we are aware that CO_2 pressure would result in a better exposure of structures, mainly by compression of lung and diaphragm. In fact, during our thymic RATS procedures, CO_2 insufflation was routinely used, thanks to the application of an RP approach.

We believe that RATS is an interesting technology that may be beneficial in lung resections. However, given its cost, it is expected to bring benefits not only to surgeons but also to patients in order to be justified. Thus, we will monitor outcomes of RATS procedures in our center. It may reveal to perform better in determined surgical gestures, as suturing. In fact, it resembles the open surgery experience, and this may facilitate procedures as sleeve resections, as reported by several authors (14–16). Thus, the positive impact of RATS may appear more significant in this kind of procedures, rather than in routine ones.

Some limits of this study can be identified. First, the cohort of patients is small and from a single center, limiting the power of our results. In addition, we are still in the learning curve phase, thus requiring more time to produce definitive data from both involved surgeons.

5. Conclusion

We found that RATS lung resections were safe and effective, and from the surgeon's standpoint, several practical advantages over VATS were observed. Results are probably premature to be correctly interpreted and, of course, we are still in the learning curve phase. At present time, we believe that the uniportal approach is not advisable because of possible conflicts between the robotic arms and the resulting risks to the patient. Further analysis of outcomes will help better understand the value of this technology.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The present study involving human participants was reviewed and approved by the ethical review board of our institution. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DT and AP contributed to the study conception. Material preparation, data collection, and analysis were performed by GM. The first draft of the manuscript was written by GM, AP, and DT, and all authors commented on the previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The publication costs for this manuscript were covered by the fund Current research—IRCCS from the Italian Ministry of Health dedicated to the IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. (2009) 34(1):17–41. doi: 10.1183/09031936.00184308

2. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. (2013) 143(5 Suppl):e166S–90S. doi: 10.1378/chest.12-2395

3. Cerfolio R, Louie BE, Farivar AS, Onaitis M, Park BJ. Consensus statement on definitions and nomenclature for robotic thoracic surgery. *J Thorac Cardiovasc Surg*. (2017) 154(3):1065–9. doi: 10.1016/j.jtcvs.2017.02.081

4. Veronesi G, Galetta D, Maisonneuve P, Melfi F, Schmid RA, Borri A, et al. Four-arm robotic lobectomy for the treatment of early-stage lung cancer. *J Thorac Cardiovasc Surg*. (2010) 140(1):19–25. doi: 10.1016/j.jtcvs.2009.10.025

5. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae

6. Feczko AF, Wang H, Nishimura K, Farivar AS, Bograd AJ, Vallières E, et al. Proficiency of robotic lobectomy based on prior surgical technique in the society of thoracic surgeons general thoracic database. *Ann Thorac Surg*. (2019) 108(4):1013–20. doi: 10.1016/j.athoracsur.2019.04.046

7. Lee BE, Korst RJ, Kletsman E, Rutledge JR. Transitioning from video-assisted thoracic surgical lobectomy to robotics for lung cancer: are there outcomes advantages? *J Thorac Cardiovasc Surg*. (2014) 147(2):724–9. doi: 10.1016/j.jtcvs.2013.10.002

8. Gómez-Hernández MT, Fuentes MG, Novoa NM, Rodríguez I, Varela G, Jiménez MF. The robotic surgery learning curve of a surgeon experienced in video-assisted thoracoscopic surgery compared with his own video-assisted thoracoscopic surgery learning curve for anatomical lung resections. *Eur J Cardiothorac Surg*. (2022) 61(2):289–96. doi: 10.1093/ejcts/ezab385

9. Gonzalez-Rivas D, Bosinceanu M, Motas N, Manolache V. Uniportal robotic-assisted thoracic surgery for lung resections. *Eur J Cardiothorac Surg*. (2022) 62(3):ezac410. doi: 10.1093/ejcts/ezac410

10. Wei B, Cerfolio RJ. Robotic lobectomy and segmentectomy: technical details and results. *Surg Clin North Am*. (2017) 97(4):771–82. doi: 10.1016/j.suc.2017.03.008

11. Zhao G, Jiang X, Wang F, Chu M, Zhang C, Zhao W, et al. Lobectomy with high-position single-intercostal two-port video-assisted thoracoscope for non-small cell lung cancer is a safe and effective surgical procedure. *J Thorac Dis*. (2020) 12(12):7346–54. doi: 10.21037/jtd-20-3469

12. Young R, McElnay P, Leslie R, West D. Is uniport thoracoscopic surgery less painful than multiple port approaches? *Interact Cardiovasc Thorac Surg*. (2015) 20(3):409–14. doi: 10.1093/icvts/ivu391

13. Louis SG, Gibson WJ, King CL, Veeramachaneni NK. Uniportal video-assisted thoracoscopic surgery (VATS) technique is associated with decreased narcotic usage over traditional VATS lobectomy. *J Vis Surg*. (2017) 3:117. doi: 10.21037/jovs.2017.08.05

14. Veronesi G, Cerfolio R, Cingolani R, Rueckert JC, Soler L, Toker A, et al. Report on first international workshop on robotic surgery in thoracic oncology. *Front Oncol*. (2016) 6:214. doi: 10.3389/fonc.2016.00214

15. Elliott IA, Yanagawa J. Can the robot overcome technical challenges of thoracoscopic bronchial anastomosis? *J Thorac Dis*. (2019) 11(Suppl 9):S1123–5. doi: 10.21037/jtd.2019.04.100

16. Liu A, Zhao Y, Qiu T, Xuan Y, Qin Y, Sun X, et al. The long-term oncologic outcomes of robot-assisted bronchial single sleeve lobectomy for 104 consecutive patients with centrally located non-small cell lung cancer. *Transl Lung Cancer Res*. (2022) 11(5):869–79. doi: 10.21037/tlcr-22-298

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 16 March 2023
DOI 10.3389/fsurg.2023.1130919

OPEN ACCESS

EDITED BY
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Alessandro Gonfiotti,
University of Florence, Italy
Davide Piloni,
San Matteo Hospital Foundation (IRCCS), Italy

*CORRESPONDENCE
Riccardo Orlandi
riccardo.orlandi@unimi.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 23 December 2022
ACCEPTED 27 February 2023
PUBLISHED 16 March 2023

CITATION
Orlandi R, Rinaldo RF, Mazzucco A, Baccelli A, Mondoni M, Marchetti F, Zagaria M, Cefalo J, Leporati A, Montoli M, Ghilardi G, Baisi A and Centanni S (2023) Early outcomes of "low-risk" patients undergoing lung resection assessed by cardiopulmonary exercise testing: Single-institution experience.
Front. Surg. 10:1130919.
doi: 10.3389/fsurg.2023.1130919

Early outcomes of "low-risk" patients undergoing lung resection assessed by cardiopulmonary exercise testing: Single-institution experience

Riccardo Orlandi[1]*, Rocco Francesco Rinaldo[2], Alessandra Mazzucco[3], Andrea Baccelli[2], Michele Mondoni[2], Francesca Marchetti[2], Mariapia Zagaria[2], Jacopo Cefalo[2], Andrea Leporati[3], Matteo Montoli[3], Giorgio Ghilardi[4], Alessandro Baisi[3] and Stefano Centanni[2]

[1]Department of Thoracic Surgery, University of Milan, Milan, Italy, [2]Respiratory Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Department of Health Sciences, University of Milan, Milan, Italy, [3]Thoracic Surgery Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, University of Milan, Milan, Italy, [4]General Surgery Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, University of Milan, Milan, Italy

Objective: Cardiopulmonary exercise testing (CPET) is currently recommended for all patients undergoing lung resection with either respiratory comorbidities or functional limitations. The main parameter evaluated is oxygen consumption at peak (VO_2peak). Patients with VO_2peak above 20 ml/kg/min are classified as low risk surgical candidates. The aims of this study were to evaluate postoperative outcomes of low-risk patients, and to compare their outcomes with those of patients without pulmonary impairment at respiratory function testing.
Methods: Retrospective monocentric observational study was designed, evaluating outcomes of patients undergoing lung resection at San Paolo University Hospital, Milan, Italy, between January 2016 and November 2021, preoperatively assessed by CPET, according to 2009 ERS/ESTS guidelines. All low-risk patients undergoing any extent surgical lung resection for pulmonary nodules were enrolled. Postoperative major cardiopulmonary complications or death, occurring within 30 days from surgery, were assessed. A case-control study was nested, matching 1:1 for type of surgery the cohort population with control patients without functional respiratory impairment consecutively undergoing surgery at the same centre in the study period.
Results: A total of 80 patients were enrolled: 40 subjects were preoperatively assessed by CPET and deemed at low risk, whereas 40 subjects represented the control group. Among the first, 4 patients (10%) developed major cardiopulmonary complications, and 1 patient (2.5%) died within 30 days from surgery. In the control group, 2 patients (5%) developed complications and none of the patients (0%) died. The differences in morbidity and mortality rates did not reach statistically significance. Instead, age, weight, BMI, smoking history, COPD incidence, surgical approach, FEV1, Tiffenau, DLCO and length of hospital stay resulted significantly different between the two groups. At a case-by-case analysis, CPET revealed a

Abbreviation
NSCLC, non-small cell lung cancer; ERS, european respiratory society; ACCP, american college of chest physicians; CPET, cardiopulmonary exercise testing; FEV1, forced expiratory volume in 1 s; DLCO, diffusing lung capacity for carbon monoxide; VO_2peak, oxygen consumption at peak; ECG, electrocardiogram; ATS, american thoracic society; PFT, pulmonary function testing; BGA, blood gas analysis; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; AT, anaerobic threshold; VE/VCO_2, minute ventilation to carbon dioxide production; BMI, body mass index; PETCO2, end-tidal carbon dioxide pressure.

pathological pattern in each complicated patient, in spite of VO_2peak above target for safe surgery.

Conclusions: Postoperative outcomes of low-risk patients undergoing lung resections are comparable to those of patients without any pulmonary functional impairment; nonetheless the formers represent a dramatically different category of individuals from the latter and may harbour few patients with worse outcomes. CPET variables overall interpretation may add to the VO_2peak in identifying higher risk patients, even in this subgroup.

KEYWORDS

cardiopulmonary exercise testing (CPET), thoracic surgery, postoperative outcomes, VO_2peak, peak oxygen uptake, cardiopulmonary complications

Introduction

Surgery is the treatment of choice for early-stage Non-Small Cell Lung Cancer (NSCLC) and for selected cases of locally advanced-stage NSCLC, since radical lung resection is nowadays a potentially curative therapy in lung cancer (1). However, surgery carries a significant burden of morbidity and mortality; therefore, patients' fitness for the intervention should be considered; otherwise, other medical or less-invasive therapies should be offered. In addition, since most lung cancers patients are smoking elderly with several comorbidities, a thorough preoperative evaluation is mandatory to refer each patient to the best possible treatment (2). Both European Respiratory Society (ERS) (3) and American College of Chest Physicians (ACCP) (4) have recommended that each surgical candidate should first undergo cardiac assessment and then pulmonary function testing to estimate perioperative risk. Currently, Cardiopulmonary Exercise Testing (CPET) is recommended by both Societies in patients with respiratory comorbidities and/or functional limitations to further stratify their perioperative risk. CPET can be defined as a holistic physiologic testing, assessing the whole patient's respiratory, cardiovascular, and metabolic response to stress. ERS (3) suggests that each patient with either forced expiratory volume in 1 s (FEV1) or diffusing lung capacity for carbon monoxide (DLCO) <80% predicted should undergo CPET; ACCP (4) recommends performing CPET in patients with either predicted postoperative(ppo)FEV1 or ppoDLCO <30%, or in case of unsatisfactory performance in a low technology exercise test. Oxygen consumption at peak (VO_2peak) is acknowledged as the most important variable for risk stratification: for values of VO_2peak >20 ml/kg/min, <20 ml/kg/min and >10 ml/kg/min, <10 ml/kg/min, risk of complications is considered low, moderate, and high, respectively. The low-risk group could potentially undergo lung resection up to pneumonectomy, without any increased risk; nonetheless, literature is still lacking univocal information on the outcomes and prognostic significance of this specific group. The primary aim of this study was firstly to evaluate postoperative outcomes (mortality and morbidity rates) of patients undergoing surgical lung resection and deemed to be at low risk on preoperative CPET. We also compared their outcomes with those of patients with normal pulmonary function testing, who are by definition standard-risk subjects.

Materials and methods

Study design

This is a retrospective, monocentric, observational study, analyzing consecutive patients who were preoperatively assessed through CPET, and underwent surgical lung resection for pulmonary nodules between January 2016 and November 2021, at San Paolo University Hospital in Milan, Italy. A case-control study was nested, comparing outcomes of enrolled patients preoperatively assessed by CPET with those of consecutive patients matched 1:1 for type of surgery, who had undergone surgical lung resections in the same time lapse at the same center without need for CPET. The study was conducted in accordance with the Declaration of Helsinki, and it was reviewed and approved by Milan Area 1 ethics committee.

Study population

Inclusion criteria were: age ≥18 years, preoperative CPET because of higher surgical risk according to 2009 ERS/ESTS Guidelines algorithm (either FEV1 or DLCO <80% predicted), VO_2peak from CPET above 20 ml/kg/min, lung resection of any extent for established or suspected lung neoplasia with radical intent.

Exclusion criteria were inoperability and VO_2peak from CPET below 20 ml/kg/min.

Inclusion criteria for patients of control group were: age ≥18 years, preoperative FEV1 and DLCO ≥80%, lung resection of any extent for established or suspected lung neoplasia with radical intent.

Exclusion criteria for patients of control group were inoperability and need for CPET.

Preoperative, intraoperative, and postoperative data were prospectively collected into institutional database and retrospectively analyzed.

Pre-admission exams

All patients routinely underwent clinical history questioning, physical examination, blood tests, 12-lead electrocardiogram (ECG), pulmonary function testing (PFT) according to ERS/American Thoracic Society (ATS) (5) guidelines using the Quark PFT modular system (Cosmed, Rome, Italy), arterial blood gas analysis (BGA), CPET.

Cardiopulmonary exercise testing

Patients underwent symptom limited CPET using bicycle ergometer and breath-by-breath gas exchange analysis was performed through medical system respiratory analyzer (Sensormedics, Vmax Spectra®, Yorba Linda, United States). Incremental protocol was applied: the increasing ramp-pattern rate (Watts/minute, W/min) has been determined individually, based on rest functional data and expected exercise tolerance, to achieve exhaustion between 8 and 12 min. All CPETs were performed at Department of Pneumology of our institution. During CPET the following parameters have been constantly measured: 12-lead electrocardiogram (ECG), gas-exchange by mouthpiece, heart rate, pulse oxygen, arterial blood pressure (6). An arterial blood sample was collected for blood gas analysis (BGA) and lactates at the peak of the exercise, as soon as patients reported to be exhausted, as previously described (7). We defined preserved exercise capacity when VO2peak ≥85% of predicted; we considered an upper limit of normal for the minute ventilation to carbon dioxide production (VE/VCO_2) slope of 30 (8).

Surgical procedures

Surgical resections were performed by the same team of three experienced thoracic surgeons: sub-lobar resections (segmentectomies and wedge resections), lobectomies, bi-lobectomies and pneumonectomies were included. Operations were performed though lateral muscle-sparing thoracotomy or bi-portal video-assisted thoracoscopy. Perioperative management followed standardized pathways of care.

Mortality and morbidity

Mortality is defined as in-hospital death or death within 30 days from surgery. Morbidity is defined as occurrence of major cardiopulmonary complications within 30 days from surgery: bronchopulmonary infections or pneumonia (typical clinical, laboratory and radiographic features), respiratory failure (partial arterial oxygen pressure <60 mmHg and/or partial arterial carbon dioxide pressure >45 mmHg) needing for mechanical ventilation, acute respiratory distress syndrome (based on Berlin criteria), atelectasis requiring bronchoscopy or mechanical ventilation, pulmonary oedema, pulmonary embolism, arrhythmia (hemodynamically unstable and requiring treatment), acute myocardial ischemia, cardiac failure needing for inotropic support, pulmonary sepsis or multi-organ failure (9, 10).

Statistical analysis

Primary outcomes were postoperative mortality and major cardiopulmonary morbidity, occurring within 30 days from surgery. Normality was confirmed for all the continuous variables, as assessed through the Kolmogorov–Smirnov test and visual plot analysis. Continuous variables are expressed as means and standard deviation, whereas nominal variables are presented as numbers with percentages. Furthermore, exploratory univariable analysis was performed to detect differences between patients deemed at low-risk by CPET and patients without need for CPET: continuous variables with normal distribution were compared using unpaired Student's t-test, whereas nominal variables were compared using chi-squared or Fisher's exact test, whenever appropriate. Data were analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, United States), version 23.0. Values of $p < 0.05$ were considered statistically significant.

Results

Globally, 723 patients underwent pulmonary resections for established or suspected lung cancer at the reference hospital during the study period. 174 (24%) were preoperatively assessed by CPET, due to either FEV1 or DLCO <80% predicted, according to 2009 ERS/ESTS guidelines (3), as presented in **Figure 1**. Among them, 40 patients (23%) had VO_2peak above 20 ml/kg/min, hence deemed to be at low risk for postoperative complications and were included in the analysis. The cohort population was matched for type of surgery with 40 consecutive patients undergoing surgical lung resections during the study period, but without functional respiratory impairment at the PFT (both FEV1 and DLCO above 80% of predicted). Demographic, clinical, surgical, and functional features of both groups, as well as comparison results, are shown in **Table 1**. Mean age was 65.2 years old, 52 patients (65%) were males. Arterial hypertension and diabetes were the most frequent comorbidities. A total of 40 sub-lobar resections (50%), 36 lobectomies (45%), 2 bi-lobectomies (2.5%), and 2 pneumonectomies (2.5%) were performed. Thoracoscopic approach was adopted in 65 cases (81%). Pulmonary nodules were diagnosed as primary lung cancer in 50 cases (62.5%), secondary lung cancer in 10 (12.5%), and non-neoplastic in 20 (25%). Age, weight, body mass index (BMI), smoke history, chronic obstructive pulmonary disease (COPD), surgical approach, FEV1 (absolute and percentage predicted), Tiffenau index, DLCO (absolute and percentage predicted), and length of hospital stay resulted significantly different between the two groups. There were significantly younger age, lower weight and BMI, higher percentage of active smokers, higher incidence of COPD, lower number of thoracoscopic procedures and longer hospital stay in the group of patients assessed by CPET. Furthermore, the same patients presented lower FEV1, Tiffenau and DLCO values than patients not assessed by CPET, as expected. In the CPET-group, within 30 days from surgery, 4 patients (10%) developed major cardiopulmonary complications, 1 of whom (2.5%) died due to heart failure. Focus on their demographic, functional, and surgical characteristics is reported in **Table 2**. The control patients experienced 5% major cardiopulmonary complications (2/40) and 0% death rates. In total, 13 major cardiopulmonary

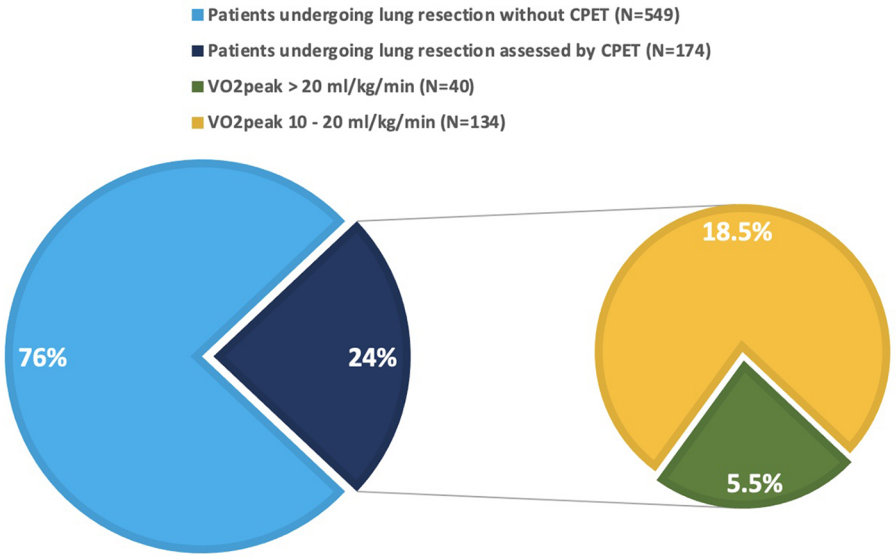

FIGURE 1
Patients undergoing lung resection for pulmonary nodules during the study period. Green slice represents the patients included in the analysis (5.5% of the whole population, 23% of the patients assessed by CPET).

complications occurred in 6 patients (0.75%) in the two groups: pneumonia (4 cases), sepsis (1 case), bronchopulmonary infection (2 cases), ARDS (3 cases), arrythmia (2 cases), heart failure (1 case). Both morbidity and mortality rates, although differing between the two groups (10% vs. 5%, and 2.5% vs. 0%, respectively), did not reach statistical significance.

Main variables provided by CPET in the cohort population are shown in Table 3. In particular, mean VO_2peak was 23.14 ± 2.59 ml/kg/min, mean VE/VCO_2 slope 30.47 ± 4.67. 21 patients (56%) displayed a VE/VCO_2 slope >30, including 9 over 12 patients affected by chronic obstructive pulmonary disease (COPD). A ventilatory limitation to exercise (defined by a breathing reserve below 15%) was observed in 9 patients. 12 patients (30%) presented a reduced exercise capacity.

Discussion

This study shows that respiratory impaired low-risk patients, as stratified by CPET assessment, have postoperative morbidity and mortality rates of 10% and 2.5%, respectively, when undergoing oncological lung resections. Furthermore, it first demonstrates that, when comparing these patients with those matched for surgical procedure without any respiratory functional impairment, no differences exist in terms of mortality and morbidity. However, differences in age, weight, BMI, smoke history, COPD, surgical approach, and length of hospital suggest that they really represent different risk categories.

PFT and CPET are two pillars of the preoperative assessment: FEV1 and DLCO, derived from PFT, allow to split standard-risk patients from those with possible increased risk, whereas VO_2peak, derived from CPET, further stratify those with possible increased risk in low, intermediate, and high risk. While lower limit of 10 ml/kg/min is a well-established cut-off for extreme perioperative risk, the higher limit allowing for safe surgery has been arbitrary defined ranging from 15 to 20 ml/kg/min (11), historically based on limited past experiences of none or minimum complications after those levels (12–14). The 20 ml/kg/min cut-off later resulted as a safe threshold for major lung resection, leading to morbidity rate lower than 10% and mortality rate of 0% (15–17). Recently, Gooseman and colleagues (18), while assessing outcomes of moderate-risk group undergoing lung surgery, have collaterally reported 19%–30% cardiopulmonary morbidity rate and 0%–4.2% mortality rate, depending on extent of resection, in low-risk patients. Furthermore, Begum and colleagues (19), while evaluating the reliability of CPET in patients undergoing thoracoscopic compared to thoracotomic lobectomy, confirmed these results, detecting cardiopulmonary morbidity rate of 29% and mortality rate of 3.5% in low-risk patients. On the other hand, Kristenson and colleagues (20) have reported 9% rate of cardiopulmonary complications or death in low-risk patients, while investigating early outcomes of moderate-risk patients undergoing lobectomy to evaluate VE/VCO_2 slope application in improving risk stratification in that category of risk. According to our experience, we reported 10% cardiopulmonary morbidity rate, which is overlapping to that shown by Kristenson and colleagues, although being lower than those presented by the other authors. Indeed, Gooseman and colleagues applied different criteria for defining low-risk patients, adopting ACCP guidelines, thus possibly including patients with greater functional impairment than ours; moreover, among their enrolled patients, more than 70% underwent surgery through open approach, thus potentially explaining the higher rate of complications registered compared to our study, where thoracoscopic approach was applied in more than 70% of cases. On the other hand, higher morbi-mortality rates detected by Begum and colleagues could be explained,

TABLE 1 Patients' characteristics and comparison between patients with functional pulmonary impairment assessed by CPET (CPET group) and patients without functional pulmonary impairment (non-CPET group). Statistically significant variables are in bold.

Variable	CPET group ($N = 40$)	Non-CPET group ($N = 40$)	p value
Demographics			
Age, mean (SD)	62.7 (10.6)	67.8 (9.6)	0.02
Gender, male (%)	24 (60)	28 (70)	0.11
Height, mean (SD)	165.7 (7.4)	166.0 (11.4)	0.88
Weight, mean (SD)	63.1 (13.8)	76.8 (16.9)	<0.01
BMI, mean (SD)	22.9 (3.9)	27.6 (4.2)	<0.01
Smoke, never/yes/former (%)	7 (17.5)/22 (55)/11 (27.5)	13 (32.5)/2 (5)/20 (50)	<0.01
Comorbidities			
Past lung surgery, yes (%)	7 (17.5)	2 (5)	0.07
COPD, yes (%)	12 (30)	1 (2.5)	<0.01
Asthma, yes (%)	1 (2,5)	5 (12.5)	0.09
ILD, yes (%)	3 (7.5)	0 (0)	0.07
Ischemic cardiopathy, yes (%)	2 (5)	5 (12.5)	0.23
Arrythmia, AF/others (%)	1 (2.5)/4 (10)	0 (0)/1 (2.5)	0.22
Heart failure, yes (%)	0 (0)	1 (2.5)	0.31
Arterial hypertension, yes (%)	17 (42.5)	22 (55)	0.26
Diabetes, yes (%)	5 (12.5)	6 (0.15)	0.74
Surgical			
Surgical approach, thoracoscopy (%)	29 (72.5)	36 (90)	0.04
Conversion, yes (%)	4 (10)	3 (7.5)	0.69
Lung resection, sublobar/lobar/bi-lobar/pneumonectomy (%)	20 (50)/17 (42.5)/1 (2.5)/2 (5)	20 (50)/19 (47.5)/1 (2.5)/0 (0)	0.62
Lung cancer histology, primary/secondary/other (%)	24 (60)/4 (10)/12 (30)	26 (65)/6 (15)/8 (20)	0.50
Functional			
FEV1, mean (SD)	2.28 (0.72)	2.82 (0.74)	<0.01
FEV1%predicted, mean (SD)	83.60 (21.15)	103.68 (14.26)	<0.01
FVC, mean (SD)	3.38 (0.93)	3.63 (0.91)	0.23
FVC %predicted, mean (SD)	97.88 (21.64)	102.35 (10.11)	0.24
Tiffenau, mean (SD)	85.74 (13.86)	98.12 (16.77)	<0.01
DLCO, mean (SD)	14.65 (3.72)	20.23 (3.99)	<0.01
DLCO %predicted, mean (SD)	60.03 (10.92)	87.65 (8.83)	<0.01
Outcomes			
Major cardiopulmonary complications, yes (%)	4 (10)	2 (5)	0.39
Death, yes (%)	1 (2.5)	0 (0)	0.32
Length of hospital stay, mean (SD)	9.00 (8.44)	6.20 (2.24)	0.04

CPET, cardiopulmonary exercise testing; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; AF, atrial fibrillation; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide.

besides the enrollment of 80% thoracotomic procedures, by their choice of applying 15 ml/kg/min as threshold for low-risk patients, thus including patients traditionally at moderate risk, who could have increased the incidence of complications. This consideration is supported by the results from Chouinard and colleagues (21), who have shown 10.4% of complication rate in patients undergoing thoracoscopic lobectomy with VO_2peak >20 ml/kg/min, which is similar to our results. Notably, the percentage of low-risk patients over the total assessed by CPET from our study (23%) is grossly comparable to that reported in literature (18, 19, 21).

