Interventional bronchoscopy in lung cancer treatment

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Shareable abstract (@ERSpublications)
Interventional bronchoscopy plays a significant role in the treatment of malignant airway stenosis and early-stage lung cancer. Successful intervention helps alleviate severe symptoms and improves the functional status of patients. https://bit.ly/4f3BMQn

Cite this article as: Rozman A, Grabczak EM, George V, *et al*. Interventional bronchoscopy in lung cancer treatment. *Breathe* 2024; 20: 230201 [DOI: 10.1183/20734735.0201-2023].

Received: 7 March 2024
Accepted: 26 June 2024

Abstract

Interventional bronchoscopy has seen significant advancements in recent decades, particularly in the context of lung cancer. This method has expanded not only diagnostic capabilities but also therapeutic options. In this article, we will outline various therapeutic approaches employed through either a rigid or flexible bronchoscope in multimodal lung cancer treatment. A pivotal focus lies in addressing central airway obstruction resulting from cancer. We will delve into the treatment of initial malignant changes in central airways and explore the rapidly evolving domain of early peripheral malignant lesions, increasingly discovered incidentally or through lung cancer screening programmes. A successful interventional bronchoscopic procedure not only alleviates severe symptoms but also enhances the patient's functional status, paving the way for subsequent multimodal treatments and thereby extending the possibilities for survival. Interventional bronchoscopy proves effective in treating initial cancerous changes in patients unsuitable for surgical or other aggressive treatments due to accompanying diseases. The key advantage of interventional bronchoscopy lies in its minimal invasiveness, effectiveness and favourable safety profile.

Educational aims

- To present methods used during interventional bronchoscopy for treating malignant central airway stenosis and early-stage lung cancer.
- To discuss indications in which performing a palliative or curative bronchoscopic procedure can alleviate symptoms and may improve survival.
- To outline the benefits and complications of bronchoscopic interventions in the treatment and palliation of lung cancer.

Introduction

The development of interventional bronchoscopy in recent decades has closely paralleled the increase in lung cancer cases. The primary objectives of this development have revolved around conducting diagnostic, therapeutic and palliative procedures in a minimally invasive fashion. Procedures can be performed using either a rigid or flexible bronchoscope, and in more intricate cases, a combination of both may be used. Considerable attention is dedicated to factors such as the anatomical location of the tumour, the risk of complications – notably bleeding – and, crucially, the available equipment, and the experience of the operator and the entire medical team. In interventional procedures, each patient is treated uniquely, reflecting the individualised approach to bronchoscopic intervention. The involvement of an anaesthetist

specialising in interventional bronchoscopy, along with other team members, is pivotal. Modern interventional bronchoscopic procedure is facilitated by state-of-the-art technical and computer equipment, demanding proficiency from the medical staff.

The overview of interventional bronchoscopy will be segmented into three main areas. The most comprehensive domain covers malignant stenosis of the central airways. Additionally, we will explore therapeutic interventions for early tumours within the central airways and treatments for small peripheral tumours. The latter area has gained significant attention in recent years due to the increased detection of small lung lesions through lung cancer screening programmes and the incidental discovery of lung nodules. Many patients are unsuitable candidates for surgical treatment due to concurrent disease or they may present with multiple small primary tumours simultaneously, rendering traditional surgical approaches impractical.

Malignant central airway obstruction

Prevalence and symptoms

The precise frequency of central airway obstruction (CAO) due to lung cancer is not well known but it is estimated to be ∼30% [1]. In one of the rare prevalence studies performed, one-third of newly diagnosed lung cancer patients had a visible endobronchial tumour and 13% already had CAO at the time of diagnosis [2]. Within the first year after diagnosis, an additional 5% of patients developed CAO [2]. The main symptoms of CAO include dyspnoea, a decline in exercise capacity and cough. Additionally, 20–30% of lung cancer patients develop complications related to CAO, such as atelectasis, pneumonia and pleural effusion [3].

The lumen of the trachea can be significantly narrowed, to a diameter of 8 mm, before the patient experiences exertional dyspnoea. Dyspnoea at rest occurs when the lumen is narrowed to <5 mm in diameter [4, 5]. Symptoms worsen gradually in line with tumour growth but there can be a sudden deterioration during a crisis, provoked either by increased respiratory demands (pneumonia) or rapid luminal narrowing (mucosal oedema, secretion or coagulum stasis). As a result, many patients with CAO seek emergency care with signs of respiratory distress.

Prognosis of patients with CAO

Patients with CAO due to lung cancer have significantly shorter survival compared to patients without CAO and suffer agonising death by slow suffocation [2]. Timely intervention can markedly impact survival in many patients but a randomised study with a control group is not feasible here due to ethical constraints. Brutinel *et al*. [6] compared the outcomes of bronchoscopic laser recanalisation of CAO with a historical cohort of patients treated before the interventional bronchoscopy was introduced into their hospital. In the untreated group, 4-month survival was 24% with no survival at 7 months; while in the treated group, the 7-month survival was 60% and the 1-year survival was 28%. Patients who underwent therapeutic bronchoscopy for the treatment of CAO and continued with systemic treatment had a prognosis similar to comparable patients without CAO [7]. Verma *et al*. [8] also demonstrated that the survival of lung cancer patients after the recanalisation of CAO is comparable to that of patients without CAO and strongly advocate bronchoscopic treatment for CAO.

Patient selection: assessment, prognostic factors and predictors of outcome

Patients with CAO often present with stridor, atelectasis, pneumonia, dyspnoea, respiratory failure requiring assisted mechanical ventilation, and haemoptysis. However, these symptoms cannot be always attributed to the airway stenosis, especially when it is peripheral, and the patient has accompanying disease such as emphysema, pleural effusion, heart failure. Therefore, a careful assessment of the patient is important before a planned procedure, weighing the benefits and potential complications of the intervention. It is advisable to recanalise the trachea and main bronchi if the distal part of the airway beyond the obstruction is patent and supplies functional lung parenchyma [9]. Equally important is the patency of the vessels supplying the affected part of the lung; if they are not patent, recanalisation only increases the dead space in the lungs and does not contribute to functional improvement. Recanalisation of lobar bronchi does not lead to significant improvement in ventilation, perfusion and the patient's functional status [9, 10]. An exception is the situation where postobstructive pneumonia is resolved, allowing the patient to undergo systemic treatment. It is also important that the computed tomography (CT) scan is not outdated and there has been no additional tumour growth in the time leading up to therapeutic bronchoscopy [11]. Endoluminal obstruction and stent placement were associated with success, whereas an American Society of Anesthesiology (ASA) score >3, renal failure, primary lung cancer, left mainstem disease and tracheo-oesophageal fistula were associated with failure [10]. Extrinsic compression, major

airway involvement and respiratory failure requiring mechanical ventilation are correlated with the poorer survival [12, 13].

