Review Article

Techniques of endoscopic airway tumor treatment

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Abstract: Interventional bronchoscopy has a predominant role in the management of both early and advanced-stage airway tumors. Given the very poor prognosis of lung cancer, there is a need for new tools to improve early detection and bronchoscopic treatment of endo-bronchial precancerous lesions. In more advanced stages, interventional bronchoscopy plays an important role, as nearly a third of lung cancers lead to proximal airway obstruction. This will cause great discomfort or even life-threatening symptoms related to local extension, such as dyspnea, post-obstructive pneumonia, and hemoptysis. Surgery for very locally advanced disease is only effective for a limited number of patients and the effects of conventional antitumor therapies, like radiation therapy or chemotherapy, are inconstant and are too delayed in a palliative context. In this review, we aim to provide pulmonologists with an exhaustive technical overview of (I) the bronchoscopic management of benign endobronchial lesions; (II) the bronchoscopic management of malignant tumors, including the curative treatment of localized lesions and palliative management of malignant proximal airway stenosis; and (III) descriptions of the emerging endoscopic techniques used to treat peripheral lung tumors.

Keywords: Interventional bronchoscopy; central airway obstruction; lung cancer; laser; brachytherapy; airway stent

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Introduction

Interventional bronchoscopy mainly concerns malignant tumors (bronchogenic carcinoma in 70% of cases, metastatic malignancies in 25% of cases in our institution) but also benign tumors (5% of cases).

Lung cancer has the particularity of being tardily symptomatic, making early diagnosis a far too rare event. No screening program has yet been validated in most countries, and improvements to the early detection of metaplastic changes in selected populations are very challenging. For the same reasons, lung cancer is usually diagnosed at an advanced stage, and frequently from symptoms related to local progression of the disease, when conventional treatments offer inconstant and delayed benefits. In contrast, new bronchoscopic approaches that visualize peripheral nodules using radial-probe endobronchial ultrasonography (RP-EBUS) and electromagnetic navigation (EMN) are paving the way towards new bronchoscopic management of early-stage peripheral lung cancers.

Herein, we present an exhaustive description of the overriding role of the interventional pulmonologist in the management of pre-invasive, localized, and locally advanced lung cancer. We will detail: (I) the place of bronchoscopy in the curative treatment of benign pediculate endoluminal tumors; (II) the specific indications, results, and limitations of the bronchoscopic tools to detect and offer a curative treatment for localized neoplastic lesions, and the management of malignant central-airway obstruction; and

(III) discuss the emerging endoscopic approaches used for curative treatment of peripheral lung cancer.

Curative treatment of endobronchial benign tumors

Bronchoscopic treatment of benign tumors should be restricted to strictly endoluminal polypoid tumors (<15 mm^2 base), without any signs of submucosal-layer infiltration. Involvement of the airway wall must be precisely assessed by a CT-scan or ideally by more precise tools. RP-EBUS should be considered before treating such benign tumors as it can detect invasion of the cartilage layer with a sensitivity of 86% and a specificity of 100% (1). In 1995, Shah *et al.* reported "very good" and "good" results in 62% and 38% of patients, respectively, after bronchoscopic management of 185 benign airway tumors. The main technique used in these cases was laser resection (2). Bertoletti *et al.* then described the usefulness and the very good results from using cryotherapy on the implantation base of 18 strictly endoluminal and typical carcinoid tumors (3). This approach can be used for other benign tumors (4,5).

Bronchoscopic techniques for the curative management of early stage non-small-cell lung cancer (NSCLC)

Techniques for detection and local staging

Given the very poor prognosis of lung cancer, efforts have been made to improve the early detection of precancerous lesions. Indeed, 37% of severe dysplasias and 87% of *in situ* carcinomas evolve into invasive cancer, although less commonly in the presence of slight or moderate dysplasia (3.5%) (6). Furthermore, close surveillance is indicated for every patient that survives an initial lung cancer, as the risk of developing a second carcinoma ranges between 2% and 14% per patient per year (7,8). Different tools are available for the early detection and follow-up of these radio-occult tumors, for the screening of other endobronchial lesions before thoracic surgery, and to guide bronchoscopic curative treatments. Local staging includes evaluation of the area and thickness of the lesion.

Autofluorescence can differentiate dysplasia and cancer lesions from normal tissues based on their respective concentrations of endogenous fluorophores. The decrease in the extracellular matrix and the increased concentration of porphyrin that characterizes dysplastic tissue will thus correspond, in the autofluorescence bronchoscopy or autofluorescence imaging, to defects in fluorescence or to magenta-colored areas, respectively (9). Nevertheless, if sensitivity is good (0.9), the major pitfall of autofluorescence is its low specificity (0.56) (10); resulting in an increased number of useless biopsies (false positives). However, the results strongly depend on the predetermined definition of "positive biopsy" (i.e., 71.1% specificity for severe dysplasia and carcinoma *in situ*) (11).

Narrow-band imaging enables analyses of submucosal microcapillary structures, with different pathologic patterns described in dysplastic or cancerous tissues (grid dotted, tortuous, abrupt-ending blood vessels) (12,13). The advantage of this technique compared to autofluorescence imaging resides in its improved specificity (90% *vs.* 52%) (14).

Probe-based confocal laser endomicroscopy may further improve the diagnostic accuracy of bronchoscopy when screening pre-invasive metaplasia. The first data suggest good sensitivity (96%) and specificity (87%), which could be increased by topical instillation of exogenous fluorophores, such as acriflavine (15).

RP-EBUS can be used to evaluate the depth of invasion within the cartilaginous layer with good specificity (77%) and sensitivity (88%) (16-18). In addition, any adjacent suspected lymph nodes can be sampled by needle aspiration using linear EBUS, which is an established technique used in lung-cancer staging.

Optical coherence tomography may also help to assess parietal extension of radio-occult lesions (19).

Techniques used for the curative treatment of pre-invasive or minimally invasive lesions

Surgical resection remains the gold standard in early-stage NSCLC (20). However, bronchoscopy offers different options for the treatment of carcinoma *in situ* or slightly invasive endo-bronchial lesions, with good results, low morbidity, and low cost. Indeed, many patients with poor lung function or other comorbidities can then avoid surgery.