According to ESTS/ERS guidelines (3), patients with both FEV1 and DLCO >80% predicted do not have to be further investigated by CPET and can undergo any extent of surgical resection with low risk for perioperative cardiopulmonary complications and deaths, whose incidence rates are about 13% and 0%, respectively (15). Nevertheless, recently, Cundrle and colleagues (22) have selectively analyzed surgical outcomes of this group of patients assessed by CPET, reporting 9% cardiopulmonary morbidity rate, mainly affecting those with lower end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and increased VE/VCO_2 slope, and suggesting to perform routinary CPET to identify these patients. Our matched control patients have experienced 5% cardiopulmonary morbidity rate and 0% mortality rate, slightly better but grossly comparable to previous results. We assumed that these rates properly define standard low-risk patients, choosing them as controls. Our cohort of CPET-assessed "low-risk" patients have shown younger age, lower weight and BMI, higher incidence of COPD, lower number of thoracoscopic procedures, and longer length of hospital stay, than controls. Although morbidity and mortality rates did not significantly differ between the two groups, we believe that they belong to physiologically different categories, which might express statistically different outcomes when enrolling greater sample sizes.

The general picture derived from the cardiopulmonary exercise testing in our cohort (Table 3) is that of an overall preserved exercise capacity (mean VO_2peak 90% predicted), associated with preserved indices of oxygen transport/utilization and normal heart rate response, highlighting a good cardiovascular response to exercise with a prevalent cardiocirculatory limitation to exercise. Not surprisingly, the ventilatory response was more frequently altered, with mean VE/VCO_2 slope of 30.5, suggesting a certain degree of ventilatory inefficiency.

The 4 patients with VO_2peak >20 ml/min/kg who experienced major postoperative complications (respiratory infections in all cases) were mostly elderly males with a significant smoking history, normal BMI, reduced DLCO and relatively preserved spirometry (Table 2). Looking at the cardiopulmonary exercise testing variables, all three patients who achieved maximal test showed normal exercise capacity, with preserved cardiovascular response to exercise. Interestingly, mild ventilatory inefficiency was observed in all cases, as indicated by the VE/VCO_2 slope; a finding which is in line with the emphysematous phenotype, as previously described (23). The two patients with the highest VE/VCO_2 slopes (35.6 and 40.5) had associated impairment of gas exchange, as evidenced by the increased alveolar-arterial gradient for O2. The fourth patient, on the other hand, exhibited reduced overall exercise capacity (VO_2peak below the normal limit of 85%), with signs of chronotropic limitation, while presenting ventilatory response at the limit of normality. The ventilatory response in complicated patients suggests a certain degree of ventilatory inefficiency, that can be interpreted as either dysregulated ventilatory drive or increased dead space ventilation, as observed in COPD patients (24). Such a pathophysiological condition might be responsible for the maladaptive cardiopulmonary response in the aftermaths of surgery, leading

TABLE 2 Characteristics of complicated patients within CPET group.

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	74	75	60	76
Gender	M	M	M	M
Height, cm	160	167	160	169
Weight, kg	50	75	59	67
BMI, kg/m^2	19.6	26.9	23.1	23.5
Smoke	Active (60 PY)	Active (50 PY)	Active (50 PY)	Never Smoker
Comorbidities	Arterial hypertension	Arrythmia, arterial hypertension	None	Arterial hypertension, peripheral artery disease
Surgical approach	VATS	Thoracotomy	VATS	Thoracotomy
Lung resection	Sub-lobar	Lobar	Lobar	Bi-lobar
Lung cancer histology	Adenocarcinoma	Squamous	Adenocarcinoma	Squamous
FEV1%predicted	96	98	149	90
FVC %predicted	119	155	155	118
Tiffenau	80	64	94	78
DLCO %predicted	64	44	71	59
Major cardiopulmonary complications	Pneumonia, sepsis, ARDS	Bronchopulmonary infection	Pneumonia, ARDS	Bronchopulmonary infection, pneumonia, ARDS, arrythmia, heart failure
Death	N	N	N	Y
Length of hospital stay, days	39	14	37	29
VO_2peak, ml/kg/min	22.6	20.2	22.1	20.7
VO_2peak %predicted	84	92	71	87
AT %predicted	45	46	50	55
VO_2/W slope, ml/min/watt	10.9	10.2	10.4	9.7
VE/VCO_2 slope	32.4	40.5	30.4	35.6
$P_{ET}CO_2$peak, mmHg	37	23	34	32
Alveolar-arterial oxygen gradient	28	58	20	35
HRpeak %predicted	86	102	61	89
O_2pulse %predicted	99	90	118	98

CPET, cardiopulmonary exercise testing; BMI, body mass index; PY, pack year; VATS, video-assisted thoracoscopic surgery; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing lung capacity for carbon monoxide; ARDS, acute respiratory distress syndrome; N, no; Y, yes; VO_2peak, peak oxygen consumption; AT, anaerobic threshold; VO_2/W, carbon dioxide production to minute work; VE/VCO_2, minute ventilation to carbon dioxide production; HR, heart rate; PETCO2, end-tidal carbon dioxide pressure.

to higher risk of cardiopulmonary complications. This is in line with previous literature, in which the VE/VCO_2 slope was identified as a predictor of respiratory complications and death after pulmonary resection surgery (25, 26). Despite being the most used parameter in thoracic surgery, VO2peak is not the only variable provided by CPET. Patients with VE/VCO_2 slope >34–35 have been demonstrated to experience higher incidence of cardiopulmonary complications and deaths (25, 27, 28) after lung surgery, likely related to increased postoperative ventilation-perfusion mismatch (28, 29), even in patients without moderate-to-severe COPD (27, 30). Our findings confirm the role of other CPET parameters (particularly VE/VCO_2 slope) as a potential additional variable to refine risk-stratification besides VO_2peak.

TABLE 3 Cohort's CPET values.

Variable	Mean	SD
VO_2peak, ml/kg/min	23.14	2.59
VO_2peak %predicted, %	91.80	14.71
AT, ml/kg/min	13.56	2.88
AT %predicted, %	52.87	12.23
VO_2/W slope, ml/min/W	11.08	0.97
Work %predicted, %	81.13	12.94
VE/VCO_2 slope, ratio	30.47	4.67
Breathing reserve, %	23.68	20.54
Alveolar-arterial oxygen gradient, mmHg	30.17	12.34
HRpeak %predicted, %	90.32	12.50
HRpeak, bpm	141.63	19.90
O_2pulse %predicted, %	98.54	22.45

CPET, cardiopulmonary exercise testing; SD, standard deviation; VO_2peak, peak oxygen consumption; AT, anaerobic threshold; VO_2/W, carbon dioxide production to minute work; VE/VCO_2, minute ventilation to carbon dioxide production; HR, heart rate.

Our study has some limitations which are worth to be considered when interpreting the results. First, its retrospective design could have led to a selection bias. We have enrolled consecutive patients both for cohort and for controls, attempting to minimize this bias. Furthermore, we have decided to match patients based exclusively on type of surgery, in order to detect any difference between the two groups, also demographically. Then, the monocentric nature of the study might prevent generalization of findings to other settings. Finally, the small sample size has precluded multivariable analysis, as well as the comparison between complicated and uncomplicated patients, thus preventing us from drawing definitive conclusions in this way.

Nevertheless, we think that our exploratory findings can have clinical and physiological implications, prompting a thorough preoperative evaluation also in patients historically deemed at low risk for better stratifying their real risk. Further prospective studies with larger sample size are required to confirm our results.

Conclusions

Thorough preoperative functional assessment is mandatory in surgical lung cancer patients to accurately stratify their perioperative risk of complications or death. Patients with functional pulmonary impairment at PFT, as expressed by FEV1 or DLCO below 80% predicted, but with preserved oxygen consumption at CPET, as manifested by VO_2peak above 20 ml/kg/min, i.e., the "low-risk" category, have cardiopulmonary morbidity and mortality rates comparable to those of patients without functional pulmonary impairment. Nevertheless, they represent a completely distinct group of individuals, who may deserve further investigations to properly identify those at increased risk. CPET variables overall interpretation may add to the VO_2peak in identifying higher risk patients, even in this subgroup.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Milan Area 1 Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RO, RR, and AB contributed to conception and design of the study. RO and RR wrote the first draft of the manuscript. RO, RR, AB, AB wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Montagne F, Guisier F, Venissac N, Baste J-M. The role of surgery in lung cancer treatment: present indications and future perspectives—state of the art. *Cancers (Basel)*. (2021) 13(15):3711. doi: 10.3390/cancers13153711

2. Salati M, Brunelli A. Risk stratification in lung resection. *Curr Surg Rep*. (2016) 4 (11):37. doi: 10.1007/s40137-016-0158-x

3. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. (2009) 34(1):17–41. doi: 10.1183/09031936.00184308

4. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest*. (2013) 143(5 Suppl):e166S–90S. doi: 10.1378/chest.12-2395

5. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. (2005) 26(5):948–68. doi: 10.1183/09031936.05.00035205

6. Di Marco F, Terraneo S, Job S, Rinaldo RF, Sferrazza Papa GF, Roggi MA, et al. Cardiopulmonary exercise testing and second-line pulmonary function tests to detect obstructive pattern in symptomatic smokers with borderline spirometry. *Respir Med*. (2017) 127:7–13. doi: 10.1016/j.rmed.2017.04.006

7. Rinaldo RF, Mondoni M, Parazzini EM, Baccelli A, Pitari F, Brambilla E, et al. Severity does not impact on exercise capacity in COVID-19 survivors. *Respir Med*. (2021) 187:106577. doi: 10.1016/j.rmed.2021.106577

8. American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. (2003) 167(2):211–77. doi: 10.1164/rccm.167.2.211

9. Fernandez FG, Falcoz PE, Kozower BD, Salati M, Wright CD, Brunelli A. The society of thoracic surgeons and the European society of thoracic surgeons general thoracic surgery databases: joint standardization of variable definitions and terminology. *Ann Thorac Surg*. (2015) 99(1):368–76. doi: 10.1016/j.athoracsur.2014.05.104

10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae

11. Lim E, Beckles M, Warburton C, Baldwin D. Cardiopulmonary exercise testing for the selection of patients undergoing surgery for lung cancer: friend or foe? *Thorax*. (2010) 65(10):847–9. doi: 10.1136/thx.2009.133181

12. Bechard D, Wetstein L. Assessment of exercise oxygen consumption as preoperative criterion for lung resection. *Ann Thorac Surg*. (1987) 44(4):344–9. doi: 10.1016/S0003-4975(10)63787-3

13. Smith TP, Kinasewitz GT, Tucker WY, Spillers WP, George RB. Exercise capacity as a predictor of post-thoracotomy morbidity. *Am Rev Respir Dis*. (1984) 129(5):730–4. doi: 10.1164/arrd.1984.129.5.730

14. Torchio R, Gulotta C, Parvis M, Pozzi R, Giardino R, Borasio P, et al. Gas exchange threshold as a predictor of severe postoperative complications after lung resection in mild-to-moderate chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis*. (1998) 53(2):127–33.

15. Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest*. (2009) 135(5):1260–7. doi: 10.1378/chest.08-2059

16. Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med*. (2007) 101(8):1790–7. doi: 10.1016/j.rmed.2007.02.012

17. Ferguson MK, Lehman AG, Bolliger CT, Brunelli A. The role of diffusing capacity and exercise tests. *Thorac Surg Clin*. (2008) 18(1):9–17; v. doi: 10.1016/j.thorsurg.2007.11.001

18. Gooseman MR, Falcoz PE, Decaluwe H, Szanto Z, Brunelli A. Morbidity and mortality of lung resection candidates defined by the American college of chest

physicians as 'moderate risk': an analysis from the European society of thoracic surgeons database. *Eur J Cardiothorac Surg*. (2021) 60(1):91–7. doi: 10.1093/ejcts/ezab028

19. Begum SS, Papagiannopoulos K, Falcoz PE, Decaluwe H, Salati M, Brunelli A. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO2 max: a case-matched analysis from the ESTS database†. *Eur J Cardiothorac Surg*. (2016) 49(4):1054–8; discussion 1058. doi: 10.1093/ejcts/ezv378

20. Kristenson K, Hylander J, Boros M, Fyrenius A, Hedman K. Ventilatory efficiency in combination with peak oxygen uptake improves risk stratification in patients undergoing lobectomy. *JTCVS Open*. (2022) 11:317–26. doi: 10.1016/j.xjon.2022.06.018

21. Chouinard G, Roy P, Blais MC, Lippens A, Pelletier É, Roy E, et al. Exercise testing and postoperative complications after minimally invasive lung resection: a cohort study. *Front Physiol*. (2022) 13:951460. doi: 10.3389/fphys.2022.951460

22. Cundrle I, Merta Z, Bratova M, et al. The risk of postoperative pulmonary complications in lung resection candidates with normal FEV1 and DLCO: a prospective multicenter study. *ERJ Open Res*. (2022).

23. Rinaldo RF, Mondoni M, Comandini S, et al. The role of phenotype on ventilation and exercise capacity in patients affected by COPD: a retrospective study. *Multidiscip Respir Med*. (2020) 15. doi: 10.4081/mrm.2020.476

24. Neder JA, Berton DC, Arbex FF, et al. Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur Respir J*. (2017) 49(3):1602036. doi: 10.1183/13993003.02036-2016

25. Shafiek H, Valera JL, Togores B, Torrecilla JA, Sauleda J, Cosío BG. Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: beyond oxygen consumption. *Eur J Cardiothorac Surg*. (2016) 50(4):772–9. doi: 10.1093/ejcts/ezw104

26. Torchio R, Guglielmo M, Giardino R, et al. Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer. *Eur J Cardio-Thoracic Surg*. (2010) 38(1):14–9. doi: 10.1016/j.ejcts.2010.01.032

27. Brunelli A, Belardinelli R, Pompili C, Xiumé F, Refai M, Salati M, et al. Minute ventilation-to-carbon dioxide output (VE/VCO2) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg*. (2012) 93(6):1802–6. doi: 10.1016/j.athoracsur.2012.03.022

28. Torchio R, Mazzucco A, Guglielmo M, Giardino R, Ciacco C, Ardissone F. Minute ventilation to carbon dioxide output (V'E/V'CO2 slope) is the strongest death predictor before larger lung resections. *Monaldi Arch Chest Dis*. (2017) 87 (3):817. doi: 10.4081/monaldi.2017.817

29. Bédat B, Koliakos E, Demarchi MS, Perentes J, Licker MJ, Triponez F, et al. Ventilatory efficiency slope is associated with cardiopulmonary complications after thoracoscopic anatomical lung resection. *Interact Cardiovasc Thorac Surg*. (2022) 35 (1):ivac039. doi: 10.1093/icvts/ivac039

30. Pele I, Mihălțan F. Cardiopulmonary exercise testing in thoracic surgery. *Pneumologia*. (2020) 69(1):3–10. doi: 10.2478/pneum-2020-0001

frontiers | Frontiers in Surgery

TYPE Mini Review
PUBLISHED 22 March 2023
DOI 10.3389/fsurg.2023.1160827

OPEN ACCESS

EDITED BY
Monica Casiraghi,
European Institute of Oncology (IEO), Italy

REVIEWED BY
Rossano Fiorelli,
Federal University of State of Rio de Janeiro, Brazil

*CORRESPONDENCE
Domenico Loizzi
✉ domenico.loizzi@unifg.it

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 07 February 2023
ACCEPTED 27 February 2023
PUBLISHED 22 March 2023

CITATION
Loizzi D, Mongiello D, Bevilacqua MT, Raveglia F, Fiorelli A, Congedo MT, Ardò NP and Sollitto F (2023) Surgical management of compensatory sweating: A systematic review. Front. Surg. 10:1160827. doi: 10.3389/fsurg.2023.1160827

Surgical management of compensatory sweating: A systematic review

Domenico Loizzi[1]*, Diletta Mongiello[1], Maria Teresa Bevilacqua[1], Federico Raveglia[2], Alfonso Fiorelli[3], Maria Teresa Congedo[4], Nicoletta Pia Ardò[1] and Francesco Sollitto[1]

[1]Department of Medical and Surgical Science, University of Foggia, Foggia, Italy, [2]Department of Thoracic Surgery, San Gerardo Hospital, Monza, Italy, [3]Department of Translation Medicine, Thoracic Surgery Unit, Università della Campania "Luigi Vanvitelli", Naples, Italy, [4]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Roma, Italy

Endoscopic thoracic sympathectomy (ETS) surgery is a highly effective treatment of primary hyperhidrosis (PH) for the palms, face, axillae. Compensatory sweating (CS) is the most common and feared side effect of thoracic sympathectomy. CS is a phenomenon characterized by increased sweating in sites distal to the level of sympathectomy. Compensatory sweating is the main problem for which many patients give up surgery, losing the chance to solve their problem and accepting a poor quality of life. There are still no treatments that offer reliable solutions for compensatory sweating. The treatments proposed in the literature are scarce, with low case histories, and with uncertain results. Factors associated with CS are extension of manipulation of the sympathetic chain, level of sympathetic denervation, and body mass index. Therapeutic options include non surgical treatment and surgical treatment. Non surgical treatments include topical agents, botulinum toxin, systemic anticholinergics, iontophoresis. Surgical treatments include clip removal, extended sympathectomy and sympathetic chain reconstruction, although the efficacy is not well-established for all the methods. In this review we provide an overview of the treatments and outcomes described in the literature for the management of compensatory CS, with focus on surgical treatment.

KEYWORDS

compensatory sweating (CS), compensatory hyperhidrosis (CH), unclipping, diffuse sympathectomy, sympathetic nerve reconstruction

Introduction

Endoscopic thoracic sympathectomy (ETS) is the standard surgical treatment for palmar, facial and axillary hyperhidrosis with a success rate greater than 95% (1).

Compensatory sweating (CS) is the most common and feared side effect of thoracic sympathectomy and is a phenomenon characterized by increased sweating in sites distal to the level of sympathectomy. CS can range from mild to severe, with a percentage that can reach 98% depending on the case (2).

Patients with intense symptoms of CS feel such discomfort that they regret surgery; they have to change their clothes several times a day. This symptom greatly affects daily and professional activities and has severe consequences for patients' quality of life.

The treatments for CS range from lifestyle control, to pharmacological, topical or systemic treatments, iontophoresis, up to surgical treatments for severe forms.

For lifestyle control we can consider weight control, non thermogenic diet, regular physical activity. Pharmacological treatments include topical agents, botulinum toxin injections, and systemic anticholinergics.

Patient choices are influenced by the severity of the side effect and the patient's compliance with the various treatments offered. Some treatments are minimally invasive, but must be performed for a long time, if not for life, while others are more invasive but have a longer duration or are expected to be definitive (2).

Several surgical techniques for CS have been proposed depending on the previous sympathetic surgery. These techniques can be grouped into three categories: (a) unclipping; (b) extended sympathectomy/sympathicotomy; (c) sympathetic nerve reconstruction.

In this review we focus on the evidence actually available in the literature on these techniques.

Materials and methods

Search strategy

In October 2022 we conducted an extensive and systematic literature search to identify all relevant studies published up to October 2022.

The following databases were searched: Pubmed, Scopus, Google Scholar.

The Keywords used were compensatory sweating, compensatory hyperhidrosis, reflex sweating, reflex hyperhidrosis.

Selection of studies and data collection

The selection of studies was performed by two reviewers. After excluding duplicate studies, the titles and abstracts were analyzed.

We analyzed in their entirety the papers where a keywords was in the main topic or was included in the title or abstract.

Inclusion criteria

We selected studies that met all of the following inclusion criteria: (1) studies published in English; (2) studies involving series of at least 5 patients undergoing surgical treatment for compensatory hyperhidrosis following ETS with patient-reported outcome; (3) studies reporting the number of patients with improvement on the total number of patients treated and with documented results; (4) the most recent study in case of duplication of data of the same author.

Data extraction

Data extraction was performed by two reviewers, using a standardized Excel form. The number of patients with improvement out of the number of total patients treated and with documented self-reported outcome was reported in the tables as satisfaction rate.

Data regarding sympathetic levels treated in the previous surgery were summarized in the tables in 3 categories: T2 and below, T3 and below, T4 and below.

Subgroup analysis

Patients treated with clips removal, reconstruction surgery or diffuse sympathectomy were separately grouped.

Results

After excluding duplicate publications, there were 4,976 studies. After analysis of the titles and the abstracts, we selected 54 studies for full analysis.

After the full text analysis, 32 studies were excluded because they were not relevant ($n = 21$), or they were case reports or with case histories less than 5 ($n = 7$), or they did not report outcomes described in the inclusion criteria ($n = 4$).

We selected 22 studies relevant for the analysys, of which 14 met the inclusion criteria for quantitative synthesis and were included in tables.

Table 1 shows the baseline characteristics of the selected studies: author, origin, year of publication, techniques for reversal (grouped in unclipping, diffusesympathectomy and nerve reconstruction), number of patients treated with documented results, kind of outcome of the reversal surgery in the study and the level of previous surgery (T2/T3/T4 and below).

Table 2 shows the outcomes of the reversal surgery with the satisfaction rate, time to reversal (range in months) and follow-up declared from reversal (range in months).

Discussion

The pathophysiological mechanism by which CS develops remains unknown to date. The risk of developing compensatory hyperhidrosis is influenced by many variables. If we consider all forms of compensatory hyperhidrosis, from the lightest to the most severe, the percentage of subjects that is affected in the literature can reach up to 98% (2, 17).

In 2006, Chou (5) suggests that changes in sweating patterns after sympathetic surgery may be attributable to a reflex response in the sweating center of the hypothalamus, and not at all to a compensatory mechanism. For this reason he suggests using the term "reflex sweating" instead of "compensatory hyperhidrosis". The distribution of sweating control pathways may show some variability in the population.

This could explain why the same surgery for primary hyperhidrosis (PH) could have different outcomes in different patients.

Several authors have pointed out that surgery for the craniofacial hyperhidrosis, therefore surgery on T2, increases the

TABLE 1 Characteristics of the studies.

Author	Origin	Year	Techniques for reversal	N patients treated, with documented results	Kind of outcome of the reversal surgery in the study	Previous surgery		
						T2 and below	T3 and below	T4 and below
Lin (3)	China	1998	Clip removal	5	Secondary	5		
Reisfeld (4)	USA	2006	Clip removal	25	Secondary	22	3	
Chou (5)	China	2006	Clip removal	13	Secondary	nd	nd	nd
Jo (6)	South Korea	2007	Clip removal	9	Secondary	3	6	
Kang (7)	South Korea	2008	Clip removal	14	Primary	12	2	
Sugimura (8)	Canada	2009	Clip removal	31	Primary	26	5	
Hynes (9)	USA	2015	Clip removal	8	Primary	5	3	
Kara (10)	Turkey	2019	Clip removal	8	Secondary	5	3	
Yamamoto (11)	Japan	2019	Diffuse sympathicotomy	8	Primary	2	5	1
Moon (12)	South Korea	2020	Diffuse sympathicotomy	44	Primary	13	25	6
Vasconcelos (13)	Brasil	2020	Diffuse sympathicotomy	12	Primary		12	
Haam (14)	South Korea	2010	Nerve reconstruction	17	Primary	12	5	
Rantanen (15)	Finland	2016	Nerve reconstruction	19	Primary	8	11	
Gebitekin (16)	Turkey	2021	Nerve reconstruction	15	Primary	nd	nd	nd

TABLE 2 Outcomes of reversal surgery.

Author	Year	Techniques for reversal	Satisfaction rate[a] (%)	Time to reversal (range in months)	F-up declared from reversal (range in months)
Lin (3)	1998	Clip removal	4/5 (80)	1–2	6–8
Reisfeld (4)	2006	Clip removal	16/25 (64)	nd	nd
Chou (5)	2006	Clip removal	10/13 (77)	nd	nd
Jo (6)	2007	Clip removal	8/9 (89)	1–2	6–30
Kang (7)	2008	Clip removal	9/14 (64)	1–2	6–65
Sugimura (8)	2009	Clip removal	15/31 (48.4)	1–57	1–72
Hynes (9)	2015	Clip removal	5/8 (62.5)	3–70	1–54
Kara (10)	2019	Clip removal	2/8 (25)	1–30	10–31
Yamamoto (11)	2019	Diffuse sympathicotomy	8/8 (100)	>6	14–22
Moon (12)	2020	Diffuse sympathicotomy	20/44 (45)	1–24	8–29
Vasconcelos (13)	2020	Diffuse sympathicotomy	8/12 (66.6)	nd	nd
Haam (14)	2010	Nerve reconstruction	9/17 (53)	4–111	1–45
Rantanen (15)	2016	Nerve reconstruction	14/19 (73.6)	6–144	6–180
Gebitekin (16)	2021	Nerve reconstruction	14/15 (93.3)	7–96	nd

[a]Satisfaction rate is described as the number of patients with improvement out of the number of total patients with documented outcome, expressed as fraction and percentage.

risk of CS (17). Sympathectomy at the T2 level probably causes interruption of the negative feedback to the hypothalamus and this seems to be shown to be the district most at risk for the development of CH (2, 18).

Some research suggests that CS is associated with extensive sympathicotomy, while others report that the extent of sympathicotomy has no association with the degree of CS.

The poor knowledge of the mechanisms underlying CS are reflected in the heterogeneity of treatments currently proposed for its treatment.

The literature actually available on the surgical treatment of compensatory hyperhidrosis is scarce and with small case series. The outcome's evaluation is not well established. The most common methods to evaluate surgery are scales of patient-reported outcome, with different questionnaires administered by different authors.

Furthermore, patients who only want to solve the CS, maintaining the benefits obtained with the first intervention, must be distinguished from patients who, in addition to the CS, regret the excessive dryness of the hands.

The objective of reversal surgery could be an attempt to return to the conditions before surgery, or an extension of the action of the surgery on the body areas affected by CS. Patients with primary palmar hyperhidrosis are more likely to have mild or moderate mental disorders, and postoperative compensatory sweating may impact the satisfaction of surgery. In addition, the personality characteristics of patients are related to compensatory sweating (19). For this reason it is recommended that all patients

should take psychological states evaluation before any kind of sympathetic surgery.

Reversal when the chain has been cut is challenging, whereas reversal when the chain has been clipped is straightforward.

The most documented technique is clip removal, and it can be performed only in patients submitted to clip placement. In our review we describe 8 series of clip removal (**Tables 1**, **2**) starting 1998, with a total of 113 patients treated and with documented results. Out of these, 69 (61%) patients were satisfied with the result of the procedure. The treatment of compensatory sweating after clipping and the evaluation of its effectiveness was described in secondary outcomes in 5 studies while it was primary outcome in the remaining 3 studies. In these series the satisfaction rate ranges from 25% to 89%, without a clear trend over the time.

The hypothesis of the regeneration of the sympathetic chain after clip removal is controversial. Some authors suggest that clip removal time, reported as the time between the placement of clips and their removal, may be a variable affecting the outcome (9, 10). In our data the differences in the time to reversal can therefore partially explain the differences in the results (satisfaction rate).

However some authors think that degenerative and irreversible changes occur at the level of the sympathetic nervous system following the placement of clips even if removed after a few days.

In a study of 2012 on a swine model, performing clipping, unclipping and extirpation with pathological examination, the authors observed Wallerian degeneration as early as 10 days after clip placement. They conclude that clipping cannot be considered a reversible technique (20).

In another 2014 animal model study, however, 12 weeks after unclipping, severe histological damage in the sympathetic trunk had clearly decreased, which suggests in theory that application of metal clips to the sympathetic chain is a reversible procedure if only the observation period is prolonged (21).

Other variables that can influence the results of the clipping technique are the degree of compression exerted by the clips and the differences between the clips themselves. For example, clips can be single-branch or dual-branch.

The satisfaction rate shows big variability as shown in **Table 2**.

In the various studies, the time to reversal can also be a variable that influences the result. In the selected studies, the time to reversal, where specified, ranges from 1 to over 70 months depending on the cases.

