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REVIEWS

The Utility of Interventional Pulmonary Procedures in Liberating Patients with Malignancy-Associated Central Airway Obstruction from Mechanical Ventilation

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Abstract
Purpose Utilization of intensive care services by patients with malignancy has risen during the past several decades. Newer cancer therapies have improved overall survival and outcomes. Patients with respiratory failure from central airway obstruction related to tumor growth were previously viewed as inappropriate candidates for ventilator support. However, an increasing number of reports suggest that interventional pulmonary (IP) procedures may benefit such patients.
Methods We reviewed the literature for case reports or case series from the past 20 years regarding the use of IP procedures for the treatment of respiratory failure from malignancy-associated central airway obstruction.
Results As a whole, IP procedures were greater than 60 % successful in liberating patients from mechanical ventilation. Moreover, IP procedures served to palliate respiratory symptoms, prolong overall survival, allow for additional cancer treatments, and reduce hospitalization costs. Nevertheless, it remains unclear who may benefit the most from these procedures.
Conclusions Although data are limited, IP procedures are generally safe and should be considered for appropriate patients with respiratory failure from malignancy-associated central airway obstruction as a potential means of liberation from mechanical ventilation.

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Keywords Central airway obstruction · Respiratory failure · Mechanical ventilation · Interventional pulmonology

Introduction

Primary or metastatic tumors involving the central airways produce airflow disruptions, which if left untreated can ultimately increase work of breathing and affect ventilation (gas exchange). Leading causes of malignant central airway obstruction (CAO) include lung, esophageal, and thyroid tumors or lymphoma. Three general types of CAO have been previously described: endoluminal (tumor within the airway), extraluminal (from the compressive effects of tumor growth), or combined (Fig. 1) [1]. The presence and severity of symptoms associated with CAO is to some extent related to tumor size, shape, and location. However, individual symptoms are influenced additionally by the presence of other disease states (cardiopulmonary, neurological, musculoskeletal, metabolic, and nutritional) as well as overall performance status. Patients with severe isolated CAO or combined with additional disease states can develop progressive respiratory insufficiency, necessitating mechanical ventilation (MV) and admission to an intensive care unit (ICU). Eventual MV liberation may be unattainable without treatment of the CAO, leading to prolonged ICU stays and translating into a high cost of care. Interventional pulmonary (IP) medicine, a relative new discipline that emerged in the 1980s, has made available new airway procedures that can treat CAO. IP utilizes advanced technologies, such as ablative therapies (laser photoresection (LPR), argon plasma coagulation (APC), electrocautery, and cryotherapy) and airway stenting. Whereas the utility of IP procedures in patients with

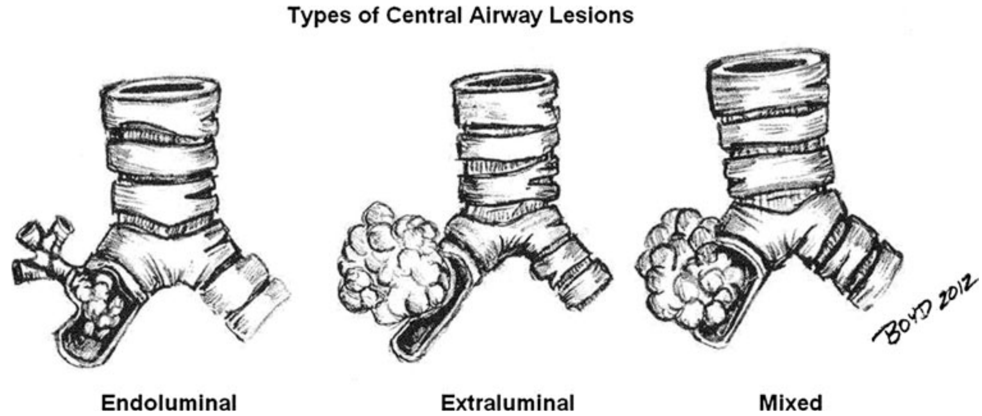

Fig. 1 Types of central airway obstruction

malignant CAO has been demonstrated, their usefulness in patients who require MV is less well known [2–7]. Hence, we offer this review of the available literature on the safety and efficacy of IP procedures in liberating patients with malignancy-associated CAO from MV.