Smokers can develop multiple pre-neoplastic lesions and synchronous or metachronous squamous carcinomas within the entire upper aerodigestive tract, based on the principle of "field cancerization" (21). The main advantage of endoscopic treatment is thus the preservation of lung parenchyma and lower morbidity mortality, whereas the major risks are potential underestimation of the extension of the tumor and a lack of care regarding lymph-node metastases (22). The best candidates for bronchoscopic treatments are patients with lesions measuring <10 mm

Table 1 Results and limitations of the main available bronchoscopic techniques used for curative treatment of endobronchial lesions

Methods	Principle	Indications	Results/advantages	Limitations
Photodynamic therapy	Local activation of a photosensitizing agent using a specific wave-length (630 nm) Phototoxic reaction	Maximum 6–7 mm depth lesions; extensive/ multiple lesions	Tumor response 70%; 5-year survival 70% for TIS or stage I; widely studied	Cost; sunburn
Brachytherapy	Radioactive isotopes (Iridium 192) delivered through a graduated radio-opaque catheter	Radio-occult lesions, <3 cm infiltration; inoperable patients; contralateral recidive after pneumonectomy; incomplete resection surgery	2 years-survival rate 92%; 2 years-local control rate 86%; depth of action; synergistic association with external radiation therapy; widely studied	Risk of fatal hemoptysis; radiation bronchitis/ necrosis/fistula/ stenosis
Cryotherapy	Cold cytotoxic effect (dehydration, crystallisation)	Endobronchial superficial lesions; no cartilaginous invasion; <3 mm depth	91% histological remission; no fire risk; cheap; no risk of stenosis or perforation	Limited thickness of action (3 mm)
Thermocaogulation	Thermic destruction of the tissue by a high-frequency electric current	From severe dysplasia to micro invasive carcinoma	80% complete response rate; cheap; quick; available in many centers	Risk of bleeding; stenosis; perforation; poor littérature

without extra-cartilaginous invasion (23). Once the histological nature and extension are assessed, different tools are available, with each having preferential indications, specific mechanisms of actions, and risks. These data are summarized in *Table 1*.

Brachytherapy

Brachytherapy is a highly localized radiation therapy that preserves healthy tissue. Radioactive isotopes (iridium-192) are delivered to the tumor through a graduated radio-opaque catheter (24). Catheters are placed through a large bronchoscope, their position controlled by fluoroscopy. The target volume is assessed based on endoscopic findings (usually helped by autofluorescence imaging) and 3D-treatment planning is then calculated from radiographic data after placement of the catheter(s). *Figure 1* shows each step during treatment of endoluminal T1 squamous-cell carcinoma in a patient recused for surgery.

Brachytherapy should be considered as a curative treatment in radio-occult lesions, endobronchial infiltration for patients with respiratory insufficiency, controlateral recurrence after pneumonectomy, or as a complementary technique for incomplete resection surgery (25-29).

The largest cohort to date included 226 patients that had undergone brachytherapy (97% squamous cell carcinomas and had been treated with high-dose rate (HDR) brachytherapy because they had contraindications for surgery or external-beam radiation therapy. Repartition was 26% Tis, 67% T1, and 0.04% T2. A complete bronchoscopic response at 3 months was observed in 93.6% of patients. The 2- and 5-year survival rates were 57% and 29%, respectively. Fatal hemoptysis occurred in 5% of cases, bronchitis in 19.5%, with 3.5% necrosis. These complications were shown to be associated with the use of two catheters and having a distal localization (27).

A combination of external-beam radiation therapy and HDR brachytherapy has also been proposed to treat endobronchial carcinomas as an alternative to surgery, and has achieved high response and survival rates. In this study, Kawamura *et al.* included 16 lesions, of which 10 were treated with HDR brachytherapy (20 Gy) combined with external-beam radiation therapy (45 Gy), and 6 lesions were treated with HDR brachytherapy alone (25 Gy). The 2-year survival and local-control rates were 92.3% and 86.2%, respectively. Local recurrences were observed in only two lesions (30).

This method is expansive and remains suited for deeper lesions compared to the techniques described below. Acute side effects of this procedure include pneumothorax, bronchospasm, hemoptysis, pneumonia, and cardiac arrhythmia. Radiation bronchitis and stenosis may occur as early and delayed complications. Interventional bronchoscopy is sometimes required in cases of