Regarding the results, the largest series found in literature is by Sugimura et al. reporting data about 31 patients undergoing unclipping in a reversal time period between 1 and 57 months and with a satisfaction rate of 48.4% (15/31). They conclude that reversal by unclipping offers acceptable results and should be considered in selected patients (8).

The best result as satisfaction rate after unclipping is reported by Jo et al. who shows 8/9 patients (89%) satisfied by the reversal surgery. They presented a new protocol for clip removal under local anesthesia. During the first surgery they place a suture between the tip and the body of the clip applicator that is fixed in the subcutaneous tissue; during reversal the clip is easily detected and removed with being pulled back (6).

From currently available data the reversibility of clipping remains controversial. The number of individual cases is minimal (5–31 patients).

The consensus of the International Society of Sympathetic Surgery states that unclipping has a placebo effect (10).

The issue about the reversibility of effects of sympathetic clipping remains empirical.

If there is little data on clip removal, even fewer are those concerning diffuse sympathectomy.

An important advantage of this technique is that it can be performed after any type of ETS already performed. It consists in the extension of the surgery on ganglia, usually at a lower level, with the aim of disrupting the activity of the ganglia responsible for the CS.

In our review only 3 studies met the inclusion criteria. These studies were published in 2019–20 and collected 64 patients. Satisfaction rate ranges from 45% to 100%. The study declaring a satisfaction rate of 100% seems to be promising, even if it involves only 8 patients (11).

In this report the authors described an original technique: patients with severe CS were treated by observing blood perfusion of the skin with laser speckle flowgraphy (LSFG), stimulating each sympathetic nerve and ganglion with an electrosurgical unit. LSFG allowed the exact identification of the ganglia corresponding to the CS areas. After identification of the ganglia responsible for the CS, ganglionectomy was performed.

In the remaining studies sympathectomy was applied to the lower sympathetic chain starting from R5 to R8 or from R5 to R11, eventually associated with lumbar sympathectomy L3 in case of severe plantar hyperhidrosis. In these studies the sympathectomy was performed without intraoperative monitoring of blood perfusion for determining the connections between ganglia and skin areas affected by CS. In these 2 studies the satisfaction rate was 45% for Moon (12) and 67% for Vasconcelos (13).

The latter concludes that extended R5–R8 thoracic sympathectomy for compensatory hyperhidrosis seems to be an effective and safe alternative to the other techniques with promising results.

Extended sympathectomy is feasible, but laser fluoroscopy equipment described by Yamamoto is not commonly available in institutions.

The efficacy of a diffuse sympathectomy can also be considered for preventive purposes, performing it directly during the first operation for sympathectomy for hyperhidrosis (17).

Han et al. designed a new sympathectomy method to prevent severe CS by expanding sympathectomy as low as possible beyond R8, even to R12. Their results showed a significantly reduced degree of CS and there were no severe CS cases without major complications (22).

Sympathetic nerve reconstruction (SNR) is a complex surgical procedure. Reports on sympathetic nerve reconstruction are also scarce. Three papers met the inclusion criteria, with a total number of 51 patients treated with documented results.

Of these, 37 (72.5%) patients were satisfied after the procedure.

Proximal and distal ends of the previously resected sympathetic chain are exposed and cut. Either sural or intercostal

nerve was used as a free graft and fibrin glue was applied to the contact surfaces. The nerve is generally anastomosed in the original direction.

The use of the intercostal nerve is preferable because it does not require additional surgical accesses, has more sympathetic nerve fibers, and can be used also as a pedicled graft harvested as a neurovascular bundle (14, 15); sural nerve can be used only as free graft and requires additional incision. Successful nerve anastomosis is generally obtained with fibrin sealant without suture technique. Rantanen and Telaranta report that approximately 75% (14/19) of their patients benefited from SNR after an average reversal time value of 87 month and that in 50% of these the improvement was significant; they conclude that SNR can be considered as a potential treatment option for patients with severe side effects from ETS which are unresponsive to conservative treatment (15).

This is a much more complex technique that requires more skills of the surgeon, more resources, and significantly longer operating times.

The results of this technique, considering the cost-benefit ratio, compared with other techniques do not actually seem to justify its use except in referral centres.

Conclusion

Severe CS is a rare but hardly treatable complication of ETS. Candidates for ETS should be informed about risk factors for developing severe CS.

The experiences on the surgical treatment of CS seem to be still few.

CS has to be managed with lifestyle control, pharmacological treatment, and iontophoresis. Surgical treatment for CS should be offered to highly motivated patients in referral centers.

There is currently no evidence of a surgical treatment for CS recognized as completely effective. Informed consent must be clear about the real expectations of success of such treatments.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Gossot D, Galetta D, Pascal A, Debrosse D, Caliandro R, Girard P, et al. Long-term results of endoscopic thoracic sympathectomy for upper limb hyperhidrosis. *Ann Thorac Surg.* (2003) 75(4):1075–9. doi: 10.1016/s0003-4975(02)04657-x

2. Wolosker N, Milanez de Campos JR, Fukuda JM. Management of compensatory sweating after sympathetic surgery. *Thorac Surg Clin.* (2016) 26(4):445–51. doi: 10.1016/j.thorsurg.2016.06.009

3. Lin CC, Mo LR, Lee LS, Ng SM, Hwang MH. Thoracoscopic T2-sympathetic block by clipping–a better and reversible operation for treatment of hyperhidrosis palmaris: experience with 326 cases. *Eur J Surg Suppl.* (1998) 580:13–6. doi: 10.1080/11024159850191067

4. Reisfeld R. Sympathectomy for hyperhidrosis: should we place the clamps at T2-T3 or T3-T4? *Clin Auton Res.* (2006) 16(6):384–9. doi: 10.1007/s10286-006-0374-z

5. Chou SH, Kao EL, Lin CC, Chang YT, Huang MF. The importance of classification in sympathetic surgery and a proposed mechanism for compensatory hyperhidrosis: experience with 464 cases. *Surg Endosc.* (2006) 20(11):1749–53. doi: 10.1007/s00464-005-0829-7

6. Jo KH, Moon SW, Kim YD, Sim SB, Cho DG, Jin U, et al. New protocol for a reversal operation in endoscopic thoracic sympathetic clamping: pulling back the suture sling linked to the clip under local anesthesia. *Surg Laparosc Endosc Percutan Tech.* (2007) 17(1):29–32. doi: 10.1097/01.sle.0000213759.61514.cc

7. Kang CW, Choi SY, Moon SW, Cho DG, Kwon JB, Sim SB, et al. Short-term and intermediate-term results after unclipping: what happened to primary hyperhidrosis and truncal reflex sweating after unclipping in patients who underwent endoscopic thoracic sympathetic clamping? *Surg Laparosc Endosc Percutan Tech.* (2008) 18 (5):469–73. doi: 10.1097/SLE.0b013e31817e91f8

8. Sugimura H, Spratt EH, Compeau CG, Kattail D, Shargall Y. Thoracoscopic sympathetic clipping for hyperhidrosis: long-term results and reversibility. *J Thorac Cardiovasc Surg.* (2009) 137(6):1370–6; discussion 1376–7. doi: 10.1016/j.jtcvs.2009.01.008

9. Hynes CF, Yamaguchi S, Bond CD, Marshall MB. Reversal of sympathetic interruption by removal of clips. *Ann Thorac Surg.* (2015) 99(3):1020–3. doi: 10.1016/j.athoracsur.2014.10.062

10. Kara M, Kose S, Ozkan B, Sertcakacilar G. Does clip removal help for compensatory hyperhidrosis complicating thoracic sympathetic clipping? *Clin Auton Res.* (2019) 29(3):353–5. doi: 10.1007/s10286-019-00599-8

11. Yamamoto H, Okada M. The management of compensatory sweating after thoracic sympathectomy. *J Thorac Cardiovasc Surg.* (2019) 158(5):1481–8. doi: 10.1016/j.jtcvs.2019.05.062

12. Moon MH, Hyun K, Park JK, Lee J. Surgical treatment of compensatory hyperhidrosis: retrospective observational study. *Medicine.* (2020) 99(42):e22466. doi: 10.1097/MD.0000000000022466

13. Vasconcelos CFM, Aguiar WS, Tavares RM, Barbosa A, Cordeiro GG, Oliveira FSC, et al. Bilateral R5-R8 sympathectomy for compensatory hyperhidrosis: complications and patient satisfaction. *Rev Col Bras Cir.* (2020) 47:e20202398. doi: 10.1590/0100-6991e-20202398

14. Haam SJ, Park SY, Paik HC, Lee DY. Sympathetic nerve reconstruction for compensatory hyperhidrosis after sympathetic surgery for primary hyperhidrosis. *J Korean Med Sci.* (2010) 25(4):597–601. doi: 10.3346/jkms.2010.25.4.597

15. Rantanen T, Telaranta T. Long-term effect of endoscopic sympathetic nerve reconstruction for side effects after endoscopic sympathectomy. *Thorac Cardiovasc Surg.* (2017) 65(6):484–90. doi: 10.1055/s-0036-1582431

16. Gebitekin C, Melek H, Cetinkaya G, Ozer E, Yenturk E, Sevinç TE, et al. Intercostal nerve reconstruction for severe compensatory hyperhidrosis: the gebitekin technique. *Ann Thorac Surg.* (2021) 111(6):e443–6. doi: 10.1016/j.athoracsur.2020.11.067

17. Raveglia F, Orlandi R, Guttadauro A, Cioffi U, Cardillo G, Cioffi G, et al. How to prevent, reduce, and treat severe post sympathetic chain compensatory hyperhidrosis: 2021 state of the art. *Front Surg.* (2022) 8:814916. doi: 10.3389/fsurg.2021.814916

18. Rde ML, Campos JR, Kang DW, Loureiro Mde P, Furian MB, Costa MG, et al. Guidelines for the prevention, diagnosis and treatment of compensatory hyperhidrosis. *J Bras Pneumol*. (2008) 34(11):967–77. doi: 10.1590/s1806-37132008001100013

19. Wang HY, Zhu YJ, Liu J, Li LW, Liu YH. The relationship between preoperative psychological evaluation and compensatory sweating. *J Cardiothorac Surg*. (2018) 13 (1):42. doi: 10.1186/s13019-018-0728-3

20. Loscertales J, Congregado M, Jimenez-Merchan R, Gallardo G, Trivino A, Moreno S, et al. Sympathetic chain clipping for hyperhidrosis is not a reversible procedure. *Surg Endosc*. (2012) 26(5):1258–63. doi: 10.1007/s00464-011-2023-4

21. Thomsen LL, Mikkelsen RT, Derejko M, Schrøder HD, Licht PB. Sympathetic block by metal clips may be a reversible operation. *Interact Cardiovasc Thorac Surg*. (2014) 19(6):908–13. doi: 10.1093/icvts/ivu311

22. Han JW, Kim JJ, Kim YH, Kim IS, Jeong SC. New sympathicotomy for prevention of severe compensatory hyperhidrosis in patients with primary hyperhidrosis. *J Thorac Dis*. (2020) 12(3):765–72. doi: 10.21037/jtd.2019.12.91

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 31 March 2023
DOI 10.3389/fsurg.2023.1150254

OPEN ACCESS

†This work was presented as oral presentation at the XXI National Meeting of the Italian Society of Thoracic Endoscopy (SIET), 29 September-01 October, 2022.

EDITED BY
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Federico Raveglia,
ASST-Monza, Italy
Evangelia Koukaki,
Sotiria General Hospital, Greece
Grigoris Stratakos,
National and Kapodistrian University of Athens, Greece

*CORRESPONDENCE
Giuseppe Marulli
✉ giuseppe.marulli@uniba.it

‡These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 23 January 2023
ACCEPTED 15 March 2023
PUBLISHED 31 March 2023

CITATION
Brascia D, De Palma A, Cantatore MG, Pizzuto O, Signore F, Sampietro D, Valentini M, Genualdo M and Marulli G (2023) Not only acute respiratory failure: COVID-19 and the post-intubation/tracheostomy upper airways lesions†.
Front. Surg. 10:1150254.
doi: 10.3389/fsurg.2023.1150254

Not only acute respiratory failure: COVID-19 and the post-intubation/tracheostomy upper airways lesions†

Debora Brascia‡, Angela De Palma‡, Mirko Girolamo Cantatore, Ondina Pizzuto, Francesca Signore, Doroty Sampietro, Mariangela Valentini, Marcella Genualdo and Giuseppe Marulli*

Unit of Thoracic Surgery, Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari "Aldo Moro", Bari, Italy

Background: An increasing number of patients have been subjected to prolonged invasive mechanical ventilation due to COVID-19 infection, leading to a significant number of post-intubation/tracheostomy (PI/T) upper airways lesions. The purpose of this study is to report our early experience in endoscopic and/or surgical management of PI/T upper airways injuries of patients surviving COVID-19 critical illness.

Materials and Methods: We prospectively collected data from patients referred to our Thoracic Surgery Unit from March 2020 to February 2022. All patients with suspected or documented PI/T tracheal injuries were evaluated with neck and chest computed tomography and bronchoscopy.

Results: Thirteen patients (8 males, 5 females) were included; of these, 10 (76.9%) patients presented with tracheal/laryngotracheal stenosis, 2 (15.4%) with tracheoesophageal fistula (TEF) and 1 (7.7%) with concomitant TEF and stenosis. Age ranged from 37 to 76 years. Three patients with TEF underwent surgical repair by double layer suture of oesophageal defect associated with tracheal resection/anastomosis (1 case) or direct membranous tracheal wall suture (2 cases) and protective tracheostomy with T-tube insertion. One patient underwent redo-surgery after primary failure of oesophageal repair. Among 10 patients with stenosis, two (20.0%) underwent primary laryngotracheal resection/anastomosis, two (20.0%) had undergone multiple endoscopic interventions before referral to our Centre and, at arrival, one underwent emergency tracheostomy and T-tube positioning and one a removal of a previously positioned endotracheal nitinol stent for stenosis/granulation followed by initial laser dilatation and, finally, tracheal resection/anastomosis. Six (60.0%) patients were initially treated with rigid bronchoscopy procedures (laser and/or dilatation). Post-treatment relapse was experienced in 5 (50.0%) cases, requiring repeated rigid bronchoscopy procedures in 1 (10.0%) for definitive resolution of the stenosis and surgery (tracheal resection/anastomosis) in 4 (40.0%).

Conclusions: Endoscopic and surgical treatment is curative in the majority of patients and should always be considered in PI/T upper airways lesions after COVID-19 illness.

KEYWORDS

COVID-19, tracheal stenosis, tracheoesophageal fistula, tracheal surgery, endoscopy

Introduction

The novel coronavirus disease 2019 (COVID-19) is a pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First cases were first reported in Wuhan, China in December 2019 and, since that time, the coronavirus outbreak was declared by the World Health Organization (WHO) as a public health emergency of international concern.

The clinical presentation of COVID-19 is highly heterogeneous, ranging from asymptomatic to severe respiratory failure, requiring invasive mechanical ventilation (IMV) for an average of 9.8%–15.2% of patients (1). Along with this increased need for IMV, an occult, silent and parallel pandemic has raised for surgeons. The mechanic and ischemic damage caused by intubation and tracheostomy on the tracheal wall is a well-known risk factor for the production of fibrotic tracheal scarring (2–4). Moreover, the SARS-CoV-2 has proved to worsen this ischemic tracheal and oesophageal mucosa damage by causing a prothrombotic and antifibrinolytic state, by producing microvascular injury and necrosis and by requiring chronic high dose systemic steroids use (5–7). Prolonged need for IMV in COVID-19 patients, along with the intrinsic capacity of the virus itself to damage the tracheal and oesophageal mucosa, have led to an increased incidence in post-intubation/tracheostomy (PI/T) upper airways lesions, including tracheal stenosis, tracheomalacia and tracheoesophageal fistulas. For this reason, the tracheal surgeon has to become familiar with tracheal lesions resulting from intubation/tracheostomy and with their treatment.

So far, most of the published literature on the COVID-19 PI/T upper airways lesions is anecdotal and mostly made up of case reports (8). We present our case series of COVID-19 patients who developed PI/T lesions after prolonged IMV and were treated at our Institution during the pandemic period.

Materials and methods

This is a prospective analysis on patients with documented PI/T tracheal injuries after intubation and invasive mechanical ventilation (IMV) due to respiratory failure resulting from SARS-CoV-2 infection who underwent endoscopic or open tracheal/oesophageal surgery between March 2020 and February 2022 in our Thoracic Surgery Unit. All patients were diagnosed with COVID-19 using real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab.

All patients with suspected or documented PI/T lesions were evaluated with CT of the neck and chest, flexible fiberoptic bronchoscopy and oesophagogastroscopy in case of suspected TEF. The features data were prospectively collected, including patients' demographics (age, body mass index, and comorbidities), length of ICU stay, duration of the endotracheal intubation, time from endotracheal intubation to tracheostomy, duration of tracheostomy and the characteristics of the PI/T lesions (type, size, and localization of the stenosis, categories of the endoscopic interventions and surgeries applied).

Before each operation, nasopharyngeal swabs were taken from the patients for SARS-CoV-2 RT-PCR testing, and only when patients tested negative, they underwent surgery. In only one patient surgery was performed even with a positive SARS-CoV-2 RT-PCR swab; this was the case of a seropositive myasthenia gravis (MGFA class IIB) patient with an ARDS due to COVID-19 infection, coupled with respiratory muscle failure, diagnosed with a TEF of 3.5 cm during her ICU stay. In this case, we considered the emergent surgical repair because of the critical clinical condition of the patient in which prolonged mechanical ventilation was expected. After initial flexible fiberoptic bronchoscopy, type, localization and residual tracheal lumen of the stenosis were assessed and the adequate treatment planned. Endoscopic treatment was considered as the first therapeutic option for those patients with simple web-like stenosis, with a cranio-caudal extent < 1 cm and without any damage to the cartilages, as a bridge-to-surgery option to manage symptomatic emergencies or for patients not eligible for surgery due to poor overall health status and comorbidities or with serious tracheomalacia. Surgery was chosen as first therapeutic option in high grade complex stenosis, with cranio-caudal extension >1 cm, intramural involvement and/or laryngo-tracheal framework impairment or in case of failure of multiple endoscopic procedures.

All patients with TEF, after endoscopic diagnosis was confirmed, underwent urgent surgical repair. Only in one case, surgical repair was delayed because of the priority for the patient, who was 20 weeks pregnant, to undergo prior abortion because of a malformed foetus.

Additionally, specimens of the trachea resected from the patients who underwent tracheal surgery were sent for pathologic examination and were compared with other similar tracheal specimens resected from patients with tracheal stenosis non-COVID-related to assess possible similarities or differences.

Endoscopic procedures

The rigid bronchoscope was inserted under general anaesthesia and the patient was ventilated through its ventilating channel. The stenosis was radially incised in two or three points with thulium and diode laser thus, the stenotic area was dilated with coring manoeuvres using rigid bronchoscopes with increasing diameters or Savary catheters. At the end of the procedure, an orotracheal tube was placed for 20 min for haemostasis and to stabilize dilatation.

Surgical procedure: tracheal resection and anastomosis

The surgical principles of tracheal resection and anastomosis (TR/A) have been already described (8). In our experience, after the two 2/0 polyglactin (Vicryl; Ethicon, Inc., Somerville, NJ, USA) traction sutures were placed in the lower tracheal tract and to the larynx, respectively, the posterior anastomosis was carried out first through a 4/0 polydioxanone (PDS; Ethicon, Inc., Somerville, NJ, USA) continuous suture on the membranous

pars; soon after, the latero-anterior cartilaginous pars was sutured with interrupted 3/0 Vicryl stitches. The traction sutures were then tied together to release tensions on the anastomosis and pretracheal muscle flaps are used to cover the anastomosis.

Surgical procedure: closure of the tracheal and oesophageal defects for tracheoesophageal fistula

The surgical principles of primary closure of the tracheal and oesophageal defects for acquired tracheoesophageal fistula have been already described (9). A gastrostomy and a jejunostomy tube should be positioned to allow both enteral feeding and gastric content drainage. Surgery should be delayed until weaning from mechanical ventilation. Postintubation fistulae are usually located in the cervical trachea, thus cervicotomy is the most frequent surgical approach. Trachea and oesophagus were dissected at the location of the fistula, and then closure of the membranous tracheal defect was accomplished directly using interrupted sutures of 4/0 PDS. The oesophageal defect was closed in two layers: the inner oesophageal mucosal layer was closed with a running suture, inverting the edges of the defect into the lumen, followed by closure of the outer oesophageal muscle over the mucosal layer with interrupted 4/0 polydioxanone sutures. A pedicled flap of pretracheal muscles or of sternocleidomastoid muscle was interposed between the oesophagus and the trachea.

Follow-up

In patients undergoing tracheal resection and anastomosis, control flexible bronchoscopies were done under conscious sedation at postoperative day 1 and day 7 to control the anastomotic suture line. In the TEFs cases, before resuming oral diet, all patients underwent contrast radiography to confirm healing of the oesophagus.

All patients were followed up after discharge with flexible bronchoscopies performed at 10 days, 1–3—6–12 months after surgery.

Statistical analysis

Continuous variables are described as mean ± standard deviation (SD) and median (intra-quartile range, IQR). Categorical variables are reported as counts and percentages. Statistical analysis was performed on STATA 14.0 statistical software (StataCorp.2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

A total of thirteen patients (8 males, 5 females) underwent endoscopic/surgical treatment for PI/T tracheal injuries after prolonged intubation and mechanical ventilation due to respiratory failure resulting from SARS-CoV-2 infection between March 2020 and February 2022. Particularly, 10 (76.9%) patients presented with tracheal/laryngotracheal stenosis, 2 (15.4%) with tracheoesophageal fistula (TEF) and 1 (7.7%) with concomitant TEF and stenosis. Age ranged from 37 to 76 years (mean 61.9 ± 12.2). The demographic and clinical characteristics of the patients are described in Table 1. Mean IMV duration (endotracheal tube and tracheostomy) was 47.0 ± 33.6 days. Eleven (84.6%) patients had undergone tracheostomy, with a mean duration of 49.2 ± 46.1 days. All patients diagnosed with TEF were already hospitalized and were sent to our Department to undergo emergency surgery; four patients (40.0%) with tracheal stenosis were admitted from the emergency department to our Unit to undergo urgent procedures and the last six patients (60.0%) were admitted to the outpatient clinic. Table 2 summarizes the bronchoscopic features of patients' tracheal stenosis and/or TEF. Figure 1 summarizes the treatment algorithm and outcomes.

Among the ten patients with stenosis, two (20.0%) underwent primary laryngotracheal resection/anastomosis, two (20.0%) had undergone multiple endoscopic interventions before referral to our Centre: in one case, at arrival, emergent tracheostomy and T-tube positioning was performed; in the other one, a previously positioned endotracheal nitinol stent causing tracheal stenosis/granulation was removed and laser resection and tracheal dilatation was performed at first. Repeated rigid bronchoscopic procedures with tracheal dilatation were performed on this patient and, at least, post-treatment relapse required tracheal resection/anastomosis. Six (60.0%) patients were initially treated with rigid bronchoscopy procedures (laser and/or dilatation). Post-treatment relapse was experienced in 5 (50.0%) cases, requiring repeated rigid bronchoscopy procedures in 1 (10.0%) and surgery (tracheal resection/anastomosis) in 4 (40.0%) for definitive resolution of the stenosis (Figure 2).

TABLE 1 Demographic and clinical characteristics of the enrolled patients.

Variable	*n* (%)
Gender	
Female	5 (38.5)
Male	8 (61.5)
Age (years)	61.9 ± 12.2
BMI (kg/m^2)	29.5 ± 4.7
Comorbidities	
COPD	5 (38.5)
Diabetes	1 (7.7)
Hypertension	5 (38.5)
Cardiopathy	2 (15.4)
Myasthenia Gravis	1 (7.7)
Cancer	1 (7.7)
Other	7 (53.8)
Time from endotracheal intubation to tracheostomy (days)	17.0 ± 5.4
Tracheostomy (*n*)	11 (84.6)
Tracheostomy duration (days)	49.2 ± 46.1; 33 (IQR 22;67.5)
Duration of the IMV (endotracheal tube and tracheostomy) (days)	47.0 ± 33.6; 43 (IQR 22;53)

TABLE 2 Bronchoscopic features of patients' tracheal stenosis and/or TEF.

Patients with tracheal stenosis	
Time from extubation to diagnosis (days)	103.2 ± 73.1; 74.5 (IQR 56;137)
Type of stenosis, *n* (%)	
Web-like	4 (40.0)
Complex	6 (60.0)
Localization *n* (%)	
Subglottic	5 (50.0)
Upper 1/3 trachea	4 (40.0)
Middle trachea	1 (10.0)
Residual lumen (mm)	6.5 ± 1.65
Number of endoscopic procedures	20
Type of procedure	
Dilatation only	3 (30.0)
Surgery only	2 (20.0)
Dilatation + Surgery	5 (50.0)
Patients with TEF	
Length of fistula (cm)	3.0 ± 0.25
Type of procedure	
Primary oesophageal/tracheal closure	2 (66.7)
Tracheal resection/anastomosis + oesophageal closure	1 (33.3)

Three patients with TEF underwent surgical repair by double layer suture of oesophageal defect associated with tracheal resection/anastomosis (1 case) or direct tracheal suture (2 cases) and protective tracheostomy with T-tube insertion.

Early postoperative complications developed in 2 cases (67%): one patient experienced a small (<5 mm) oesophageal suture leak in the immediate postoperative course, managed by using endoscopic through-the-scope clips (TTSC). The other patient, instead, experienced a TEF relapse successfully managed by redo-surgery. Particularly, the relapse was firstly managed through the endoscopic placement of a self-expanding covered nitinol stent (Ultraflex, Boston Scientific, MA, USA) without resolution of the fistula. Two more surgeries were then needed to perform a faringostomy and upper oesophageal exclusion by cervicotomy with protection tracheostomy with T-tube insertion. Definitive surgery was performed after three months, allowing complete oesophageal recanalization and tracheostomy closure.

During long-term follow-up, only one patient (33.3%) treated for TEF developed a minor complication, that is to say bacterial infection of the cervicotomy treated with local medications and systemic antibiotic therapy.

Early postoperative complications developed in 20.0% of patients who underwent TR/A; they experienced postoperative low-grade laryngeal oedema in the immediate postoperative course, successfully managed by low-dose systemic corticosteroids and delayed extubation. During long-term follow-up, only 1 case of the TR/A treated patients developed non-obstructive postoperative granulation tissue at the anastomosis, successfully regressed with medical therapy including inhaled beclometasone and low-dose systemic corticosteroids. In all the other cases, long-term follow-up highlighted no major complication.

Intraoperative and postoperative patients' features are summarized in Table 3.

The pathologic examination of the tracheal segments resected from the patients who underwent tracheal surgery revealed fibrosis, inflammation, degeneration and ischemic necrosis of the tracheal rings but, in comparison with other tracheal specimens resected from non-COVID-19 related patients, no particular differences were observed.