Types of stenosis and methods of treatment

Obstruction of the central airways in lung tumours is classified based on location, degree of obstruction and the type of obstruction (intraluminal, extrinsic due to external compression or combined) [14]. The choice of bronchoscopic treatment depends on these factors [3]. In the case of intraluminal obstruction, tumour tissue can be removed using hot and/or cold methods, and if technically successful, immediate symptom improvement can be achieved. Stenosis dilation and stenting are options for extrinsic compression caused by pressure on the airway from outside. If the patient is in respiratory distress, a method with an immediate effect should be chosen, but if not, a delayed-effect method, usually less aggressive, may be used instead (table 1). A precondition for improving the patient's symptoms and prognosis is the technical success of the therapeutic bronchoscopic procedure (reopening of the airway lumen) [15, 16]. Of great importance is the finding that the likelihood of technical success of therapeutic bronchoscopy is not significantly different when using different techniques and there is no single best method in terms of ablative techniques [10]. A summary of the bronchoscopic treatment methods and their indications is presented in table 2.

Endoscopic laser resection

Bronchoscopic laser resection is considered an effective treatment modality for airway obstruction with an immediate effect and, therefore, it is deemed appropriate in life-threatening situations [17]. "Laser" stands for "light amplification by stimulated emission of radiation". A laser emits a high energy density beam of light with very similar wavelengths, which causes tissue damage dependent on the beam's irradiance (power density) and exposure time [18]. To achieve tissue destruction, it uses various gases (carbon dioxide, potassium titanyl phosphate, neodymium-doped yttrium aluminium garnet (Nd:YAG), argon ion, excimer or alexandrite) [19].

Bronchoscopic laser resection is indicated in airway obstruction due to localised endobronchial exophytic lesions rather than extrinsic compression or submucosal tumours. A pacemaker is not a contraindication for laser treatment [19]. In interventional pulmonology, it is performed under general anaesthesia, and the laser beam is applied through a combination of rigid and/or flexible bronchoscope straight to the lesion [17, 20].

The laser's penetration length depends on the type of laser and its emission wavelength, and generally varies between 0.23 mm (CO_2 laser) and 2 mm (Ar) [21]. Despite the presumably short penetration length, there is general advice for noncontract treatment (*i.e.* the distance between the probe and the target should be ~1 cm) and limiting the power to <40 W to avoid a perforation of the tracheobronchial wall with a subsequent fistula and/or mediastinitis [17, 22, 23].

Bronchoscopic laser resection poses the risk of airway fire in an oxygen-enriched atmosphere, where a resulting fire can cause extensive airway injury; therefore, a reduction of inhaled oxygen fraction (F_{IO_2}) is required during laser activation. Since 2006, six reports of airway fire during bronchoscopic laser resection were received by the Emergency Care Research Institute [22]. The literature shows that the risk of airway fire appears beyond the F_{IO_2} threshold of 40% [24].

Following laser resection, patients have an immediate improvement of symptoms, arterial blood gases, spirometry and quality of life [23, 25].

TABLE 1 Comparison of treatment modalities regarding tumour location and time of therapy effect

	Immediate effect	Delayed effect
Endoluminal tumour	Laser	Cryotherapy
	Electrocautery/APC	Photodynamic therapy
	Cryoextraction	Brachytherapy
	Mechanical debulking	External irradiation
Extraluminal compression	Dilatation and stent placement	External irradiation

APC: argon plasma coagulation.

Electrocautery

Electrocautery involves the delivery of a high-frequency alternating electric current through a probe straight to the tumour tissue, where it generates heat [17]. It can cut, coagulate or vaporise the target tissue depending on the power setting, the surface area and the contact time [23, 24]. It is indicated in endobronchial lesions rather than extrinsic compression. There are several instruments available for electrocautery, including rounded probes, snares, knives and forceps [26]. The electrocautery probe can be employed for both coagulation and cutting purposes. A wire snare is effective for removing pedunculated endobronchial lesions with thin stalks by placing it over the lesion, wrapping it around the stalk and cutting while simultaneously ensuring haemostasis. The electrocautery knife is used to cut web-like stenoses before dilation. "Hot" forceps are typically used for mechanical debridement of highly vascularised tumours.

The contraindication maybe a pacemaker that presents electric interference [19]. The electrocautery probe can be applied through flexible and/or rigid bronchoscopes with general anaesthesia or conscious sedation [17, 23, 24] and unlike the laser, it should be in close contact with the target tumour. The penetration depth is reported as a few millimetres; however, it has not been directly compared to that of the laser

TABLE 2 Summary of different treatment modalities, their specific roles and their aims of treatment

Treatment modality	Indications/specific role	Aim of treatment	Indication for life-threatening situations
Laser	Debulking in endobronchial tumours	Debulking and relief of airway obstruction with immediate effect	Yes
Electrocautery	Debulking in endobronchial tumours	Debulking and relief of airway obstruction with immediate effect	Yes
APC	Debulking in endobronchial tumours	Debulking and relief of airway obstruction with immediate effect	Yes
Cryoextraction/ cryotherapy	Debulking in endobronchial tumours	Debulking and relief airway obstruction with immediate effect	Yes
Mechanical debulking	Debulking in endobronchial tumours	Debulking and relief of airway obstruction with immediate effect	Yes
Balloon dilatation	Extraluminal compression	Relief of airway obstruction with immediate effect	Yes
Stent	Extraluminal compression	Relief of airway obstruction with immediate effect	Yes
Photodynamic therapy	Endobronchial treatment in inoperable lung cancer	Local disease control	No
Brachytherapy	Treatment in early invasive mucosal or submucosal NSCLC in nonsurgical candidates Locally advanced centrally located lung cancer Endobronchial boost to full-course external beam radiation therapy with incomplete response/recurrence	Local disease control	No
MWA	Preparation for the debulking of endobronchial tumours	Relief of airway obstruction with immediate effect in combination with mechanical debulking	Yes
Intratumoural therapy	Administration of cytotoxic agents within the tumours with EBUS	Local disease control	No

APC: argon plasma coagulation; MWA: microwave ablation; NSCLC: nonsmall cell lung cancer; EBUS: endobronchial ultrasound.

modalities [21]. Similarly to laser applications, the risk of airway fire decreases significantly below the F_{IO_2} threshold of 40% [23, 24, 27]. There are no randomised controlled trials (RCTs) comparing the efficiency of electrocautery *versus* laser in debulking, recurrence and quality of life, so the choice of their application relies on departmental availability and bronchoscopist's experience [17–27].