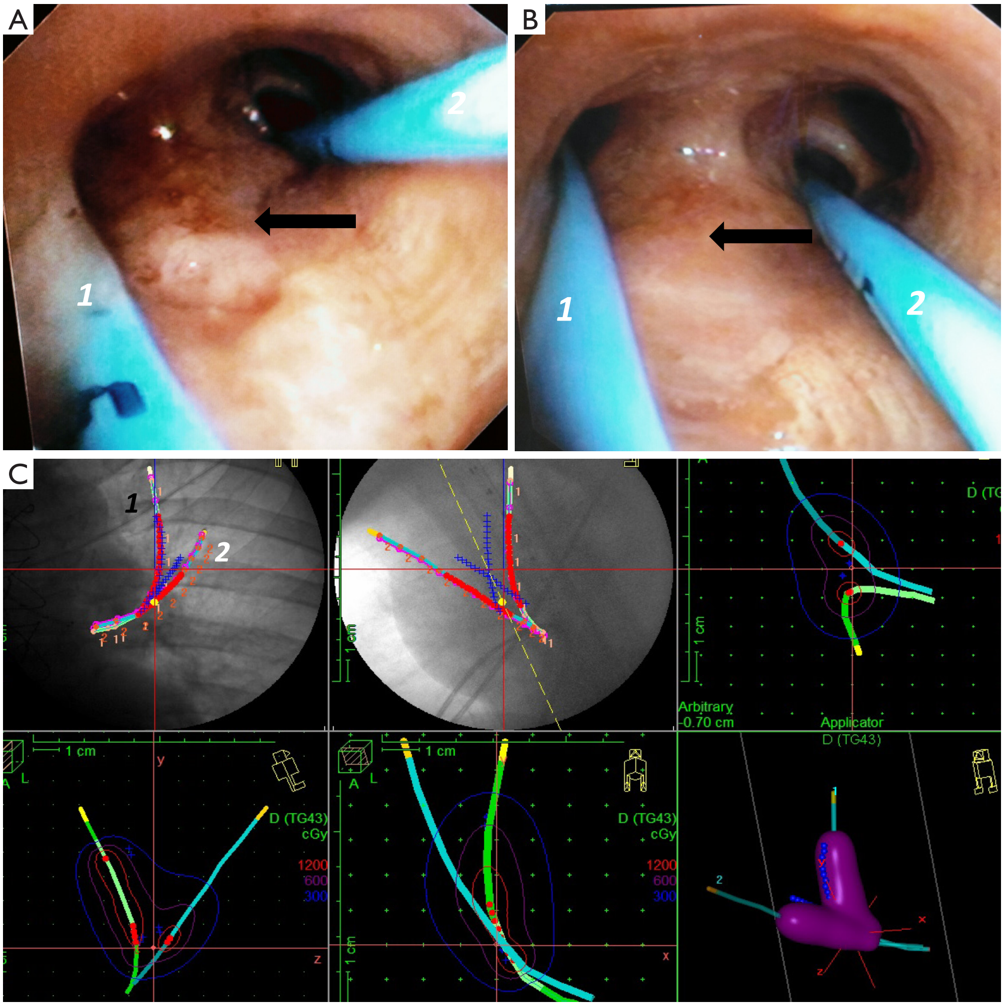

Figure 1 Example of brachytherapy for an endobronchial infiltration of the upper left lobe. Bronchoscopic view of the two catheters (1= apical of the culminal bronchus; 2= anterior segment of the culminal bronchus); showing local dramatic improvement: before (A) and after (B) the three first fractions (6 Gy); (C) planning of dose distribution from radiographic images.

symptomatic stenosis (balloon dilatation, laser resection, or airway stenting) (31).

It is sometimes difficult to differentiate complications linked to tumor progression from those related to brachytherapy (32). The most serious potential side-effects from brachytherapy are fatal hemoptysis and fistula formation. Death from massive hemoptysis has been reported in up to 7% of patients (n=342), but occurred mainly within palliative settings, and this complication seems rarer in the context of minimally invasive lesions (33).

Photodynamic therapy (PDT)

The principle of bronchoscopic PDT resides in the local activation of a photosensitizing agent (most commonly a hematoporphyrin derivative) using a light source with a specific wave-length (630 nm) that induces a phototoxic reaction and cell death (24,31-33). Bronchoscopic PDT for lung cancer is a two-step procedure: photosensitization and illumination. After intravenous injection of a photosensitizer (photosensitization) and a 72-h latent period, bronchoscopic illumination is carried out. Other photosensitizers have been tried (ALA or Npe6) (34). The depth of action is 6–7 mm and the surface diffusion of light allows, in theory, treatment of slightly more extensive lesions than other techniques. Moreover, this technique can still be used when the tumor area cannot be precisely identified by narrow-band imaging or autofluorescence imaging. Depending on the number and extent of the treated lesions, PDT can be performed under local or general anesthesia, sometimes secured by rigid bronchoscopy.

Many studies have reported on the efficiency of PDT in treating central-airway obstructions (reported in the next chapter), and early stage and minimally invasive endobronchial tumors. Corti *et al.* reported a 5-year survival rate of 60% amongst 40 patients with CIS or minimally invasive diseases (35). Moghissi *et al.* collected data from PDT used for early-stage NSCLC in 13 studies (n=523 patients). Tumor response to treatment was observed in >70%. The 5-year survival amongst patients that experienced complete remission after treatment of TIS or stage-I diseases was 70%. After exclusion of deaths not related to cancer, the 5-year survival was 90% for TIS (36).

PDT is generally well tolerated. Skin photosensitivity is the most common side effect (8–28% of cases), which is usually grade I, justifying avoiding sunlight for the 6 weeks after treatment (31,36). Dyspnea may be caused by airway obstruction from necrotic debris, local airway edema, or delayed strictures, but these complications are less common in the context of early-stage disease than in a palliative situation. Fatal hemorrhage and fistulas were also very rarely reported in this indication.

Cryotherapy

Cryotherapy is the application of very low temperatures (89.5 ℃) using cryogenic liquid gas (N_2O, N_2, CO_2) to destroy tumor tissues (24,34,35,37). The mechanisms of action are associated with immediate (dehydration and cellular crystallization) (31,37-40) and delayed (apoptosis, ischemia caused by microthrombi formation) effects (31,39,41). At least three cycles of freezing and thawing are applied to the treatment area through the tip of a flexible or rigid cryoprobe. The whole surface should be treated with 5-mm spacing between each new application of the probe (31).

Deygas *et al.* reported 91% histological remission rate at one month in a multicenter study (n=35). Local recurrence was observed in 28% of cases within 4 years (41). Noppen *et al.* also reported favorable outcomes in four patients (42). Cryotherapy possesses many advantages: it is very cheap and safe (41) because the risk of airway ignition, perforation, or delayed stenosis is non-existent, and it has a good hemostatic effect (35,43). Its major pitfalls are the narrowness of the treatment area and the depth of its cytotoxic action, which is limited to 3 mm (44).

Thermocoagulation

Electrocoagulation (or electro-cautery) is a coagulation technique. A high-frequency electric current is delivered through the tumor tissue, which generates heat and destroys it (24). The probe is placed in close contact to the target tissue area and the energy setting can then be changed depending on the expected effect. A small study that included 15 <1 cm endobronchial lesions in 13 patients showed an 80% complete-response rate and no recurrences after 22 months of follow-up (45). It can be applied through flexible or rigid probes, under local or general anesthesia (46). It is inexpensive and available in all surgical wards, but some complications can occur, such as bleeding.

In conclusion, all of these methods show promising outcomes. Brachytherapy seems to be most suited to deeper lesions and PDT to extensive and/or multiples lesions, especially when the tumor area cannot be precisely identified. Nevertheless, more prospective controlled studies need to be conducted to help clinicians choose the right technique for each specific case. Associations of these different tools together with stereotactic radiotherapy or systemic treatment should also be evaluated.

Available techniques for the management of central-airway obstruction

Between 20% and 30% of lung cancers cause central-airway obstruction (CAO), resulting in dramatic alterations to quality of life and a poor prognosis. CAO can be linked to purely endoluminal tumors, extrinsic compression, or a combination of both. Multiple bronchoscopic tools are available to relieve these obstructions depending on the mechanism of the stenosis, and can be split into four main categories: (I) mechanical debulking, usually used with other techniques for intraluminal lesions; (II) thermal techniques, which have an immediate effect on severe and/or very symptomatic intraluminal stenoses; (III) thermal techniques that have a delayed effect on non-threatening intraluminal stenoses; and (IV) airway stenting for extrinsic compressions.

