Review of the clinical outcomes of therapeutic bronchoscopy for central airway obstruction

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Abstract: Central airway obstruction (CAO) is a debilitating condition with a significant impact on patient's quality of life and risk of hospitalization from respiratory failure. The causes of CAO can be both benign and malignant. Benign CAO may be idiopathic or secondary to other disease processes (infection, intubation, tracheostomy, etc.). Malignant central airway obstruction (MCAO) may occur in patients with primary lung malignancy as well as metastasis from other malignancies including renal cell, colon, and breast. In a cohort review, MCAO was found in up to 13% of patients with newly diagnosed lung cancer. The obstruction may occur either due to endoluminal disease, extrinsic compression, or a combination of both. Several bronchoscopic tools are available to manage such obstruction. Practice patterns and tools used to relieve CAO vary between institutions and may depend on physician preference, patient characteristics, emergency nature of the procedure, and nature of the obstruction. To quantify the effect and added value of such interventions, it is crucial to understand the clinical impact these interventions have on patients. The clinical impact of therapeutic bronchoscopy (TB) must then be weighed against the potential complications to justify its value. Early studies of TB for CAO included patients with both malignant and benign etiologies. The study population's heterogeneity makes it difficult to determine how TB affects clinical outcomes, as clinical outcomes are disease specific. The impact of TB for a MCAO may be different when compared to a benign CAO. Similarly, the clinical outcome of treating an idiopathic benign CAO may be different than that of a post tracheostomy airway obstruction. In this article, we will focus on the clinical outcomes of TB in MCAO. TB has been shown to have a clear impact on weaning from mechanical ventilation, dyspnea, health-related quality of life, survival and quality adjusted survival. The potential impact of TB on these outcomes should be weighed against the potential risk of complications. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

Keywords: Therapeutic bronchoscopy (TB); malignant airway obstruction; clinical outcomes

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Introduction

Central airway obstruction (CAO), defined as obstruction of the trachea and/or mainstem bronchi, is a debilitating condition with a significant impact on patient's quality of life and risk of hospitalization from respiratory failure (1). The causes of CAO can be both benign and malignant. Benign CAO may be idiopathic or secondary to other disease processes (infection, intubation, tracheostomy, etc.). Malignant central airway obstruction (MCAO) may occur in patients with primary lung malignancy as well as metastasis from other malignancies including renal cell, colon, and breast (2). In a cohort review, MCAO was found in up to 13% of patients with newly diagnosed lung cancer (3). The obstruction may occur either due to endoluminal disease, extrinsic compression, or a combination of both. Several bronchoscopic tools are available to manage such obstruction. For endoluminal disease, hot and cold ablative therapies as well as mechanical debulking may help reestablish patency of the airway (4). Airway stenting may be beneficial in cases of extrinsic compression. In cases of MCAO due to a combination of extrinsic and endoluminal disease, a combination of the aforementioned modalities may be used. Practice patterns and tools used to relieve CAO vary between institutions and may depend on physician preference, patient characteristics, emergency nature of the procedure, and nature of the obstruction (5).

To quantify the effect and added value of such interventions, it is crucial to understand the clinical impact these interventions have on patients. The clinical impact of therapeutic bronchoscopy (TB) may have must then be weighed against the potential complications to justify its value. Early studies of TB for CAO included patients with both malignant and benign etiologies (1,6-9). The study population's heterogeneity makes it difficult to determine how TB affects clinical outcomes, as clinical outcomes are disease specific. The impact of TB for a MCAO may be different when compared to a benign CAO. Similarly, the clinical outcome of treating an idiopathic benign CAO may be different than that of a post tracheostomy airway obstruction. In this article, we will focus on the clinical outcomes of TB in MCAO.

TB has been shown to have a clear impact on weaning from mechanical ventilation, dyspnea, health-related quality of life, survival and quality adjusted survival. The potential impact of TB on these outcomes should be weighed against the potential risk of complications. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

Clinical outcomes

Clinical outcomes are quantifiable improvements in health, function, or quality of life following a specific intervention. Outcomes may be immediate (e.g., technical success), short term (e.g., dyspnea post procedure), or long term (e.g., quality-adjusted survival). Priority should be given to examining how an intervention affects patient-centered, clinically significant outcomes. Measuring the success of an intervention by merely the technical aspect of it may overestimate the true value of the intervention.

A more challenging question to answer is how much improvement in a particular clinical outcome following TB would justify its potential complications. While that may not be an easy question to answer, understanding the effect of TB on these clinical outcomes and the factors that may impact outcomes may help individualize the decision as to whether an intervention is warranted. Clinical outcomes that have been studied for TB in MCAO include technical success, weaning from mechanical ventilation, dyspnea, health related quality of life (HrQOL), survival, and quality adjusted survival.