Materials and Methods

A literature search was performed using Medline for the period from January 1991 to January 2011. The search was limited to English using a combination of terms: CAO AND respiratory failure AND MV AND intensive care AND critical care AND interventional pulmonology. All abstracts were reviewed, and only those studies or case reports of patients who required MV were selected. References were reviewed to identify any additional publications not identified within Medline. One additional abstract was included (authors own work). All of the studies included in this review are retrospective case reviews or cohort analyses (Table 1).

Review of Interventional Pulmonology Procedures

Ablative Therapies

The first report suggesting the potential use of LPR for the treatment of malignant CAO requiring MV was in 1987. Six patients with subtotal airway obstruction of the trachea or mainstem bronchi were successfully liberated from MV by using neodymium-yttrium-aluminum-garnet (Nd:YAG) laser and survived to have additional therapies [8]. In 1993, the utility of ablative IP procedures for the treatment of respiratory failure due to malignant CAO was specifically examined in 17 patients with lung cancer. The authors reported the overall success of LPR in liberation from MV was 9 of 17 (53 %). Those with endoluminal disease (12 patients) were more likely to benefit from LPR compared with patients with submucosal invasion and extraluminal compression (5 patients). Those freed from MV had improved survival (98 vs. 8.5 days) [9].

Airway Stenting

Successful liberation from MV using a metallic stent was first described in a patient with thymic carcinoma. The patient died 2 months after the procedure [10]. Since this report, the use of expandable metal stents to facilitate extubation in patients with malignant CAO has been examined in several limited studies and case reports [11–16]. The largest investigated the utility of self-expandable metallic stents (SEMS) deployed via flexible bronchoscopy in 21 patients with malignancy-associated CAO requiring MV. Five patients with benign disease were included in this study (for a total of 26 patients). Although not clearly divided into distinct cohorts, the overall success of liberation from MV was 53.8 %. The primary factor associated with failure was severe pneumonia [11]. In a similar study of 50 patients (39 with lung cancer and 11 patients with metastatic cancer), airway stenting facilitated liberation in 7 of 8 patients (87.5 %) requiring MV. Additionally, immediate resolution of symptoms occurred in 36 patients (72 %). Reported complications included granuloma (4 %), infection (10 %), migration (4 %), hemoptysis (16 %), and disease recurrence (10 %) [12]. In a retrospective chart review, airway stenting facilitated liberation in 100 % of patients receiving MV: five with extraluminal compression and one with endoluminal disease [13]. Similar results were reported in four patients with CAO from esophageal cancer. All patients were liberated within 1 day of stent placement and were eventually discharged from the hospital [14]. Successful liberation was reported in one of two patients who required MV for respiratory failure due to malignant CAO. The liberated patient lived an additional 3.5 months. The other patient died of sepsis 48 hours after stent placement [15]. In a recent report, three of seven patients with malignant CAO were liberated from MV after

Table 1 Articles related to interventional pulmonology, respiratory failure, and mechanical ventilation

