Review Article

Management of malignant central airway obstruction

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Abstract: Malignant central airway obstructions (MCAOs) generally consist of lesions occupying a large percentage of the luminal wall within the trachea, mainstem bronchi, bronchus intermedius, or lobar bronchus. These obstructions can often be dangerous and debilitating, causing serious hemodynamic instability and severe reduction in quality of life. Advanced bronchoscopic techniques offer an ability to tackle these lesions in an attempt to restore airway patency while simultaneously improving hemodynamic stability and alleviating symptoms. A large number of bronchoscopic therapies are available to date. Choice of a modality is widely dependent on the clinical picture and type of obstruction at hand. Therefore, this review focuses on the developments made in the field of interventional pulmonology, providing insight into possible advanced bronchoscopic therapies to combat these MCAOs.

Keywords: Interventional pulmonology; advanced bronchoscopy; malignant central airway obstruction (MCAO)

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Clinical background

Central airway obstructions are generally defined as luminal obstructions of more than 50% in the trachea, mainstem bronchi, bronchus intermedius, or a lobar bronchus (1,2). Further, not only can these obstructions be categorized by the location in the central airway, but also by the type of tumor seen. Therefore, malignant central airway obstructions (MCAO) are further classified into intraluminal tumor growth (intrinsic), extraluminal tumor compression (extrinsic), or a combination of both (mixed) (3).

Locally advanced primary lung cancer is the most common etiology of MCAO (4). Of the roughly 200,000 new cases of primary lung cancer per year in the United States (5), an estimated 30% will develop clinically evident endoluminal disease (5-7). Other primary malignancies of the lung or airway that lead to MCAO include adenoid cystic carcinoma, mucoepidermoid carcinoma, and carcinoid tumors (8-10). Structures adjacent to the lungs including esophageal, thyroid, and primary mediastinal tumors have also been described as causes of MCAO (11). Although locally advanced lung cancer remains the most likely etiology of MCAO, airway metastases from virtually any malignancy have been reported as well, particularly thyroid, breast, colon, renal cancer, and melanoma (11).

Presentation

The aggressiveness and location of the tumor will cause variation in patient presentation. Expiratory wheezing suggests intrathoracic airway obstruction, often distal to the carina. Stridor is generally a sign of extrathoracic obstruction (8). Mild symptoms of MCAO include cough, wheezing and exertional dyspnea (12). These symptoms may often be mistaken for obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD)

and may lead to a delay in diagnosis.

Most often, MCAO presents with clear signs and symptoms. In addition to wheeze or stridor, patients may have resting dyspnea, hemoptysis, or a history of post obstructive infections (13,14). However, CAO can be asymptomatic and occasionally found incidentally on chest imaging (8,15,16).

Non-bronchoscopic management techniques

Non-bronchoscopic management of MCAO includes chemotherapy, external radiation, and surgical resection. Both chemotherapy and radiation are frequently employed to manage central airway obstructions, but have limitations in the acute setting. Both modalities attempt to achieve the goal of tumor size reduction, but also require an ample amount of time to observe any symptom relief, if at all. Therefore, these modalities alone are often not feasible due to the severe progression of patients' symptoms and most likely obstruction during inspection of the airway. Furthermore, chemo- and radio-therapy alone seldom can alleviate airway obstruction due to non-small cell lung cancer (NSCLC) (17).

Surgery may play a role in curative intent, although most malignant airway lesions are surgically inoperable due to advanced disease stage and therefore, require multimodality palliation (18).

Introduction to bronchoscopic techniques

Patients with MCAO may present with various symptoms that require emergent (e.g., in cases of hemorrhage or acute respiratory failure) or non-emergent (e.g., ongoing or worsening dyspnea) intervention. Bronchoscopic techniques offer an ability to allow restoration of airway patency and improve palliative outcomes, regardless of the level of urgency (19). These options are often safer, cost effective, and pose less risk than benefit compared to invasive surgical options (20).

In patients that may tentatively undergo surgical intervention, these techniques may also provide great benefit through providing better visualization of the airways, resolution of atelectasis, and subsequent ability to treat post obstruction infections, eventually optimizing candidacy and decreasing risk of failure (21,22).