Technical success

Technical success of TB, typically defined as reopening the airway lumen to >50% of normal, has been used as a primary outcome to assess its effectiveness (10). Ost *et al.* examined the technical success of 1,115 procedures on 947 patients. Technical success was achieved in 93% of procedures (10). Similar success rates were seen in other studies (11,12). The odds of technical success decreased with increase in the severity of the obstruction (13). Factors associated with success included endobronchial obstruction and stent placement. On the other hand, American Society of Anesthesiology (ASA) score 3, renal failure, primary lung cancer and left mainstem involvement were associated with failure. In a different study, distal patent airway on CT scan and during bronchoscopy, non-smokers, and decreased time from radiographic finding of CAO to intervention increased the likelihood of technical success (13,14). The likelihood of technical success of TB was not significantly different between centers using different techniques and there was no single best method in terms of ablative techniques (10). Stenting was found to be associated with a higher technical success. This finding, however, should be interpreted with caution as it may not necessarily be a causal association and may be confounded by indication (Physician may decide a stent is of no value in a patient with extensive disease that goes beyond the central airways). In addition, the technical success of stenting must be weighed against the risks of long-term complications that may arise from keeping the stent (15). In the study by Ost *et al.*, those whom dyspnea scores were measured, clinically significant improvement in dyspnea occurred in 48% of patients. This suggests that technical success of TB does not always translate into clinical improvement (10).

Weaning from mechanical ventilation

Patients with MCAO may develop respiratory failure requiring intubation and mechanical ventilation. The ability of TB to allow for a rapid weaning from the ventilator is an objective short-term outcome that has been assessed in prior studies. Colt *et al.* retrospectively reviewed 32 patients with MCAO. Of the 32 patients, 19 patients were mechanically ventilated. Bronchoscopic intervention allowed immediate discontinuation of mechanical ventilation in 10 (52.6%) (16). Murgu *et al.* examined the outcomes of 12 consecutive intubated and mechanically ventilated patients with inoperable or unresectable CAO from non-small cell lung cancer (NSCLC). TB resulted in immediate extubation in 9 patients (75%) (12). These studies demonstrate the impact of TB on the ability to wean patients with malignant CAO from the ventilator. Weaning from mechanical ventilation may allow for time for additional systemic treatment and provide time for the patient to discuss further goals of care.

Dyspnea

Dyspnea is the main symptom of MCAO and may result in sleep impairment, increase fatigue, and decrease functional performance (17). Improvement in dyspnea can be measured via standardized scoring systems including Borg score, San Diego Shortness of breath questionnaire or via a visual analog scale (10,17-19). Objective improvement in dyspnea using forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and 6-minute walk test (6MWT) has also been demonstrated (20). Overall, TB for MCAO has been shown to improve dyspnea in 48–75% of cases depending on the patient characteristics, nature and location of the obstruction (19,21,22). Various factors have been found to be associated with increased likelihood of improvement in dyspnea. In a retrospective study of 301 therapeutic bronchoscopies, a visible distal airway on CT and shorter time to intervention from radiographic CAO were associated with increased success rate (13). Ong *et al.* found that a higher baseline Borg score was associated with greater improvement in dyspnea (11). Similarly, greater baseline dyspnea was associated with improvement in dyspnea, whereas smoking, having multiple cancers and lobar obstruction were associated with smaller improvements (10). These findings suggest that significant functional impairment due to shortness of breath should not preclude bronchoscopic intervention provided that there is significant dyspnea, dyspnea is likely caused by the airway obstruction and that dyspnea is impacting the patient's functional status. Stenting the esophagus as well as the airway in cases of esophageal malignancy has also led to improvement in both dysphagia and respiratory symptoms. The lack of comparator limits the ability to clearly measure the value of double stenting (23).

Dutau *et al.* assessed the impact of silicone stent placement after successful TB in symptomatic MCAO without extrinsic compression and concluded that silicone stent placement maintained the benefit of the TB after one year on dyspnea score as well as obstruction recurrence, although data should be interpreted carefully as the study was not able to recruit the target number (24).

HrQOL

HrQOL is a multifaceted outcome that incorporates physical, mental, emotional, and social function. This outcome is broader and is not solely dependent on dyspnea (17). HrQOL is frequently measured by various questionnaires and scales including European Organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30), 36-item short form survey (SF-36), and SF-6D HrQOL (10,11,18,25). Initial studies examining the impact of TB on quality of life were small, and did not find a significant improvement in HrQOL. Amjadi *et al.* in prospective study of 24 patients found that while dyspnea scores improved in 85% of patients, HrQOL, measured by the EORTC did not change for the group as a whole (17). Similarly, Oviatt *et al.* did not find a significant difference overall in HrQOL measured in 19 patients who underwent TB for MCAO despite 84% of patients maintaining airway patency (20). However, larger studies have demonstrated HrQOL improvement after TB for MCAO in both prospective and retrospective fashion (10,11,17,26). A retrospective study of 1,115 patients by Ost *et al.* found that Greater baseline dyspnea was associated with improved HrQOL whereas lobar obstruction was associated with smaller improvements (10). The data for HrQOL was only available in a subset of patients (183 patients) from select centers, therefore generalizability of these findings may need to be verified. In addition, retrospectively assessing the impact of TB on HrQOL can be confounded by indication, as the intention of a TB may be to avoid future potential worsening of an airway obstruction rather than for immediate relief. In the former case the impact on HrQOL may not be significant.