Author	Patients (*n*)	MV (*n*)	Cause of CAO	Primary interventional modality	Liberated from MV/ total pts. on MV (%)	Complications all patients and types
Gelb and Epstein [8]	70	NR	70 Malignant	Laser photoresection	6 / NR (not included in total)	Death—Hemorrhage 1/70 (1.4 %) Death—Respiratory failure 1/70 (1.4 %)
Stanopoulos et al. [9]	17	17	17 Malignant	Laser photoresection	9/17 (52.9 %)	Minor
Zannini et al. [10]	6	6	1 Malignant	Stent	1/1 (100 %)	None
Lin et al. [11]	26	26	21 Malignant	Stent	14/26 (53.8 %) (5 pts. with benign disease included in total)	Granuloma 7/26 (26.9 %) Mucus plugging 1/26 (3.8 %) Pneumothorax 1/26 (3.8 %) Stent migration 1/26 (3.8 %)
Saad et al. [12]	50	8	50 Malignant	Stent	7/8 (87.5 %)	Granuloma 2/50 (4 %) Infection 5/50 (10 %) Stent migration 2/50 (4 %) Hemoptysis 8/50 (16 %) Disease recurrence 5/50 (10 %)
Shaffer and Allen [13]	8	8	2 Benign 6 Malignant	Stent	7/8 (87.5 %)	None
Chan et al. [14]	11	4	11 Malignant	Stent	4/4 (100 %)	Stent migration 2/11 (18 %)
Lippman et al. [15]	3	3	1 Benign 2 Malignant	Stent	2/3 (66 %)	Sepsis 1/3 (33 %)
Razi et al. [16]	50	7	50 Malignant	Stent	3/7 (42.8 %)	Mucus plugging 2/50 (4 %) Stent migration 2/50 (4 %) Disease recurrence 5/50 (10 %)
Colt and Harrell [17]	32	19	18 Benign 14 Malignant	Combined laser and stent	10/19 (52.6 %)	Mucus plugging 3/32 (9 %) Stent migration 5/32 (15.6 %) Granuloma 3/32 (9 %)
Kovitz et al. [18]	14	14	14 Malignant	Combined laser and stent	14/14 (100 %)	None
Jeon et al. [19]	36	NR	36 Malignant	Combined laser and stent	NR (not included in total)	Hemoptysis 1/36 (2.7 %) Sepsis 3/36 (8.3 %)
Totals	323	112			71/112 (63.4 %)	Death 2/323 (0.6 %) Granuloma 12/323 (3.7 %) Infection/sepsis 9/323 (2.7 %) Pneumothorax 1/323 (0.3 %) Stent migration 12/323 (3.7 %) Hemoptysis 9/323 (2.7 %) Disease recurrence 10/323 (3 %) Mucus plugging 6/323 (1.8 %) All 61/323 (18.8 %)

airway stenting. In two of the four patients who required continued ventilator support, superior vena cava syndrome was present. The two liberated patients lived between 3 and 6 months, whereas the others died within 20 days after the procedure [16].

Combined Modalities

The use of LPR, airway stenting, and dilatation was examined in 14 lung cancer patients with CAO (12 with combined and 2 with endoluminal disease). All interventional procedures were considered successful in alleviating the CAO; however, only 2 of 11 patients who required MV (18 %) were liberated and 1 patient who was not initially on MV, subsequently required intubation [17]. The authors concluded that although IP procedures could palliate respiratory symptoms, facilitate liberation, and lower healthcare costs, in patients with more advanced cancers, there should be consideration for the early institution of comfort measures. In a similar study, 14 patients with malignant CAO (12 with lung primaries) underwent IP ablative therapies and 100 % were liberated from MV. Eleven patients were extubated within 24 hours, and 86.6 % (12/14) subsequently returned home. Rapid liberation was found to reduce ICU costs [18]. A more recent retrospective cohort analysis examined 36 patients with malignant CAO referred for severe dyspnea. All patients required intubation or supplemental oxygen. It is unclear whether all patients required ICU monitoring. Rigid bronchoscopy was performed within 24 h of presentation. Sixteen patients (44.4 %) had endoluminal disease, 2 (5.6 %) had extraluminal compression, and 18 (50 %) had mixed lesions. Patients underwent airway dilatation, LPR, and stenting depending on the lesion type. IP interventions were 94.4 % effective in alleviating dyspnea. Tracheal perforation occurred in one patient, requiring surgical repair. Further analysis found that 21 of 36 patients (58.3 %) received additional definitive therapies. Survival was significantly longer in those who received additional therapy versus those who did not (median survival, 38.2 vs. 6.3 months, $p < 0.001$) [19].