Argon plasma coagulation

Argon plasma coagulation (APC) is similar to the electrocautery method but does not require contact with the tissues it destroys. It can be introduced *via* rigid and/or flexible bronchoscopy, and be applied at a safe distance of 2–5 mm from the target tumour [23]. For APC, we can use axial, radial or lateral electrodes to more accurately direct the desired effect, depending on the lesion type or position. Its penetration length is more superficial that electrocautery and, therefore, it is better suited for superficial and spreading endobronchial lesions [24]. Its noncontact application makes it a better modality for rapid coagulation as the bronchoscopy field is easier to preserve [23, 24]. Complications from APC are rare, and include airway fire and airway perforation. Gas embolism, though rare, is a serious complication of bronchoscopic APC. Ablation in the trachea and bronchi can lead to gas formation in the right and left atria, potentially causing cerebral gas embolism, stroke or cardiac arrest. Direct mucosal contact with the APC probe can result in submucosal gas deposition, likely leading to gas entering the intravascular space. Therefore, APC should be used in a strictly noncontact manner, with the shortest pulse duration and lowest gas flow rate, to minimise these risks [28].

Mechanical debulking and balloon dilatation

Mechanical debulking and/or balloon dilatation are safe and effective methods with an immediate effect for treating central airway obstructions (CAOs) caused by endobronchial tumour growth or extrinsic compression (figure 1). The procedure is typically conducted by a rigid bronchoscope, which ensures airway protection, facilitates anaesthesia, enables reduction of tumour mass and extraction of large tumour parts, controls bleeding by mechanical compression and by aspiration with large-bore suction catheters [29–31].

In endobronchial tumour cases, debulking involves "coring", a process where the rigid bronchoscope is screwed through the soft tissue [29]. The fragmented tissue is then extracted using forceps, suction or cryoprobe. Conversely, in extrinsic compression, the bronchoscope is carefully advanced past the

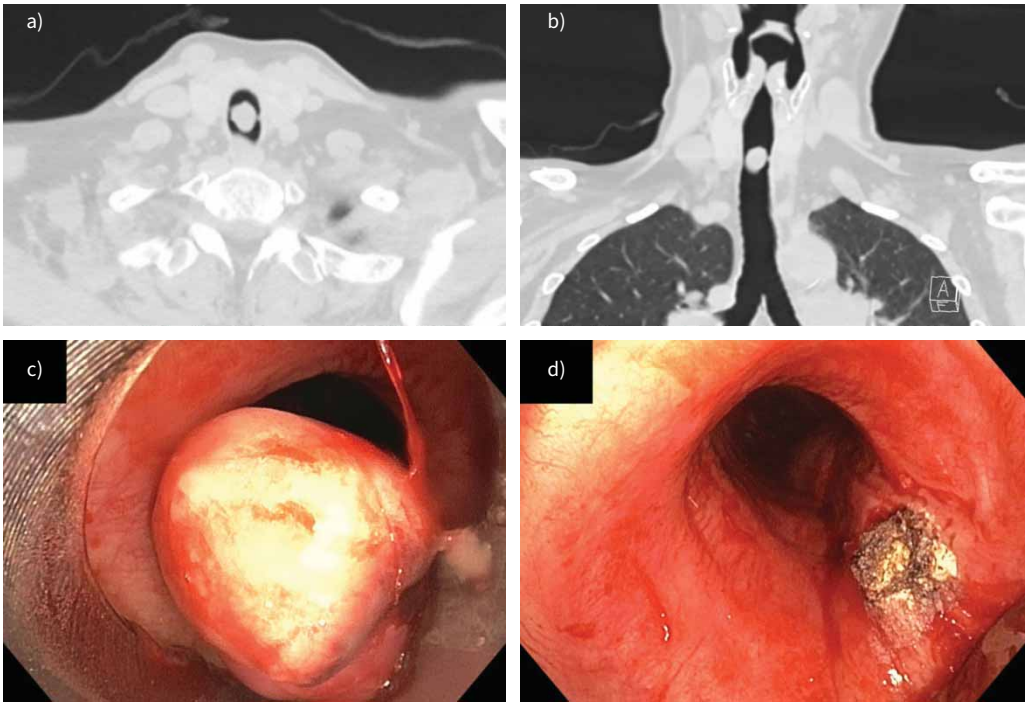

FIGURE 1 a and b) Computed tomography images of polypoid metastasis in the trachea of a patient with severe dyspnoea and haemoptysis. c) Tumour was removed by coring with rigid bronchoscope. d) Basis of the tumour was treated by argon plasma coagulation to stop bleeding and prevent recurrence.

constricted bronchus or high-pressure balloon dilatation is applied on the stenosis [32]. Mechanical recanalisation, while not commonly used as a standalone intervention, is frequently accompanied by airway stenting in clinical practice.

Vishwanath *et al*. [29] reported an 87.1% success rate in a cohort of 23 patients, with manageable bleeding complications. Thermal ablative therapies (laser, electrocautery and APC) are recommended for persistent bleeding.

Mechanical debulking provides immediate relief and improves the performance status of patients. Lee *et al*. [33] found that it significantly enhanced the Eastern Cooperative Oncology Group (ECOG) scale score, allowing 70% of patients to undergo additional treatments like radiotherapy and/or systemic therapy.

Airway stents

Tracheobronchial stents play a crucial role in the treatment of CAO, primarily or entirely resulting from extraluminal compression on the airway, with an immediate effect. An ideal stent must have sufficient mechanical strength to resist external pressure without collapsing and enough elasticity to adapt to the physiological properties of the trachea during coughing [34].