As an explorative analysis, the non-COVID-related PI/T treated at out Department in the same years were reviewed. A

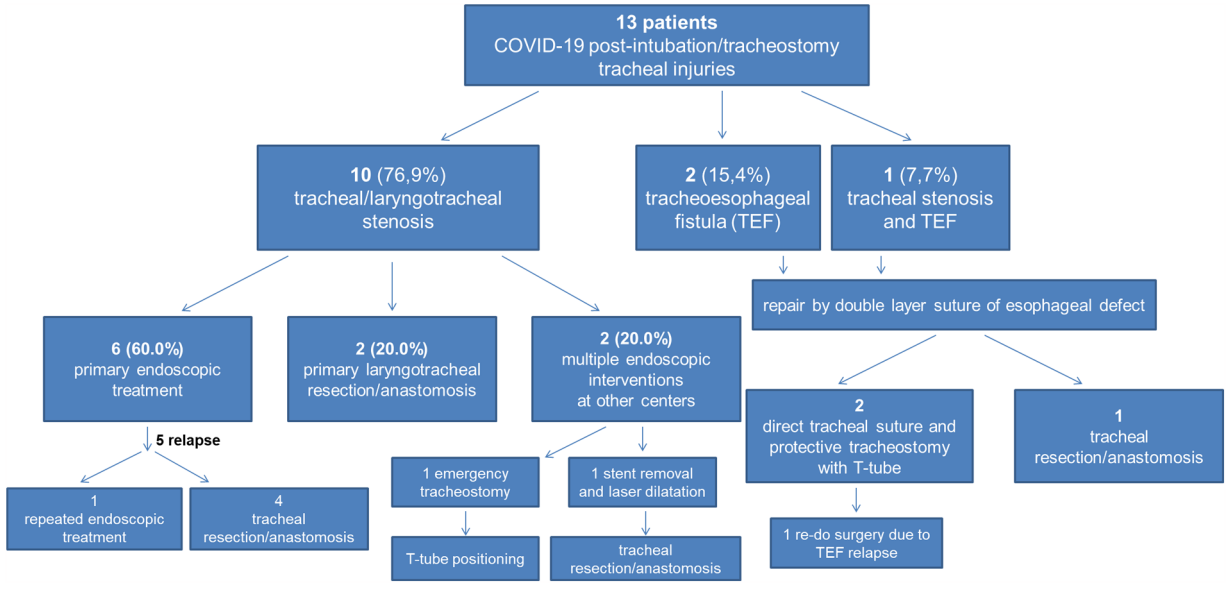

FIGURE 1
Treatment algorithm and outcomes in our patients with COVID-19 post-intubation/tracheostomy tracheal injuries.

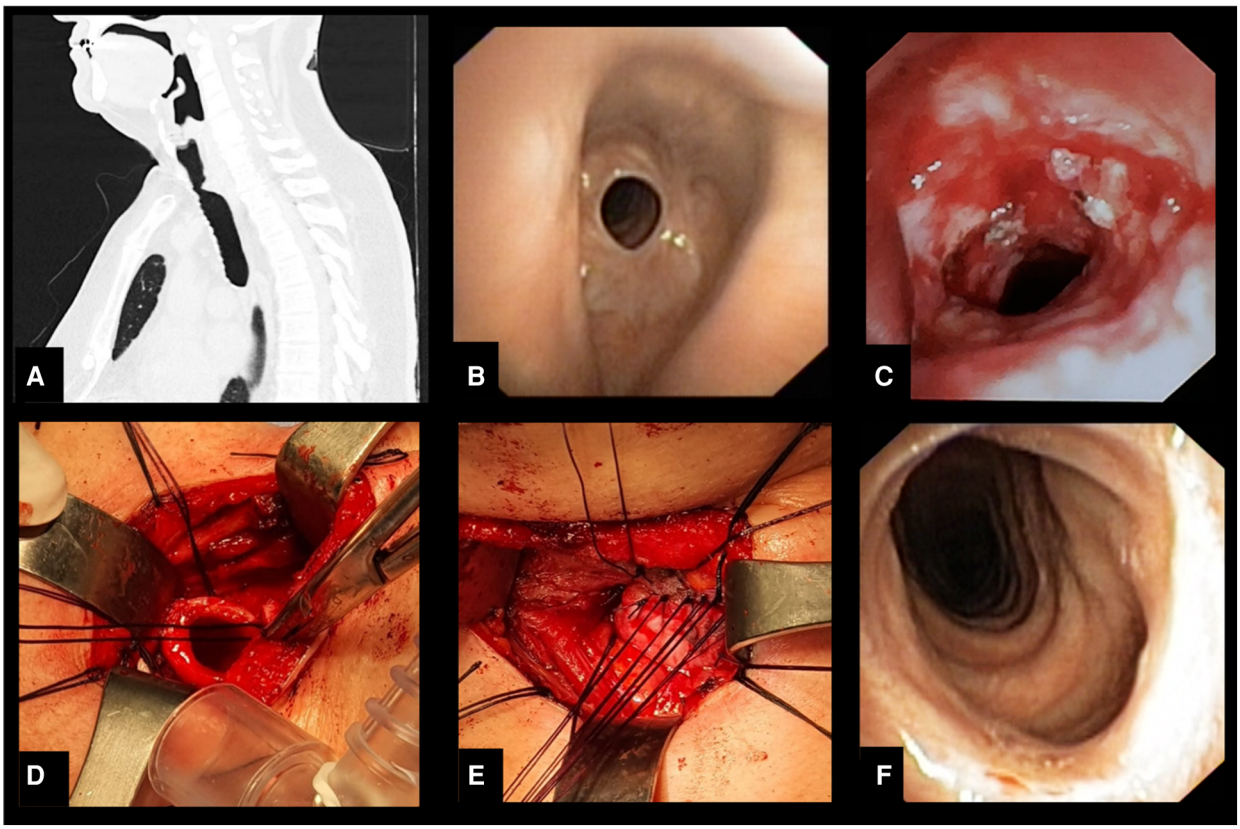

FIGURE 2
(A) Sagittal computed tomography image showing stenosis of the upper third of trachea. (B) Bronchoscopic appearance of the stenosis. (C) Endoscopic appearance of the recurrence of stenotic tracheal segment after endoscopic treatment with laser and dilation. (D) Intraoperative photo after resection of the stenotic tracheal segment. (E) Intraoperative appearance of the tracheal anastomosis. (F) Bronchoscopic appearance 3 months after surgery.

TABLE 3 Intraoperative and postoperative patients' features.

Endoscopic dilatation	*n* (%)
Mean duration of procedure (min)	36.3 ± 16.3
Tracheal resection/anastomosis	
Mean duration of operation (min)	252.9 ± 46.8
Postoperative ICU-stay (patients)	6 (85.7)
Postoperative ICU LOS (days)	1.6 ± 1.3
In-hospital LOS (days)	7.7 ± 0.5
Complications	
Anastomotic	
Granulation tissue	1 (14.3)
Non-anastomotic	
Laryngeal oedema	2 (28.6)
Closure of TEFs	
Time from diagnosis to surgery (days)	9.3 ± 6.7
Mean duration of operation (min)	261.7 ± 79.7
ICU-stay (patients)	2 (66.7)
ICU LOS (days)	5.3 ± 6.1
Postoperative LOS (days)	50.3 ± 34.6;
Complications	
Recurrent TEF	1 (33.3)
Dysphagia	2 (66.6)
Wound infection	1 (33.3)

total of 28 patients had presented with tracheal stenosis, of them 7 (25%) patients presented with idiopathic stenosis and 21 (75%) with post-intubation/tracheostomy non-COVID-related stenosis. One (3.6%) patient underwent primary laryngotracheal resection/anastomosis, while the others 27 (96.4%) had undergone primary endoscopic treatment (laser and/or dilatation); among them, 3 (11.1%) patients had already undergone multiple endoscopic interventions before referral to our Centre. Post-treatment relapse was experienced in 9 (33.3%) cases, requiring repeated rigid bronchoscopy procedures in 5 (18.5%) and surgery (tracheal resection/anastomosis) in 4 (14.8%) for definitive resolution of the stenosis (Figure 3).

Discussion

The recent COVID-19 pandemic has raised new medical and surgical challenges. The virus contagiousness, morbidity, and mortality have forced the clinicians to study new therapeutic options in the field of pneumology and infectious diseases, but surgery too has been forced to adapt to new scenarios and needs. As a consequence of prolonged IMV due to COVID-19 severe

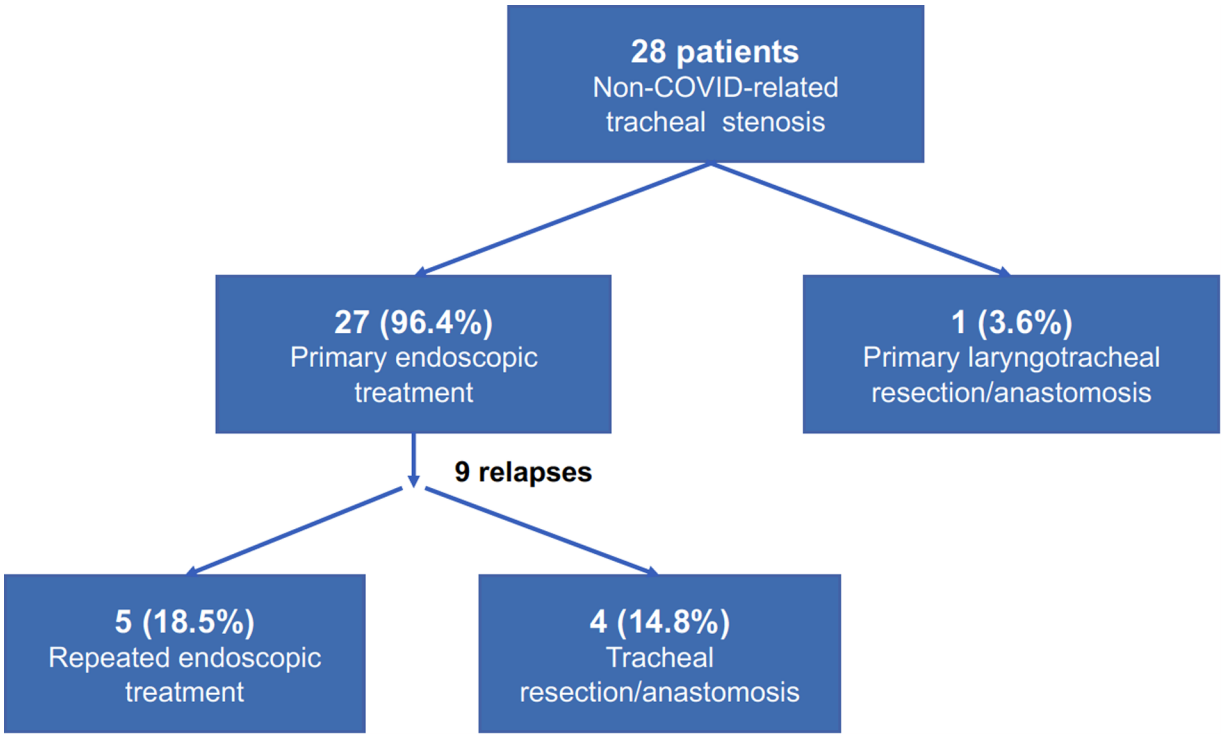

FIGURE 3
Treatment algorithm and outcomes in our patients with non-COVID-related tracheal injuries.

acute respiratory syndrome (SARS), in fact, a significant number of PI/T upper airways lesions has been detected, including both tracheal/laryngotracheal stenosis and tracheoesophageal fistulas. During the pandemic, around 10%–20% of infected patients have developed a severe disease requiring IMV for an average of 18 days (10–12) thus leading to an increase rate of upper airways lesions. Although the described incidence rates of tracheal stenosis following laryngotracheal intubation and tracheostomy range from 6% to 21% and 0.6% to 21% respectively in literature (13–17), recent studies have described the occurrence of PI/T lesions in almost half of the COVID-19 treated with prolonged IMV (18). Fiacchini et al. (19), in fact, compared 30 COVID-19 patients and 45 non-COVID-19 patients who both underwent prolonged IMV, and they found that 47% of COVID-19 patients developed PI/T upper airways complications compared to 2% of the control group. Many mechanisms have been regarded as responsible of the tracheal and oesophageal mucosal damage: the prothrombotic and antifibrinolytic state caused by SARS-CoV-2 virus producing microvascular injury and necrosis, high viral replication within the mucosa itself, chronic high dose systemic steroids use and the hypoxic damage and pronation manoeuvres used during the ICU stay which increase the pressure on the tracheal walls (1, 5, 6). Moreover, while generally tracheostomy should be performed 7 to 14 days after intubation to promote faster weaning and reduce IMV complications, during the COVID-19 period, tracheostomies were delayed until the patients were clear from the virus (3 to 4 weeks) because of the high risk of cross-infection of healthcare professionals, the need for continuation of prone position ventilation and the death of patients prior to the first 14 days. Also in our series, along with the worldwide records, in fact, mean duration time from intubation to tracheostomy was 17 days. Moreover, past case reports have shown times to onset from 28 days to 6 months (20). Shin et al. (21), in their study on 117 post-intubation tracheal lesions, reported a mean time from tracheal trauma to diagnosis of 1.8 months. Similarly, Beyoglu et al. (22) found a time to diagnosis of 42.0 days in the COVID-19 group with no statistically significant difference when comparing it with the non-COVID-19 group. In our case series, time from extubation to diagnosis was longer than the previous reports, around 100 days in mean.

Furthermore, a strict correlation between COVID-19, obesity and IMV has already been described (23) and, also in our study, most of patients were overweight with a mean BMI of 29.5. In our experience, in more than one case, surgical tracheal resection was delayed in favour of multiple endoscopic dilatations because of obesity, and patients were warned to lose weight before surgery. In COVID-19 population avoiding tracheal stenting has been suggested, because of its potential tissue damage on the airway wall causing an inflammatory response with granulation and causing delaying of surgical treatment (24). In our study, in fact, a patient had been admitted to our Centre with a previously positioned endotracheal nitinol stent for stenosis/granulation and, after removal, the inflammatory response of the tracheal wall had caused multiple relapses requiring multiple endoscopic dilatation and, at least, after maturation of the stenosis, tracheal resection

and anastomosis was performed. Some recent reports have suggested that open surgical approaches should be avoided as primary choice in the COVID-19 population because of the high risk for comorbidities linked to the infection itself (25). In our experience, the distance from vocal cords did not influence the choice of treatment; half of our patients, in fact, had a subglottic stenosis and their treatment did not differ from the others. Type and grade of stenosis, instead, along with the patient characteristics, had guided the choice of treatment; in almost all cases an endoscopic dilatation attempt was made at first while upfront surgery was chosen for two patients with complex stenosis who had recovered from COVID-19 infection for at least 5 months and had developed a mature stenosis, in the absence of other serious comorbidities. Stratakos et al. (26) recently presented their case series on 23 COVID-19 patients diagnosed with post-intubation tracheal stenosis and TEF; in this study 65% of patients was initially treated with rigid bronchoscopic modalities and/or stent placement and 35% with tracheal resection-anastomosis, presenting rates similar to ours.

In literature, success rates of laser/mechanical dilatation of simple stenosis varies from 60% to 100% (27–29), with relapse rates after dilatation as high as 90%, especially in complex stenoses.

Cavaliere et al. (30) reported good results in 66% of benign tracheal stenosis cases treated with endoscopic manoeuvres, whereas Galluccio et al. (27) reported success rates of 96% and 69% for simple and complex stenoses, respectively. When looking at our results of the tracheal procedures in non-COVID patients, we experienced success rates of primary endoscopic procedures of approximately 67%. In our COVID-19-related case series, instead, recurrence developed in 6 out of 8 patients (75%) initially treated with mechanical tracheal dilatation and endoscopic dilatation was performed for a minimum of 1 and a maximum of 5 sessions due to symptomatic stenosis. It could be speculated that the pathologic alterations produced by the virus could impact on the capacity of the mucosa itself to heal properly because of the microvascular injury and the high viral replication within the mucosa itself. However, at the pathologic examinations, no particular differences were observed and more studies are needed to properly assess this issue.

In literature, TR/A complication rates range from 15% and 45% (22). In our study, only 1 patient presented small granulation tissue formation at the anastomotic site, which did not require any invasive treatment; laryngeal edema presenting in the immediate postoperative period was transient and regressed after 24–48 h.

TEF is a rare clinical entity, accounting for 0.5% of patients requiring prolonged IMV; recent series have proved an increase in its incidence during the COVID-19 pandemic, with rates increasing from 0.5 to 1.5% (31). Nonoperative mortality rate for TEFs is as high as 80% (32). In literature, many different approaches have been proposed for TEFs but, due to the rarity of this entity, no consensus exists, especially for the COVID-19 patients. Many authors have proposed conservative treatment for small TEFs, by temporarily bypassing the fistula with a tracheostomy tube, perform percutaneous jejunostomy and wait for healing, but all these approaches have showed high failure rates, always requiring definitive surgery (33–36). In our experience, all TEFs cases were managed urgently with surgery. Due both to the novelty and the rarity of TEF occurrence in COVID-19 patients, most of the published experience is anecdotal. Most of case reports (34–38) describe a conservative treatment, followed by delayed surgical repair of TEFs as the preferred option in COVID-19 patients. Gomez Zuleta et al. (31) described their series of 14 COVID-19 patients with TEF treated by either surgical (6 patients) or endoscopic (8 patients) repair; they found that 42.8% of the patients died due to infectious complications, with two patients dying before receiving surgical management. Palacios et al. (39), instead, described their series on 20 patients with TEF who were all managed by direct closure; only two patients (3.2%) developed dehiscence of the surgery site. Along with this last experience, we preferred timely surgical closure in all our TEF cases, since we feared that the virus could worsen ischemic damage of both the tracheal and oesophageal wall and enlarge the defect, preventing an effective surgical closure. Two out of three patients with TEF in our study experienced minor complications, all successfully managed with medical treatment. In one case, the patient experienced a primary failure of the surgical repair requiring a redo-surgery.

In conclusion, PI/T upper airways lesions during the COVID-19 pandemic have showed an increase in their incidence because of the longer need for IMV and the consequent delay of tracheostomies, the SARS-CoV-2 virus itself producing microvascular injury and necrosis, the high dose systemic steroids use and the hypoxic damage and pronation manoeuvres used during the ICU stay. Surgeons should be comfortable with all the therapeutic strategies, which do not differ from those for upper airways lesions in general. Firstly, the endoscopic evaluation is of paramount importance in the treatment plan, since the location, length, and severity of the stenosis or damages should guide the proper surgical or endoscopic management. Secondly, surgery should always be considered, when feasible, both for tracheal stenosis and for tracheoesophageal fistulas. TEFs in particular should always be treated as soon as possible, since the virus itself could weak and damage tracheal and oesophageal wall, preventing future surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DB—introduction, materials and methods, evaluation of results, discussion, writing, literature, critical review and final approval of the manuscript. AD—introduction, materials and methods, evaluation of results, discussion, writing, literature, critical review and final approval of the manuscript. MGC—introduction, materials and methods, evaluation of results, discussion, writing, literature and final approval of the manuscript. OP—discussion and final approval of the manuscript. FS—discussion and final approval of the manuscript. DS—discussion and final approval of the manuscript. MV—discussion and final approval of the manuscript. MG—discussion and final approval of the manuscript. GM—introduction, materials and methods, evaluation of results, discussion, critical review and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor SR declared a past collaboration with the author ADP.

Publisher's note

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5

2. Sue RD, Susanto I. Long-term complications of artificial airways. *Clin Chest Med*. (2003) 24:457–71. doi: 10.1016/S0272-5231(03)00048-0

3. Wood DE, Mathisen DJ. Late complications of tracheotomy. *Clin Chest Med*. (1991) 12:597–609. doi: 10.1016/S0272-5231(21)00806-6

4. Wain JC Jr. Postintubation tracheal stenosis. *Semin Thorac Cardiovasc Surg*. (2009) 21:284-9. doi: 10.1053/j.semtcvs.2009.08.001

5. Minonishi T, Kinoshita H, Hirayama M, Kawahito S, Azma T, Hatakeyama N, et al. The supine-to-prone position change induces modification of endotracheal tube cuff pressure accompanied by tube displacement. *J Clin Anesth*. (2013) 25:28–31. doi: 10.1016/j.jclinane.2012.05.007

6. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. (2020) 220:1–13. doi: 10.1016/j.trsl.2020.04.007

7. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu h, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington state: a case series. *Lancet*. (2020) 396:320–32. doi: 10.1016/S0140-6736(20)31305-2

8. Scholfield DW, Warner E, Ahmed J, Ghufoor K. Subglottic and tracheal stenosis associated with coronavirus disease 2019. *J Laryngol Otol*. (2021) 135:656–8. doi: 10.1017/S0022215121001134

9. Marulli G, Rizzardi G, Bortolotti L, Loy M, Breda C, Hamad AM, et al. Single-staged laryngotracheal resection and reconstruction for benign strictures in adults. *Interact Cardiovasc Thorac Surg*. (2008) 7:227–30. doi: 10.1510/icvts.2007.168054

10. Marulli G, Loizzi M, Cardillo G, Battistella L, De Palma A, Ialongo P, et al. Early and late outcome after surgical treatment of acquired non-malignant tracheo-oesophageal fistulae. *Eur J Cardio-Thor Surg*. (2013) 43:e155–61. doi: 10.1093/ejcts/ezt069

11. Senturk M, El Tahan MR, Szegedi LL, Marczin N, Karzai W, Shelley B, et al. Thoracic anesthesia of patients with suspected or confirmed 2019 novel coronavirus infection: preliminary recommendations for airway management by the European association of cardiothoracic anaesthesiology thoracic subspecialty committee. *J Cardiothorac Vasc Anesth*. (2020) 34:2315–27. doi: 10.1053/j.jvca.2020.03.059

12. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. COVID-19 Lombardy ICU network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. *JAMA*. (2020) 323:1574–81. doi: 10.1001/jama.2020.5394

13. Elsayed HH, Hassaballa AS, Ahmed TA, Gumaa M, Sharkawy HY, Moharram AA. Variation in outcome of invasive mechanical ventilation between different countries for patients with severe COVID-19: a systematic review and meta-analysis. *PLoS One*. (2021) 16:e0252760. doi: 10.1371/journal.pone.0252760

14. Sarper A, Ayten A, Eser I, Ozbudak O, Demircan A. Tracheal stenosis aftertracheostomy or intubation: review with special regard to cause and management. *Tex Heart Inst J*. (2005) 32:154–8. PMID: 16107105.

15. Grillo HC, Donahue DM, Mathisen DJ, Wain JC, Wright CD. Postintubation tracheal stenosis. Treatment and results. *J Thorac Cardiovasc Surg*. (1995) 109:486–92. doi: 10.1016/S0022-5223(95)70279-2

16. Diaz-Jimenez JP, Lisbona RML. Benign tracheal and bronchial stenosis. In: JP Díaz-Jimenez, RML Lisbona, editors. *Interventions in pulmonary medicine*. New York: Springer (2013). p. 165–184.

17. Papla B, Dyduch G, Frasik W, Olechnowicz H. Post-intubation tracheal stenosis–morphological-clinical investigations. *Pol J Pathol*. (2003) 54:261–6. PMID: 14998295.

18. Esteller-More E, Ibanez J, Matino E, Adema JM, Nolla M, Quer IM. Prognostic factors in laryngotracheal injury following intubation and/or tracheotomy in ICU patients. *Eur Arch Otorhinolaryngol*. (2005) 262:880–3. doi: 10.1007/s00405-005-0929-y

19. Fiacchini G, Tricò D, Ribechini A, Forfori F, Brogi E, Lucchi M, et al. Evaluation of the incidence and potential mechanisms of tracheal complications in patients with COVID-19. *JAMA Otolaryngol Head Neck Surg*. (2021) 147:70–6. doi: 10.1001/jamaoto.2020.4148

20. Liu J, Zhang CP, Li Y, Dong S. Post-intubation tracheal stenosis after management of complicated aortic dissection: a case series. *J Cardiothorac Surg*. (2015) 10:148. doi: 10.1186/s13019-015-0357-z

21. Shin B, Kim K, Jeong BH, Eom JS, Song WJ, Kim H. Clinical implications of differentiating between types of post-tracheostomy tracheal stenosis. *J Thorac Dis*. (2017) 9:4413–23. doi: 10.21037/jtd.2017.10.99

22. Beyoglu MA, Sahin MF, Turkkan S, Yazicioglu A, Yekeler E. Complex post-intubation tracheal stenosis in COVID-19 patients. *Indian J Surg*. (2022) 84:805–13. doi: 10.1007/s12262-022-03498-x

23. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)*. (2020) 28:1195–9. doi: 10.1002/oby.22831

24. Gaissert HA, Grillo HC, Wright CD, Donahue DM, Wain JC, Mathisen DJ. Complication of benign tracheobronchial strictures by self-expanding metal stents. *J Thorac Cardiovasc Surg United States*. (2003) 126:744–7. doi: 10.1016/S0022-5223(03)00361-1

25. Mattioli F, Marchioni A, Andreani A, Cappiello G, Fermi M, Presutti L. Post-intubation tracheal stenosis in COVID-19 patients. *Eur Arch Otorhinolaryngol*. (2021) 278:847–8. doi: 10.1007/s00405-020-06394-w

26. Stratakos G, Anagnostopoulos N, Alsaggaf R, Koukaki E, Bakiri K, Emmanouil P, et al. COVID-19 Patients presenting with post-intubation upper airway complications: a parallel epidemic? *J Clin Med*. (2022) 11:1719. doi: 10.3390/jcm11061719

27. Galluccio G, Lucantoni G, Battistoni P, Paone G, Batzella S, Lucifora V, et al. Interventional endoscopy in the management of benign tracheal stenoses: definitive treatment at long-term follow-up. *Eur J Cardiothorac Surg*. (2009) 35:429–33. doi: 10.1016/j.ejcts.2008.10.041

28. Dalar L, Karasulu L, Abul Y, Ozdemir C, Sokucu SN, Tarhan M, et al. Bronchoscopic treatment in the management of benign tracheal stenosis: choices

for simple and complex tracheal stenosis. *Ann Thorac Surg*. (2016) 101:1310–7. doi: 10.1016/j.athoracsur.2015.10.005

29. Dutau H, Breen DP. Endobronchial laser treatment: an essential tool in therapeutic bronchoscopy. *Eur Respir Monogr*. (2010) 48:149–60.

30. Cavaliere S, Bezzi M, Toninelli C, Foccoli P. Management of post-intubation tracheal stenoses using the endoscopic approach. *Monaldi Arch Chest Dis*. (2007) 67:73–80. doi: 10.4081/monaldi.2007.492

31. Gomez Zuleta MA, Gallego Ospina DM, Ruiz OF. Tracheoesophageal fistulas in coronavirus disease 2019 pandemic: a case report. *World J Gastrointest Endosc*. (2022) 14:628–35. doi: 10.4253/wjge.v14.i10.628

32. Gaissert HA, Lofgren RH, Grillo HC. Upper airway compromise after inhalation injury. Complex strictures of the larynx and trachea and their management. *Ann Surg*. (1993) 218:672. doi: 10.1097/00000658-199321850-00014

33. Roomi S, Talib U, Farooq S, Chohan A, Siddique M, Saeed R, et al. Tracheoesophageal fistula: a rare complication of prolonged intubation in COVID-19. *Chest*. (2020) 158:A2596–7. doi: 10.1016/j.chest.2020.09.191

34. Pereira C, Silva R, Campello GC, Moura F. Tracheoesophageal fistula in a COVID-19 patient. *Saudi J Anaesth*. (2021) 15:447–9. doi: 10.4103/sja.sja_294_21

35. Negaresh M, Hoseininia S, Samadi Takaldani AH, Feyzi-Khankandi I, Mohammadzadeh Germi B, Ghobadi H. Implanting jejunostomy tube as conservative management of tracheoesophageal fistula in a COVID-19 patient. *Clin Case Reports*. (2021) 9:e05151. doi: 10.1002/ccr3.5151

36. Cuaño PMGM, Pilapil JCA, Larrazabal RJB, Villalobos RE. Acquired tracheoesophageal fistula in a pregnant patient with COVID-19 pneumonia on prolonged invasive ventilation. *BMJ Case Rep*. (2021) 14:e244016. doi: 10.1136/bcr-2021-244016

37. Rosati R, De Nardi P, Dell'Acqua A, Calvi MR, Elmore U, Scarparo E, et al. Tracheoesophageal Fistula in a COVID-19 ventilated patient: a challenging therapeutic decision. *Case Rep Surg*. (2021):6645518. doi: 10.1155/2021/6645518

38. Granata A, Martucci G, Rizzo GEM, Arcadipane A, Traina M. Combined endoscopical treatments for tracheo-esophageal fistula developed during V-V ECMO for severe COVID-19: a case series. *Artif Organs*. (2022) 46:506–8. doi: 10.1111/aor.14101

39. Palacios JM, Bellido DA, Valdivia FB, Ampuero PA, Figueroa CF, Medina C, et al. Tracheal stenosis as a complication of prolonged intubation in coronavirus disease 2019 (COVID-19) patients: a Peruvian cohort. *J Thorac Dis*. (2022) 14:995–1008. doi: 10.21037/jtd-21-1721

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 04 April 2023
DOI 10.3389/fsurg.2023.1156465

OPEN ACCESS

EDITED BY
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Salvatore Andrea Mastrolia,
Umberto 1 Hospital, Italy
Maria Teresa Gomez Hernandez,
University of Salamanca, Spain

*CORRESPONDENCE
Angela De Palma
angela.depalma@uniba.it

This work was presented as oral presentation at the XXI National Meeting of the Italian Society of Thoracic Endoscopy (SIET), 29 September–01 October, 2022.