Direct mechanical modalities

Bronchoscopy

Both rigid and flexible bronchoscopy are able to provide diagnostic and therapeutic interventions. The preference of scope may depend on many factors such as better control of the airway or larger size of working channel. These scopes are often combined during a procedure with flexible bronchoscopy performed through the rigid barrel to allow distal airway access or more nuanced articulation.

Rigid bronchoscopy has historically served as an important mechanical modality for dealing with MCAO. The use of rigid bronchoscopy has especially been useful in patients with an acute, unstable, airway (8). We often find that this tool serves to provide immediate relief and stabilization through the ability of securing the airway. A clear advantage of its use is the large channel allowing for entry of different therapeutic tools, ease of airway stenting, suctioning through the tube, all while providing ventilation throughout the procedure (23). The bevel of the bronchoscope itself can be used for debulking or "coring out" of an obstruction (24). Furthermore, the barrel of the bronchoscope in itself can be utilized to tamponade bleeding central lesions seen in malignant obstructions (25).

Cryorecanalization

While the cryoprobe may be used for standard probe cryotherapy with freeze-thaw cycles that serves as an indirect or delayed therapy, it may also be utilized for cryorecanalization (26). Contrary to the mechanism of freeze-thaw cycles used in standard cryotherapy, cryorecanalization involves application of the cryoprobe directly applied to the tumor continuously for approximately 3–20 seconds, allowing freezing and adherence (26-30) (*Figure 1*). Quick removal of the cryoprobe then removes any frozen tissue still adherent to the probe (31). Cryorecanalization allows for retrieval of the frozen tumor for pathology while simultaneously debulking the obstruction with rapid withdrawal of the cryoprobe (26). The main advantage of this approach is immediate debulking of the tumor, with a lower risk of perforation or residual stenosis (26,29). The maneuver is most often done with flexible cryoprobes via flexible bronchoscopy.

The main disadvantage is removal of the specimen

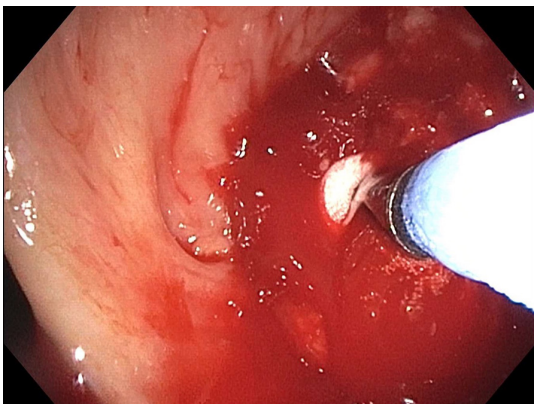

Figure 1 Cryorecanalization with 2.4 mm cryo probe (Erbe).

en bloc with the bronchoscope as the frozen tumor is too large to pull through the working channel of the flexible bronchoscope. This leads to temporary loss of airway visualization and limited ability to inspect for hemorrhage and stop bleeding until the specimen is thawed in saline and the bronchoscope is re-introduced (28). This limitation can be mitigated with the use of suction via a rigid bronchoscope or alternating with a second bronchoscope, when available. Serious bleeding can occur using this technique and should be used with caution at centers without experience managing pulmonary hemorrhage.

Microdebrider

This instrument is passed under direct telescopic guidance through rigid a bronchoscope or laryngoscope into the airway (3). Airway debulking is purely mechanical and performed by a rotating blade at the distal tip of the instrument (8). No pathologic specimen is obtained during the debulking process. The benefits of the microdebrider are the ability to rapidly and efficiently debulk while maintaining direct visualization through suctioning (8,27,32,33). Contrary to thermal modalities, the device does not pose a risk of airway fire and thus does not require a fraction of inspired oxygen (FiO_2) less than 40% (24,32). As the microdebrider is a relatively new tool for debulking, further studies are required to evaluate safety and long-term outcomes.

Stents

Airway stenting for MCAO is indicated in patients with pure extrinsic compression or a mixed obstruction where there is still significant obstruction after endoluminal debulking (34). Metallic and silicone are the two main types of airway stents currently available (35). Compared to silicone stents, metallic stents have better internal-external diameter ratio and therefore lead to larger airway lumens, are radio-opaque, making them easy to spot in imaging, and lower incidence of migration (36,37). However, silicone stent offer more choices in shape and size, including the ability to stent multiple airways with a single stent.