Survival

Survival is a longer-term outcome when compared to dyspnea. It is one of the most important outcomes when evaluating any drug, intervention, or procedure in oncological clinical trials (27). This outcome is clear, unambiguous, and unbiased. When MCAO is managed with TB, survival is reported to be no different compared to patients with advanced NSCLC without MCAO (28). When compared with patients with MCAO who refused TB, patients who underwent TB had a longer survival after matching for age, comorbidities, type of malignancy and type of obstruction (4±3 and 10±9 months respectively) (25). The impact of specific tools on survival has been evaluated. Brutinel *et al.* found that laser resection improved survival when compared to historical controls that received radiation (40% mortality at 7 months and 72% at 1 year compared to 76% and 100% respectively) (29). Similarly, Macha *et al.* sought to evaluate the impact of endobronchial laser resection in addition to radiation therapy on survival in 75 patients with MCAO and compared them to a retrospective cohort that received external radiation alone for the same indications. Laser resection did not influence the overall survival, however, in patients who had complete recanalization, survival was prolonged by more than 4 months compared to those whom recanalization failed, although the risk of bleeding was higher (30). Desai *et al.* found no difference in survival between patients who received laser plus radiotherapy compared to those who received radiotherapy alone, although significant increase in survival was noted in patients who underwent emergent laser compared to emergent radiation in patients with critical MCAO (31). Stratakos *et al.* in a prospective study showed a significant improvement in survival in patients who underwent TB compared to those who declined the intervention after matching for comorbidities (10±9 and 4±3 months respectively) (25). This may be due to the potential improvement in their functional status which would allow patients to receive further anti-cancer therapy.

Additionally, the effect of stenting on survival has been studied. Saji *et al.* retrospectively reviewed 65 patients with MCAO that underwent airway stenting. Airway stenting provided acute relief of symptoms, although overall survival was not significantly changed (32). While Razi *et al.* found that timely stenting was associated with improved survival in patients with intermediate and poor performance status when compared to historical controls (33). Other studies suggested that stenting was associated with worse survival (14,22). Given the retrospective nature of the majority these studies, these results may be confounded by indication (e.g., stents may not be placed when the disease is very extensive) and therefore results should be interpreted with caution.

Poor survival following TB was associated with underlying chronic pulmonary disease, poor performance status, extended lesion, extrinsic or mixed lesion as well as not receiving adjuvant treatment following bronchoscopic intervention (34). Patients who underwent additional adjuvant treatment following TB, and those with obstruction limited to one lung seem to have better survival (34,35). Guibert *et al.* retrospectively studied data from 204 patients and concluded that reduced survival was associated with high American Society of Anesthesiologists (ASA) score, non-squamous histology, and metastatic tumors (36). A distinction between patients with high ASA due to CAO and those due to other organ dysfunction should be made, as patients with high ASA due to CAO seem to benefit from TB (36).

Quality adjusted survival

Quality adjusted survival is an important indicator to assess the cost-effectiveness of an intervention and the true impact on quality of life (37-41). Although TB may prolong life, most patients benefit from the improvement in quality of life during that time. Quality-adjusted life day is calculated as the area under the utility curve with time on the x-axis and quality of life on the y-axis (42). The impact of TB on long term quality-adjusted survival has not been studied until recently. Ong *et al.* performed a prospective observational study of 102 consecutive patients with MCAO that underwent TB. The median quality adjusted survival was 109 quality-adjusted life-days. Factors associated with longer quality-adjusted survival included better functional status, treatment naïve tumor, endobronchial disease, less dyspnea at baseline, shorter time from cancer diagnosis to TB, absence of cardiac disease, bronchoscopic dilation, and receiving chemotherapy post intervention (11).

Complications

Although proven to be very effective in treatment of MCAO, TB is not without complications. Reported complications and adverse events are bleeding, pneumothorax, worsening hypoxia, remaining on the ventilator, airway injury, and stent related complications (18,22,43). The overall complication rate of TB for MCAO is reported to be 3.9%. Procedure-related death has been reported between 0.5% and 1.3% (22,34). Moderate sedation, high ASA, urgent or emergent bronchoscopy, and redo bronchoscopy were associated with increased risk of complications (22).

Conclusions

TB for MCAO should be considered as part of the multimodality approach to the management of the disease due to its overall positive impact on dyspnea, survival as well as long term quality of life. However, it is clear based on the available data that not every patient may benefit from such intervention, and the procedure is not without risks. Therefore, it is important to take into account the likelihood of technical success, the potential impact of technical success on dyspnea and how long is that impact expected to last, and how that will ultimately affect long-term HRQOL. The potential benefits should then be weight against the potential complications of the intervention. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

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Footnote

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