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 01 February 2023
ACCEPTED 07 March 2023
PUBLISHED 04 April 2023

CITATION
Quercia R, De Palma A, De Blasi F, Carleo G, De Iaco G, Panza T, Garofalo G, Simone V, Costantino M and Marulli G (2023) Catamenial pneumothorax: Not only VATS diagnosis. Front. Surg. 10:1156465. doi: 10.3389/fsurg.2023.1156465

Catamenial pneumothorax: Not only VATS diagnosis

Rosatea Quercia†, Angela De Palma*†, Francesco De Blasi, Graziana Carleo, Giulia De Iaco, Teodora Panza, Giuseppe Garofalo, Valentina Simone, Michele Costantino and Giuseppe Marulli

Unit of Thoracic Surgery, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy

Background: Catamenial pneumothorax (CP) is a rare type of spontaneous, recurring pneumothorax occurring in women, from the day before menstruation until 72 hours after its beginning. Conservative treatment is generally associated with recurrence of CP. Video-assisted thoracic surgery (VATS) approach allows not only to obtain diagnosis but also to guide definitive treatment of causing lesions, such as ectopic endometrial implants or diaphragmatic defects and fenestrations. We report our experience in VATS management of CP to focus on its role in CP.
Materials and methods: In this retrospective observational study, we collected data from women referred to our center for CP, from January 2019 to April 2022. All patients underwent VATS approach, with muscle-sparing thoracotomy when diaphragmatic fenestrations were detected, to perform selective diaphragmatic plication and/or partial diaphragmatic resection. Results were analyzed in terms of pneumothorax recurrence after surgical treatment. All patients were referred to gynecologists for medical therapy.
Results: Eight women (median age 36 years, range: 21–45), all with right side CP, were included; three already had pelvic endometriosis and two had already undergone lung apicectomy at other institutions. VATS allowed us to detect diaphragmatic fenestrations in seven patients (87.5%) and apical bullae in five (62.5%). Apicectomy was performed in five cases (62.5%), selective diaphragmatic plication in two (25%), and partial diaphragmatic resection in five (62.5%). Chemical pleurodesis with talc was performed in all to minimize the risk of recurrence. Pathological diagnosis of endometriosis on the resected diaphragm was achieved in five patients (62.5%). No recurrence occurred, except for one woman who stopped medical treatment for endometriosis.
Conclusions: In the management of patients with CP, VATS should be recommended not only to obtain an explorative diagnosis of ectopic endometrial implants or diaphragmatic fenestrations but also to allow the most appropriate surgical treatment and obtain pathological specimens for confirmation and definitive diagnosis of thoracic endometriosis. Medical therapy to achieve ovarian rest is mandatory in the postoperative period and should not be discontinued.

KEYWORDS
catamenial pneumothorax, thoracic endometriosis, VATS, diagnosis, surgical treatment

1. Introduction

Endometriosis is a common, benign condition characterized by the localization of endometrial-like glands and stroma outside the uterine cavity. The thoracic cavity is the most common site of endometriosis outside of the abdominal-pelvic cavity, where it can produce a range of clinical and radiological manifestations including catamenial

pneumothorax (CP), catamenial hemothorax, catamenial hemoptysis, and pulmonary nodules, also known as thoracic endometriosis syndrome (TES) (1–3).

CP is the most common manifestation (73%) of TES and is a rare type of spontaneous, recurring pneumothorax occurring in women of reproductive age (4), from 24 hours before menstruations until 72 hours after their beginning (5), but the literature indicates also other time criteria, up to 7 days before and after monthly bleeding (6). CP could be characterized by the presence or not of thoracic endometriosis (7, 8) (**Table 1**).

Differently from primary spontaneous pneumothorax (9), the mean age of women with CP is 34–37 years (6, 7, 10, 11). The experienced symptoms are comparable to those of spontaneous pneumothorax and consist of pleuritic chest pain, cough, and shortness of breath (9). Diaphragmatic irritation may produce referred pain to the periscapular region or radiation to the neck (most often right-sided). In most cases (95%), there is involvement of the right hemithorax, in 5% of cases of the left hemithorax, and in 3% bilateral involvement (11).

Chest x-ray is the first imaging exam for the diagnosis of pneumothorax. CP may be associated with thoracic endometriosis or diaphragmatic fenestrations (6, 12), and computed tomography (CT) or magnetic resonance imaging (MRI) could show small diaphragmatic defects, called "air-filled bubble" perforations (13). In particular cases, when patients suffer from abdominopelvic symptoms, abdominal MRI may be helpful in the diagnosis of endometriosis and subsequently of TES.

The gold standard diagnostic tool and treatment for CP is video-assisted thoracic surgery (VATS) (11, 14–17), which allows multiple treatment modalities depending upon the characteristics of identified lesions. In cases of superficial endometriotic implants, lesions could be fulgurated using bipolar diathermy, CO^2 laser, Nd–YAG laser, argon laser, or plasma energy, while deeper endometriotic implants should be excised using sharp dissection (15, 16, 18–20), lung wedge resection with a stapling device, segmentectomy, or in rare cases lobectomy (14, 16, 21, 22). Pleurodesis, which can be accomplished chemically with talc or mechanically with pleural abrasion and partial pleurectomy, decreases the recurrence rate of CP after VATS by 20%–25% (16, 23–26). Proper CP diagnosis, especially if done with histological confirmation of the endometrial foci in the pleura, pulmonary parenchyma, or diaphragm, may be crucial to the patient even after surgical treatment of pneumothorax, because hormonal therapy may contribute to the avoidance of CP recurrence (27, 28).

We report our experience in VATS management of CP to focus on the role of VATS not only in obtaining the definitive diagnosis of endometriosis but also in selecting the most appropriate surgical treatment.

TABLE 1 Classification of recurrent spontaneous pneumothoraces in women of reproductive age referred for surgical treatment, in the absence of a known underlying disease [modified from Visouli et al. (8)].

Definition	Criteria	Percentage	Total percentage
Catamenial/endometriosis-related	Recurrent, in temporal relationship with menses with evidence of thoracic endometriosis	15.4	23.7
Catamenial/non-endometriosis-related	Recurrent, in temporal relationship with menses without evidence of thoracic endometriosis	8.3	
Non-catamenial/endometriosis-related	Occurring in the intermenstrual period with evidence of thoracic endometriosis	7.7	76.3
Non-catamenial/non-endometriosis-related	Occurring in the intermenstrual period without evidence of thoracic endometriosis	68.6	

2. Materials and methods

In this retrospective observational study, we collected data from women of reproductive age referred to our center for recurrent spontaneous pneumothorax, from January 2019 to April 2022, selecting those having temporal relation with menses, compatible with CP.

Data were collected about age at first pneumothorax and at recurrence, onset symptoms, side of CP, history of smoke, time relationship with menses, medical history of endometriosis, imaging used for diagnosis, number of episodes of pneumothorax before surgical treatment, type and time of surgical treatment, results of VATS approach, complications after surgery, and hormonal therapy after surgery.

All patients underwent VATS approach, with muscle-sparing thoracotomy when diaphragmatic fenestrations were detected, to perform selective diaphragmatic plication and/or partial diaphragmatic resection.

Results were analyzed in terms of pneumothorax recurrence after surgical treatment.

All patients were referred to gynecologists for medical therapy. A telephone questionnaire was also submitted, regarding the gynecological therapeutic follow-up.

Continuous variables are reported as medians with range and categorical variables as counts and percentages.

3. Results

Twenty-two women of reproductive age were referred to our center for recurrent spontaneous pneumothorax. Eight (36.4%) of them had temporal relation with menses, compatible with CP.

The group of eight women had a median age of 37 years (range: 21–45) at the onset of symptoms, that is at the time of first pneumothorax episode, and the same at the time of recurrence, when they were operated on. No difference in the age of CP presentation was found between patients with and those without pelvic endometriosis. In one case, there was SARS-CoV-2 infection concurrent with the first episode of pneumothorax, but the recurrence occurred a month later.

Onset symptom was chest pain in all cases, associated with dyspnea in three. In all cases, the pneumothorax was on the

right side. Two patients were smokers, while the remaining six consisted equally of three non-smokers and three ex-smokers.

In one patient, the pneumothorax occurred 1 day before the start of the menses, while in the other cases 48 hours after the start of the menses.

Three patients already had a diagnosis of pelvic endometriosis and all of them had already undergone abdominopelvic surgery. Estrogen–progestin therapy had been taken by these three patients (37.5% of the sample) for diagnosis of pelvic endometriosis, but this therapy was not for ovarian rest.

Half of the cases were women with a history of pregnancies with a median number of 2 (range: 1–2) deliveries.

In all patients, standard two-view chest x-ray was performed as first imaging exam for diagnosis (Figure 1). In three cases, preoperative chest CT was done, too: in one case, with recent SARS-CoV-2 infection, to exclude pneumonia or thromboembolic complications and in two cases because the patients had previously undergone surgery for recurrent pneumothorax at other institutions, without evidence of thoracic endometriosis. In the case with recent SARS-CoV-2 infection, CT was extremely helpful, revealing small diaphragmatic defects ("air-filled bubble" perforations) (Figure 2).

The median number of episodes of pneumothorax before surgical treatment was 3 (range: 2–4).

All patients underwent VATS surgical treatment. The median time to surgery, calculated as the difference between the date of admission and the date of surgery, was 2 days (range: 0–6 days).

VATS approach allowed to diagnose seven cases (87.5%) of CP thoracic endometriosis-related, with diaphragmatic fenestrations (Figure 3), associated with lung apical blebs and/or bullae in four of them and one case (12.5%) of CP non-thoracic endometriosis-related, with dystrophic apex only (Figure 4).

Because of the detection of diaphragmatic fenestrations, through a muscle-sparing thoracotomy, selective diaphragmatic plication was performed in two cases (25%) and partial diaphragmatic resection in five (62.5%) cases, with apposition of a prosthetic mesh in one of them (Figure 5). Lung apicectomy was performed in five cases (62.5%) for the evidence of dystrophic apex with blebs and/or bullae. In order to minimize the risk of recurrence, in all cases not only mechanical pleurodesis with electrocautery and/or brossage was performed, but also chemical pleurodesis, nebulizing sterile medical talc powder (Figures 6, 7).

No postoperative complications occurred. Pathological diagnosis of endometriosis on the resected diaphragm was achieved in five patients (62.5%).

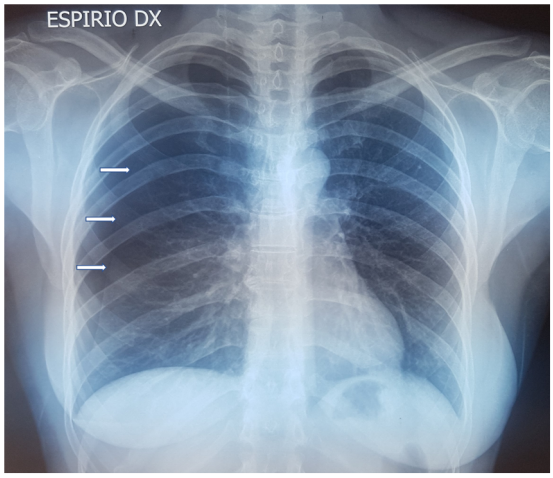

FIGURE 1
Chest x-ray showing CP on the right side: white arrows indicate the collapsed lung. CP, catamenial pneumothorax.

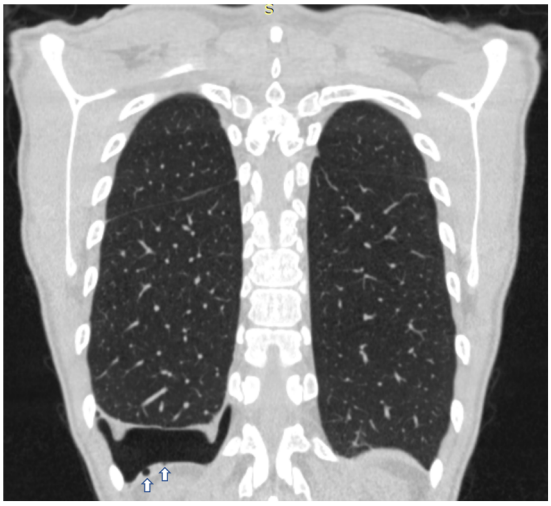

FIGURE 2
Coronal chest CT scan of a patient with CP showing on the right side small diaphragmatic defects, called "air-filled bubble" perforations (indicated by white arrows). CT, computed tomography; CP, catamenial pneumothorax.

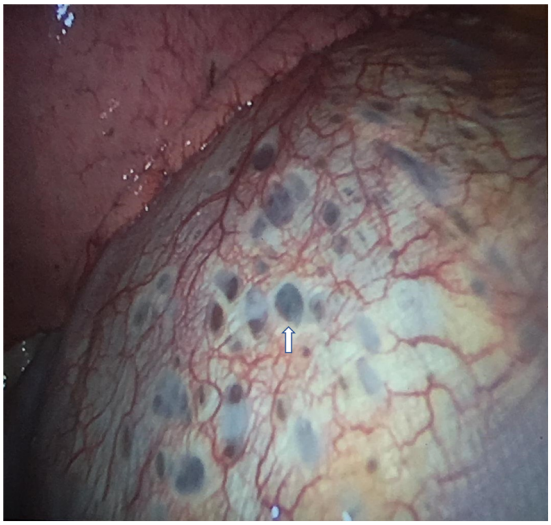

FIGURE 3
VATS intraoperative finding of typical diaphragmatic fenestrations (one indicated by white arrow), located at the central tendon of the diaphragm, in a patient with CP thoracic endometriosis-related. VATS, video-assisted thoracic surgery; CP, catamenial pneumothorax.

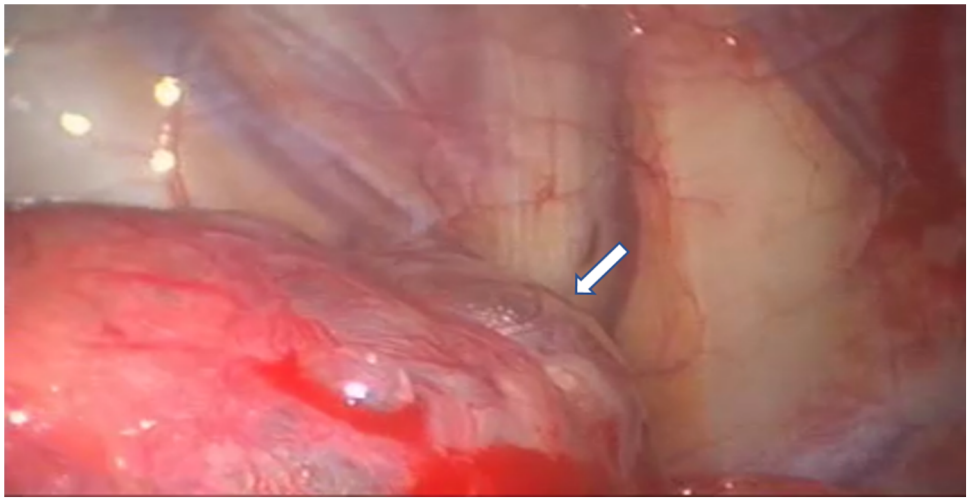

FIGURE 4
VATS intraoperative finding of dystrophic lung apex, characterized by the presence of apical blebs (indicated by white arrows), in a patient with CP non-thoracic endometriosis-related. VATS, video-assisted thoracic surgery; CP, catamenial pneumothorax.

All patients started hormonal therapy with estrogen–progestins after surgical treatment of pneumothorax, to be continued for at least 12–18 months.

The median follow-up period was 26 months (range: 7–55 months).

No recurrence of pneumothorax occurred after surgical treatment, except for one woman, approximately 32 months (970 days) later, who stopped medical treatment for endometriosis; this recurrence was simply and successfully treated with bed rest.

In two cases, medical therapy for endometriosis was discontinued, on average 3.5 years after thoracic surgery, due to unresponsiveness of pelvic endometriosis to treatment; thus, both women underwent hysteroannessiectomy. Another patient, after gynecological consultation, discontinued therapy 6 months after initiation, without presenting recurrence at 16 months.

4. Discussion

In our experience, at the onset of symptoms, the median age of patients with the first episode of CP was 37 years, similar to the literature (reported mean: 36.5 ± 6.8 years), and the median age at recurrence was the same (28).

No correlation was found with cigarette smoking or with/without previous deliveries.

All CP presented as unilateral and right-sided, in agreement with the literature (28).

Two-view chest x-ray was always performed in our patients, less often chest CT, and rarely abdominal MRI to look for pelvic endometriosis. There are no specific imaging diagnostic criteria, but chest CT sometimes can be helpful revealing small diaphragmatic defects called "air-filled bubbles" (13).

Diagnosis of CP is made mainly on the medical history (synchronicity with menses), while the diagnosis of thoracic endometriosis-related pneumothorax is based on intraoperative visual inspection and appropriate histological examination of the characteristic lesions.

The most frequent pathological findings reported in the literature were endometrial implants, present in 59.3% of patients, followed by diaphragmatic fenestrations in 57% and blebs/bullae in 25% (28). In our experience instead, seven patients (87.5%) had multiple diaphragmatic defects, usually located at the central tendon of the diaphragm, often adjacent to coexisting nodules and in four cases (50%) associated with dystrophic apex; in a patient, we found apical bullae only. Characteristic findings such as endometrial implants or diaphragmatic fenestrations may be absent in cases of CP, and blebs/bullae may be the only pathological findings, as in our last patient, while in some cases, there is no identifiable thoracic pathological abnormality (8).

Disease awareness (the size and the number of the characteristic lesions) with correct VATS timing in relationship

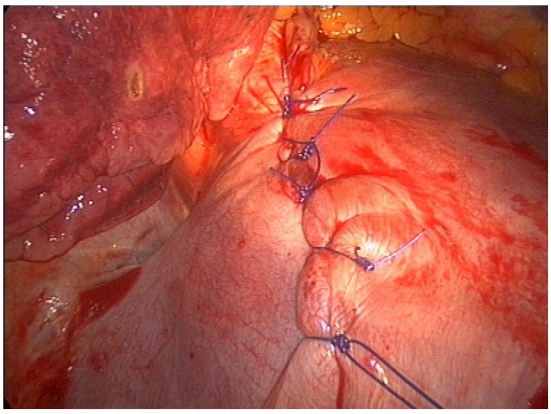

FIGURE 5
Selective diaphragmatic plication for VATS intraoperative finding of diaphragmatic fenestrations. VATS, video-assisted thoracic surgery.

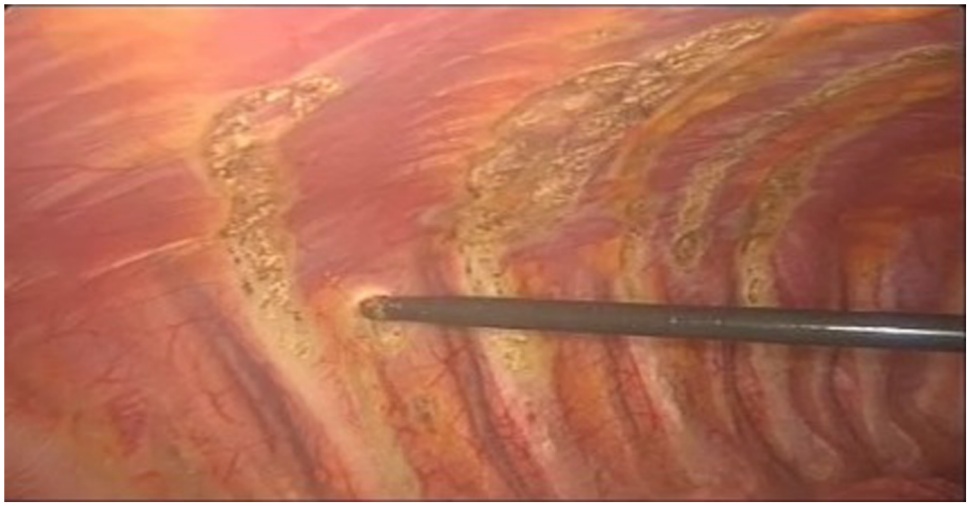

FIGURE 6
VATS mechanical pleurodesis with electrocautery on the parietal pleura to minimize the risk of CP recurrence. VATS, video-assisted thoracic surgery; CP, catamenial pneumothorax.

with the menstrual cycle and meticulous inspection of the thorax, including the diaphragm, are important factors that need to be considered.

VATS approach is considered the treatment of choice, as it allows a better visualization of the endometriotic lesions, resection of all visible lesions and pleurodesis, and provides samples for pathological examination (11, 14–17). Moreover, VATS achieves better treatment results, mainly in term of less recurrences, in comparison to medical treatment alone (11, 14–17).

When extensive diaphragmatic repair is required, a video-assisted mini-thoracotomy or a muscle-sparing thoracotomy may offer better access to the diaphragm (8).

In our patients, the median time to surgery, calculated as the difference between the date of admission and the date of surgery, was 2 days. Such a short period from admission to intervention turns out to be essential to recognize endometriotic lesions which, by their own characteristics, are evident in the menstrual period. Thus, in our experience, in all patients, surgery was performed almost concurrently with the menses.

Histologic examination on samples collected during surgery was performed in 5/7 (71.4%) of our patients with CP thoracic endometriosis-related, with diaphragmatic lesions, and in all cases we obtained pathological diagnosis of thoracic endometriosis; in the remaining 2/7 patients (28.6%), only diaphragmatic plication was performed, without removal of tissues for histologic examination. Histologic examination was performed also in cases in whom diaphragmatic lesions were associated with intraoperative finding of blebs and/or bullae, and

FIGURE 7
VATS chemical pleurodesis, nebulizing sterile medical talc powder on the pleura, to minimize the risk of CP recurrence. VATS, video-assisted thoracic surgery; CP, catamenial pneumothorax.

in the case with dystrophic apex only, but no endometriotic tissue nearby or within the bleb(s) and/or bulla(e) was found. Because of this last finding, we were able to diagnose a case of CP non-thoracic endometriosis-related.

In agreement with the literature, as we did in most of our patients (62.5%), in order to avoid recurrences, diaphragmatic resection with removal of endometrial implants is preferable to diaphragmatic plication; moreover, diaphragmatic coverage with a polyglactin or polypropylene mesh, a polytetrafluoroethylene (PTFE) mesh, or a bovine pericardial patch have been reported with good mid-term results (8). In our experience, the criteria used for performing a plication or a partial resection of the diaphragm were dependent on the extent of the involvement of the diaphragm: in case of diaphragmatic fenestrations involving an isolated area $\leq 5\ cm^2$ of the diaphragm, we preferred to perform a partial resection, while in case of diaphragmatic fenestrations involving an area $>5\ cm^2$ or multiple diaphragmatic fenestration at different sites (potentially requiring multiple resection of the diaphragm), we decided to perform a plication.

All patients underwent ovarian rest therapy after surgical treatment of pneumothorax. Medical treatment of endometriosis utilizes gonadotropin-releasing hormone (GnRH) analogs, which block the ovarian hormones leading to amenorrhea (8); low doses of such drugs should be combined with female hormones (i.e., low-dose progestins) to reduce climacteric-like symptoms and improve tolerability and adherence to therapy (29). Most authors suggest administering this therapy in the immediate postoperative period, for 6–12 months, in all patients with proven catamenial and/or endometriosis-related pneumothorax (8). Low-dose oral contraceptives (estrogen–progestin) can also be used to treat endometriosis, but the literature data are conflicting (29). However, these treatments do not eradicate the disease. Moreover, one-third of the women with endometriosis do not respond to estrogen–progestins, which may be in part due to progesterone resistance (29, 30).

A period of exposure to hormonal therapy of at least 18 months along with surgical treatment was found to be essential to avoid posttreatment recurrence (8).

In a review by Bricelj et al., recurrence was observed in 26.9% of patients after treatment (28). In our patients, the median follow-up period was 26 months and no recurrence occurred, regardless the type of surgery, except for one patient (12.5%), approximately 32 months from surgery. This woman had discontinued medical therapy for endometriosis and presented with a recurrence of marginal pneumothorax, which did not require treatment with pleural drainage but was simply and successfully treated with bed rest.

Two out of eight patients underwent gynecologic surgery (hysteroannessiectomy) for recurrence of pelvic endometriosis due to unresponsiveness to medical treatment. In another case, the patient had estrogen–progestin therapy for 6 months only, according to the gynecological specialist indication, presenting a relapse-free period, in the absence of medical therapy for 16 months.

The combination of hormonal treatment with surgical approach turns out to be crucial for the diagnostic framing of the patient, the proper gynecologic specialist treatment of the patient, and lowering the risk of disease recurrence.

To the best of our knowledge, our study is the first to evaluate the specific role of VATS in CP not only to obtain visual diagnosis of endometriotic lesions but also to select the most appropriate surgical treatment and particularly to provide pathological specimens for definitive diagnosis of thoracic endometriosis.

One limitation of our study is the low number of cases, mainly related to the rarity of CP. However, due to the lack of guidelines in diagnosis and treatment of TES and CP, multicenter studies are recommended in order to define guidelines shared by thoracic surgeons and gynecologists, for a correct and optimal diagnostic and therapeutic management of these patients.