Metallic stents can be divided into covered and uncovered, as well as self-expandable metallic stents (SEMS) or fixed-diameter stents requiring balloon dilation. Although uncovered stents in theory do not interrupt the mucociliary clearance, they can be difficult to remove due to tumor or granulation tissue overgrowth through the stent fenestrations. SEMS can be placed using prepackaged deployment catheters through existing airways such as by laryngeal mask airway or rigid bronchoscope with real time guidance using a small flexible bronchoscope or by fluoroscopy (36,38-45). Smaller stent deployment catheters can now fit through the 2.8 mm working channel of a therapeutic bronchoscope, allowing for easy direct visualization of stent deployment.

The main pitfalls of all stents are due to the rate of complications. Common complications include granulation tissue at the stent edges, epithelialization with incorporation into the mucosa, obstruction of the stent with mucous, stent migration with potential airway obstruction, airway injury with hemoptysis or perforation (37,46-50). Complications from stenting, including stent migration and stent obstruction by granulation tissue or secretions vary from approximately 20% to 50% (23,49). Regardless of the rates of complications, the overall mortality from stent placement is very low (38,51).

Direct thermal therapies

Similar to mechanical interventions, thermal techniques can provide immediate therapeutic relief through direct tissue destruction and relief of stenosis. Laser therapy, contact electrocautery, argon plasma coagulation (APC), and Corecath (Medtronic) have all been noted to be viable options for direct thermal intervention.

Laser therapy

Light amplification of stimulated emission of radiation (LASER), uses its properties to deliver a precise beam

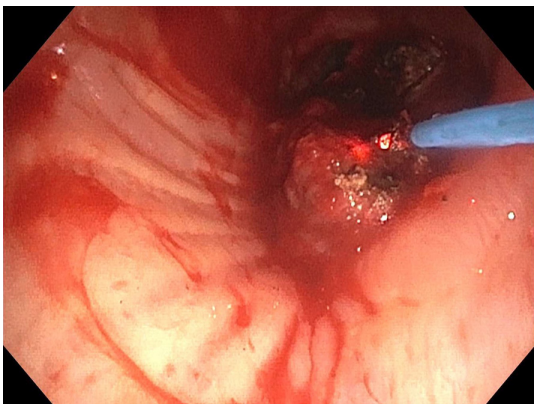

Figure 2 Neodynmium-Yttrium-Aluminum-Garnet (Nd:YAG) laser tumor cautery and vaporization.

of thermal energy through a thin fiber to coagulate and vaporize tissue (4,52-54). The coagulative properties of laser can be helpful in providing hemostasis with superficial hemorrhagic lesions while the ablative properties of the laser are beneficial in debulking endoluminal masses (24). Flexible laser fibers can be positioned within the airway through the use of a flexible or rigid bronchoscope.

Tissue coagulation can be provided by a shallow laser effect at low power settings whereas high power settings allow for more penetration with more resultant carbonization and vaporization (24). Position of the laser fiber further (1 cm or greater) cause superficial penetration and better coagulation whereas closer distances (3–4 mm) cause deeper penetration and more efficient vaporization (24,52).

Several large studies have demonstrated the utility and effectiveness of neodymium-yttrium-aluminum-garnet (Nd:YAG) laser photoradiation in airway tumor debulking. The technique involves a flexible fiber inserted through either rigid or flexible bronchoscope to emit the light beam (4). As the tissue penetration of Nd:YAG laser is approximately 10 mm, comparatively deeper than electrocautery and APC, the laser is directed parallel to the airway wall to reduce perforation and bronchovascular fistula (4,7,52) (*Figure 2*). Drawbacks included the inability to use this modality with higher oxygen requirements (FiO_2 >40%), similar to other thermal ablative techniques (55).

The use of Nd:YAG laser in the treatment of MCAO provides immediate palliation of symptoms (24,56-59), while allowing for minimal bleeding during debulking (55). If done with proper precautions, NDYAG has an excellent safety record (57,60-66).