All these methods can be used alone or in combination (47). The precise place of each technique and the eventual superiority of one over another remains undefined, as no large clinical trials or comparative studies have been conducted. The choice of technique thus depends on the choice of the operator and the techniques available. The principles, results,

Table 2 Principles, results, and pitfalls of the techniques available for the bronchoscopic management of malignant central-airway obstructions

Methods	Principle	Indication	Advantages	Limitations
Mechanical debulking	Resection with the beveled end of rigid tubes and rigid forceps	Proximal, slightly hemorrhagic intraluminal lesions	Rapidity; cost	20% severe complications (bleeding, perforation)
Thermal techniques with immediate effect				
Laser	Short pulsations in the bronchial axis	Critical intraluminal obstructions	Rapid, immediate, and prolonged effect	Cost; perforation and fistula risks
Electrocoagulation + argon plasma coagulation	High-frequency electric current +/− argon as a carrier gas (APC)	Intraluminal proximal obstructions	Cost; low risk of perforation; APC: extended and hemorrhagic lesions	Risk of cicatricial stenosis if circumferential treatment; cost for APC
Thermal techniques with delayed effect				
Cryotherapy	Expansion of a cryogenic gas; cycles of rapid freezing and slow thawing	Non-critical endoluminal obstructions (except cryoextraction and spray cryotherapy)	Low cost; easy procedure; no perforation; prolonged efficacy	Delayed effect (except cryoextraction and spray cryotherapy); retention of tumor material
Photodynamic therapy	Activation of a photosensitizer by light; phototoxic reaction, cell death	Intraluminal or mixed nonthreatening obstructions	Good symptom control (hemoptysis) ; prolonged efficacy	Delayed effect; retention of tumor material; cleaning bronchoscopy; phototoxicity; cost
Stents				
Silicone stent	Inserted via rigid tube; adjustment with a forceps	Extrinsic or mixed obstructions	Good tolerance; few local granulomatous and ischemic reactions; easily removable	Systematic general anesthesia and rigid bronchoscopy; altered ciliary clearance; risk of migration (rare, except in case of purely extrinsic compression)
Metallic stent	Under radiographic or bronchoscopic control; flexible or rigid bronchoscopy; self-expandable	Second intention, except in cases of highly necrotic lesions, fistula or high distortion	Easy placement; preserved clearance	Risk of granuloma, perforation; hardly removable

APC, argon plasma coagulation.

and pitfalls of each technique are summarized in *Table 2*. Two examples of scanographic and bronchoscopic results after mechanical debulking, thermo-coagulation, and airway stenting are represented in *Figures 2* and *3*.

Indications

Interventional bronchoscopy is an invasive treatment and should only be used in cases of symptomatic obstruction and in the presence of a viable downstream bronchial tree and parenchyma. A CT-scan and flexible bronchoscopy are thus the two essential tools to both check the viability of the distal airways and the precise mechanism of the stenosis. Significant improvement to quality of life and symptoms can be expected for obstruction involving large airways (trachea, main bronchi, *bronchus intermedius*). Interventional bronchoscopy for a more distal tumor must only be proposed to control hemoptysis or draining-retentional pneumonia (48). Beyond this technical aspect, selection of the patient that will benefit most from this treatment is crucial, but is sometimes difficult. We reported some strong predictive factors for sustained efficiency in a retrospective analysis of 204 patients (49). A study is currently recruiting patients to prospectively validate these results on survival and, above all, will try to identify the predictive factors for improvement to quality of life. We hope this study will help

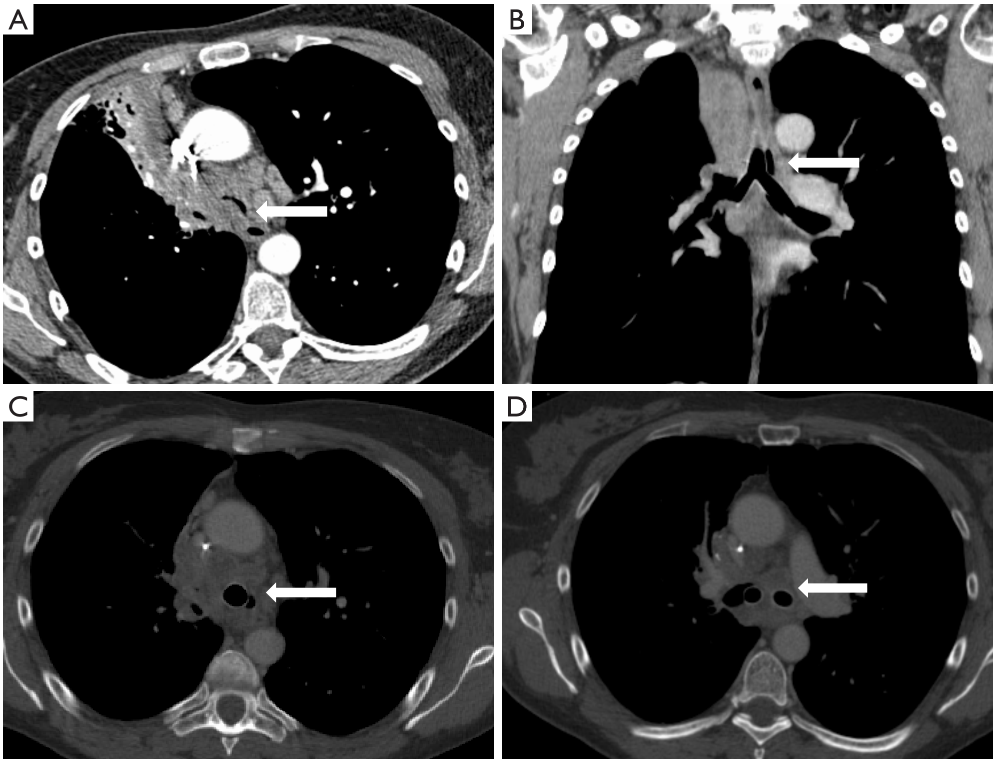

Figure 2 Example of a scanographic result after laser treatment, mechanical debulking, and airway stenting (a Dumon Y stent®) of a life-threatening malignant central-airway obstruction involving the carina (A); (B) frontal view after airway stenting; (C,D) scanographic sagittal views after airway stenting.