Essentially, there are two types of stents: silicone and metallic stents, each with its own advantages and disadvantages [35]. Uncovered metallic stents were adapted from the gastrointestinal and vascular fields but have evolved significantly over time [36]. Recently, nitinol metal stents have become popular due to their two important properties: shape memory and elasticity [37]. Shape memory allows the stent to be compressed for insertion and then expand to its original shape once placed (self-expandable). Elasticity makes the stent resistant to high pressures (*e.g.* during coughing) and enables it to conform to the irregular anatomy of the airways, thereby distributing pressure more evenly on the surrounding tissues. Modern self-expanding metal stents (SEMSs) are coated with a polyurethane membrane or silicone, earning them the designation of hybrid stents. The benefits of this design include preventing tumour tissue from growing into the lumen and easier removal. However, they also have drawbacks such as reduced mucus clearance and biofilm formation.

Silicone stents have good mechanical strength and elasticity but are more challenging to introduce. Their advantage lies in the possibility of additional pre-insertion customisation based on the anatomical situation, and they cause less tissue irritation, resulting in fewer inflammatory granulations. Unlike uncovered metallic stents, tumour tissue does not grow into the metal mesh, making them relatively easy to remove even after an extended period.

The most common issues with both types of stents include reduced secretion clearance, biofilm deposits, migration and ingrowth of granulation tissue on both ends [36, 38, 39]. Metal stents are additionally associated with stent fracture and erosion into the surrounding tissue.

Based on their shape, stents are primarily divided into two groups: cylindrical stents and Y-stents. The former are inserted into the trachea or main bronchi, while the latter are placed in the area of the main carina and, less frequently, at the site of secondary carinas. Cylindrical stents migrate more often than Y-stents.

Introducing a silicone stent requires rigid bronchoscopy under general anaesthesia with prior dilation, either with a bronchoscope or using a dilation balloon [35, 36, 38]. SEMSs can also be introduced with a flexible bronchoscope under moderate sedation, although rigid bronchoscopy is recommended.

The indication for a stent is symptomatic extramural compression. If the tumour grows within the lumen and can be removed, this method is preferred, as the stent is essentially a foreign object in the airways and is used when no other options are available [40]. Stenting is performed in the trachea and main bronchi, and the effectiveness at the level of the lobar bronchi is questionable and often does not outweigh potential complications [41].

Stents are mostly inserted in the late stage of the disease when the patient has exhausted other therapeutic options. However, the performance of patients often improves to the extent that they can undergo oncological treatment (irradiation and systemic therapy) after stent insertion, further improving their prognosis (figure 2) [33]. Recently, patients with CAO who undergo stent insertion and subsequent modern treatments (immunotherapy and targeted therapy) are experiencing stable and prolonged

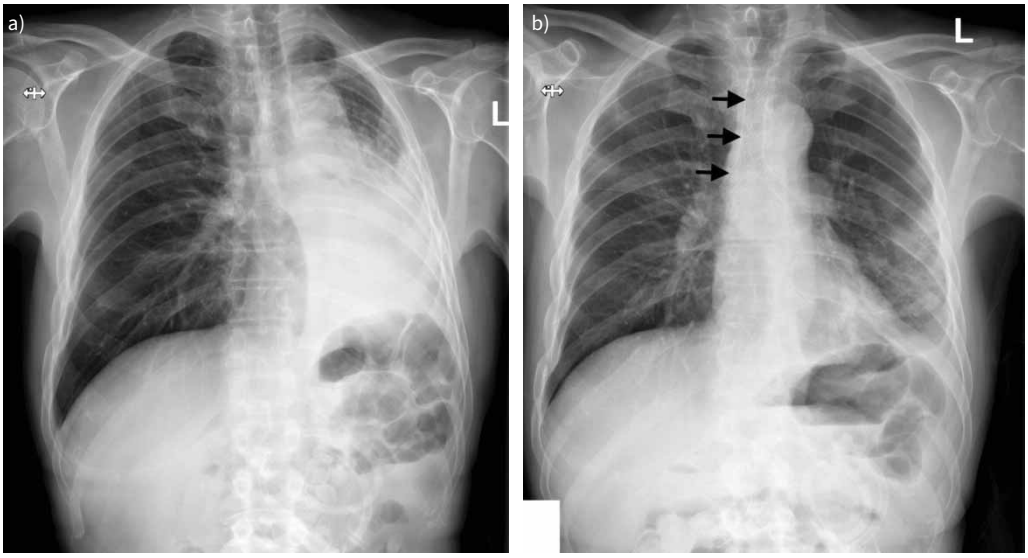

FIGURE 2 a) Atelectasis of the left lung as a consequence of combined (endobronchial/extramural compression) malignant stenosis of the left main bronchus. b) Atelectasis was resolved after stent placement and the patient improved enough to receive further multimodal treatment.

remissions, leading to an increasing tendency to consider stent removal. In such cases, when bridging is planned, stents that are easier to remove (silicone or Bronchus AER SEMSs) are preferred (figure 3).

Recently, there have been reports of biodegradable and three-dimensionally printed stents, although they have not yet found their place in the treatment of malignant CAO.

Endobronchial brachytherapy

Endobronchial brachytherapy (EBBT) is a method of local treatment of malignancy by endobronchial application of a radioactive source in close proximity to a tumour to provide high doses of radiation to the tumour and less to nearby tissue. An afterloading catheter, equipped with a radiopaque wire, is placed transnasally under direct visualisation beyond the obstruction site, ensuring dose uniformity and minimising complications [42]. The catheter's fluoroscopic position is verified, secured to the patient's nose and the bronchoscope is removed [43]. High dose rate iridium-192 is commonly used, with total doses ranging from 5 to 60 Gy [44, 45]. Successful EBBT requires the tumour to allow distal catheter passage for the radiation source. Treatment effects, expected in ∼3 weeks, necessitate patient life expectancy of >3 months. Initial EBBT may cause temporary deterioration, emphasising the need for caution, especially in life-threatening situations, where it should be considered after local ablative therapy [46–48].

Brachytherapy is performed as a sole treatment method or can be combined with other therapeutic approaches (external beam radiation therapy (EBRT), laser resection, cryotherapy or stents). Application of EBBT may result in substantial symptom improvement in 20–98% of patients [49–51]. The effect is best expressed in the case of haemoptysis (86–100%) and less pronounced in dyspnoea (improvement in 57–75% of patients) or cough (34–88%) [50–52]. However, when patients' survival is concerned, the benefits of EBBT are not so clear. The meta-analyses performed by Reveiz *et al.* [53] including >950 patients showed no evidence of survival benefit associated with the EBBT alone compared to EBRT and Nd:YAG laser or for the combination of EBBT with chemotherapy.