Electrocautery

The utility of electrocautery devices is their simplicity, rapid palliation, and immediate tumor debulking (67). Through the use of a probe or device targeting tissue, electrocautery permits high-frequency electrical currents to be converted to heat energy for tissue coagulation or dissection of tumor tissue (68). The effects of thermal heat delivered through the use of electrocautery are dependent on the power and voltage of the electrocautery, tissue resistance, temperature at the tissue, and duration (52). Those factors will delineate if coagulation, hemostasis, carbonization, or vaporization will occur (69).

Electrocautery can be performed with either flexible bronchoscope or rigid bronchoscopy (55). Soft or forced coagulation is used at 20 to 40 Watts in short bursts of >5 seconds with the blunt probe (70). This facilitates coagulation, at which point tissue can be removed through mechanical debridement. Increasing the activation and therefore contact time may also lead to tissue carbonization and vaporization (52). For lesions resting on a "stalk", a snare may be utilized around the stalk to cut and subsequently coagulate the stalk, remove the tumor en mass. An electrocautery knife allows for more precise debulking of tumor (69). Electrocautery forceps allow for simultaneous tissue biopsy and subsequent cauterization though care must be taken to minimize thermal damage to sampled tissues (4,71).

Potential complications include hemorrhage, airway perforation, airway fire, and scarring/stenosis (72). Care should be taken maintain an FiO_2 level of less than 40%, and a power setting of less than 80 W, and application times greater than 5 seconds (54,69).

The Corecath (Medtronic) is a new electrocautery device that can be used with a flexible bronchoscope for therapeutic debulking of MCAOs. Through the use of flexible bronchoscopy, the Corecath allows for an electrosurgical means to debulk obstructions, provide hemostasis, and surgical smoke and blood evacuation through its integrated suction (73) (*Figure 3*).

Overall, electrocautery is a cost friendly, efficacious, and safe modality in management of MCAO (20,74-76), with a success rate comparable to Nd:YAG laser, APC, and cryotherapy (69,77).

APC

The use of APC began fairly recently within the realm of

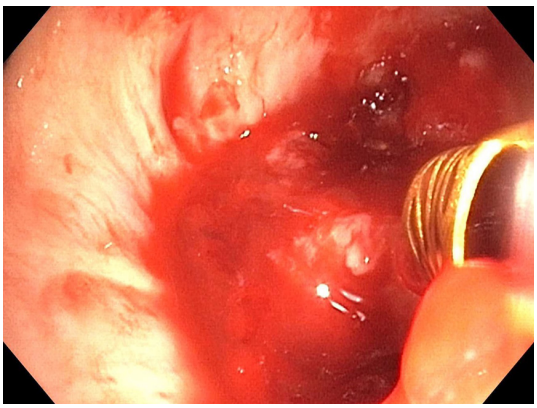

Figure 3 Corecath (Medtronic) electrocautery and tumor debulking.

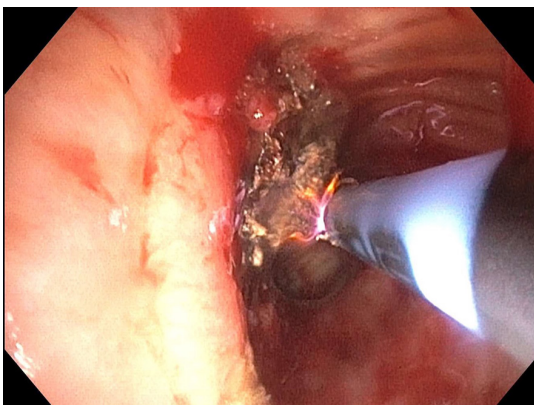

Figure 4 Argon plasma coagulation (APC) cautery using a straight fire probe (Erbe USA).

interventional pulmonology. The technique utilizes argon, a colorless, odorless, and chemically inert gas to pass down the probe (4). An ionized monopolar current is formed with argon gas and a high-voltage electrical field, targeting tissue and subsequently causing tissue coagulation or hemostasis (69) (*Figure 4*).

A variety of probe styles exist to optimize energy delivery depending on the anatomy of the MCAO and position of the bronchoscope that best achieves visualization (52). As with electrocautery, the power setting, during of activation, and probe distance will delineate the type of tissue effect APC will have.