Discussion

Malignant CAO is primarily due to lung cancer, followed by esophageal tumors, thyroid cancer, and lymphoma. Other tumors also can metastasize, resulting in CAO (Fig. 2). CAO may be the result of endoluminal tumor growth, extraluminal compression, or a combined process (Fig. 1). It is believed that 20–30 % of all primary lung cancers will at some point develop airway involvement, but the true incidence of malignancy associated CAO remains unknown [20, 21]. The best approach for therapy requires an individual assessment of the tumor causing CAO, with attention to size, location, and degree/type of airway involvement. Based on our review, it is clear that no single modality is appropriate for all cases. LPR was demonstrated to be effective in liberating patients from MV when endoluminal disease was present, whereas tracheobronchial stenting was better suited to treat extrinsic compression. Combined modalities may be necessary in mixed lesions.

The effect of CAO on any given patient's respiratory status is variable. The burden of parenchymal tumor involvement, presence of postobstructive pneumonia, or associated pleural effusion may be additive. Additionally, comorbidities, such as chronic obstructive pulmonary disease, cardiac disease, and neurological dysfunction, may contribute to impairments in oxygenation and increase work of breathing. Finally, factors, such as performance and/or nutritional status, also influence tolerance to sustained breathing efforts. In attempting to liberate these patients from MV, all contributing processes that impair ventilation and oxygenation must be addressed. Relief of CAO without concomitant treatment of associated pathology may only allow these weakened patients to support their ventilation for a transient period. The reports cited do not fully describe the associated factors that may have contributed to the need for MV. Only one study notes pneumonia as contributing to failed extubation [12]. Future studies should address these issues.

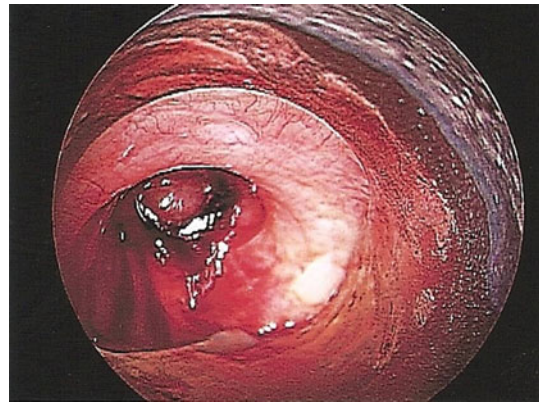

Fig. 2 Endobronchial tracheal lesion (non-small-cell lung cancer) resulting in respiratory failure

Complications related to IP procedures performed specifically in patients requiring MV are difficult to assess from the available literature, because individual procedures are not clearly described. In both MV and non-MV patients, it would seem that complications can be divided into immediate and delayed. Immediate procedural-related complications occurred in 6.3 % of patients and included hemoptysis, pneumothorax (rare), infection, and death from respiratory failure or hemorrhage. It is unclear whether these complications were higher in the MV cohort. Delayed complications included granuloma formation (3.7 %), stent migration (3.7 %), disease recurrence (3 %), and mucus plugging (1.8 %; Table 1). The studies also show a significant difference in the incidence of these complications from study to study. The occurrence of immediate complications, although important in this population, remains low when considering the severity and complexity of such cases. Granulation tissue formation is a delayed response and should occur more commonly in patients with longer survival. It is the experience of the authors that granulation complications can be minimized by routine reinspection of the airway and early removal of stents when appropriate (i.e., when additional therapies have succeeded in controlling local disease). Stent migration may be an acute or delayed complication. The experience of the operator plays a role in this, as well as the fact that adjuvant therapy may lead to decreased local tumor burden, facilitating stent migration. For these reasons, early bronchoscopic reinspection of the airways should be performed. Mucous plugging also can be both an acute or delayed complication, which may be mitigated by implementing aggressive pulmonary toilet from the beginning. In general, acute complications appear uncommon and overall indicate that IP techniques are generally safe and appropriate interventions to facilitate liberation from MV. Perhaps, future studies should better standardize how to define these complications while also providing adequate standardization of implemented measures to prevent them.