Complications of EBBT may rate from 5% to 40% [49]. Early complications are connected with bronchoscopy, and late complications comprise mainly radiation bronchitis, airway stenosis and bleeding. According to the American Society for Radiation Oncology evidence-based clinical practice guideline, EBBT is not recommended as either sole or adjunct therapy for routine palliation of airway obstruction [54].

Photodynamic therapy

Photodynamic therapy (PDT) is a minimally invasive endobronchial treatment with delayed effect approved for inoperable endobronchial cancer [55, 56]. It involves administering a photosensitising drug,

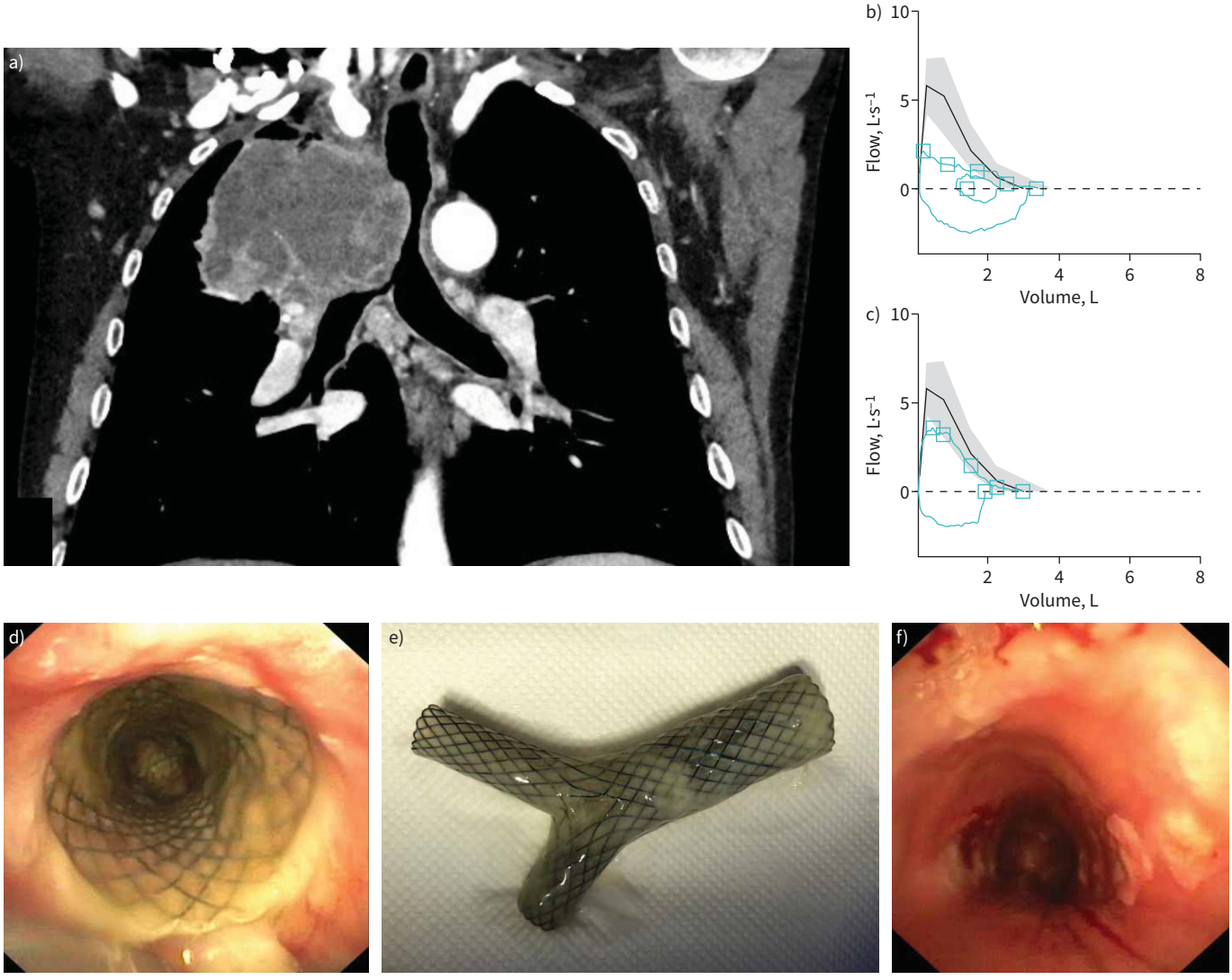

FIGURE 3 Patient with severe central airway stenosis due to extramural tumour compression. a) Computed tomography image in which stenosis of trachea and right main bronchus is evident. b) Flow–volume loop before stent placement. c) Flow–volume loop after stent placement. d) Stent in the trachea several months later after successful chemoradiotherapy with almost complete remission. e) Removed stent. f) Trachea after stent removal is fully patent.

commonly porphyrin sodium, which selectively accumulates in malignant tissue. Typically, 48–72 h after drug administration, bronchoscopy is performed by illuminating the tumour with laser light (wavelength 620–640 nm). The depth of penetration depends upon the type of photosensitiser used and wavelength of laser light (usually 5–10 mm penetration). The activated photosensitiser destroys tumour cells mostly by generating reactive oxygen species and it may also induce an inflammatory reaction leading to a host antitumour immune response [57–59]. The effects of PDT are not immediate and debris removal is recommended 24 h post-PDT to ensure airway patency. Complications may include haemorrhage and photosensitivity reactions lasting up to 6 weeks [55, 56, 60, 61]. Other reported complications include bleeding, airway obstruction 24–48 h after the procedure due to debris or airway oedema, and fistula formation [61–63].

PDT can at least partly reduce tumour stenosis, and improve dyspnoea, performance, haemoptysis and post-obstructive pneumonia [62–66]. Combining PDT with external radiation, brachytherapy or chemotherapy can enhance its effectiveness [67, 68]. PDT prior to external radiotherapy provides better local control (reduction in respiratory symptoms and improvement in the quality of life) than external radiotherapy alone [69]. An RCT comparing PDT and Nd:YAG laser treatment showed comparable

effectiveness and safety in the palliation of symptoms, with a significantly longer time until treatment failure and longer median survival (possibly due to differences in the tumour stages between the groups) of patients treated with PDT [70].