As penetration is relatively minimal, this modality provides coagulation and good control of hemorrhage (4,70,78,79). APC has the ability for hemostasis even if the precise origin of bleed is not known (23,70,78,80).

Although highly effective in coagulation or granulation tissue debridement, the superficial penetration does not allow for effective vaporization or large scale tumor debulking (53). A risk unique to APC is argon gas embolism into the systemic circulation due to high gas pressure (69,81-83). Keeping flow to less than 0.80 L/minute has been shown to minimize the risk of gas embolism (84). Akin to other thermal modalities, other risks include airway fire and airway perforation.

Indirect therapeutic modalities

Probe cryotherapy

Cryotherapy, a cold ablative therapy, is able to destroy tumor tissues through the use of cryogenic liquid gas (N2O, N2, CO_2) utilizing a pattern of freeze-thaw cycles (41,85-88). A cryogen is defined as a substance used to produce very low temperatures. As gas is released from high pressure to the tip of a flexible or rigid probe, it expands and thus creates rapid cooling of the distal tip by the Joule-Thompson effect (26). The degrees of temperature variation depend on the cryogen gas utilized. Low temperatures result in the immediate effect of dehydration and cellular crystallization as well as delayed effects of apoptosis and ischemia due to microthrombi formation (8,41,89-92).

The cryoprobe can be used either through flexible or rigid bronchoscopy (8). It is recommended to have at least 3 to 5 repeated 60-second freeze-thaw cycles to the lesion to facilitate increased cellular damage (8,93,94). After the last completed cycle, the probe is retracted from the tissue, and placed several millimeters adjacent to the site for another three cycles, creating an overlap of treated area (86,95). Necrotic tissue can be removed on a subsequent bronchoscopy (86,96).

Advantages of cryotherapy include the relatively low cost, virtually no risk of delayed stenosis, and positive hemostatic effect (88,92,97). Cartilage-like tissue, collagen, and poorly vascularized tissue are cryoresistant, and in turn decrease the risk of airway perforation, making cryotherapy one of the safest ablation techniques (8). Disadvantages include its delayed effects as stated previously, as well as limited depth of its cytotoxic action (8). The safety and efficacy of the therapy, incorporating factors such as successful removal of the obstruction, symptomatic improvement, and level of complications, indicate a highly effective therapeutic modality in MCAOs (26,96,98-104).

Cryospray is a related technology where liquid nitrogen (N2) is rapidly forced through a disposable catheter that fits down the working channel of a flexible bronchoscope. The cryogen will spray directly on the tissue to cause an extreme cooling effect with passive thawing. The rapid expansion of such compressed gas requires an open ventilator circuit to avoid pneumothorax or other barotrauma. Preliminary studies are promising but the technique has not been widely described in large cohorts (26).

Photodynamic therapy (PDT)

Since 1911, porphyrin-based photosensitizers have been extensively researched for its utility in providing non-thermal laser light to cause a phototoxic reaction which leads to cell death (23,89,105,106). This process is called PDT, with porfirmer sodium (Photofrin) currently being the most widely used agent (8,53,107,108). The mechanism involves direct cell damage by singlet oxygen, apoptosis, and indirect effect due to vascular stasis, inflammation, and immune response (8,89).

Intravenous photosensitizer is injected in the systemic circulation that is the absorbed mostly by metabolically active cells including malignant cells, skin, liver, and spleen (109). A light probe is inserted through a flexible bronchoscope, activated at the target lesion to a specific wavelength to achieve a penetration depth of 5–10 mm (24,110). A repeat bronchoscopy is required to clean debris and necrotic tissue 72 hours after light therapy, with repeat PDT cycles performed if needed (23,24,54,111). To limit toxicity, light therapy is performed approximately 48–72 hours after administration of photosensitizer to ensure clearance out of most normal tissue. Patients are advised to avoid light exposure due to partial retention of the compound for approximately 6 weeks (112).