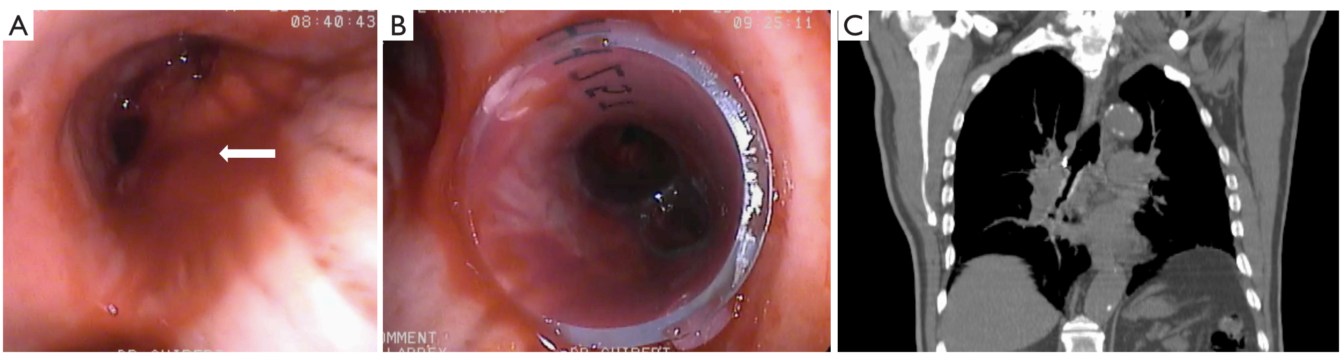

Figure 3 Example of a bronchoscopic result after stenting of the primary main carina for a malignant stenosis of the right main bronchi. (A) Extrinsic compression of the right main bronchus; (B) result after airway stenting (a Dumon Oki stent®); (C) CT-scan after stenting.

clinicians to select the best candidates and to avoid giving an invasive treatment to others.

Modalities

Rigid bronchoscopy offers advantages in terms of airway control, the ability to easily remove large volumes of tumor, and to deploy silicone stents: this method should, in our opinion, always be favored. Treatment through a flexible bronchoscope and local anesthesia, or under slight sedation and a laryngeal mask, may be considered for small, nonthreatening, and slightly hemorrhagic tumors, when the expected time of procedure is short. When rigid bronchoscopy is chosen, different types of ventilation can be proposed: i.e., manual with a bag-valve mask, or jet ventilation (high frequency, high pressure, low volume) (48).

Techniques with an immediate effect

In cases of threatening and/or very symptomatic intra-luminal CAO, an immediate, rapid, and safe technique must be chosen. Mechanical debulking, electrocoagulation, and laser are the most widely used techniques in this context.

Mechanical debulking

Rapid debulking of intraluminal tumors can be obtained with either the beveled end of different-caliber rigid tubes or with a large clamp. However, except in cases of proximal and low-risk hemorrhage tumors, this approach usually needs to be combined with one of the thermal techniques described below, as it is associated with high rates of complications when used alone (i.e., ~20% of cases), such as pneumothorax, hemoptysis, and pneumonia (50). For example, an ideal sequence is, combined with a laser: (I) hemostasis by tumor coagulation at 30 W; (II) mechanical debulking; (III) destruction of the residual tumor tissue at 50 W; and (IV) final treatment at 20–30 W on the implantation base for a prolonged cytotoxic effect (51,52). A minimum of 15–20 supervised procedures are required to reach autonomy with a rigid bronchoscopy (53).

Thermocoagulation

This method offers rapid relief from malignant proximal intrinsic compressions. A high-frequency electric current is delivered to the endoluminal tumor obstruction through a flexible or rigid probe of varying diameter and form, such as a coagulation electrode, loop, or hot-biopsy forceps (24,31,54-56). New-generation generators can be set to different modes (55). The "soft-coagulation" mode prevents airway fire, maintaining relatively low temperatures (<200 °C). "Forced coagulation" is more risky but allows rapid debulking by tissue carbonization. Symptomatic palliation is obtained in 96% of cases and concords with functional improvement (55,56). Major complications are rare, and the particular risks of perforation and ignition are non-existent in soft-coagulation mode (55,57-59). Circumferential thermocoagulation of an airway may result in scarring stenosis (53,60,61). Thermocoagulation must therefore been considered as the first-line treatment for intra-luminal tumors as it is highly efficient, only moderately expensive, and is very safe.

Argon-plasma coagulation

The limitations of electrocoagulation include restricted access to the most apical segments and loss of efficacy when there is active bleeding. These two drawbacks are overcome by using argon as a carrier gas (non-contact method), but this technique requires an additional probe and a generator (24,31,57,62). Argon (and thus electric current) is transported to the affected vessels through the bloodstream, allowing good control of the hemorrhage (100%) (62,63), even if the origin of bleeding cannot be precisely identified (24,53,55,64,65). This makes this tool particularly suited for extensive and hemorrhagic lesions.

Laser

This method is the fastest and thus the most suitable technique for life-threatening intraluminal critical obstruction. It uses different gases (CO_2, potassium titanyl phosphate, Nd:YAG, and a diode laser) to rapidly photocoagulate and destroy tumors (24,53). An immediate bronchoscopic result (92% of cases) is usually obtained, and the more proximal the tumor, the better the result (66). This re-permeabilization results in constant and significant improvement in symptoms, quality of life, arterial blood gas, and spirometric analyses (67,68). The results are globally equivalent to those reported with thermo-coagulation (55,69) but laser treatment may shorten the procedure, even though these two techniques have not been prospectively compared. The risk of airway fire only appears beyond the 0.4 FiO_2 level and can thus be prevented by good communication between the anesthesiologist and pulmonologist (68,70). Hemorrhages are not rare, but can be usually efficiently controlled by cold serum, adrenaline, local instillation of terlipressin, compression with the tube, or short electrical pulses of <30 W. Severe hemoptysis only occurs in 1% of cases (52,67,70).

The major potential lethal complication, related to a high depth of action, is perforation of the tracheobronchial wall to cause a vascular fistula, gas embolism, and/or mediastinitis (70,71). This event can be avoided by respecting a tangential axis of treatment and a non-contact treatment (1 cm). Although the mortality rate is low [reported as <1% (31,68,69,71)], one pitfall of this technique is its high cost, which may be prohibitive in some centers due to the price of the generator and because of the single-use probes, with costs much higher than for electro-coagulation (54,64,69).

Cryotherapy with an immediate effect

Cryotherapy can be delivered through a flexible or rigid probe (40,72,73). This procedure is known to have delayed effects (74) and, thus, is not suitable for cases of threatening stenosis. Nevertheless, two modalities can still be considered in this context.