Interstitial photodynamic therapy (I-PDT) is a novel approach for treating deeply seated or extrabronchial tumours causing malignant central airway obstruction. In I-PDT, light-diffuser fibres are inserted into the tumour using endobronchial ultrasound (EBUS) transbronchial needle guidance to achieve intratumoural illumination. Personalised treatment planning using computational methods optimises the delivered irradiance [71, 72]. Although findings are based on a small single-arm phase 1 study, I-PDT has demonstrated safety, positive effects on immune response, and potential benefits for survival [59].

Cryotherapy

Cryoprobes are used in rigid or flexible bronchoscopy [73, 74]. By rapid CO_2 or nitrous oxide expansion in the probe tip, it reaches temperatures below −30°C, freezing the surrounding tissue up to 1 cm deep [75]. While the tissue dies, it maintains its structure, making it beneficial for cryobiopsies. Cryoprobes are most commonly used for cryoextraction of intraluminal tumour tissue, which is devitalised beforehand using hot methods to reduce bleeding [76]. It is rarely used as the sole treatment method for malignant CAO because freezing alone does not yield immediate effects [77, 78]. It is useful for ablating granulations on stent ends that could be damaged using hot methods. When using cryoprobes, there is no need to reduce F_{IO_2}. In cases of pedunculated tumours, we treat the tumour base with a cryoprobe after tumour removal, achieving a deep effect while avoiding perforation due to tissue matrix preservation (figure 4).

Microwave ablation

Microwave ablation (MWA) is a technology that heats tissue by creating an oscillating electromagnetic field around an ablation device. Tumour debulking post-MWA requires less time as it enables the removal of large pieces without haemorrhage [79].

MWA has recently been introduced in treatment of central airway tumours and the first studies with small patient numbers indicate that MWA is a safe and efficient method. Trigiani *et al*. [80] reported seven cases of airway stenosis from extrinsic compression, applying MWA through a rigid needle placed through the airway wall. Senitko *et al*. [81] successfully recanalised obstructing intrinsic tumours in eight cases using an MWA endobronchial ablation catheter, with no complications.

Intratumoural therapy

Endobronchial intratumoural chemotherapy, an alternative to systemic treatment for centrally located nonsmall cell lung cancer (NSCLC), achieves highly cytotoxic concentrations within the tumour while minimising toxicity outside it. It can be safely performed through EBUS-guided transbronchial needle

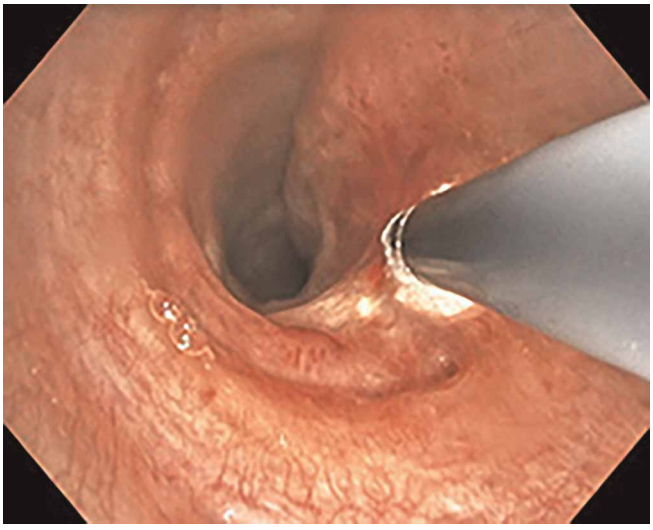

FIGURE 4 Cryotherapy is effective for additional treatment of the basis of removed polypoid tumours or minor lesions in the central airways. Its effect extends deeply, with a low risk of perforation.

injection and few adverse events have been reported [82]. Studies have shown success in relieving obstruction (69–88%) with repeated cisplatin and ethanol injections, but the optimal dose and regimen are yet to be determined [83–86]. For smaller tumours, one or two injections may suffice, while larger tumours benefit from multiple injection sites [87]. Additionally, pre-debulking intratumoural alcohol injection aids in cases with a large tumour burden by inducing necrosis and microcirculatory embolisation [88].

Clinical outcomes

When assessing the justification for therapeutic bronchoscopy, quantitative monitoring of clinical outcomes plays a crucial role in improving the patient's health and quality of life. Important clinical outcomes in bronchoscopic treatment of CAO include technical success, weaning from mechanical ventilation, dyspnoea, health-related quality of life (HRQoL), survival and quality-adjusted survival [89].

Ost *et al*. [10] analysed a registry of therapeutic bronchoscopies from 15 bronchoscopy centres. Technical success (reopening the airway lumen to >50% of normal) was achieved in 93%. Clinically significant improvement in dyspnoea was achieved in 48% and in HRQoL, in 42%. Worse baseline dyspnoea was associated with a greater improvement in both parameters. Similar technical success rate, and improvement in dyspnoea, HRQoL and spirometry were observed in other studies, and were maintained long-term [15, 90]. The patients who benefit the most in terms of survival are those with purely endoluminal lesions, in whom technical success was achieved and those whose cancer-specific treatment was initiated after intervention [91].

Due to sudden deterioration with respiratory failure, intubation and mechanical ventilation are sometimes necessary for patients who are later diagnosed with malignant CAO. Rapid weaning from the ventilator allows some patients to initiate therapy or at least gain some time for making independent decisions regarding care goals. Interventional procedures with stenting or removal of intraluminal tumour enables weaning from the ventilator in 52.6–75% of patients [15, 92].

Stratakos *et al*. [93] compared the survival of patients after recanalisation of CAO with a group of patients who refused therapeutic bronchoscopy. Mean±SD survival for intervention and control group was 10±9 and 4±3 months, respectively. Quality of life and the degree of dyspnoea were consistently better in the intervention group throughout the follow-up period. The median quality-adjusted survival was 109 quality-adjusted life-days after successful recanalisation of malignant CAO in a study by Ong *et al*. [90].