Although death may be delayed by the use of IP, issues related to quality versus quantity of life (QOL) must to be considered. In a recent study in 37 non-ventilated patients with malignant CAO (>50 % reduction in luminal tracheal or mainstem bronchus diameter), QOL measurements related to spirometry, 6-minute walk distance, and dyspnea were all significantly improved at 30 days subsequent to receiving IP therapies [22]. It is unclear whether similar findings could be demonstrated in patients requiring MV. Many confounders in these critically ill patients would likely influence their response to similar therapies and the measurement of these outcomes. As such, other outcomes regarding QOL might need to be considered in this particular patient cohort. Only one of the presented studies examined the long-term benefits of IP in malignant CAO with respiratory failure. After IP procedures, 21 of 36 (58.3 %) patients went on to receive additional definitive therapies (9 surgical resections). Those who received additional therapies survived significantly longer. This should be one of the goals of IP procedures in these patients. Furthermore, identifying risk factors that prohibit additional therapies may help to decide who should be offered IP services. Recent studies that examined prognostic factors in patients with lung cancer have suggested CAO as a negative prognostic factor. These do not describe the type of CAO (endoluminal, extraluminal, or mixed), nor do they report whether IP services were available or attempted [23–26]. It would be interesting to know whether this negative prognostic factor could be improved by the presence of an IP program.

Additional therapies may be facilitated by an initial IP procedure and appear to confer further benefit in prolonging overall survival [19]. In this regard, while radiation therapy has not been studied specifically in this cohort of patients, the use of endobronchial brachytherapy has been shown to help control endoluminal airway lesions. The latter should be considered complimentary to other interventional pulmonology techniques [27–29]. It is necessary to point out that the effects of brachytherapy are not immediate and frequently require several treatments [30]. Additionally, the initial response to this localized radiation may produce an acute inflammatory response. Patients may develop airway stenosis, bronchospasm, and/or pneumonitis, which may cause worsening of these patients with already pronounced respiratory failure [30]. This makes brachytherapy, as an isolated modality, less well suited to facilitate expeditious liberation from MV. Nevertheless, in combination with ablative therapy and/or airway stenting, brachytherapy may convey an added benefit allowing longer term control of localized tumor involvement/recurrence.

Institutions providing dedicated IP services in large markets, as those in this review, can expect to see approximately *six* patients each year. The incidence in smaller markets is unknown. From a research perspective, this is important due to two main factors. One is that experience performing interventional procedures may impact outcomes. The other is that the limited number of cases per center suggests that research to investigate the utility of IP malignant CAO associated respiratory failure will likely require a multicenter approach.

It is necessary to point out that dedicated IP services are few and in many cases unavailable. The number of IP programs has increased, but still few pulmonologists have training and experience in this discipline. Certainly less complex airway processes may be within the limits of self-trained and experienced pulmonologist, but higher risk airway lesions that will require the full therapies of an IP physician should be considered carefully and referred to centers that are able to offer all of these services. The establishment of regional IP programs in the United States should be considered.

There are ethical concerns regarding the performance of randomized, controlled trials, given the success reported by the currently available studies. Additionally, the effectiveness of IP procedures in both MV and non-MV patients with malignant CAO is highlighted in the new ACCP lung cancer guidelines [31]. Nevertheless, a retrospective case-control study may be possible considering as controls those patients admitted to facilities that do not offer these IP services (although identifying these patients may be difficult) or patients refusing further interventions.

Conclusions

The available literature on the use of IP to treat patients with malignant CAO with respiratory failure is limited and based on retrospective cohorts. Therefore, definitive conclusions regarding the utility of IP procedures in these patients are not possible. Nevertheless, the overall effectiveness of IP procedures to liberate patients from MV appears to be greater than 60 % (Table 1). Complications are minor, with the procedures being generally safe. To further minimize complications, these procedures should be performed by experienced dedicated IP physicians with adequate training. Patient selection is not clear and should be explored further. Both survival and quality of life are improved in most cases. Furthermore, IP approaches may facilitate the implementation of additive therapies, which may play a significant role in prolonging survival. In malignant disease the value of prolonged survival must be individualized and should be discussed openly. Based on this review, IP should be at least considered in every case of malignant CAO resulting in respiratory failure, with interventions pursued in appropriate cases.

Conflict of interest None.

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