(I) Spray cryotherapy is a technique that enables low-pressure liquid nitrogen (−196 ℃) to be administered, and produces immediate effects. The treatment area is extensive and the hemostatic effect is excellent. This technique, like APC, should therefore be preferentially used in cases of hemorrhagic and extensive tumors, especially when the origin of bleeding is not easily identifiable. Nevertheless, this technique still requires validation and does not appear suitable for voluminous tumors, given that this intervention has a long duration (73).

(II) Cryoextraction uses a large probe (2.3 mm) and is another modality used to treat obstructive stenosis without risking perforation or residual stenosis; it has a low incidence of other complications (74).

Endoscopic dilatation

Balloons placed at the center of a malignant stenosis can allow mechanical debulking and dilatation by controlled inflating (3 to 6 atm. pressure) (75-77). However, the effect is transient, and this tool should only be considered as a complement with other techniques, especially as a first step before stent placement when there is an impassable obstruction.

Microdebrider

The microdebrider is mainly used by rhino-laryngologists and involves a rotating blade and suction. This combination shortens the procedure, as tumor debris are simultaneously aspirated, and allows for rapid and efficient debulking [98% of cases (78,79)].

Techniques with a delayed effect

When there is a nonthreatening and slightly symptomatic malignant stenosis, the indications for interventional bronchoscopy must be carefully discussed. Indeed, it depends on the other therapeutic options and the probability of these conventional therapies (radiation therapy, chemotherapy) succeeding (47). Histological subtype and its supposed chemosensitivity should especially be taken into account. In this context, cryotherapy is the most attractive tool due to its low cost, good efficiency, safety, and prolonged effects. Other techniques have been reported but, in our opinion, should not be considered as first-line treatments in the context of palliative management of central-airway obstruction, like PDT or HDR brachytherapy.

Cryotherapy with a delayed effect

Except for particular cases of cryo-recanalization and spray cryotherapy (described previously), this technique is indicated in cases of non-obstructive and slightly symptomatic obstructions without acute respiratory distress, because of its delayed effects (24,55). This procedure offers good control of symptoms (especially hemoptysis), and improves quality-of-life scores, arterial blood gas, and spirometric parameters (35,37,80). A normal airway caliber can be recovered in 61–91% of cases (72,81,82), allowing for resolution of 57% and 76% of cases of total and lobar atelectasis, respectively (81). Its prolonged effect, strengthened by repetitive cryotherapy sessions, is related to an associated cytotoxic effect (74,83,84).

One major advantage of this tool is its safety. Mortality rate is low, reaching 1.2%, and is rarely directly linked to cryotherapy (80). The total complication rate is less than 10% (72,82). The risk of perforation is non-existent, as the cartilage is extremely cryo-resistant (31,72). This technique also has a low cost and a synergistic association with chemotherapy (85,86). The major caveat is its delayed effect, resulting in retention of tumoral material, which then needs bronchial aspiration performed at 1–2 days after (31,62,87).

PDT

The principle of bronchoscopic PDT resides in local activation of a photosensitizing agent (most commonly a hematoporphyrin derivative) using a light source with a specific wave-length (630 nm), which induces a phototoxic reaction and cell death (24,31,38,43,88). Like cryotherapy, PDT achieves good but delayed improvement, and is therefore contraindicated in cases of critical obstruction. This technique is particularly effective in controlling hemoptysis (99%) and dyspnea, and offers good bronchoscopic results and significant functional improvement (89-91). A synergistic effect with radiation therapy is probable (92).

However, this technique has major limitations. The drug is eliminated from most tissues within 72 hours, yet remains preferentially stored in the skin, liver, spleen (and in malignant cells), explaining the phototoxic reactions observed in 5–28% of patients. Avoidance to sunlight is recommended during the 6 weeks after treatment (52,91); however, this preventive measure appears to be

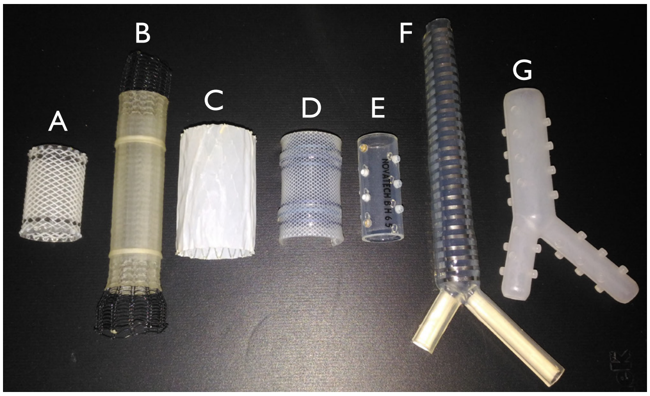

Figure 4 Examples of stents available: from left to right: (A) Polyflex®; (B) Covered Ultraflex®; (C) Silmet stent®; (D) Nova-Stent®; (E) Dumon stent®; (F) Dynamic Freitag® stent; (G) Hood stent®.

overly restrictive in a palliative context. In addition, a second bronchoscopy must be performed at 1–2 days later to remove necrotic tumor tissue and again at 5–7 days after to expose residual tissue to a second illumination (83,88,89,93,94). Furthermore, hemoptysis is a relatively frequent complication, reported in 18% of cases, of which 2.2% are fatal (89); the mortality rate is not negligible, reaching 9% during the first month (91).

Brachytherapy

Although brachytherapy, as described previously, still constitutes an interesting option for early-stage lung cancer, in our opinion, it should no longer be used for the palliative treatment of malignant obstructions. Symptomatic and functional improvements have been reported in older studies, with delayed efficiency, but the risk of severe complications has been major, reported at between 13 and 20% (33,95). Up to 7% of patients died after massive hemoptysis (33). Radiation bronchitis, which frequently exhibits a fatal evolution due to bronchial necrosis followed by abscess formation, affected 14–35% of patients (96,97). Nevertheless, experimental groups have reported good results and slightly better tolerance to this treatment. Interestingly, in a very large cohort (n=648) of patients divided into two groups that received a single fraction of 10 or 22.5 Gy in three fractions once a week, the clinical improvement was globally equivalent (98).