Lastly, it is important to mention that malignant CAO often worsens performance status to the extent that the patient cannot receive specific oncological treatment. A study by Lee *et al*. [33] showed that 70% of patients who were previously in ECOG groups 3 and 4 could subsequently receive specific oncological treatment due to symptom improvement. Interventional bronchoscopy is thereby a part of new integrated multimodal therapeutic approaches that further extend the survival of patients with lung cancer and CAO [94, 95]. Our experience indicates that after successful combination of radiotherapy and new systemic treatments, endobronchial stents from several patients have been removed due to a stable disease remission.

Complications

Despite the fact that patients with malignant CAO are often in poor general condition, sometimes even in respiratory failure, the complication rate during interventional procedures is low. Procedure-related mortality ranges from 0.4% to 1.3%, and the overall rate of severe complications is 3.9–18.1% [1, 96, 97]. Early complications include bleeding, pneumothorax, worsening hypoxaemia, and injury to the vocal cords, larynx or airway. Late complications are often associated with stents (granulation tissue blockage, lung atelectasis due to mucous plugs, migration and infection) [1, 96–98]. Urgent and emergent procedures, ASA score >3, redo therapeutic bronchoscopy, and moderate sedation instead of general anaesthesia are risk factors for complications [98].

Small tumours within the central airways

Centrally located early lung cancer (CLELC) is defined as localised lung cancer no more distal than the segmental bronchi, diagnosed as squamous cell carcinoma (SCC) *in situ* or SCC with no invasion beyond the bronchial cartilage (figure 5) [99]. TNM-8 classification for NSCLC categoriss these as Tis, T1a, T1b and T2a lesions (if involving the main bronchus) with no lymph node or distant metastases, corresponding to stage Ia and Ib disease [100].

Surgical resection is the gold standard for CLELC treatment; however, stereotactic or external beam radiotherapy is considered for patients unwilling or unable to undergo surgery [99]. Due to the proximal

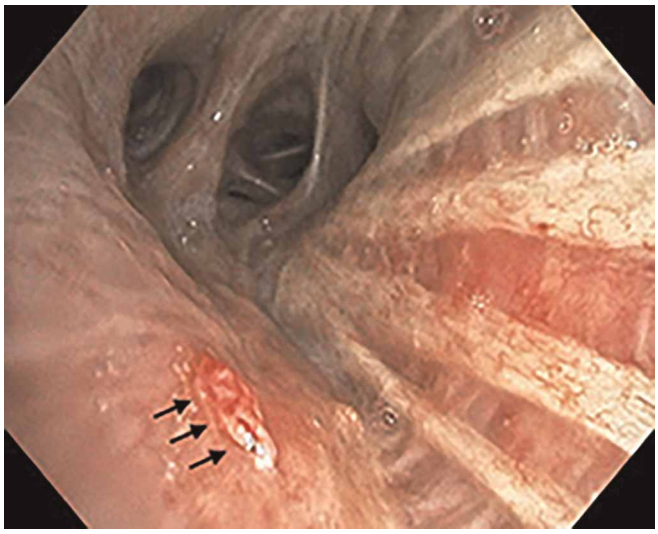

FIGURE 5 Early squamous cell carcinoma in the central airways (arrows), discovered accidentally.

location, resection often requires removing substantial unaffected lung parenchyma, with lobectomy (74%), bilobectomy (20%) and pneumonectomy (6%) [101].

CLELC patients, typically older male smokers with a high COPD prevalence, may be ineligible for surgery or radiotherapy due to significant comorbidity [102, 103]. Rate of up to 28.6% synchronous and metasynchronous lung SCC in treated patients have been reported [101]. Endoscopic therapy suits high-risk candidates, preserving lung parenchyma but potentially increasing local recurrence [104]. However, recruiting participants for well-powered RCTs is challenging due to the small subset of NSCLC cases ineligible for surgery or definitive radiotherapy.

Photodynamic therapy

PDT is currently the best studied of the available endoscopic treatment options for CLELC [99, 105, 106]. Despite this, the data are limited to a mixture of small single-centre studies without a comparator arm. A total of 542 patients underwent PDT across 13 studies in bronchoscopy literature. Most studies used the photosensitiser Photofrin, but two Japanese studies employed the second-generation agent NPe6, believed to achieve deeper antitumour effects due to its longer wavelength. However, there has been no head-to-head trial to evaluate this [102, 107]. Complete response is observed in 70–100%, with subsequent local recurrence in 6.3–33% of cases. The 5-year overall survival rate ranges from 50.6% to 80% in newer studies [108]. A single-centre study demonstrated complete response rates of 91% in lesions $\leqslant$2 cm when using EBUS to assist in pre-treatment evaluation of the depth of invasion [109]. The only study consisting solely of operable patients with CLELC included 48 patients with superficial lesions $\leqslant$1 cm and showed a 94% complete remission rate, 20% local recurrence rate and an overall survival rate of 81% at 5 years [108]. Adverse effects of PDT are uncommon, with 5–32% experiencing mild cutaneous phototoxicity in the weeks afterwards.

High-dose brachytherapy

There is no clear consensus regarding the best protocol and dosing of high-dose brachytherapy for CLELC and protocols vary throughout the published data. Complete response occurs in 59.4–96% with subsequent local recurrence occurring in 5–37% of cases. The 5-year overall survival rate ranges from 24% up to 29% [99]. Grade $\geqslant$3 toxicity occurs at rates of 4.4–10.5%, with significant rates of haemoptysis and pneumothorax, and a few cases of treatment-related mortality [99].

Electrocautery

One pilot study from 1998 was published on the use of electrocautery in which 12 patients with <1-cm CLELCs were treated with curative intent. Complete response was achieved in 80% of patients without recurrence over a median follow-up of 22 months. There were no direct significant complications associated with the procedure in this study [110].

Cryotherapy

There is only one published study on cryotherapy in CLELC with curative intent, which reported 35 patients treated over a period of 12 years in multiple French centres [111]. Complete response was achieved in 91%. There was a recurrence in 28% of the patients over 4 years of follow-up. 4-year overall survival was 50%. There were no serious adverse events noted [111].

Radiofrequency ablation

In 2022 a pilot study of EBUS-guided radiofrequency ablation in five patients with central, early-stage NSCLC was performed in a single centre in Canada [112]. Further data are required to delineate both safety and efficacy.

Other methods of treatment

To date, there have been limited published data for use of laser ablation therapy or APC as a definitive treatment modality for central early-stage NSCLC [113, 114].

