Malignant airway obstruction: treating central airway obstruction in the oncologic setting

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Obstruction of the central airways, the trachea and main stem bronchi, may result from many disease processes including malignant growths. It is estimated that in the United States, malignant neoplasms will cause central airway obstruction (CAO) in 80,000 cancer patients a year. It is estimated that 20% of these patients will experience significant morbidity due to persistent cough, dyspnea, and obstructive pneumonia, and as many as 35-40% of lung cancer patients die due to complications resulting from locoregional disease. While most treatments for malignant CAO are not curative, they have been shown to improve respiratory function, avoid mortality, and improve quality of life. Many different strategies for managing malignant airways exist. Choosing the best one depends on patient factors such as presence of co-morbidities, medical stability, the nature of the underlying tumour, and overall prognosis. Non-patient related factors such as expertise of medical staff and availability of technology also greatly impact the mode of treatment chosen. This article presents current treatment options for malignant CAO, specifically, therapeutic bronchoscopy, radiotherapy, and surgical resection.

CAUSES OF MALIGNANT CENTRAL AIRWAY OBSTRUCTION

The most common malignant causes of central airway obstructions are direct extension into the airway lumen by extrinsic tumours (fig. 1b). Of these tumours the most common types are bronchogenic carcinomas (i.e. small cell lung cancer and non-small cell lung cancer), followed by esophageal and thyroid carcinomas. Primary tumours of the trachea and bronchi, or intrinsic central airway tumours (fig. 1a) are relatively rare. Seventy to eighty percent of these tumours are of squamous cell or adenoid cystic carcinoma type. Squamous cell carcinomas typically occur later in life and more frequently in men and smokers, while adenoid cystic carcinomas are found in younger patients and are not related to exposure to smoking or to the sex of the patient.

Occasionally, but less frequently, metastases from carcinomas of the breasts, kidneys, colon, thyroid and esophagus may spread to the respiratory system and cause CAO.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of malignant CAO depend on size, location, and the rate of progression of airway obstruction. Moreover, the patient’s underlying health status and ability to compensate for decreased airflow will influence the extent to which symptoms appear. If encroachment into the airway is minor, then there will be little impact on airflow and patients will likely be asymptomatic and never brought to clinical attention. The majority of patients that experience symptoms of CAO have advanced disease and a history of underlying malignancy. Thus, symptoms of CAO are late findings and include dyspnea, cough, wheezing, stridor and frequently, pneumonia. Because these symptoms overlap with those found in asthma and COPD, patients with malignant CAO are commonly misdiagnosed. However, a strong indication that symptoms are due to CAO is that they are unresponsive to inhaled steroids and bronchodilators. Other advanced CAO symptoms are related to signs of decreased ventilation such as tachycardia, diaphoresis and increased work of breathing. Symptoms of bradycardia, cyanosis and obtundation suggest that the airway lumen is severely compromised and in need of immediate intervention in order to avoid imminent respiratory failure.

Evaluation and diagnosis of malignant airways is often based on clinical examinations as well as a tissue biopsy and radiological studies to confirm the diagnosis. While chest radiographs have little diagnostic value, they may be used to quickly rule out other causes of breathing difficulty such as tracheal deviations or a pneumothorax. Chest and neck computed tomography (CT) scans make it possible to estimate tumour size, depth of invasion, and the ability to see if the airway distal to obstruction is still patent, providing important information for treatment planning. CT scans are typically always performed in conjunction with bronchoscopy, the gold standard for evaluating CAO. Bronchoscopy allows for direct visualization of the tumour, evaluation of tumour length and location, differentiation between an intrinsic endobronchial and extrinsic tumours, and most importantly, is equipped to provide a tissue diagnosis. Moreover, if needed, diagnostic bronchoscopy may be quickly converted to therapeutic bronchoscopy for CAO management.

Figure 1: Schematic diagram of intrinsic (a) and extrinsic (b) tumour obstruction of the central airways. Each demonstrates 50% occlusion. Adapted from Bollinger et al. Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents (2006).
TREATMENT MODALITIES

1) Therapeutic bronchoscopy:

Therapeutic bronchoscopy utilizes the rigid stainless steel bronchoscope to visualize, treat and debulk tumours. Its wider diameter facilitates ventilation allowing for a variety of procedures to be performed, including tumour debulking, laser resection, argon-plasma electrocoagulation, balloon bronchoplasty, and stent insertion to re-canalize the airway.\(^2,7,8\)

i) Tumour debulking:

The sharp bevelled tip of the rigid bronchoscope is used to core out the tumour and apply pressure to airway walls promoting clot formation. However, inadvertent damage to surrounding airways during treatment is a risk and complications may include cutting the lips, gums, larynx or airway mucosa or cartilage during intubation. Perforation of the mediastinum may also occur if the scope is not in line with the airway lumen.\(^8\)

ii) Laser Resection:

Laser energy delivered by optical fibres is used to resect obstructing tumours. The main type of laser used during bronchoscopic resection is the Neodymium:yttrium aluminium garnet (Nd:YAG) laser which transmits light energy at 1,064 nm wavelength to the target tissues.\(^2,7\) The thermal energy from the Nd-YAG laser is absorbed into the core of tissue where temperatures may reach up to 100°C.\(^3\) The heat is then transmitted and scattered around into surrounding tissues so that total tissue effects may extend up to 10mm below the surface of laser administration.\(^1,2,7,8\) Darker pigments, such as those found in blood maximally absorb energy from Nd:YAG lasers. As a result, tissues exposed to the laser energy are devascularized—a process otherwise known as electrocoagulation.\(^7\) Additional administration of the Nd-YAG laser causes charring and eventual vaporization, which is removed by ventilation from the bronchoscope.\(^2,8\) If tissue is not completely vaporized, it may be mechanically debulked. Because total tissue effects are not immediately visible during treatment and may extend well past the depth of the tumour, complications include late devascularisation of adjacent healthy tissues well after the treatment is completed.\(^2,8\)

iii) Argon-Plasma Electrocoagulation:

Argon-Plasma Electrocoagulation (APE), as opposed to laser electrocoagulation, is a form of non-contact electrocoagulation. Using a 5,000-6,000 volt spark at the tip of the probe, argon gas, also released at the tip, becomes an ionized plasma that finds the nearest grounded tissues producing coagulative necrosis.\(^1\) Advantages of APE are that it may treat tumours lateral to or around a corner from the tip of the probe that would not otherwise be accessible for laser therapy.\(^1,9\) The electron energy utilized by APE, however, does not penetrate tissues as deeply as laser energy resulting only in superficial necrosis opposed to the deep tissue necrosis created by Nd-YAG lasers.\(^9\) This may be desirable for treating superficial squamous cell carcinomas or if major blood vessels are close to the tumour bed.\(^9\)

iv) Balloon Bronchoplasty:

Balloon bronchoplasty uses a balloon to evenly dilate the airway with minimal trauma and subsequent granulation tissue formation in mucosal tissues. While most rigid bronchoscope techniques require general anaesthetic, balloon bronchoplasty may be performed with a flexible bronchoscope under conscious sedation.\(^1\) Dilation is immediately effective and may be used for both intrinsic and extrinsic airway obstructions. The results of balloon bronchoplasty are not typically sustained and dilation is usually followed by stenting or laser resection. Complications include airway rupture resulting in pneumothorax, mediastinitis and bleeding.\(^1\)

v) Airway stent insertion:

Airway stents are made of silicone, metal or a combination of both and are used to mechanically prop open obstructed airways. Stents restore airway patency, improve ventilation, and allow for the clearance of airway secretions.\(^2,7,8\) They can be used as standalone treatment or in conjunction with debulking and they do not interfere with subsequent radiation treatments, brachytherapy, or chemotherapy if any are needed.\(^8\) Moreover, if the patient’s ventilation status improves following treatment, silicon stents can be removed.\(^2\) However, metal stents are very difficult to extract and are essentially permanent.\(^2,8\) One of the greatest advantages to using stents is that they may counteract compression by tumours extrinsic to the airway. Complications include stent migration, more commonly seen with silicon stents, and stent obstruction by recurrent tumour growth or granulation tissue formation (typically seen with metal stents).\(^2,8\) Newer metal stents used for malignant airway obstruction have silicon coverings and are made of Nitinol, a flexible elastic biomaterial, to help avoid stent obstruction.\(^2\) Additionally, newer silicone stents are meshed for flexibility and shaped or studded to prevent stent migration.\(^2\)

Indications for therapeutic bronchoscopy are the presence of symptoms of advanced CAO.\(^8\) Necrosis, bleeding and cartilaginous destruction are not contraindications for treatment.\(^8\) In emergency settings, therapeutic bronchoscopy may provide more immediate improvement of the patient’s ventilator status and stabilize them enough for further treatment with radiation or chemotherapy.\(^8\) Drawbacks to the use of a rigid bronchoscope are that it requires patients to be under general anaesthetic. Thus, therapeutic bronchoscopy, balloon bronchoplasty withstanding, can only be used in patients that have enough remaining respiratory capacity to tolerate sedation.

2) Radiation Treatment:

Radiation has long been used to decrease tumour size and improve symptoms that result from a large tumour burden, especially in palliative settings. For malignant CAO, radiation may be delivered in one of two methods: intrinsic radiation treatment (i.e. brachytherapy) or external beam radiotherapy (EBRT).

i) Brachytherapy:

Brachytherapy refers to the placement of a radiation source within or adjacent to the tissues being treated. This is achieved by placing radiation seeds directly into the tumour (interstitial brachytherapy) or inserting catheters into the lumen of the organ being treated such as an airway.\(^8\) For the treatment of malignant CAO, an empty catheter is inserted into lumen of the airway approximately two centimetres beyond the estimated distal end of a target area that includes the tumour.\(^7\) The catheter is then secured at the nostril and a radiation source, most commonly iridium-192, is then loaded into the catheter.\(^2,6\) The area targeted by radiation can be several centimetres long depending on whether high-dose radiation (HDR) or low-dose radiation (LDR) is used.\(^2\) However, LDR has fallen out of favour and HDR is most commonly used as it utilizes the greatest advantage of the brachytherapy technique, that is, the radiation delivered directly at the site of target tissues minimizes radiation exposure to nearby healthy organs otherwise exposed during external beam radiotherapy. In this way HDR brachytherapy exposes vital structures near the airway—such as the esophagus, thyroid, mediastinum and aorta— to minimal amounts of radiation while enabling larger radiation doses to be delivered to the target tissue sites. A typical HDR regimen delivers a fraction dose of 7,000-8,000 cGy administered once a week for three weeks; however, the exact dose and number of fractions (radiation treatments) will depend on the size of the tumour and its location.\(^2,8\) Each fraction lasts between 3 to 30 minutes allowing brachytherapy to be delivered as
an outpatient procedure. Brachytherapy is contraindicated for tumours that invade major arteries or other structures within the mediastinum. Complications include early and late radiation effects such as radiation bronchitis, hemoptysis, bronchial stenosis, and bronchial fistulas.

ii) External beam radiotherapy:
External beam radiotherapy (EBRT) has variable efficacy for treating CAO and the therapeutic effects may be quite delayed. However, EBRT continues to be a mainstay of treatment for CAO especially in patients with highly advanced disease or comorbidities that preclude them from undergoing general anaesthetic. Palliative doses of EBRT for the treatment of CAO are typically 3,000 cGy in 10 consecutive fractions. Side-effects also include early and late radiation effects. Early effects are radiation dermatitis to the overlying skin and fatigue. Long-term effects mainly involve thoracic structures close to the airway (such as the lungs), which may undergo fibrosis as a result of inadvertent radiation exposure. However, current techniques in EBRT such as intensity-modulated radiation therapy in conjunction with shielding or stereotactic body radiotherapy effectively minimize radiation exposure to surrounding tissues.

3) Surgical resection:
Surgical resection is usually reserved for tracheal tumours that have not yet metastasized to other areas of the body. If surgical resection is successful at removing the entire tumour and achieving negative margins, it may be a curative treatment for cancer. The procedure involves removal of the tumour and the involved tracheal segment followed by re-anastomosis or reconstruction of the tracheal tube. Tumours that involve the carina or subglottic larynx can be successfully resected while preserving ventilation and vocal functioning. In addition, it is possible to remove up to 50% of the cervical or intrathoracic tracheal length without compromising anastomotic healing. While its advantage is that it is a potentially curative treatment for cancer, surgical resection cannot be performed if complete tumour removal threatens the healing of the anastomosis, if the tumour length exceeds 50% of the trachea or if vital structures such as the aorta or heart are involved. Moreover, the presence of CAO symptoms that alert clinicians to the need for treatment typically appear at advanced stages of disease when metastatic spread has likely to have already occurred. Although surgical resection cannot be performed after the mediastinum has received a high-dose of radiation (due to impaired tissue healing), it may be followed by adjuvant radiation therapy to decrease the likelihood of loco-regional disease reoccurrence.

DISCUSSION
Interventions for malignant CAO are highly technical and require a large amount of medical resources and teams of well-trained medical personnel. Often the widespread availability of these treatments is limited to patients within a reasonable distance of specialized centers. However, many studies have shown that these treatments are effective, improve patient quality of life, and may be life-saving in emergent situations. In a prospective cohort study of 20 patients with symptomatic CAO, all patients demonstrated improvements in airway diameter and 16 patients achieved greater than 80% patency using therapeutic bronchoscope techniques. Moreover, the study demonstrated that Nd:YAG laser therapy alone, airway stenting alone, and a combination of stenting, laser, and/or cryotherapy were each individually effective at re-establishing airway patency and improving symptoms. Similar positive results were demonstrated for the treatment of CAO using stent insertion and radiotherapy. Authors of a multicenter trial found that silicone mesh, studded stents re-established patency, and improved functional capacity, dyspnea, and global functioning at 1 month and 3 months after stent placement. HDR brachytherapy has also been found to be successful in prospective cohort studies at improving symptoms of CAO by more than 90%. Lastly, for patients eligible for surgical resection, surgery offers a high rate of curative success. While most of these trials compared intervention to no treatment and were not randomized control trials, they have demonstrated that interventions may improve symptoms and quality of life. However, to date there are no best practice guidelines available on which interventions should be used. It has been frequently observed that the best approach includes a combination of treatment interventions, and although many centers are already utilizing these interventions to manage malignant CAO, choice of treatment is heterogeneous and centre-specific.

As incidences of cancer and specifically bronchogenic tumours continue to rise, it can only be expected that a growing number of patients will need to be managed for malignant CAO. Signs and symptoms of malignant CAO occur at advanced stages of disease and patients suffering from CAO almost always have a positive history for underlying malignancy. Symptoms of CAO may be treated with a number of techniques including therapeutic bronchoscopy, radiotherapy, or surgical resection. Each modality has been shown to improve symptomology, decrease morbidity, and improve quality of life. There are currently no best practice guidelines for managing malignant CAO. While patient factors will contribute to the decision making process, the choice of intervention may be most determined by centre resources and availability of skilled personnel.

REFERENCES