Local instillation of chemotherapy and gene therapy

Local intra-tumoral injection of chemotherapy has been attempted in the context of malignant central-airway obstruction. Celikoğlu *et al.* reported re-permeabilization in more than 80% of patients using different cytotoxic agents (5FU, mitomycin, methotrexate, bleomycin, mitoxantrone, cisplatin) (99-101). More recently, Mehta *et al.* also described good bronchoscopic results (defined as >50% reduction in airway stenosis from baseline) after intratumoral injection of cisplatin in 15/21 patients (102). Khan *et al.* obtained complete PET/CT remission of locally recurrent lung cancer after an EBUS-guided transbronchial needle-injection of cisplatin in a hilar lymph node (103).

Another promising approach is the bronchoscopic delivery of a recombinant adenovirus that carries wild-type *p53* into patients with NSCLC and that harbor the *p53* mutation. After monthly injections, 50% (6/12) of patients had airway obstruction improved by >25%, and 25% of patients showed a partial response (104). Combined with external radiation therapy (60 Gy), this strategy enabled 63% of cases to obtain local and complete-response rates (105).

Stents

Airway stenting is the only procedure available for the relief of extrinsic compression or trachea-esophageal fistulas (75,106,107). It has been widely used since Dumon designed a silicone stent, derived from Montgomery's T-shaped tracheal stent (which required a tracheotomy) (83,108). Self-expandable metallic stents dedicated to airways were concomitantly developed, after the transient use of endovascular stents (Gianturco), which were associated with a high risk of ischemic mucosal necrosis and thus of perforation (109). The ideal prosthesis should (I) be cost-effective; (II) be easy to place and remove; (III) not migrate; (IV) be rigid enough to resist airway compression, yet still flexible enough to mimic airway physiology; (V) not impair mucociliary clearance, and (VI) not induce granulomatous reactions (38,106,110). The most widely used stents are represented in *Figure 4*.

Experts suggest that a minimum of 5–10 procedures per year after 10–20 supervised procedures are required to maintain competence of airway stenting (24,55).

Silicone stents

In the context of malignant central-airway obstruction, we recommend silicone stents as the first-line treatment (109,111). Indeed, they are easy to place and remove, they are well tolerated, have a marked vault effect, and cause few granulomatous reactions (24,106,108). The Dumon (Tracheobronxane®, Novatech, La Ciotat, France) is the most widely used stent (108). Alternatives are the Polyflex® stent (silicone expandable stent) (Boston Scientific, Natick, MA, USA), the Hood stent® (Hood Laboratories, Pembroke, MA, USA), and the Noppen stent (Reynders Medical Supply, Lennik, Belgium).

The Dynamic Freitag® (Rüsch, Kernen, Germany) stent has a flexible posterior wall that mimics the physiological behavior caused during coughing. This stent should theoretically be associated with a lower risk of granuloma because of the more homogeneous distribution of pressures (112,113). Silicone stents can be straight or bifurcated for stenoses that involve the carina or primary right carina (Oki stent) (106,114). The diameter and size are chosen based on scanographic and per-operative bronchoscopic data, which are then adjusted by cutting (37,75,108,115-117).

Symptoms and quality of life are immediately improved in the vast majority of cases (52,75). Symptomatic granuloma is rare (1%, n=306) (10,118). Migration risk mainly concerns short and purely extrinsic stenoses (24,38,118,119) and immediate subglottic stenoses are relatively rare in cases of obstructions of malignant origin [2–6% (119) of cases *vs.* 18% with benign stenoses (120)]. The overall complication rate has been reported as 9.4% (52).

The few limitations of silicone stents compared to self-expandable metallic stents are caused by a narrower internal diameter due to wall thickness, which results in altered mucociliary clearance (38,106): i.e., obstruction by secretions (14% of patients) (64,111), favored by bacterial colonization (121), which can be avoided by nebulizations and good hydration (24).

Self-expandable metallic and hybrid stents

Self-expandable metallic stents (Ultraflex®, Boston Scientific; Alveolus®, Charlotte, NC, USA, Aerstent® Leufen, Germany) can be placed under video-bronchoscopic or radioscopic guidance (122). Their advantages include a lower risk of migration, better preserved mucociliary clearance, and larger internal diameter (106). They also offer rapid and good control of symptoms, and improved quality-of-life scores and spirometric parameters (85,107,110). However, even if these stents can be placed under flexible bronchoscopy, we do not recommend this approach (except in cases of intubated patients with no access to rigid bronchoscopy), as the control of obstructive or hemorrhagic complications is more rapid under rigid bronchoscopy. Self-expandable coated stents are particularly suitable for trachea esophageal fistulas, for tight and highly distorted stenoses, and for highly necrotic stenoses, as they avoid the need to bypass the stenosis with a rigid tube (which increases the risk of perforation) (107,109,118,123).

Major limitations include the risk of granulomatous reactions at the extremities (118); epithelialization with incorporation into the mucosa, thus rendering the stent difficult to remove after 3–6 weeks (116); a weaker vault effect (111); and an increased risk of perforation (109). The rate of significant complications is often high for these stents, reaching 16% in the first month and 13% afterwards (124). Early complications include pneumothorax, pneumonia, and migration (118). Hemoptysis and infections are seen in 10% of patients (125). At later stages, symptomatic granuloma formation is observed in 15% (118) to 27% of cases (126).

Drug-eluting stents

These may be an interesting way to prevent granuloma and malignant-tissue formation. This approach has mostly been evaluated in gastrointestinal endoscopy, with anticancer or antiproliferative (mTOR inhibitors) agents (127). A biodegradable cisplatin-eluting stent has been designed, dedicated to the central airways, but has not yet been tested in humans (128). The main pitfall of such a prosthesis may be an enhanced risk of a fistula caused by its antiproliferative action.

Bronchoscopic management of endobronchial metastases

Endobronchial metastasis of other solid tumors is relatively rare; it usually occurs tardily after the initial diagnosis (median 56 months) (129). A classification has been proposed to described their mechanisms: (I) type I is a directly endoluminal metastasis; (II) type II corresponds to bronchial invasion by a parenchymal lesion; (III) type III is the result of bronchial invasion by a mediastinal or hilar lymph node; and (IV) type IV are peripheral lesions extending along the proximal bronchus (129). Most frequently involved malignancies are breast, colon, and renal-cell carcinomas (130).