5. Conclusions

In the management of patients with CP, VATS should be recommended not only to obtain an explorative diagnosis of ectopic endometrial implants or diaphragmatic fenestrations but also to allow the most appropriate surgical treatment and obtain pathological specimens for confirmation and definitive diagnosis of endometriosis. Gynecological consultation is recommended and medical therapy to achieve ovarian rest is mandatory in the postoperative period and should not be discontinued, in order to reduce the risk of recurrence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RQ and ADP: introduction, materials and methods, evaluation of results, discussion, writing, literature, critical review, and final approval of the manuscript. FDB and GC: introduction, materials and methods, evaluation of results, discussion, writing, literature, and final approval of the manuscript. GDI, TP, GG, VS, and MC: discussion and final approval of the manuscript. GM: introduction, materials and methods, evaluation of results, discussion, critical

review, and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. *Am J Med*. (1996) 100:164–70. doi: 10.1016/S0002-9343(97)89454-5

2. Nezhat C, King LP, Paka C, Odegaard J, Beygui R. Bilateral thoracic endometriosis affecting the lung and diaphragm. *JSLS*. (2012) 16:140–2. doi: 10.4293/108680812X13291597716384

3. Nezhat C, Main J, Paka C, Nezhat A, Beygui RE. Multidisciplinary treatment for thoracic and abdominopelvic endometriosis. *JSLS*. (2014) 18(3):e2014.00312. doi: 10.4293/JSLS.2014.00312

4. Fonseca P. Catamenial pneumothorax: a multifactorial etiology. *J Thorac Cardiovasc Surg*. (1998) 116:872–3. doi: 10.1016/S0022-5223(98)00434-6

5. Rousset-Jablonski C, Alifano M, Plu-Bureau G, Camilleri-Broet S, Rousset P, Regnard JF, et al. Catamenial pneumothorax and endometriosis-related pneumothorax: clinical features and risk factors. *Hum Reprod*. (2011) 26:2322–9. doi: 10.1093/humrep/der189

6. Marjański T, Sowa K, Czapla A, Rzyman W. Catamenial pneumothorax—a review of the literature. *Kardiochir Torakochirurgia Pol*. (2016) 13(2):117–21. doi: 10.5114/kitp.2016.61044

7. Alifano M, Jablonski C, Kadiri H, Falcoz P, Gompel A, Camilleri-Broet S, et al. Catamenial and noncatamenial, endometriosis-related or nonendometriosis-related pneumothorax referred for surgery. *Am J Respir Crit Care Med*. (2007) 176(10):1048–53. doi: 10.1164/rccm.200704-587OC

8. Visouli AN, Zarogoulidis K, Kougioumtzi I, Huang H, Li Q, Dryllis G, et al. Catamenial pneumothorax: from diagnosis to treatment. *J Thorac Dis*. (2014) 6(S4):S448–60. doi: 10.3978/j.issn.2072-1439.2014.08.49

9. Ghisalberti M, Guerrera F, De Vico A, Bertolaccini L, De Palma A, Fiorelli A, et al. Age and clinical presentation for primary spontaneous pneumothorax. *Heart Lung Circ*. (2020) 29(11):1648–55. doi: 10.1016/j.hlc.2020.05.107

10. Bagan P, Le Pimpec Barthes F, Assouad J, Souilamas R, Riquet M. Catamenial pneumothorax: retrospective study of surgical treatment. *Ann Thorac Surg*. (2003) 75(2):378–81. doi: 10.1016/S0003-4975(02)04320-5

11. Korom S, Canyurt H, Missbach A, Schneiter D, Kurrer MO, Haller U, et al. Catamenial pneumothorax revisited: clinical approach and systematic review of the literature. *J Thorac Cardiovasc Surg*. (2004) 128(4):502–8. doi: 10.1016/j.jtcvs.2004.04.039

12. Visouli AN, Darwiche K, Mpakas A, Zarogoulidis P, Papagiannis A, Tsakiridis K, et al. Catamenial pneumothorax: a rare entity? Report of 5 cases and review of the literature. *J Thorac Dis*. (2012) 4:17–31. doi: 10.3978/j.issn.2072-1439.2012.s006

13. Rousset P, Rousset-Jablonski C, Alifano M, Mansuet-Lupo A, Buy JN, Revel MP. Thoracic endometriosis syndrome: CT and MRI features. *Clin Radiol*. (2014) 69(3):323–30. doi: 10.1016/j.crad.2013.10.014

14. Alifano M, Roth T, Camilleri-Broet S, Schussler O, Magdeleinat P, Regnard JF. Catamenial pneumothorax: a prospective study. *Chest*. (2003) 124(3):1004–8. doi: 10.1378/chest.124.3.1004

15. Alifano M, Trisolini R, Cancellieri A, Regnard JF. Thoracic endometriosis: current knowledge. *Ann Thorac Surg*. (2006) 81(2):761–9. doi: 10.1016/j.athoracsur.2005.07.044

16. Nezhat C, Nicoll LM, Bhagan L, Huang JQ, Bosev D, Hajhosseini B, et al. Endometriosis of the diaphragm: four cases treated with a combination of laparoscopy and thoracoscopy. *J Minim Invasive Gynecol*. (2009) 16(5):573–80. doi: 10.1016/j.jmig.2009.06.012

17. Marshall MB, Ahmed Z, Kucharczuk JC, Kaiser LR, Shrager JB. Catamenial pneumothorax: optimal hormonal and surgical management. *Eur J Cardiothorac Surg*. (2005) 27(4):662–6. doi: 10.1016/j.ejcts.2004.12.047

18. Shirk GJ, Brumsted JR, Gimpelson RJ. Operative laparoscopy with the Nd:YAG laser in the treatment of endometriosis and pelvic adhesions. *Lasers Surg Med*. (1991) 11(3):297–300. doi: 10.1002/lsm.1900110314

19. Corson SL, Woodland M, Frishman G, Batzer FR, Gocial B, Maislin G. Treatment of endometriosis with a Nd:YAG tissue-contact laser probe via laparoscopy. *Int J Fertil*. (1989) 34(4):284–8.

20. Nezhat C, Kho KA, Morozov V. Use of neutral argon plasma in the laparoscopic treatment of endometriosis. *JSLS*. (2009) 13(4):479–83. doi: 10.4293/108680809X12589998403967

21. Terada Y, Chen F, Shoji T, Itoh H, Wada H, Hitomi S. A case of endobronchial endometriosis treated by subsegmentectomy. *Chest*. (1999) 115:1475–8. doi: 10.1378/chest.115.5.1475

22. Kristianen K, Fjeld NB. Pulmonary endometriosis causing haemoptysis: report of a case treated with lobectomy. *Scand J Thorac Cardiovasc Surg*. (1993) 27(2):113–5. doi: 10.3109/14017439309098701

23. Lang-Lazdunski L, de Kerangal X, Pons F, Jancovici R. Primary spontaneous pneumothorax: one-stage treatment by bilateral videothoracoscopy. *Ann Thorac Surg*. (2000) 70(2):412–7. doi: 10.1016/S0003-4975(00)01552-6

24. Hatz RA, Kaps MF, Meimarakis G, Loehe F, Muller C, Furst H. Long-term results after video-assisted thoracoscopic surgery for first-time and recurrent spontaneous pneumothorax. *Ann Thorac Surg*. (2000) 70(1):253–7. doi: 10.1016/S0003-4975(00)01411-9

25. Light RW, O'Hara VS, Moritz TE, McElhinney AJ, Butz R, Haakenson CM, et al. Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax. Results of a department of veterans affairs cooperative study. *JAMA*. (1990) 264(17):2224–30. doi: 10.1001/jama.1990.03450170072025

26. Chen JS, Tsai KT, Hsu HH, Yuan A, Chen WJ, Lee YC. Intrapleural minocycline following simple aspiration for initial treatment of primary spontaneous pneumothorax. *Respir Med*. (2008) 102(7):1004–10. doi: 10.1016/j.rmed.2008.02.006

27. Celik S, Erşen E. Catamenial pneumothorax. In: K Amer, editor. *Pneumothorax*. London: Intechopen (2009). p. 1–14.

28. Bricelj K, Srpcic M, Razem A, Snoj Z. Catamenial pneumothorax since introduction of videoassisted thoracoscopic surgery: a systematic review. *Wien Klin Wochenschr*. (2017) 129(19–20):717–26. doi: 10.1007/s00508-017-1237-4

29. Barbara G, Buggio L, Facchin F, Vercellini P. Medical treatment for endometriosis: tolerability, quality of life and adherence. *Front Glob Womens Health*. (2021) 2:729601. doi: 10.3389/fgwh.2021.729601

30. Donnez J, Dolmans MM. Endometriosis and medical therapy: from progestogens to progesterone resistance to GnRH antagonists: a review. *J Clin Med*. (2021) 10:1085. doi: 10.3390/jcm10051085]

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 25 April 2023
DOI 10.3389/fsurg.2023.1123329

OPEN ACCESS

EDITED BY
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Duilio Divisi,
University of L'Aquila, Italy
Edoardo Bottoni,
University of Milan, Italy

*CORRESPONDENCE
Oliver J. Harrison
✉ ojharrison@doctors.org.uk

SPECIALTY SECTION
This article was submitted to Thoracic Surgery, a section of the journal Frontiers in Surgery

RECEIVED 13 December 2022
ACCEPTED 30 March 2023
PUBLISHED 25 April 2023

CITATION
Harrison OJ, Maraschi A, Routledge T, Lampridis S, LeReun C and Bille A (2023) A cost analysis of robotic vs. video-assisted thoracic surgery: The impact of the learning curve and the COVID-19 pandemic.
Front. Surg. 10:1123329.
doi: 10.3389/fsurg.2023.1123329

A cost analysis of robotic vs. video-assisted thoracic surgery: The impact of the learning curve and the COVID-19 pandemic

Oliver J. Harrison[1,2]*, Alessandro Maraschi[1], Tom Routledge[1], Savvas Lampridis[1], Corinne LeReun[3] and Andrea Bille[1]

[1]Thoracic Surgery Department, Guys Hospital, London, United Kingdom, [2]Department of Thoracic Surgery, University Hospital Southampton, Southampton, United Kingdom, [3]Conseil en Analyse Statistique et Modélisation économique, Sainte-Anne, Guadeloupe

Introduction: Robot-assisted thoracoscopic surgery (RATS) is an alternative to video-assessed thoracoscopic surgery (VATS) for the treatment of lung cancer but concern exists regarding the high associated costs. The COVID-19 pandemic added further financial pressure to healthcare systems. This study investigated the impact of the learning curve on the cost-effectiveness of RATS lung resection and the financial impact of the COVID-19 pandemic on a RATS program.

Methods: Patients undergoing RATS lung resection between January 2017 and December 2020 were prospectively followed. A matched cohort of VATS cases were analyzed in parallel. The first 100 and most recent 100 RATS cases performed at our institution were compared to assess the learning curve. Cases performed before and after March 2020 were compared to assess the impact of the COVID-19 pandemic. A comprehensive cost analysis of multiple theatre and postoperative data points was performed using Stata statistics package (v14.2).

Results: 365 RATS cases were included. Median cost per procedure was £7,167 and theatre cost accounted for 70%. Major contributing factors to overall cost were operative time and postoperative length of stay. Cost per case was £640 less after passing the learning curve ($p < 0.001$) largely due to reduced operative time. Comparison of a post-learning curve RATS subgroup matched to 101 VATS cases revealed no significant difference in theatre costs between the two techniques. Overall cost of RATS lung resections performed before and during the COVID-19 pandemic were not significantly different. However, theatre costs were significantly cheaper (£620/case; $p < 0.001$) and postoperative costs were significantly more expensive (£1,221/case; $p = 0.018$) during the pandemic.

Discussion: Passing the learning curve is associated with a significant reduction in the theatre costs associated with RATS lung resection and is comparable with the cost of VATS. This study may underestimate the true cost benefit of passing the learning curve due to the effect of the COVID-19 pandemic on theatre costs. The COVID-19 pandemic made RATS lung resection more expensive due to prolonged hospital stay and increased readmission rate. The present study offers some evidence that the initial increased costs associated with RATS lung resection may be gradually offset as a program progresses.

KEYWORDS

lung cancer, robot—assisted thoracic surgery, video assisted thoracic surgery, cost analyses, COVID—19, learning curve

1. Introduction

Surgery remains the gold standard treatment for early stage lung cancer a with 5-year survival rate of 90%. In the 1990s, video-assisted thoracoscopic surgery (VATS) was introduced and became the standard surgical approach offered for the treatment of early stage lung cancer (1). More than 20 years after its introduction, the VIOLET trial and other randomized studies have demonstrated that VATS is associated with shorter length of hospital stay and fewer complications compared to open surgery (2, 3).

Concurrently, over the last two decades robot-assisted thoracoscopic surgery (RATS) has evolved into thoracic surgical practice. Several retrospective studies have demonstrated the potential benefits of RATS over VATS and open surgery including improved the lymph node clearance, fewer conversions and reduced length of hospital stay (4–6). However, there are concerns regarding the increased costs associated with RATS, particularly vs. VATS, which have been further exacerbated by studies demonstrating similar outcomes between RATS and VATS (7–9). Due to a lack of randomized trials, there is still an open debate regarding the best and most cost-effective minimally invasive approach in the treatment of lung neoplasms.

In current times more than ever there is intense scrutiny on postoperative outcomes and the cost-effectiveness of new technologies and devices. A cost analysis is hugely important to better understand if the potential benefits of RATS surgery can be cost-effective for patients and national health systems. Upfront costs of purchasing a robotic system are steep and the additional operative time taken to get over the learning curve absorbs further resources. Indeed, evidence from urological surgery suggests that learning robotic surgery is costly, but these costs can be attenuated by high volume exposure to flatten the learning curve (10). There is certainly a desire among the robotic surgical community to explore this concept further (11).

Our center is currently the highest volume thoracic unit for lung cancer resection in the UK National Health Service with over 70% of cases performed minimally invasively (12). RATS was introduced in 2017 and our center is now one of the highest volume robotic thoracic units in Europe. Our impression is that after completing the learning curve, RATS may have similar or even improved cost-effectiveness compared to VATS. Similarly, in March 2020 the COVID-19 pandemic began to have a huge impact on the provision of lung cancer care in the UK.

The primary aim of this study was to determine the impact of the learning curve on the cost-effectiveness of RATS vs. VATS lung resection. The secondary aim was to assess impact of the COVID-19 pandemic on postoperative costs in patients who had minimally invasive lung cancer surgery and assess if RATS could help to contain some of the increased cost burden inflicted by the COVID-19 pandemic.

2. Materials and methods

2.1. Patient selection

This study was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study the need for written consent was waivered by the institutional review board. Patients who underwent RATS lobar or sublobar lung resection for neoplasm between January 2017 and December 2020 were identified and included in the analysis. Patients who had undergone prior VATS or thoracotomy, a pneumonectomy or chest wall resection were excluded. VATS lobar and sublobar resections performed between April 2015 to December 2020 were used as comparison group. Patient demographics, clinical data and outcomes were accessed from the Thoracic Surgery department prospective database (IRB approval number: 13197, January 2021). Complications were classified according to the Clavien-Dindo scale (13). Operative time was measured from skin incision to the completion of wound closure. Requirement for blood transfusion and rate of conversion to open were also captured. All RATS procedures were performed by two high volume robotic surgeons using the same technique. VATS procedures were performed by one of the two surgeons with a high-volume experience in VATS lobectomy. Cost calculations were performed using our institutional cost codes.

To evaluate the impact of learning curve on cost, patients were grouped into the first 100 RATS cases performed and most recent 100 RATS cases performed by the two surgeons combined. To evaluate the impact of COVID-19 on cost, patients undergoing operations before March 2020 vs. those performed during and after March 2020 were analyzed separately. A comparative cost analysis of VATS and RATS was also performed using two subgroups matched on performance status and subtype of procedure, which were all performed by a single surgeon.

2.2. Surgical technique

All RATS cases were performed using the Da Vinci Model Xi (Intuitive Surgical, USA) using a 4-arm approach: 2×8 mm ports, 2×12 mm ports and 1×15 mm assistant port. Insufflation of CO_2 was used at a pressure of 6 mmHg in all cases. Fenestrated bipolar forceps, permanent cautery spatula and Cadiere forceps were the standard instruments used together with the SureForm^{TM} 45 EndoWrist stapler. VATS lung resections were performed using a 3-port approach according to the Mckenna Technique (14). Manual ENdoGIA staplers (Covidien/Medtronic, UK) were used in all cases. Intercostal nerve block was performed for each case and a single 28 Fr chest drain was positioned at the end and suction (-2 KPa) was applied for the first 24 h.

2.3. Cost analysis

The primary financial outcome was to analyse the direct cost related to RATS surgery and to compare this with VATS costs. Total direct costs were defined as the cost of specific items used in the patient care intraoperatively. All unit costs of consumables were provided by Intuitive and Guy's and St Thomas NHS Foundation trust. The cost of all reusable instruments, devices and staplers were included in the analysis.

Operating theatre time (cost per minute) was based on NHS Improvement data (15). The cost of blood transfusion and readmission were based on the NICE Costing Statement (16). The cost of hospital stay on the ward and in the intensive care unit (ICU) were based on the National Schedule of NHS costs 2018–2019 (17). The cost of complications was based on previously published figures (18, 19).

The postoperative management was identical for RATS and VATS patients and therefore not accounted for in the cost-analysis. Costs related to 30-day readmission were also included. Capital costs of the robotic systems VATS sets and vision stack were not included in this analysis. A full list of costing and sources can be found in **Supplementary Table S1**.

2.4. Statistical analysis

Categorical variables were presented as frequencies and percentage and were analyzed using Chi-squared tests. Continuous variables were reported as means ± standard deviations and median. Mean and median costs were calculated by multiplying the average resources used by each patient by the corresponding unit costs. Costs were compared between groups using Mann-Whitney *U* tests. When comparing the cost of RATS and VATS procedures, the first 100 cases (learning curve cases) were excluded. Data analysis was performed with Stata (v14.2; StataCorp LLC, USA).

3. Results

365 consecutive RATS lung resections were included in the analysis: 132 (36.2%) patients were male with a median age of 71. 355 (97.8%) patients underwent an anatomical lung resection. Patient characteristics are summarized in **Table 1**. The median operating time was 127 min. An R0 resection was achieved in 362 cases (99%). In 15 cases the robotic procedure was converted to open due to oncological reasons ($n = 9$) or bleeding ($n = 6$). Only 6 patients required a blood transfusion. The median time to chest drain removal was 2 days and median length of hospital stay was 5 days. 36.8% of patients experienced postoperative complications. Nineteen patients (5.2%) required an unplanned ICU admission. A detailed report of complications is given in **Supplementary Table S2**.

TABLE 1 Patient characteristics of the RATS cohort.

	RATS ($N = 365$)
Age (years)*	69.7 +/− 9.8 (71)
Gender (*n*)	
Male	132 (36.2%)
Female	233 (63.8%)
Performance Status (ECOG; *n*)	
0	121 (33.2%)
1	176 (48.2%)
2	68 (18.6%)
Procedure (*n*)	
Lobectomy	278 (76.2%)
Bilobectomy	7 (1.9%)
Segmentectomy	70 (19.2%)
Wedge resection	10 (2.7%)
Histology (*n*)	
Adenocarcinoma	226 (61.9%)
Squamous cell carcinoma	49 (13.4%)
Other NSCLC	4 (1.1%)
Metastasis	46 (12.6%)
Carcinoid	33 (9.0%)
Other	6 (1.6%)
Adenocarcinoma, SCLC	1 (0.3%)
Duration of chest drain (days)*	3.7 +/− 5.0 (2)
Length of stay (days)*	6.7 +/− 8.4 (5)
Planned ICU admission	
Number of patients	16 (4.4%)
Days in ICU*	1.8 +/− 1.5 (1)
Unplanned ICU admission	
Number of patients	19 (5.2%)
Days in ICU*	9.6 +/− 10.0 (6)
Complications (Clavien-Dindo grade; *n*)	
0	233 (63.8%)
I	55 (15.1%)
II	50 (13.7%)
III	17 (4.7%)
IV	6 (1.6%)
V	4 (1.1%)

*mean ± standard deviation (median). ECOG: Eastern Cooperative Oncology Group; ICU: Intensive care unit; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer.

3.1. Cost of RATS and the learning curve

The median cost per RATS procedure was £7,167, with theatre costs comprising just over two-thirds of the total cost (NB. an outlier value heavily skewed the postoperative costs; **Table 2**). The median theatre cost per robotic procedure was £4,606 and the median postoperative cost was £2,035. The two major factors influencing total cost were the OR time and length of hospital stay.

The impact of the learning curve on procedure cost was evaluated. A significantly higher cost during the learning curve could be attributed to theatre time, requirement for blood transfusion and conversion rate (**Table 3**). The theatre cost per procedure after completion of the learning curve was significantly lower at £4,406 vs. £5,046 pre-learning curve ($p < 0.001$). There was a trend towards increased postoperative costs largely due to significantly increased cost of complications. This could be attributed to a possible selection bias (e.g. increased performance status and cancer stage) secondary to the effect of the COVID-19 pandemic on patient presentation as discussed in more detail below.

3.2. Cost of RATS vs. VATS

The cost-effectiveness of RATS and VATS surgery in lung cancer patients was evaluated. Robotic procedures during learning curve were excluded and 101 RATS vs. 101 VATS lung resections were matched and compared. Patient characteristics were similar in both groups (**Table 4**). Mean operative time was

TABLE 2 Costs associated with RATS lung resection.

	ALL RATS (*N* = 365)
Theatre costs	
OR time (in minutes)	2,637 +/− 775 (2540)
Blood transfusion (units of blood)	8 +/− 67 (0)
Staplers	1,264 +/− 0 (1264)
Instrument	467 +/− 0 (467)
Patient drape	10 +/− 0 (10)
Robot drape	250 +/− 0 (250)
Assistant port	48 +/− 0 (48)
Drain	8 +/− 0 (8)
Conversion	97 +/− 455 (0)
TOTAL Theatre cost	*4,789 +/− 1,011 (4606)*
Length of stay	
General ward	2,480 +/− 2,684 (1628)
ICU	633 +/− 3,415 (0)
Complications	1,606 +/− 2,539 (0)
Re-admission	164 +/− 607 (0)
TOTAL Postoperative costs	*4,884 +/− 7,169 (2035)*
Overall	
TOTAL COST PER PATIENT	9,673 +/− 7,329 (7167)

Mean ± standard deviation (median) per patient. All costs in £GBP. ICU, Intensive care unit; OR, Operating room.

TABLE 4 Patient characteristics of RATS and VATS lung resections.

	RATS (*N* = 101)	VATS (*N* = 101)	*p*-value
Age*	69.5 +/− 9.1	69.9 +/− 9.0	0.757
Gender (*n*)			
Male	39 (38.6%)	39 (38.6%)	1.000
Female	62 (61.4%)	62 (61.4%)	
Performance Status (ECOG; *n*)			
0	22 (21.8%)	22 (21.8%)	1.000
1	55 (54.5%)	55 (54.5%)	
2	24 (23.8%)	24 (23.8%)	
Smoking status (*n*)			
Non-smoker	20 (19.8%)	13 (12.9%)	0.155
Ex-smoker	59 (58.4%)	72 (71.3%)	
Smoker	22 (21.8%)	16 (15.8%)	
Comorbidity (*n*)			
Pulmonary comorbidity	29 (28.7%)	31 (30.7%)	0.758
Cardiac comorbidity	50 (49.5%)	55 (54.5%)	0.481
Renal comorbidity	6 (5.9%)	6 (5.9%)	1.000
Endocrine comorbidity	18 (17.8%)	17 (16.8%)	0.853
FEV1 (%)*	93.1 +/− 22.2	90.7 +/− 23.6	0.459
TLCO (%)*	75.6 +/− 21.3	74.9 +/− 19.3	0.807
Procedure (*n*)			
Lobectomy	72 (71.3%)	72 (71.3%)	1.000
Bilobectomy	2 (2.0%)	2 (2.0%)	
Segmentectomy	27 (26.7%)	27 (26.7%)	

*Mean ± standard deviation. ECOG: Eastern Cooperative Oncology Group; FEV1: Forced expiratory volume in 1 s; TLCO: Transfer capacity (Lung) for Carbon Monoxide.

similar in the VATS and RATS groups (115.7 and 115.8 min respectively; $p = 0.98$), as was blood transfusion requirement (0.03 and 0.01 units/case respectively; $p = 0.52$) and number of stapler loads used (8.3 and 8.2 respectively; $p = 0.88$; Table 5). The conversion rate was 4% in the RATS groups and 2% in the VATS group but this was not significantly different. The median length of stay was significantly longer in the RATS group at 5 days vs. 4 days in the VATS group ($p = 0.025$). Complication rate was similar between the two groups (38.6% for RATS and 34.7% for VATS; $p = 0.433$) but the readmission rate was higher in the RATS group (12.9% and 4.0% respectively; $p = 0.04$). All RATS cases for this sub-analysis were performed during the COVID-19 pandemic and 85% of the VATS cases were performed before it.

The overall average cost of a RATS procedure was significantly higher than the cost of a VATS procedure (approximately £1,000/

TABLE 3 Analysis of cost related to the learning curve. Mean ± standard deviation (median) per patient. All costs in £GBP. OR: Operating room.

	100 EARLIEST RATS (*N* = 101)	100 LATEST RATS (*N* = 101)	*p*-value
Theatre costs			
OR time (in minutes)	3,052 +/− 737 (3000)	2,338 +/− 579 (2360)	<0.001
Blood transfusion (units of blood)	25 +/− 118 (0)	0 +/− 0 (0)	0.024
Staplers	1,264 +/− 0 (1264)	1,264 +/− 0 (1264)	–
Instrument	467 +/− 0 (467)	467 +/− 0 (467)	–
Patient drape	10 +/− 0 (10)	10 +/− 0 (10)	–
Robot drape	250 +/− 0 (250)	250 +/− 0 (250)	–
Assistant port	48 +/− 0 (48)	48 +/− 0 (48)	–
Drain	8 +/− 0 (8)	8 +/− 0 (8)	–
Conversion	200 +/− 639 (0)	0 +/− 0 (0)	0.002
TOTAL Theatre cost	*5,323 +/− 1,113 (5046)*	*4,384 +/− 579 (4406)*	*<0.001*
Length of stay			
General ward	2,173 +/− 1,525 (1628)	2,381 +/− 1,679 (2035)	0.350
ICU	396 +/− 1,322 (0)	583 +/− 3,618 (0)	0.389
Complications	1,192 +/− 2,185 (0)	2,108 +/− 2,966 (0)	0.012
Re-admission	216 +/− 690 (0)	168 +/− 615 (0)	0.603
TOTAL Postoperative costs	*3,978 +/− 4,288 (2035)*	*5,240 +/− 6,078 (3621)*	*0.053*
Overall			
TOTAL COST PER PATIENT	9,301 +/− 4,688 (7441)	9,624 +/− 6,132 (7481)	0.790

Mean ± standard deviation (median) per patient. All costs in £GBP. ICU, Intensive care unit; OR, Operating room.

TABLE 5 Comparison of theatre and postoperative data from RATS and VATS lung resections.

	RATS ($N = 101$)	VATS ($N = 101$)	*p*-value
Theatre costs			
OR time (minutes)*	115.7 +/− 38.1 (110)	115.8 +/− 25.1 (120)	0.983
Blood transfusion (units per case)*	0.03 +/− 0.3 (0)	0.01 +/− 0.1 (0)	0.528
Staple loads (*n*)*	8.3 +/− 2.4 (8)	8.2 +/− 2.4 (8)	0.883
Conversion rate	4.0%	2.0%	0.683
Other costs			
Length of stay (days)	9.5 +/− 13.9 (5)	6.2 +/− 5.0 (4)	0.025
Number of days in general ward	*8.3 +/− 10.8 (5)*	*5.9 +/− 4.9 (4)*	*0.048*
Number of days in ICU	*1.2 +/− 5.3 (0)*	*0.2 +/− 0.9 (0)*	*0.062*
Complication rate (Clavien-Dindo grade)			
None	61.4%	65.3%	0.433
I	16.8%	14.9%	
II	10.9%	11.9%	
III	5.9%	7.9%	
IV	2.0%	0%	
V	3.0%	0%	
Re-admission rate	12.9%	4.0%	0.040

*Mean ± standard deviation (median) per patient. ICU, Intensive care unit; OR, Operating room.

case; $p = 0.045$; Table 6). The relatively high standard deviation associated with postoperative (and hence total) cost in the RATS group, suggests that the average costs are influenced by a few outlier values and so the median values were used for the comparison. Theatre and postoperative costs individually were not significantly different for RATS and VATS lung resections. Of note, stapler cost per case was significantly lower in the RATS group (£1264 vs. £1782; $p < 0.001$).

3.3. Effect of the COVID-19 pandemic on the cost of RATS

A cost comparison of RATS procedures performed before and during the COVID-19 pandemic was performed on two subgroups of patients (Table 7). The overall cost of procedures performed during the pandemic was similar to those performed before the pandemic (Table 8). Total theatre and postoperative

TABLE 6 Cost comparison of RATS and VATS lung resections.