As PDT is a non-thermal ablative therapy, its use is advantageous in patients requiring higher oxygen demands, as the risk of airway fire is negligible compared to thermal therapies. Disadvantages of the therapy consist of photosensitivity, mucosal sloughing causing subsequent respiratory failure, repeated bronchoscopies to evacuate debris, as well as hemoptysis, bronchitis, pneumonias, and severe endotracheal candidiasis (113,114). Our practice is to observe patients for 48 hours post treatment with a repeat bronchoscopy to clear debris before discharge. An additional disadvantage is its high cost (23,85,111). The delayed effect of the therapy essentially rules out the ability of immediate support in imminent respiratory failure.

Brachytherapy

Brachytherapy is an indirect therapeutic option using iridium-192 beads to provide localized radiation therapy within or alongside a tumor in the airway with the assistance of graduated radiopaque catheter and bronchoscope (8,23,53). The gamma radiation emitted through brachytherapy does not cause direct killing of cells, but rather causes breaks within DNA and therefore lead to apoptosis and decreased cell proliferation (89,91).

Unfortunately, at this time, patient selection remains ambiguous, as there is lack of evidence to support dose-rate methods or prediction of tumor response (4).

Clinical evidence of efficacy

Bronchoscopic interventions are often safer, promote superior cost effectiveness, and pose a better benefit to risk profile compared to open surgical options (20). These therapies are known to be effective in MCAO with further evidence showing it is the preferred method of palliative relief (27,59,68,115-117).

Studies have indicated significant improvement of 6-minute walk test, FEV1, and FVC, dyspnea, and Quality of Life (QoL) by day 30 of post-intervention (17,59,118). Technical success rate has been recorded to be approximately 88–100%, while procedural related complications were recorded to be 3% to 20.4% and mortality of 1–3.1% (17,68,115,116,119-123). Stenting was in fact, recorded to have better success rates compared to ablative techniques (115).

While complications and mortality rates vary, the patient population receiving interventions are frequently those with late-stage cancer and no further options for targeted treatment (123). The type of obstruction, extent, location, mechanism, symptoms, and stability of the patient need to be accounted for prior to choosing intervention (1,2,115,124). Utilizing rigid bronchoscopy for airway stabilization, followed by direct therapies such as mechanical debulking, thermal tools, cryorecanalization, and cryotherapy to combat endoluminal obstruction, with airway stenting to maintain airway patency when feasible, are an accepted approach for rapid restoration of the airway (8). Delayed bronchoscopic measures such as

PDT and brachytherapy in addition to therapies used for rapid restoration, can also be utilized in non-emergent obstructions (4). Overall, evidence supports the use of multimodality and multidisciplinary approach that focuses on a combination of interventions rather than just one in order to produce successful results (125,126).

Future directions

As we move into the future, new modalities give hope to additional effective and precise options while aiming to decrease risks and complications. New directions include but not limited to intratumoral chemotherapy (ITC) and transbronchial needle injection (TBNI), drug eluting and biodegradable stents.

ITC and TBNI are two new modalities that are showing promise in reducing tumor size, and improving airway lumen (127). Through the use of endobronchial ultrasonography (EBUS), needle catheters are used for drug delivery directly into luminal tumors or lymph nodes (128). Currently, a new micro-infusion device, Blowfish™ (Mercator MedSystems, Emeryville, CA, USA) is being investigated for its utility (128). Drugs being examined include, but are not limited to, cisplatin, 5-fluorouracil, bleomycin, carboplatin, para-toluenesulfonamide, and paclitaxel (128-131). Advantages of these modalities include better precision of drug delivery and higher tumor concentration (132). There remains mixed evidence on systemic effects and toxicity such as neutropenia in patients exposed to the intratumoral injection at this time (133). No other major side effects have been noted (128). Evidence demonstrates ITC and TBNI as a feasible therapeutic option in a multimodal approach of restoring airway patency in MCAO, although further studies on drug of choice and modality are warranted (133-136).

Thus far, endeavors towards drug eluting airway stents remains suboptimal and may in part be due to other bronchoscopic modalities already available for palliation in patients with MCAO and concurrent low performance status (137). Therefore, as we approach the idea of airway drug eluting stents, prerequisites should be met in order to make the most ideal drug eluting airway stent. The stent should provide sufficient strength to maintain airway patency, be biocompatible so mucosal irritation will be negligible, have the ability to be biodegradable in order to prevent necessity of removal, and finally, provide drug therapy that in an effective manner (137).

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