In a cohort of 24 patients undergoing bronchoscopic management of endobronchial metastasis from colorectal cancer, dramatic symptomatic and functional improvement was observed and median survival after the procedure was 14 months (131). Dalar *et al.* reported results from the bronchoscopic management of 20 procedures in nine patients suffering from endoluminal metastases of renal-cell carcinoma. The procedure was efficient in most cases with

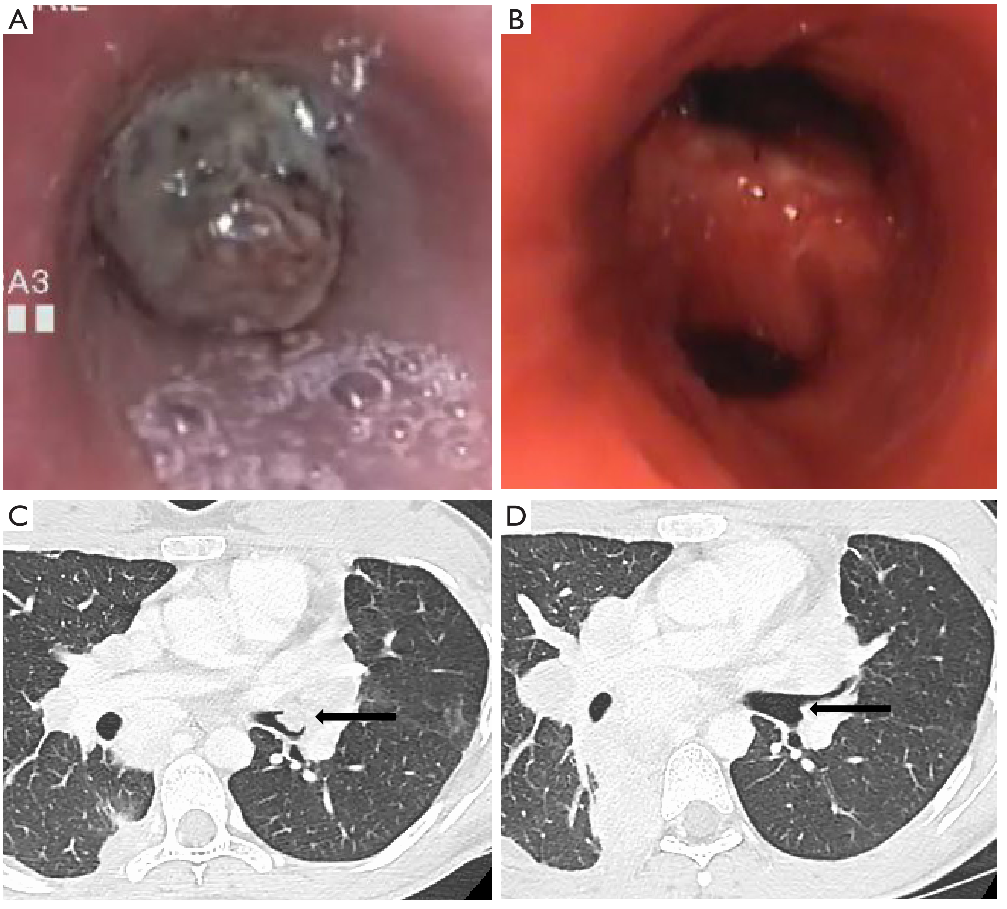

Figure 5 Bronchoscopic management of an airway metastasis (type I) from a fibrolamellar hepatocellular carcinoma. (A and C) Complete intraluminal obstruction of the left main bronchus (bronchoscopic and scanographic views); (B and D) results after laser and mechanical debulking.

median survival after the intervention of 8.7 months. The operator facing this histology has to be particularly prepared to face hemoptysis (60% of hemorrhagic procedures in this cohort) (12/20) (132). Bronchoscopic treatment of airway metastases from a melanoma is also usually efficient and does not show any technical particularities. Median survival after the procedure is 6 months (n=18) (133). *Figure 5* represents the results after bronchoscopic management of a type-I airway metastasis.

Emerging bronchoscopic techniques for the management of peripheral lung cancer

Although surgery remains the gold-standard treatment for early-stage lung cancer, alternative options have been developed to treat the most vulnerable and inoperable patients. Stereotactic body-radiation therapy has been evaluated the most and, thus, is the non-surgical treatment of choice, followed by percutaneous thermoablation. New bronchoscopic techniques that access distal nodules, mainly RP-EBUS, are paving the way towards new options to treat early-stage peripheral cancer (134).

Trans-bronchial CT-guided brachytherapy has been described in a few cases of peripheral lung cancer. Barium was injected through a catheter, placed under bronchoscopic control, to check its position with a CT-scan. Lateral and frontal X-rays allowed brachytherapy to be planned and iridium-92 was delivered using the HDR after-loading system. One of the two patients experienced a 75% decrease in tumor burden after a single dose of 15 Gy whereas the other patient did not respond after three fractions given at weekly intervals (total 24 Gy) (135). HDR brachytherapy (three fractions of 5 Gy) was also delivered to a patient through a catheter that was placed using both EMN and RP-EBUS: this resulted in a durable partial response and a complete histological response in RP-EBUS-guided biopsy specimens at 12 months (136).

Because radiofrequency ablation has a high risk for pneumothorax, bronchoscopy-guided radiofrequency ablation has been reported as a safe alternative for selected patients. Amongst 23 peripheral lung cancers in 20 patients, 11 tumors showed significantly reduced tumor size and eight cases showed stability, resulting in a disease-control rate of 82.6% and a 5-year overall survival of 61.5%. Given these interesting results, we can anticipate a role for EMN and/or RP-EBUS to guide and thus improve the precision of this new strategy.

Other techniques should be evaluated for the treatment of peripheral early lung cancers, such as cryotherapy or PDT, which would be delivered through small cryoprobes/laser fibers after confirmation of the tumor location by EMN of RP-EBUS.

Finally, bronchoscopy has been evaluated as a tool for the placement of fiducial markers to guide real-time tumor-tracking radiation therapy for peripheral lung nodules (137). This option could also be improved by EMN of RP-EBUS.

In conclusion, the interventional pulmonologist holds an increasingly important place within each step of managing lung cancer. The early detection of pre-invasive endo-bronchial lesions is a current challenge, justifying the recent development of several tools with increased diagnostic accuracy and of mini-invasive techniques that have curative treatments.

In more advanced stages of lung cancer, interventional bronchoscopy offers many different possibilities to relieve central-airway obstruction when it is associated with a poor prognosis, and it greatly increases quality of life. The choice of technique ultimately depends on both the mechanism and the respiratory repercussions of the stenosis.

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Footnote

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