	RATS ($N = 101$)	VATS ($N = 101$)	*p*-value
Theatre costs			
OR time (in minutes)	2,314 +/− 763 (2200)	2,316 +/− 502 (2400)	0.479
Blood transfusion (units of blood)	5 +/− 49 (50)	2 +/− 17 (0)	0.994
Staplers	1263.6 +/− 0 (1263.6)	1,782 +/− 479 (1738)	<0.001
Instrument	467 +/− 0 (467)	–	–
Patient drape	9.6 +/− 0 (9.6)	9.6 +/− 0 (9.6)	–
Robot drape	250 +/− 0 (250)	–	–
Alexis	–	25 +/− 0 (25)	–
Assistant port	48 +/− 0 (48)	–	–
Port	–	16 +/− 0 (16)	–
Drain	8 +/− 0 (8)	8 +/− 0 (8)	–
Conversion	88 +/− 435	44 +/− 311	0.408
TOTAL Theatre cost	*4,456 +/− 1,075 (4246)*	*4,202 +/− 885 (4037)*	*0.053*
Length of stay (days)			
General ward	3,365 +/− 4,377 (2035)	2,410 +/− 2,004 (1628)	0.221
ICU	1,361 +/− 5,783 (0)	261 +/− 948	0.974
Complications	1,918 +/− 3,073 (0)	1,358 +/− 1,902 (0)	0.504
Re-admissions	309 +/− 807 (0)	95 +/− 470 (0)	0.023
TOTAL Postoperative costs	*6,953 +/− 11,461 (3256)*	*4,124 +/− 3,776 (2035)*	*0.155*
Overall			
TOTAL COST PER PATIENT	11,406 +/− 11,619 (7467)	8,325 +/−4,153 (6425)	0.045

Mean ± standard deviation (median) per patient. All costs in £GBP. ICU, Intensive care unit; OR, Operating room.

TABLE 7 Demographics of patients undergoing RATS lung resection before and during the COVID-19 pandemic.

	BEFORE COVID (*N* = 171)	DURING COVID (*N* = 194)
Age*	69.7 +/− 10.6 (71)	69.7 +/− 9.1 (71.5)
Gender (*n*)		
Male	59 (34.5%)	73 (37.6%)
Female	112 (65.5%)	121 (62.4%)
Performance Status (ECOG; *n*)		
0	59 (34.5%)	62 (32.0%)
1	80 (46.8%)	96 (49.5%)
2	32 (18.7%)	36 (18.6%)
Procedure (*n*)		
Lobectomy	146 (85.4%)	132 (68.0%)
Bi lobectomy	5 (2.9%)	2 (1.0%)
Segmentectomy	20 (11.7%)	50 (25.8%)
Wedge resection	–	10 (5.2%)
Histology (*n*)		
Adenocarcinoma	110 (64.3%)	116 (59.8%)
Squamous cell carcinoma	26 (15.2%)	23 (11.9%)
Other NSCLC	2 (1.2%)	2 (1.0%)
Metastasis	13 (7.6%)	33 (17.0)
Carcinoid	17 (9.9%)	16 (8.2%)
Other	2 (1.2%)	4 (2.1%)
Adenocarcinoma, SCLC	1 (0.6%)	0 (0%)
Duration of chest drain (days)*	3.6 +/− 5.3 (2)	3.7 +/− 4.7 (2)
Length of stay (days)*	5.6 +/− 4.6 (4)	7.6 +/− 10.6 (5)
Planned ICU admission		
Number of patients	10 (5.8%)	6 (3.1%)
Days in ICU*	1.6 +/− 0.7 (1.5)	2.0 +/− 2.4 (1)
Unplanned ICU admission		
Number of patients	6 (3.5%)	13 (6.7%)
Days in ICU*	8.8 +/− 5.4 (7.5)	9.9 +/− 11.7 (4)
Complications (Clavien-Dindo grade)		
0	119 (69.6%)	114 (58.8%)
I	18 (10.5%)	37 (19.1%)
II	24 (14.0%)	26 (13.4)
III	8 (4.7%)	9 (4.6%)
IV	2 (1.2%)	4 (2.1%)
V	0 (0%)	4 (2.1%)

*mean ± standard deviation (median). ECOG: Eastern Cooperative Oncology Group; ICU: Intensive care unit; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer.

TABLE 8 Effect of the COVID-19 pandemic on cost.

	BEFORE COVID (*N* = 171)	DURING COVID (*N* = 194)	*p*-value
Theatre costs			
OR time (in minutes)	2,932 +/− 730 (2940)	2,377 +/− 720 (2360)	<0.001
Blood transfusion (units of blood)	13 +/− 87 (0)	4 +/− 43 (0)	0.325
Staplers	1,264 +/− 0 (1264)	1,264 +/− 0 (1264)	–
Instrument	467 +/− 0 (467)	467 +/− 0 (467)	–
Patient drape	10 +/− 0 (10)	10 +/− 0 (10)	–
Robot drape	250 +/− 0 (250)	250 +/− 0 (250)	–
Assistant port	48 +/− 0 (48)	48 +/− 0 (48)	–
Drain	8 +/− 0 (8)	8 +/− 0 (8)	–
Conversion	130 +/− 523 (0)	69 +/− 385 (0)	0.196
TOTAL Theatre cost	*5,122 +/− 969 (5026)*	*4,496 +/− 957 (4406)*	*<0.001*
Length of stay			
General ward	2,104 +/− 1,509 (1628)	2,811 +/− 3,368 (2035)	0.045
ICU	444 +/− 2,092 (0)	799 +/− 4,253 (0)	0.878
Complications	1,259 +/− 2,080 (0)	1,913 +/− 2,855 (0)	0.055
Re-admissions	154 +/− 591 (0)	173 +/− 623 (0)	0.768
TOTAL Postoperative costs	*3,961 +/− 4,529 (1628)*	*5,697 +/− 8,800 (2849)*	*0.018*
Overall			
TOTAL COST PER PATIENT	9,082 +/− 4,784 (7234)	10,193 +/− 8,976 (7099)	0.947

Mean ± standard deviation (median) per patient. All costs in £GBP. ICU, Intensive care unit; OR, Operating room.

costs demonstrate a paradoxical significant decrease and increase respectively in the during vs. before pandemic groups. Theatre and postoperative costs before the pandemic were £620 more expensive ($p < 0.001$) and £1,221 cheaper ($p = 0.018$) respectively than during the pandemic. A detailed summary of the complications that occurred in the before and during COVID-19 pandemic groups can be found in **Supplementary Table S3**.

4. Discussion

In the last two decades the number of lung resections performed through thoracotomy has decreased rapidly (20). Minimally invasive surgery represents the gold standard in the treatment of early stage lung cancer and limited lung metastases. VATS has become the favored approach for anatomical lung resection in respect of better postoperative outcome compared to open surgery with similar long term outcome (2). However, in the last two decades RATS has been introduced with possible advantages including better lymph node dissection, less blood loss, higher complete resection rate, lower conversion rate, less postoperative complications and better quality of life. However, prohibitively high start-up costs and concern regarding ongoing maintenance and disposable costs remain (5).

The median cost of robotic procedures in our institution was £7,167 which is significantly lower than the costs published in a recent systematic review (21, 22). This is likely partly due to our institutions higher case volume (over 700 lung cancer resections per annum) and also the impact of higher costs associated with early robotic experience which these studies describe (12). As with the introduction of most new technologies, during the learning curve the procedure cost is generally higher which is largely attributable to longer operative time. The impact of operative time on the cost of robotic surgery had been documented previously (23). To the best of our knowledge, the present study demonstrates the effect of learning curve on cost of RATS lung resection for the first time. After completing the learning curve, the operative time was shorter and both transfusion requirement and conversion rate were lower with a median saving of £640 per case.

In our series, after completion of the learning curve, VATS and RATS lung resection demonstrated no significant difference

in theatre cost as previously reported by Kneuertz et al. (9). Interestingly however, overall cost of RATS vs. VATS was significantly higher largely due to postoperative cost differences. It was necessary to exclude the procedures performed during the learning curve for this analysis, therefore all RATS procedures included in this comparison were performed during the COVID-19 pandemic. However, due to data availability, 85% of the matched VATS procedures took place before the pandemic. Thus, comparisons of the postoperative costs may have been biased by the pandemic which precipitated complex social issues together with reduced support for patients in the community. This in turn increased the length of stay and readmission rate.

The postoperative cost of performing a RATS lung resection was significantly higher (over £1,200/case) during the COVID-19 pandemic vs. before. However, overall costs were comparable due to the significantly reduced theatre costs which occurred in parallel. One might expect the pandemic to increase theatre costs (e.g., with prolonged time needed for aerosol clearance following intubation/extubation). However, the converse was demonstrated in our study. As mentioned previously, the most recent RATS cases were those performed during the COVID-19 pandemic and thus would have been performed after the learning curve had been passed. Therefore, the reduced theatre costs during the pandemic are most likely a reflection of the learning curve process, particularly given the reduction in theatre cost is primarily due to shorter OR time which comes with experience. For this reason, the true extent of the benefit of reduced costs after passing the learning curve in RATS lung resection may be masked in this study. The actual cost savings may be far greater than we report. Furthermore, we demonstrated a significantly reduced stapler cost per case with RATS vs. VATS (approx. £500/case saving). This is most likely due to more frequent fissure dissection with RATS than VATS surgery which saves stapler loads.

The pandemic might be expected to increase postoperative costs and this study confirmed a significant increase of around £1,200/case compared to the pre-pandemic period ($p = 0.018$). This difference is mostly due to a significant increase in the costs associated with length of stay, readmissions and a trend towards an increased cost of complications. In our institution, complications significantly increased in 2020 and 2021 compared to previous years. In-hospital complications were observed in 40.9% of RATS procedures in 2020/2021 compared to the year before (29.7%), a statistically significant increase ($p = 0.028$). Surgical complications increase the total cost of care and this is supported by the findings of this study (24). The reasons for this, highlighted previously include more complex social issues and reduced provision of community support post-discharge.

The strength of this study is that data from a large cohort of patients was prospectively collected and analyzed. The population were homogeneously managed in a single, high volume institution with a detailed and accurate cost analysis. However, the study has several limitations. It is an observational study with a disproportionately high number of robotic procedures performed during the COVID-19 pandemic, which likely introduced bias. Similarly, the cases performed after the learning curve were performed during the pandemic and likely confounded one another. Furthermore, the high capital costs of RATS surgery were not considered. This was largely because the robotic system is also used by other specialties, which makes it challenging to divide these costs accurately between the different specialties.

In conclusion, prior to passing the learning curve, RATS lung resection is associated with increased average procedure cost. When the learning curve is passed, theatre costs become significantly lower and are comparable with VATS. This study likely underestimates the true cost benefit of passing the learning curve due to the effect of the COVID-19 pandemic. The COVID-19 pandemic made RATS lung resection more expensive due to prolonged hospital stay and increased readmission rate. The true postoperative costs of RATS surgery may be similar or even lower than VATS, however further studies are required to elucidate this. The present study offers some evidence that the initial increased costs associated with RATS lung resection may be gradually offset as a program matures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

OH—Writing and reviewing manuscript. AM—Writing and reviewing manuscript. TR—Study design, data collection and reviewing manuscript. SL—Writing and reviewing manuscript. CL—Statistical analysis. AB—Study design, data collection and reviewing manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to acknowledge the high level of care and support provided by the Thoracic Surgery nursing, allied health professionals and administrative staff to the patients on a daily basis and especially through the challenges of the COVID-19 pandemic.

Conflict of interest

AB and TR are proctors for Intuitive Surgical. Intuitive Surgical provided a monetary grant to fund the independent statistical analysis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1123329/full#supplementary-material.

References

1. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol*. (2009) 27(15):2553–62. doi: 10.1200/JCO.2008.18.2733

2. Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, et al. Video-Assisted thoracoscopic or open lobectomy in early-stage lung cancer. *NEJM Evidence*. (2022) 1(3):EVIDoa2100016. doi: 10.1056/EVIDoa2100016

3. Long H, Tan Q, Luo Q, Wang Z, Jiang G, Situ D, et al. Thoracoscopic surgery versus thoracotomy for lung cancer: short-term outcomes of a randomized trial. *Ann Thorac Surg*. (2018) 105(2):386–92. doi: 10.1016/j.athoracsur.2017.08.045

4. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-Assisted, video-assisted thoracoscopic and open lobectomy: propensity-matched analysis of recent premier data. *Ann Thorac Surg*. (2017) 104(5):1733–40. doi: 10.1016/j.athoracsur.2017.06.020

5. Nelson DB, Mehran RJ, Mitchell KG, Rajaram R, Correa AM, Bassett RL Jr., et al. Robotic-Assisted lobectomy for non-small cell lung cancer: a comprehensive institutional experience. *Ann Thorac Surg*. (2019) 108(2):370–6. doi: 10.1016/j.athoracsur.2019.03.051

6. Park BJ, Flores RM. Cost comparison of robotic, video-assisted thoracic surgery and thoracotomy approaches to pulmonary lobectomy. *Thorac Surg Clin*. (2008) 18 (3):297–300., vii. doi: 10.1016/j.thorsurg.2008.05.003

7. Emmert A, Straube C, Buentzel J, Roever C. Robotic versus thoracoscopic lung resection: a systematic review and meta-analysis. *Medicine (Baltimore)*. (2017) 96 (35):e7633. doi: 10.1097/MD.0000000000007633

8. Swanson SJ, Miller DL, McKenna RJ Jr., Howington J, Marshall MB, Yoo AC, et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database (premier). *J Thorac Cardiovasc Surg*. (2014) 147(3):929–37. doi: 10.1016/j.jtcvs.2013.09.046

9. Kneuertz PJ, Singer E, D'Souza DM, Abdel-Rasoul M, Moffatt-Bruce SD, Merritt RE. Hospital cost and clinical effectiveness of robotic-assisted versus video-assisted thoracoscopic and open lobectomy: a propensity score-weighted comparison. *J Thorac Cardiovasc Surg*. (2019) 157(5):2018–26.e2. doi: 10.1016/j.jtcvs.2018.12.101

10. Steinberg PL, Merguerian PA, Bihrle W 3rd, Seigne JD. The cost of learning robotic-assisted prostatectomy. *Urology*. (2008) 72(5):1068–72. doi: 10.1016/j.urology.2007.11.118

11. Ielpo B, Podda M, Burdio F, Sanchez-Velazquez P, Guerrero MA, Nunez J, et al. Cost-Effectiveness of robotic vs. Laparoscopic surgery for different surgical procedures: protocol for a prospective, multicentric study (ROBOCOSTES). *Front Surg*. (2022) 9:866041. doi: 10.3389/fsurg.2022.866041

12. Royal College of Physicians L. National Lung Cancer Audit. Lung cancer clinical outcomes publication 2019 (for 2017 audit period). 2019. https://nlca.rcp.ac.uk/LCCOP (Accessed December 8, 2022).

13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae

14. McKenna RJ Jr., Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. *Ann Thorac Surg*. (2006) 81(2):421–5; discussion 5–6. doi: 10.1016/j.athoracsur.2005.07.078

15. NHS Improvement. Operating theatres: opportunities to reduce waiting lists. 2019. https://allcatsrgrey.org.uk/wp/download/surgery/Theatre_productivity_report__Final.pdf (Accessed December 8, 2022).

16. NICE NIfCE. NICE Guideline NG24: Blood Transfusion. 2015. www.nice.org.uk/guidance/NG24 (Accessed December 8, 2022).

17. NICE NIfCE. Intermediate care, Appendix C3: Economic report. 2020. https://www.nice.org.uk/guidance/ng74/documents/guideline-appendix-2 (Accessed December 8, 2022).

18. Brunelli A, Drosos P, Dinesh P, Ismail H, Bassi V. The severity of complications is associated with postoperative costs after lung resection. *Ann Thorac Surg*. (2017) 103 (5):1641–6. doi: 10.1016/j.athoracsur.2016.10.061

19. Rouanet P, Mermoud A, Jarlier M, Bouazza N, Laine A, Mathieu Daudé H. Combined robotic approach and enhanced recovery after surgery pathway for optimization of costs in patients undergoing proctectomy. *BJS Open*. (2020) 4 (3):516–23. doi: 10.1002/bjs5.50281

20. Nguyen DM, Sarkaria IS, Song C, Reddy RM, Villamizar N, Herrera LJ, et al. Clinical and economic comparative effectiveness of robotic-assisted, video-assisted thoracoscopic, and open lobectomy. *J Thorac Dis*. (2020) 12(3):296–306. doi: 10.21037/jtd.2020.01.40

21. Nasir BS, Bryant AS, Minnich DJ, Wei B, Cerfolio RJ. Performing robotic lobectomy and segmentectomy: cost, profitability, and outcomes. *Ann Thorac Surg*. (2014) 98(1):203–8.; discussion 8–9. doi: 10.1016/j.athoracsur.2014.02.051

22. Singer E, Kneuertz PJ, D'Souza DM, Moffatt-Bruce SD, Merritt RE. Understanding the financial cost of robotic lobectomy: calculating the value of innovation? *Ann Cardiothorac Surg*. (2019) 8(2):194–201. doi: 10.21037/acs.2018.05.18

23. Deen SA, Wilson JL, Wilshire CL, Vallières E, Farivar AS, Aye RW, et al. Defining the cost of care for lobectomy and segmentectomy: a comparison of open, video-assisted thoracoscopic, and robotic approaches. *Ann Thorac Surg*. (2014) 97 (3):1000–7. doi: 10.1016/j.athoracsur.2013.11.021

24. Geller AD, Zheng H, Mathisen DJ, Wright CD, Lanuti M. Relative incremental costs of complications of lobectomy for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. (2018) 155(4):1804–11. doi: 10.1016/j.jtcvs.2017.11.025

frontiers | Frontiers in Surgery

TYPE Original Research
PUBLISHED 15 June 2023
DOI 10.3389/fsurg.2023.1115696

OPEN ACCESS

EDITED BY
Sara Ricciardi,
San Camillo Forlanini Hospital, Italy

REVIEWED BY
Maria Teresa Congedo,
UOC di Chirurgia Toracica Fondazione Policlinico Gemelli IRCCS, Italy
Angela De Palma,
University of Bari Medical School, Italy

*CORRESPONDENCE
Valentina Marziali
✉ vale.marziali95@gmail.com

RECEIVED 04 December 2022
ACCEPTED 01 June 2023
PUBLISHED 15 June 2023

CITATION
Marziali V, Frasca L, Ambrogi V, Patirelis A, Longo F and Crucitti P (2023) Prognostic significance of uncertain resection for metastasis in the highest mediastinal lymph node after surgery for clinical N0 non-small cell lung cancer.
Front. Surg. 10:1115696.
doi: 10.3389/fsurg.2023.1115696

Prognostic significance of uncertain resection for metastasis in the highest mediastinal lymph node after surgery for clinical N0 non-small cell lung cancer

Valentina Marziali[1]*, Luca Frasca[2,3], Vincenzo Ambrogi[1], Alexandro Patirelis[1], Filippo Longo[2] and Pierfilippo Crucitti[2]

[1]Department of Thoracic Surgery, University Tor Vergata, Rome, Italy, [2]Department of Thoracic Surgery, University Campus Bio-Medico, Rome, Italy, [3]Microbiology, Immunology, Infectious Diseases, and Transplants (MIMIT), University Tor Vergata, Rome, Italy

Background: The International Association for the Study of Lung Cancer defined types of surgical resection and considered the positivity of the highest mediastinal lymph node resected a parameter of "uncertain resection" (R-u). We investigated the metastases in the highest mediastinal lymph node, defined as the lowest numerically numbered station among those resected. We aimed to evaluate the prognostic value of R-u compared with R0.
Materials and methods: We selected 550 patients with non-small cell lung cancer at clinical Stage I, IIA, IIB (T3N0M0), or IIIA (T4N0M0) undergoing lobectomy and systematic lymphadenectomy between 2015 and 2020. The R-u group included patients with positive highest mediastinal resected lymph node.
Results: In the groups of patients with mediastinal lymph node metastasis, we defined 31 as R-u (45.6%, 31/68). The incidence of metastases in the highest lymph node was related to the pN2 subgroups ($p < 0.001$) and the type of lymphadenectomy performed ($p < 0.001$). The survival analysis compared R0 and R-u: 3-year disease-free survival was 69.0% and 20.0%, respectively, and 3-year overall survival was 78.0% and 40.0%, respectively. The recurrence rate was 29.7% in R0 and 71.0% in R-u (p-value < 0.001), and the mortality rate was 18.9% and 51.6%, respectively (p-value < 0.001). R-u variable showed a tendency to be a significant prognostic factor for disease-free survival and overall survival (hazard ratio: 4.6 and 4.5, respectively, p-value < 0.001).
Conclusions: The presence of metastasis in the highest mediastinal lymph node removed seems to be an independent prognostic factor for mortality and recurrence. The finding of these metastases represents the margin of cancer dissemination at the time of surgery, so it could imply metastasis into the N3 node or distant metastasis.

KEYWORDS

non-small cell lung cancer (NSCLC), R classification, complete resection, uncertain resection, high mediastinal lymph node metastases, pN2 disease

Introduction

According to the European Society for Medical Oncology (ESMO), the treatment for clinical Stage I, IIA, IIB (T3N0M0), or IIIA (T4N0M0) non-small cell lung cancer (NSCLC) is the anatomic surgical resection of the involved lobe together with systematic node dissection (1, 2). The resection status after surgery has been proven to be an

important predictor of prognosis and has an impact on the choice of further treatments. The residual tumor (R) classification includes: R0 (no residual tumor), R1 (microscopic residual tumor), and R2 (macroscopic residual tumor) (3). The International Association for the Study of Lung Cancer redefined the resection status into the categories: complete resection, incomplete resection, and uncertain resection. The last one included all cases without microscopic disease on resection margins but with one of the following criteria: lymphadenectomy less rigorous than systematic or lobe-specific nodal dissection, positive highest mediastinal node removed, carcinoma *in situ* on the bronchial margin, or positive pleural lavage cytology (4). Few previous studies focused attention on the impact of metastases in the highest mediastinal lymph node (HMLN) removed on prognosis. Moreover, the definitions of HMLN varied among these studies, leading to differences in patient selection and survival analysis. IASLC considered the highest mediastinal lymph node among those resected (3, 5).

We retrospectively reviewed patients who underwent lobectomy and systematic lymph node dissection. In patients with mediastinal nodal metastases, we investigated those who were HMLN positive. To avoid bias of the differences in the dissection of the right and left mediastinal nodal stations, because of anatomical difference (6), and according to IASLC, we defined HMLN as the lowest numerically numbered station among resected lymph node stations. These patients were defined as R-uncertain (R-u). We aimed to evaluate the prognostic value of R-u, compared with R0, in a population of patients with mediastinal node metastases.

Material and methods

Patient selection

We retrospectively reviewed 550 patients with NSCLC Stage I, IIA, IIB (T3N0M0), or IIIA (T4N0M0) who underwent lobectomy with systematic lymphadenectomy between January 2015 and December 2020. We excluded synchronous cancer or history of another cancer; neoadjuvant chemotherapy and/or radiotherapy; neuroendocrine lung tumors benign neoformations; cN2 or cM1-M1; R1–2 resection; segmentectomy, wedge, and pneumonectomy; and lymph node sampling. Other causes of "uncertain resection" as carcinoma *in situ* on the bronchial margin or positive pleural lavage cytology were also excluded.

After surgery, the follow-up consisted of a computed tomography (CT) scan at 6 months for the first 2 years and then at 12 months. The median time for follow-up was 26 months (range 12–72 months).

Preoperative staging was achieved by CT scan and synchronized CT with 18-fluorodeoxyglucose-positron emission tomography (18FDG-PET/CT) scanning, dated no more than 30 days. Before surgery, the histologic diagnosis was obtained by CT-guided transthoracic biopsy or intraoperative frozen section. Endobronchial ultrasound (EBUS) biopsy was performed for the suspected lymph node: diameter greater than 10 mm in the short axis at CT scan (7) or standardized uptake value (SUV) max score greater than 2.0 at 18FDG-PET/CT (8). Negative histologic biopsies on suspected lymph nodes were considered cN0. Invasive lymph node staging was executed if the tissue from the endobronchial biopsy was inadequate for the histological diagnosis. The choice between mediastinoscopy and thoracoscopy was guided by lymph node position.

All patients underwent lobectomy with hilar and mediastinal lymphadenectomy through thoracotomy (posterior or anterolateral) or video-assisted thoracoscopic surgery (VATS).

Pleural lavage cytology was performed in all patients to detect those with "uncertain resection" and could focalize the attention on R-u for metastases in the highest mediastinal lymph node. Systematic nodal dissection was carried out in all patients sampling at least three mediastinal lymph node stations (always including station 7) (9). If the lymphadenectomy did not fulfill the criteria of systematic nodal dissection was considered sampling.

Whenever possible, lymph nodes were resected *en bloc* with the surrounding fat. If a lymph node was fragmented, all parts were considered as the same node station for the histological analysis. The number of resected lymph nodes was evaluated in every patient as the sum of lymph nodes located within the resected lobe and the others resected during lymphadenectomy. If lymph nodes were fragmented, each fragment was counted as another lymph node.

The pathological classification was based on the 2015 World Health Organization Classification of Lung Cancer and pathological staging was based on the 8th edition of the lung cancer TNM (Tumor Node Metastases) (10, 11).

R classification

According to the new category of resection proposed by IASLC (4), the cohort of patients was reassigned to the R-u category if they met at least one of the following criteria: lymphadenectomy less rigorous than systematic, metastases on the highest mediastinal lymph node resected, pleural lavage cytology positive, or carcinoma *in situ* in the bronchial margin. We included only systematic lymph node dissection in our population to avoid selection bias.

To focus attention on the role of metastasis in the highest mediastinal lymph node, patients with positive pleural lavage cytology or carcinoma *in situ* on the bronchial margin were excluded from the R-u group. Finally, the R-u category was composed of only patients with positive higher mediastinal nodes.

Statistical analysis

Statistical data analysis was conducted using the SPSS Statistics program version 26.0 (IBM Corp., Armonk, NY, United States). Student's T test was used for continuous variables and Pearson's chi-squared test for discontinuous variables. The threshold of significance was set at p-value = 0.050. The major outcomes for

survival were overall survival (OS) and disease-free survival (DFS)). OS was calculated as the time from surgery to death or last follow-up. DFS was defined from surgery to the evidence of relapse or metastasis. Survival was graphically represented with Kaplan–Meier curves. Independent prognostic factors for OS and DFS were then evaluated with a Cox proportional hazard regression model. Univariate analysis and multivariate analysis, using the backward stepwise method, were carried out with the variables that influenced the various survivals.

Results

We selected 550 patients with clinical N0 lung cancer. The baseline characteristics are presented in Table 1. The mean age was 69.70 years (SD 8.2), 343 patients (62.4%) were male and 454 (82.5%) were current or past smokers. The patient's distribution for pT and pN classifications were as follows: pT1 296 (53.8%), pT2 174 (31.6%), pT3 58 (10.6%), and pT4 22 (4.0%); pN0 426 (77.5%), pN1 56 (10.2%), and pN2 68 (12.3%). The pN2 classification was divided into subgroups: pN2a2 39 (57.4%); pN2a1, or skip metastases, 15 (22.1%); and pN2b 14 (20.6%). The most frequent histology was adenocarcinoma (442 patients, 80.4%). VATS was performed in 385 patients (70.0%). The mean number of resected lymph nodes was 19.50 (SD 13.1), while the mean number of lymph node ratio was 22.60 (SD 17.0). The right upper lobe was the most frequently affected lobe (36.4%) while the right middle lobe was the less affected one (3.6%). Regarding the R classification in the whole population, 31 patients (5.6%) were R-u while the remaining 519 (94.4%) were R0.