Small peripheral tumours

While lobectomy is the standard for early-stage lung cancer, the rise in incidental discovery of small lung nodules, especially in peripheral areas, prompts a re-evaluation of treatment options. Nodules often contain premalignant or early-stage lung cancers, leading to consideration of less invasive local treatments like sublobar resection, stereotactic body radiation therapy (SBRT) and percutaneous ablation. Bronchoscopic ablation for peripheral lung cancer has been explored due to its minimally invasive nature. In some patients, however, such as those with severe COPD and extensive pulmonary fibrotic changes, SBRT might also be contraindicated [115, 116]. Thermal ablation modalities include RFA, MWA, bronchoscopy thermal vapour ablation (BTVA) and PDT.

Guided by navigational bronchoscopy, often using virtual bronchoscopy or electromagnetic navigation, these procedures benefit even more from hybrid theatres with cone-beam CT (CBCT) and fluoroscopy for precise planning. Post-ablation CT scans assess lesion incorporation, ablation zone size and achieved minimal margin. Double ablation techniques, like reablation, pull-back and reablate, or renavigation followed by reablation, may be employed [117]. Trials without CT guidance use fluoroscopy and radial EBUS for sheath position verification [118].

Radiofrequency ablation

RFA relies on high-frequency alternating currents for tissue damage and coagulative necrosis. Innovations like saline-irrigated RFA catheters optimise the procedure, achieving wider and more uniform ablation zones [119]. Ongoing advancements in catheters and protocols focus on thermal energy delivery and saline irrigation volume [120]. Koizumi *et al.* [121] demonstrated an 82.6% local disease control rate and 61.5% 5-year survival, surpassing results with SBRT [119].

Microwave ablation

MWA uses electromagnetic waves (900–2500 MHz) generating heat to cause cell death. MWA is less affected by tissue impedance, which is relatively high in the lungs, and produces larger and faster ablation zones with less heat sink [117, 119]. Air-rich lesions, such as ground-glass nodules, are more suitable for MWA [122]. Trials with MWA combined with image guidance (navigational bronchoscopy and CBCT) reported 100% technical success and efficacy ranging from 73% to 100%. Safety and feasibility are primary outcome measures, with limited long-term survival data. In a study conducted by Pritchett *et al.* [123], no tumour recurrence occurred during 12-month follow-up of 10 stage I lung cancer patients with ⩽20-mm tumours treated the image-guided transbronchial MWA, and a 2-year local control rate of 71.4% and median progression-free (PFS) survival of 33 months was described by Xie *et al.* [124]. Severe adverse events are rarely reported, but may include post-ablation fever reaction with fever, chest pain/pleuritis and pneumothorax requiring drainage. Pritchett *et al.* [123] reported one death of unknown cause on the 15th day following ablation, which led the sponsor to halt enrolment of their study.

Bronchoscopic thermal vapour ablation

BTVA is well-established in emphysema but also has potential in lung tumours. The study by Steinfort *et al.* [125] study introduced the novel BTVA-C system with higher thermal energy delivery in peripheral lung tumours but maintaining a comparable safety profile.

Photodynamic therapy

The disease control rate of small peripheral tumours treated with PDT is very high, with several cases with complete response after PDT, and one study reported 1-year PFS of 100% in seven cases treated [126].

Possible new treatments

Transbronchial cryoablation, laser interstitial thermal therapy and brachytherapy are being explored for inoperable lung tumours, mainly in research settings [43, 127].

Irreversible electroporation is a nonthermal technique inducing cell death through electric pulses [128].

Conclusions

Interventional bronchoscopy has been used in the diagnosis, treatment and palliation of malignant diseases in the airways since its inception. In recent years, it has experienced accelerated development and has become established as a crucial component of multidisciplinary lung cancer treatment. With its broad array of methods and utility, interventional bronchoscopy, particularly with its relatively low invasiveness, opens possibilities for patients with advanced disease, conditions in anatomically challenging locations, and especially those who are polymorbid or have a reduced performance status.

Its therapeutic capabilities contribute to improved patient outcomes, reduced invasiveness and a more personalised treatment experience. As research and innovation continue to unfold, interventional bronchoscopy holds the promise of reshaping the landscape of lung cancer management, offering more hope to patients.

Key points

- Using interventional bronchoscopy, we perform both palliative and curative procedures for malignant stenosis of the central airways and early-stage lung cancer (both central and peripheral).
- Using a rigid and/or flexible bronchoscope, various devices are introduced into the airways to destroy and remove tumour tissue.
- In cases of extramural compression, airway dilation and stent insertion can be carried out.
- The purpose of interventional bronchoscopic procedures is to alleviate severe symptoms and improve the functional status of the patient, enabling them to undergo multimodal treatment and thereby enhancing their survival.
- Interventional bronchoscopy provides treatment for a subgroup of patients with early forms of lung cancer who, due to accompanying diseases, are not candidates for surgical or other aggressive treatments.

Self-evaluation questions

1. What is the main goal of bronchoscopic treatment for malignant stenosis of the central airways?
   a) Successfully inserting an endobronchial stent
   b) Restoring lung function to ⩾75% of normal values
   c) Alleviating symptoms and improving the functional status of the patient
   d) Preventing further tumour growth along the airways
2. In which scenario is the insertion of endobronchial stent indicated?
   a) A patient with a 50% stenosis of the left main bronchus as preparation for radiotherapy
   b) A dyspnoeic patient with a large tumour in the right lower lobe
   c) A patient with 90% stenosis of the distal part of the trachea with a polypoid tumour
   d) A dyspnoeic patient with a 75% obstruction of the distal part of the trachea due to the pressure from enlarged lymph nodes on the trachea
3. What is a significant risk factor in the treatment of an initial malignant lesion in the central airways with a laser?
   a) Jet ventilation of anesthetised patient with F_{IO_2} 100%
   b) Pacemaker
   c) Previous report that the patient had haemoptysis
   d) Pleural effusion on the same side
4. What is not the method of choice for treating an endobronchially growing tumour that obstructs 90% of the airway?
   a) Laser resection
   b) Electrocautery followed by cryoextraction of necrotic tissue
   c) Mechanical coring by rigid bronchoscope followed by APC
   d) EBBT

Conflict of interest: V. George reports receiving a research grant from Olympus Australia Pty Ltd., outside the submitted work. A. Trojnar reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca and MSD, outside the submitted work. The remaining authors have nothing to disclose.

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Suggested answers

1.c
2.d
3.a
4.d