The association between R classification and clinical variables in the pN2 group is displayed in Table 2. The lymph node ratio (LNR) was evaluated as the ratio between positive lymph nodes and all resected lymph nodes. The incidence of metastases in the highest mediastinal lymph node was related to the pN2 subgroups ($p < 0.001$). No relation was found for pT classification (p-value = 0.60), histology (p-value = 0.94), number of resected lymph nodes (p-value = 0.31), lymph node ratio (p-value = 0.18), affected lobe (p-value = 0.42), and tumor diameter (p-value = 0.62).

Table 3 shows the topographic distribution of lymph node metastasis for each affected lobe. In the right upper lobe, station 2 was the most frequent highest positive lymph node station (53.8%), while station 4 was the most frequent (100%) for the right middle lobe. In the right lower lobe, the highest positive station was found in station 7 (50.0%). Station 4 was the most common (50.0%) for the left upper lobe. In the left lower lobe, station 5 and station 7 were equally common (50.0%).

The median follow-up time was 33.9 months (SD 14.8). Postoperative survival analysis in patients with N2 disease, comparing R0 and R-u resections, is shown in Table 4. Kaplan–Meier curves are illustrated in Figure 1. The recurrence rate was 29.7% (11/37) in the R0 group, while in the R-u group it was 71.0% (22/31); 3-year DFS was 69.0% (mean time to relapse of 15.5 ± 7) and 20.0% (mean time to relapse of 9.9 ± 6.6), respectively. The mortality rate was 18.9% (7/37) in the R0 group, while in the R-u group it was 51.6% (16/31); 3-years OS was 78.0% (mean time to relapse of 23.1 ± 6.) and 40.0% (mean time to relapse of 12.7 ± 8.2), respectively.

The univariate analysis for DFS and OS, in the N2 population, included the variable listed in Table 5. The R-u variable showed a

TABLE 1 Clinical and pathological characteristics of the cohort population.

Variables	Total
Age	69.7 (SD 8.2)
Sex	
Male	343 (62.4%)
Female	207 (34.3%)
Smoke habit	
Non-smoker	95 (17.3%)
Smoker	454 (82.5%)
pT	
1	296 (53.8%)
2	174 (31.6%)
3	58 (10.6%)
4	22 (4.0%)
pN	
0	426 (77.5%)
1	56 (10.2%)
2	68 (12.3%)
pN2 subgroups	
2 a2	39 (57.4%)
2 a1	15 (22.1%)
2 b	14 (20.6%)
Histology	
Adenocarcinoma	442 (80.4%)
Squamous cell carcinoma	108 (19.6%)
Open	385 (70.0%)
VATS	165 (30.0%)
No. lymph nodes	19.5 (SD 13.1)
Lymph node ratio	22.6 (SD 17.0)
Lobe	
RUL	200 (36.4%)
RML	20 (3.6%)
RLL	106 (19.3%)
LUL	136 (24.7%)
LLL	88 (16.0%)
Tumor diameter at CT	27.9 (SD 17.0)
SUVmax tumor	
< 5	265 (48.2%)
> 5	285 (51.8%)
Lymph node diameter at CT	
<1 cm	494 (89.8%)
>1 cm	56 (10.2%)
SUVmax mediastinal lymph nodes	
<2	506 (92.0%)
>2	44 (8.0%)
R classification	
R-u	31 (5.6%)
R0	519 (94.4%)

CT, computed tomography; LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; VATS, video-assisted thoracic surgery; SD, standard deviation; SUV, standardize.

10.3389/fsurg.2023.1115696

TABLE 2 Association between R classification and clinical variables in the pN2 group.

Variables	Total	R0 (*n*, 37)	R-u (*n*, 31)	*p*-value
Age	69.7 (SD 8.2)	68.1 (SD 7.9)	73.0 (SD 6.7)	0.71
Sex				0.52
Male	41 (60.3%)	21 (56.8%)	20 (64.5%)	
Female	27 (39.7%)	16 (43.2%)	11 (35.5%)	
Smoke habits				0.52
Non-smoker	11 (16.2%)	5 (13.5%)	6 (19.4%)	
Smoker	57 (83.8%)	52 (86.5%)	25 (80.6%)	
pT				0.6
1	26 (38.2%)	13 (35.1%)	13 (41.9%)	
2	34 (50%)	20 (54.1%)	14 (45.2%)	
3	7 (10.3%)	4 (10.8%)	3 (9.7%)	
4	1 (1.5%)	0 (0.0%)	1 (3.2%)	
pN subgroups				**<0.001**
2a2	39 (57.4%)	30 (81.1%)	9 (29.0%)	
2a1	15 (22.0%)	2 (5.4%)	13 (42.0%)	
2b	14 (20.6%)	5 (13.5%)	9 (29.0%)	
Histology				0.94
Adenocarcinoma	59 (86.8%)	32 (86.5%)	27 (87.1%)	
Squamous cell carcinoma	9 (13.2%)	5 (13.5%)	4 (12.9%)	
Open	16 (23.5%)	6 (16.2%)	10 (32.3%)	0.12
VATS	52 (76.5%)	31 (83.8%)	21 (67.7%)	
No. lymph nodes	19.5 (SD 13.1)	21.5 (SD 12.3)	19.1 (SD 10.6)	0.31
Lymph node ratio	22.6 (SD 17.0)	21.5 (SD 12.4)	24.1 (SD 15.3)	0.18
Lobe				0.42
RUL	24 (35.3%)	11 (29.7%)	13 (41.9%)	
RML	4 (5.9%)	2 (5.4%)	2 (6.5%)	
RLL	17 (25.0%)	9 (24.3%)	8 (25.8%)	
LUL	16 (23.5%)	12 (32.4%)	4 (12.9%)	
LLL	7 (10.3%)	3 (8.1%)	4 (12.9%)	
Tumor diameter at CT	27.9 (SD 17.0)	26.4 (SD 9.3)	27.2 (SD 12.6)	0.62
SUVmax tumor				0.12
< 5	5 (7.4%)	1 (2.7%)	4 (12.9%)	
> 5	63 (92.6%)	36 (97.3%)	27 (87.1%)	
Lymph node diameter at CT				0.12
<1 cm	52 (76.5%)	31 (83.8%)	21 (67.7%)	
>1 cm	16 (23.5%)	6 (16.2%)	10 (32.3%)	
SUVmax mediastinal lymph nodes				0.31
<2	48 (70.6%)	28 (75.7%)	20 (64.5%)	
>2	20 (29.4%)	9 (24.3%)	11 (35.5%)	

CT, computed tomography; LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; VATS, video-assisted thoracic surgery; SD, standard deviation; SUV, standardize uptake value.
Bold indicate statistical significative value.

tendency to be a significant prognostic factor. The hazard ratio (HR) for DFS and OS of the R-u group was higher if compared with the R0 group [DFS: HR 4.6 (95% CI 2.2–9.6), *p*-value < 0.001; OS: HR 4.5 (95% CI 1.8–10.9), *p*-value < 0.001]. The multivariable analysis was evaluated using variables with a significant *p*-value at univariate analyses (Table 6). R-us remained a significant prognostic factor for DFS and OS [DFS: HR 3.2 (95% CI 1.4–7.4), *p*-value = 0.008; OS: HR 2.0 (95% CI 0.7–6.1), *p*-value < 0.001].

TABLE 3 Topographic distribution of lymph node metastasis for each affected lobe.

Positive stations	RUL	RML	RLL	LUL	LLL
2	7 (53.8%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
4	6 (46.2%)	2 (100%)	3 (37.5%)	2 (50%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	2 (50.0%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
7	0 (0.0%)	0 (0.0%)	4 (50.0%)	0 (0.0%)	2 (50.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**13**	**2**	**8**	**4**	**4**

LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe.
Bold indicate statistical significative value.

The univariate analysis was also carried out in the R-u group (Table 7). We consider lymph node macro-metastases when the metastatic part is bigger than 2 mm. Variables that showed a tendency to be significant prognostic factors were pT [OS: HR 1.9 (95% CI 1.1–3.6), *p*-value = 0.02], pN2 subgroups [DFS: HR 1.7 (95% CI 0.9–2.9), *p*-value = 0.04; OS: HR 1.9 (95% CI 1.0–3.9), *p*-value = 0.03], number of resected lymph nodes [DFS: HR 0.9 (95% CI 0.9–1.0), *p*-value = 0.03], lymph node ratio [DFS: HR 1.0 (95% CI 1.0–1.0), *p*-value = 0.04], number of the positive lymph node in the higher station [DFS: HR 0.4 (95% CI 0.2–1.1), *p*-value = 0.03], macro-metastases [DFS: HR 30.5 (95% CI 3.9–240.0), *p*-value < 0.001; OS: HR 3.9 (95% CI 1.1–14.0), *p*-value = 0.01], and tumor diameter at CT scan [DFS: HR 1.0 (95% CI 1.0–1.1), *p*-value = 0.02]. In multivariable analysis, evaluated using the variables that had a significant *p*-value at univariate analyses, variables that confirmed to be significant prognostic factors were pT [OS: HR 1.9 (95% CI 0.9–3.7), *p*-value = 0.04] and macro-metastases (DFS: HR 28.8 (95% CI 3.5–239.5), *p*-value = 0.002; OS: HR 3.5 (95% CI 0.9–12.6), *p*-value = 0.05] (Table 8).

Discussion

It is known that the diffusion of metastatic cells through the lymphatic pathway generally follows a specific pattern: intrapulmonary nodes, hilar nodes (N1), mediastinal nodes (N2) in the caudal–cranial direction, final to the supraclavicular (N3) nodes and distant organs (12). As previous studies evaluated, the pN2 groups are heterogeneous with regard to prognosis. The difference could come from the number of involved lymph nodes and stations and the specific patterns of lymphatic spread (13, 14).

At the time of surgery, the highest mediastinal lymph node resected represents the margin of cancer dissemination. Therefore, a metastasis in this station could be considered as a positive margin. The rationale lies in the possibility of cranial lymph node involvement or distant micro-metastases. Thereby, the involvement of cervical nodes or a more extensive mediastinal involvement may be underestimated. The finding of metastasis in the highest mediastinal lymph node dissected might be an important parameter to differentiate this subgroup of patients with a poor prognosis.

TABLE 4 Survival analysis in patients with N2 disease comparing R0 and R-u resections.

Group	*N*	Recurrence	3-year DFS	Mean time to relapse (Months ± SD)	Mortality	3-year-OS	Mean time to death (months ± SD)
R0	37	11 (29.7%)	69.0%	15.5 ± 7.1	7 (18.9%)	78.0%	23.1 ± 6.1
R-u	31	22 (71.0%)	20.0%	9.9 ± 6.6	16 (51.6%)	40.0%	12.7 ± 8.2

DFS, disease-free survival; OS, overall survival; SD, standard deviation.

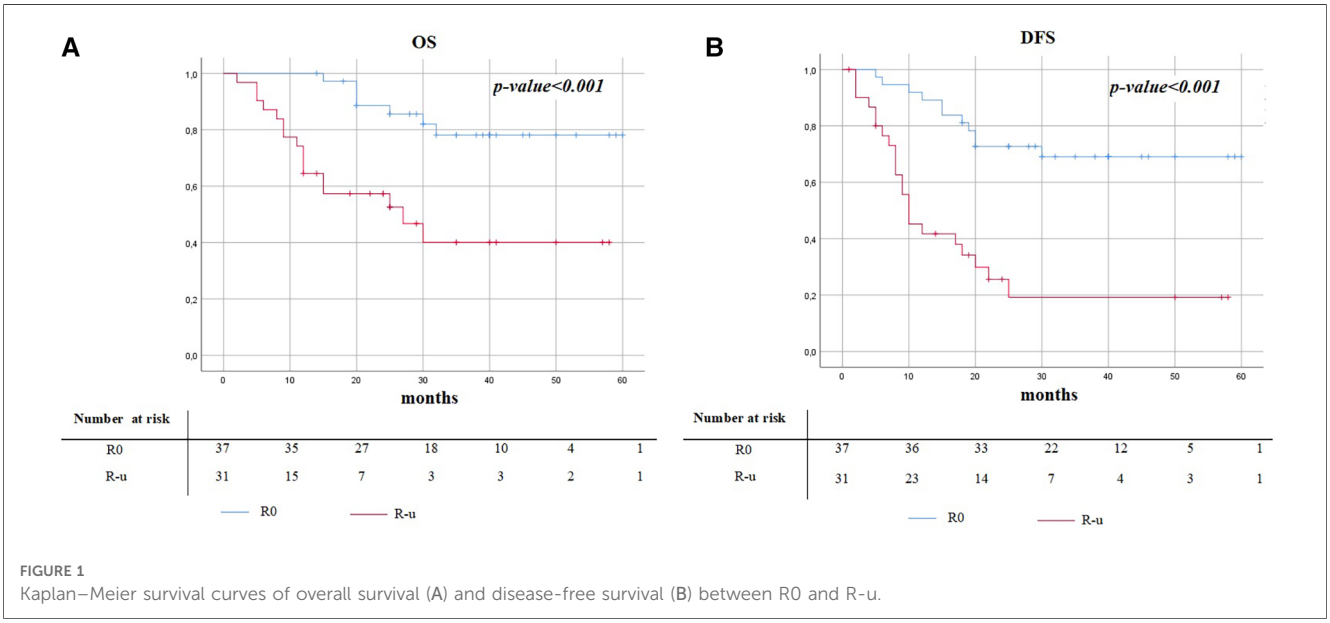

FIGURE 1
Kaplan–Meier survival curves of overall survival (A) and disease-free survival (B) between R0 and R-u.

Previous studies investigated the difference in prognosis between complete and uncertain resection. In the study by Zheng et al., R0 and R-u 5-year survival rate and median survival time were 29% and 36.48 months vs. 13% and 24.43 months, respectively ($p < 0.0001$) (6). Osarogiagbon et al. found similar results: mean OS in R0 was 62 months, while in R-u it was 32 months (p-value < 0.0001) (15). In the literature, few studies paid attention to the prognostic impact of the highest mediastinal lymph node metastases and, as previously said, the definition of HMLN varied among studies. Gagliasso et al. used the IASLC definition of HMLN, so they found a better 5-year survival rate compared to less rigorous lymph node evaluation and carcinoma *in situ* in the bronchial margin (28.8% vs. 44.2% and 40.0%, respectively) (16).

Ren et al., following the IASLC definition, considered being HMLN positive as an independent risk factor for DFS and OS: among patients with N2 metastases, those with positive HMLN

TABLE 5 The univariate analysis for DFS and OS in the N2 population.

Univariate analysis	DFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.1 (1.0–1.1)	**0.04**	1.0 (1.0–1.5)	**0.02**
Sex	0.9 (0.5–1.9)	0.83	0.6 (0.2–1.4)	0.24
Smoke	0.4 (0.2–0.9)	0.06	0.9 (0.3–2.9)	0.96
pT	1.8 (1.2–2.9)	**0.02**	2.3 (1.3–4.0)	**0.005**
pN2 subgroups	1.9 (1.3–2.8)	**0.001**	1.9 (1.2–3.0)	**0.006**
Histology	1.5 (0.6–3.6)	0.39	1.9 (0.7–5.1)	0.20
Open vs. VATS	1.9 (0.9–3.9)	0.09	1.5 (0.6–3.5)	0.41
No. lymph nodes	0.9 (0.9–1.0)	0.12	0.9 (0.9–1.0)	0.75
Lymph node ratio	1.0 (1.0–1.0)	**<0.001**	1.0 (0.9–1.0)	0.06
Lobe	1.1 (0.8–1.4)	0.54	0.9 (0.7–1.3)	0.91
Tumor diameter at CT	1.0 (1.0–1.1)	**0.01**	1.0 (0.9–1.1)	0.07
SUVmax tumor	0.3 (0.1–0.9)	**0.02**	0.5 (0.2–1.7)	0.26
Lymph node diameter at CT	1.4 (0.7–2.9)	0.40	1.1 (0.5–2.9)	0.79
SUVmax mediastinal lymph nodes	0.8 (0.4–1.7)	0.52	0.6 (0.2–1.6)	0.31
R classification	4.6 (2.2–9.6)	**<0.001**	4.5 (1.8–10.9)	**<0.001**

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; VATS, video-assisted thoracic surgery; SUV, standardize uptake value.
Bold indicate statistical significative value.

TABLE 6 The multivariate analysis for DFS and OS in the N2 population.

Multivariate analysis	DFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.0 (0.9–1.1)	0.75	1.1 (0.9–1.1)	**0.05**
pT	1.5 (0.9–2.5)	0.13	2.0 (1.2–3.5)	**0.008**
pN2 subgroups	1.4 (0.9–2.4)	0.16	2.1 (1.2–3.7)	**0.007**
Lymph node ratio	1.0 (1.0–1.0)	**0.03**	—	—
Tumour diameter at CT	1.0 (0.9–1.1)	0.19	—	—
SUVmax tumor	0.4 (0.1–1.0)	0.06	—	—
R classification	3.2 (1.4–7.4)	**0.008**	2.0 (0.7–6.1)	**0.002**

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; SUV, standardize uptake value.
Bold indicate statistical significative value.

TABLE 7 The univariate analysis for DFS and OS in the R-u group.

Univariate analysis	DFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.0 (0.9–1.1)	0.97	0.6 (0.2–1.8)	0.39
Sex	0.9 (0.3–2.6)	0.9	1.0 (0.9–1.1)	0.31
Smoke	0.9 (0.3–2.9)	0.96	1.4 (0.4–4.9)	0.6
pT	1.5 (0.9–2.6)	0.1	1.9 (1.1–3.6)	**0.02**
pN2 subgroups	1.7 (0.9–2.9)	**0.04**	1.9 (1.0–3.9)	**0.03**
Histology	0.8 (0.2–2.7)	0.72	1.8 (0.5–6.3)	0.35
Open vs. VATS	1.3 (0.5–3.1)	0.57	1.1 (0.4–2.9)	0.9
No. lymph nodes	0.9 (0.9–1.0)	**0.03**	0.9 (0.9–1.0)	0.61
Lymph node ratio	1.0 (1.0–1.0)	**0.04**	1.0 (0.9–1.0)	0.57
No. lymph nodes higher station	1.1 (0.8–1.4)	0.64	1.2 (0.9–1.6)	0.12
Lymph node ratio higher station	0.9 (0.9–1.0)	0.15	1.6 (1.0–2.5)	0.35
No. positive lymph node higher station	0.4 (0.2–1.1)	**0.03**	1.2 (0.4–3.1)	0.78
Macro-metastases	30.5 (3.9–240.0)	**<0.001**	3.9 (1.1–14.0)	**0.01**
Lobe	1.1 (0.8–1.4)	0.53	1.1 (0.8–1.5)	0.56
Tumour diameter at CT	1.0 (1.0–1.1)	**0.02**	3.1 (0.7–13.7)	0.08
SUVmax tumor	0.5 (0.2–1.7)	0.28	0.7 (0.2–2.5)	0.6
Lymph node diameter at CT	1.2 (0.5–2.9)	0.64	0.8 (0.3–2.3)	0.68
SUVmax mediastinal lymph nodes	0.7 (0.3–1.8)	0.49	0.5 (0.2–1.6)	0.21

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HR: hazard ratio; OS, overall survival; VATS, video-assisted thoracic surgery; SUV, standardize uptake value.
Bold indicate statistical significative value.

TABLE 8 The multivariate analysis for DFS and OS in the R-u group.

Multivariate analysis	DFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
pT		—	1.9 (0.9–3.7)	**0.04**
pN2 subgroups	1.2 (0.6–2.6)	0.66	1.8 (0.8–3.7)	0.14
No. lymph nodes	0.9 (0.9–1.0)	0.09	—	—
Lymph node ratio	1.0 (0.9–1.0)	0.69	—	—
No. positive lymph node higher station	0.5 (0.2–1.4)	0.16	—	—
Macro-metastases	28.8 (3.5–239.5)	**0.002**	3.5 (0.9–12.6)	**0.05**
Tumour diameter at CT	1.0 (0.9–1.1)	0.8	—	—

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.
Bold indicate statistical significative value.

had significantly worse survival compared to R0 (DFS: 36 vs. 44 months, $p < 0.001$; OS: 50 vs. 59 months, $p < 0.001$) (17).

Sakao et al. defined HMLN as nodes lying above a horizontal line at the upper rim of the left innominate vein. They found that, in patients with advanced N2 disease, patients with positive HMLN had a 5-year survival rate of 21.0% compared to 52.0% of negative HMLN. Furthermore, patients with negative HMLN, even if they have multilevel N2 status, positive cN status, or T2–3 tumor status, had a better prognosis (18).

Two studies found no prognostic difference regarding survival between complete and incomplete resection. Both studies used a stricter definition of HMLN: for the right side they considered 2R, and for the left side 4l, 5, or 6. In these studies, the metastasis on HMLN did not show survival differences in completely resected N2 NSCLC (19, 20).

The results of our study support the idea that the presence of metastases in the highest mediastinal lymph node among those resected is a negative prognostic factor for DFS and OS. R-u had a higher recurrence and mortality rate compared to R0.

This study has some limitations. First, the retrospective nature of the study and the small cohort of patients may have affected the validity of the study. The category of R-u is wide; we focused only on the metastases on the highest mediastinal lymph nodes. Other studies should be done to compare the prognostic value of these subgroups and to evaluate the necessity of a specific adjuvant therapy. Future prospective for developing a preoperative evaluation of the lymphatic pathway and the sentinel node might be useful (21). So far, we suggest a systematic lymph node dissection for a better staging of the mediastinal lymph node status.

Conclusion

The group of pN2 is not homogeneous from a prognostic point of view. R classification proposed by IASLC showed a significant improvement in survival discrimination. R-u delineates the crossing area between complete resection (R0) and incomplete resection (R1 and R2). The R-u for the presence of metastasis in the HMLN removed seems to be an independent prognostic factor for mortality and recurrence. The definition of HMLN varied among studies, whereby standardization of the definition was needed. The finding of metastasis in the HMLN represents the margin of cancer dissemination at the time of surgery, so it could imply metastasis into the N3 node or distant metastasis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VM, LF, PC, and VA contributed to the conception and design of the study. AP and FL organized the database. VM and AP performed the statistical analysis. VM, LF, and AP wrote the first

draft of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* (2017) 28 (suppl_4):iv1–21. doi: 10.1093/annonc/mdx222

2. Barnes H, See K, Barnett S, Manser R, et al. Surgery for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev.* (2017) 4(4):CD011917. doi: 10.1002/14651858.CD011917.pub2

3. Hermanek P, Wittekind C. Residual tumor (R) classification and prognosis. *Semin Surg Oncol.* (1994) 10(1):12–20. doi: 10.1002/ssu.2980100105

4. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer.* (2005) 49(1):25–33. doi: 10.1016/j.lungcan.2005.01.001

5. Edwards JG, Chansky K, Van Schil P, Nicholson AG, Boubia S, Brambilla E, et al. The IASLC lung cancer staging project: analysis of resection margin Status and proposals for residual tumor descriptors for non-small cell lung cancer. *J Thorac Oncol.* (2020) 15(3):344–59. doi: 10.1016/j.jtho.2019.10.019

6. Zheng H, Hu XF, Jiang GN, Gao W, Jiang S, Xie HK, et al. Define relative incomplete resection by highest mediastinal lymph node metastasis for non-small cell lung cancers: rationale based on prognosis analysis. *Lung Cancer.* (2011) 72(3):348–54. doi: 10.1016/j.lungcan.2010.10.003

7. Kirmani BH, Volpi S, Aresu G, Peryt A, Win T, Coonar AS, et al. Long term and disease-free survival following surgical resection of occult N2 lung cancer. *J Thorac Dis.* (2018) 10(8):4806–11. doi: 10.21037/jtd.2018.07.125

8. Miao H, Shaolei L, Nan L, Yumei L, Shanyuan Z, Fangliang L, et al. Occult mediastinal lymph node metastasis in FDG-PET/CT node-negative lung adenocarcinoma patients: risk factors and histopathological study. *Thorac Cancer.* (2019) 10(6):1453–60. doi: 10.1111/1759-7714.13093

9. Lardinois D, De Leyn P, Van Schil P, Porta RR, Waller D, Passlick B, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg.* (2006) 30(5):787–92. doi: 10.1016/j.ejcts.2006.08.008

10. Travis WD, Asamura H, Bankier AA, Beasley MB, Detterbeck F, Flieder DB, et al. The IASLC lung cancer staging project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol.* (2016) 11(8):1204–23. doi: 10.1016/j.jtho.2016.03.025

11. Brierley JD, Gospodarowicz MK, Ch W. *UICC TNM classification of malignant tumours.* 8th ed. Oxford: Wiley-Blackwell (2017). p. 10–1.

12. Topol M, Masłoń A. Some variations in lymphatic drainage of selected bronchopulmonary segments in human lungs. *Ann Anat.* (2009) 191(6):568–74. doi: 10.1016/j.aanat.2009.08.008

13. Casali C, Stefani A, Natali P, Rossi G, Morandi U, et al. Prognostic factors in surgically resected N2 non-small cell lung cancer: the importance of patterns of mediastinal lymph nodes metastases. *Eur J Cardiothorac Surg.* (2005) 28(1):33–8. doi: 10.1016/j.ejcts.2005.03.016

14. Marziali V, Frasca L, Ambrogi V. Non-lobe specific metastases in occult N2 after lobectomy for clinical N0 non-small cell lung cancer. *Int J Can Med.* (2022) 6 (2):58–68.

15. Osarogiagbon RU, Faris NR, Stevens W, Fehnel C, Houston-Harris C, Ojeabulu P, et al. Beyond margin status: population-based validation of the proposed international association for the study of lung cancer residual tumor classification recategorization. *J Thorac Oncol.* (2020) 15(3):371–82. doi: 10.1016/j.jtho.2019.11.009

16. Gagliasso M, Migliaretti G, Ardissone F. Assessing the prognostic impact of the international association for the study of lung cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery. *Lung Cancer.* (2017) 111:124–30. doi: 10.1016/j.lungcan.2017.07.013

17. Ren Y, She Y, Tang H, Deng J, Jiang G, Wu C, et al. Prognostic evaluation of the proposed residual tumor classification in a Chinese non-small cell lung cancer population. *J Surg Oncol.* (2022) 125(6):1061–70. doi: 10.1002/jso.26810

18. Sakao Y, Miyamoto H, Yamazaki A, Oh T, Fukai R, Shiomi K, et al. Prognostic significance of metastasis to the highest mediastinal lymph node in nonsmall cell lung cancer. *Ann Thorac Surg.* (2006) 81(1):292–7. doi: 10.1016/j.athoracsur.2005.06.077

19. Park SY, Byun GE, Lee CY, Lee JG, Kim DJ, Paik HC, et al. Clinical implications of uncertain resection in scenarios of metastasis of the highest or most distant mediastinal lymph node station following surgical treatment of non-small-cell lung cancer. *Lung Cancer.* (2019) 138:1–5. doi: 10.1016/j.lungcan.2019.09.018

20. Wang SD, Liu GW, Li X, Sui XZ, Yang F, Wang J, et al. Propensity-matched analysis of clinical relevance of the highest mediastinal lymph node metastasis. *Ann Thorac Surg.* (2021) 111(1):277–82. doi: 10.1016/j.athoracsur.2020.05.027

21. Marziali V, Frasca L, Longo F, Vega R, Crucitti P. The wide range of uses of indocyanine green in thoracic surgery: state of art. *J Surg.* (2022) 7:1529. doi: 10.29011/2575-9760.001529

Frontiers in Surgery

Explores and improves surgical practice and clinical patient management

A multidisciplinary journal which explores surgical practices - from fundamental principles to advances in microsurgery and minimally invasive techniques. It fosters innovation and improves the clinical management of patients.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact