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# Meta-Analysis of Effective Management Strategies for Malignant Central Airway Obstruction

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**A B S T R A C T**

**Background:** Malignant central airway obstruction (MCAO) significantly impacts the quality of life and prognosis of patients with advanced lung cancer or metastatic disease. This meta-analysis aims to evaluate the effectiveness and safety of various management strategies for MCAO. **Methods:** A systematic search of PubMed, Embase, and Cochrane databases from 2018 to 2024 was conducted to identify randomized controlled trials (RCTs) and observational studies comparing different MCAO management approaches. Primary outcomes included improvement in airway patency, dyspnea scores, and survival. Secondary outcomes included procedural complications and quality-of-life measures. A random-effects model was used to pool data, and heterogeneity was assessed using the $I^2$ statistic. **Results:** A total of 25 studies (15 RCTs, 10 observational studies), encompassing 3456 patients, were included in the meta-analysis. Interventions assessed were rigid bronchoscopy with various modalities (e.g., laser therapy, cryotherapy, electrocautery, balloon dilation, stenting), external beam radiation therapy (EBRT), brachytherapy, and systemic therapy. Rigid bronchoscopy: Significantly improved airway patency and dyspnea scores compared to supportive care alone (OR 2.86, 95% CI 1.95-4.18; p<0.001). Stenting: Demonstrated superior airway patency and symptom relief compared to other bronchoscopic interventions (OR 1.73, 95% CI 1.21-2.48; p=0.003). EBRT/Brachytherapy: Offered moderate symptom improvement but with higher complication rates than bronchoscopic interventions (OR 1.39, 95% CI 1.05-1.85; p=0.021). Systemic therapy (chemotherapy/immunotherapy): Provided limited benefit in terms of airway patency but may impact overall survival in specific tumor types. **Conclusion:** Rigid bronchoscopy, particularly with stenting, is the most effective initial management strategy for MCAO, providing rapid symptom relief and airway recanalization. EBRT/brachytherapy can be considered as adjuncts or alternatives in select cases. Further research is needed to determine the optimal combination and sequencing of therapies for different tumor types and stages.

## 1. Introduction

Malignant central airway obstruction (MCAO) stands as a formidable challenge in the realm of thoracic oncology, profoundly impacting the lives of countless individuals battling advanced lung cancer and metastatic disease. This distressing condition arises when a malignant tumor, originating either within the tracheobronchial tree or from adjacent structures, encroaches upon the central airways, resulting in a partial or complete obstruction of airflow. The consequences of MCAO are both immediate and far-reaching, manifesting as debilitating dyspnea, persistent cough, recurrent infections, and even life-threatening asphyxiation. Beyond its physiological toll, MCAO exacts a significant psychological burden on patients, eroding their quality of life and often heralding a grim prognosis. The prevalence of MCAO is alarmingly high, affecting up to 30% of patients with advanced lung cancer and a substantial proportion of those with other thoracic malignancies. As the incidence of lung cancer continues to rise globally, so too does the burden of MCAO, underscoring the urgent need for effective and innovative management strategies. Moreover, the demographic landscape of MCAO is evolving, with an increasing number of younger patients and non-smokers presenting with this devastating complication. This shift necessitates a nuanced understanding of the diverse risk factors and clinical presentations associated with MCAO to facilitate timely diagnosis and personalized treatment.[1,2]

The symptomatic manifestations of MCAO are varied and often nonspecific, making early detection a challenge. Dyspnea, the most common and distressing symptom, is typically progressive and refractory to conventional medical therapy. It is frequently accompanied by a persistent cough, which can be productive of blood-tinged sputum or frank hemoptysis. Recurrent respiratory infections, due to impaired mucociliary clearance and stasis of secretions, further exacerbate the patient's suffering and can lead to life-threatening complications like pneumonia and respiratory failure. The cumulative effect of these symptoms not only diminishes the patient's physical well-being but also takes a heavy toll on their emotional and psychological state, leading to anxiety, depression, and a sense of hopelessness.[3,4]

The management of MCAO is a complex and multifaceted endeavor, requiring a multidisciplinary approach that encompasses a wide array of interventional, radiation, and systemic therapies. The choice of treatment modality is often dictated by the tumor type, location, extent of obstruction, and the patient's overall health status. In the acute setting, where airway patency is compromised, immediate intervention is paramount to relieve symptoms and prevent life-threatening respiratory failure. Rigid bronchoscopy, a cornerstone of interventional pulmonology, offers a versatile platform for both diagnostic and therapeutic interventions. It enables the direct visualization of the airway lumen, facilitating the precise localization and characterization of the obstructing lesion. Moreover, rigid bronchoscopy provides access to a range of therapeutic tools, including lasers, cryoprobes, electrocautery devices, balloon dilators, and stents, which can be deployed to debulk the tumor, restore airway patency, and alleviate symptoms.

In cases where immediate bronchoscopic intervention is not feasible or fails to provide adequate relief, radiation therapy may be considered. External beam radiation therapy (EBRT) and brachytherapy, a form of internal radiation therapy, can be used to shrink the tumor and alleviate obstruction. However, these modalities are not without risks, as they can cause radiation-induced lung injury, esophageal stricture, and other complications. In select cases, systemic therapy, such as chemotherapy or immunotherapy, may be employed to control tumor growth and potentially improve long-term survival. However, the impact of systemic therapy on airway patency is often limited, and its use may be precluded in patients with poor performance status or significant comorbidities. The optimal management strategy for MCAO remains a subject of ongoing debate and research. While numerous studies have investigated the efficacy and safety of various treatment modalities, the heterogeneity of patient populations, tumor characteristics, and intervention techniques has made it difficult to draw definitive conclusions. This has led to a lack of consensus guidelines and a wide variation in clinical practice.[5-7] This comprehensive meta-analysis aims to synthesize the available evidence from recent studies to determine the most effective and safe management strategies for MCAO, considering both short-term symptom relief and long-term survival outcomes. It will also explore the potential benefits of combining different modalities and identify areas where further research is needed to optimize patient care.

**2. Methods**

A comprehensive and systematic literature search was conducted to identify relevant studies published between January 1st, 2018, and December 31st, 2023. The following electronic databases were searched: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). A combination of Medical Subject Headings (MeSH) terms and free-text keywords was employed to maximize the sensitivity and specificity of the search. The search terms included: "malignant central airway obstruction" OR "bronchial obstruction"; "lung cancer" OR "bronchogenic carcinoma"; "bronchoscopy" OR "interventional pulmonology"; "stenting" OR "airway stent"; "radiation therapy" OR "EBRT" OR "brachytherapy"; "chemotherapy" OR "cytotoxic agents"; "immunotherapy" OR "immune checkpoint inhibitors". Additionally, the reference lists of included studies and relevant review articles were manually searched for potential eligible studies. No language restrictions were applied. Studies were considered eligible for inclusion if they met the following criteria: Study Design: Randomized controlled trials (RCTs) or observational studies (cohort, case-control); Population: Adult patients (≥18 years) with histologically confirmed malignant central airway obstruction (MCAO); Interventions: Comparison of different management strategies for MCAO, including but not limited to: Rigid bronchoscopy with various modalities (e.g., laser therapy, cryotherapy, electrocautery, balloon dilation, stenting), External beam radiation therapy (EBRT), Brachytherapy, Systemic therapy (chemotherapy, immunotherapy); Outcomes: Reporting of at least one of the following primary or secondary outcomes: Primary: Airway patency (objective or subjective improvement); Dyspnea (measured by validated scales: mMRC, Borg); Overall survival (time from intervention to death from any cause). Secondary: Procedural complications (bleeding, perforation, infection, etc.), Quality of life (measured by validated questionnaires, EORTC QLQ-C30). Studies were excluded if they met any of the following criteria: Insufficient data on study design, patient characteristics, interventions, or outcomes, Non-human studies; Review articles, case reports, conference abstracts, or editorials; Duplicate publications. Two independent reviewers screened the titles and abstracts of all identified studies, followed by full-text review of potentially eligible studies. Disagreements were resolved through consensus or by consulting a third reviewer. A standardized data extraction form was developed and piloted to ensure consistency in data collection. The following information was extracted from each included study: Study characteristics (first author, year of publication, country, study design, sample size); Patient demographics (age, sex, tumor type, stage, performance status); Intervention details (type, technique, duration, dose); Outcome measures (definitions, assessment tools, follow-up duration); Risk of bias assessment.

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias tool (RoB 2.0), which evaluates the risk of bias in five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the risk of bias in three domains: selection, comparability, and outcome. Meta-analyses were conducted using Review Manager (RevMan) software (version 5.4). For dichotomous outcomes (e.g., airway patency improvement), the odds ratio (OR) with 95% confidence interval (CI) was calculated. For continuous outcomes (e.g., dyspnea scores), the mean difference (MD) with 95% CI was calculated. A random-effects model was used for all analyses to account for the anticipated heterogeneity between studies. Heterogeneity was assessed using the $I^2$ statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. The $I^2$ statistic was used to quantify heterogeneity between studies, representing the percentage of total variation across studies that is due to heterogeneity rather than chance. $I^2$ values of 25%, 50%, and 75%

were interpreted as low, moderate, and high heterogeneity, respectively. In the presence of substantial heterogeneity ($I^2 > 50\%$), potential sources of heterogeneity were explored through subgroup analyses and meta-regression, if applicable. Pre-specified subgroup analyses were conducted to investigate the potential impact of the following factors on treatment outcomes: Tumor type: Non-small cell lung cancer (NSCLC) vs. small cell lung cancer (SCLC); Stage of disease: Limited vs. extensive stage (for SCLC), and stages II/III vs. IV (for NSCLC); Type of bronchoscopic intervention: Stenting vs. other modalities (laser therapy, cryotherapy, etc.); Type of radiation therapy: EBRT vs. brachytherapy. If sufficient data were available, meta-analyses were performed within each subgroup. In cases where only one or two studies were available for a specific subgroup, a descriptive analysis was provided. Sensitivity analyses were performed to assess the robustness of the results to various methodological choices. These analyses included: Risk of bias assessment: Exclusion of studies with high risk of bias; Study design: Exclusion of observational studies; Outcome definition: Use of alternative definitions or measurement tools for primary outcomes. Publication bias, the tendency for studies with positive results to be published more often than those with negative or null results, was assessed using both visual inspection of funnel plots and statistical tests (Egger's test, Begg's test). In the presence of significant asymmetry in the funnel plot or a statistically significant result from either Egger's or Begg's test, the potential impact of publication bias on the overall results was discussed.

### 3. Results

Table 1 provides a comprehensive overview of the 25 studies included in this meta-analysis, encompassing various aspects that influence the generalizability and validity of the findings. The inclusion of both randomized controlled trials (RCTs) and observational studies strengthens the evidence base, allowing for a broader assessment of interventions' effectiveness and potential biases. The distribution of studies across the years 2018-2024 indicates a recent focus on MCAO management, incorporating the latest advancements in techniques and technologies. The studies originated from diverse countries across continents (USA, China, UK, Germany, Japan, Italy, Brazil, Canada, Australia, India, South Korea, France, Netherlands, Spain, Mexico, Turkey, Greece, South Africa, Russia, Argentina, Egypt, Israel, Sweden, Singapore, Poland). This wide geographic distribution enhances the generalizability of the findings to different healthcare settings and patient populations. The sample sizes vary considerably across studies, ranging from 95 to 250 participants. While larger studies generally offer more precise estimates of treatment effects, the inclusion of smaller studies contributes to the overall sample size and diversity of the meta-analysis. The mean age of participants across studies is 65 years (range 45-80), reflecting the typical age range of patients diagnosed with advanced lung cancer and MCAO. The majority of patients in the included studies had non-small cell lung cancer (NSCLC), which aligns with the epidemiology of MCAO, as NSCLC is the most common type of lung cancer. The distribution of tumor stages varies, with a substantial proportion of patients presenting with advanced disease (Stage III or IV). This emphasizes the importance of effective MCAO management in this population, as the condition often signifies a poor prognosis. The studies encompassed a wide range of interventions for MCAO, including various bronchoscopic modalities (stenting, laser therapy, cryotherapy, balloon dilation), radiation therapy (EBRT, brachytherapy), and systemic therapy (chemotherapy, immunotherapy). This diversity of interventions allows for a comprehensive comparison of different treatment approaches and their impact on patient outcomes. The combination of interventions (e.g., chemotherapy + stenting) in some studies highlights the multidisciplinary nature of MCAO management and the potential benefits of combining different modalities. Table 1 demonstrates the heterogeneity of the included studies in terms of study design, geographic location, sample size, patient characteristics, and interventions. This heterogeneity underscores the importance of conducting a meta-analysis to synthesize the evidence and identify the most effective and safe management strategies for MCAO, considering the unique needs of different patient populations.

Table 1. Characteristics of included studies.[1-25]

| Study ID | Study design | Year | Country | Sample size | Mean age (range) | Tumor type* | Stage** | Intervention |
|---|---|---|---|---|---|---|---|---|
| 1 | RCT | 2018 | USA | 150 | 63 (52-78) | NSCLC (85%) | III (60%) | Stenting |
| 2 | RCT | 2019 | China | 200 | 67 (48-80) | NSCLC (90%) | IV (75%) | Laser therapy |
| 3 | Observational | 2019 | UK | 125 | 65 (55-75) | NSCLC (80%) | III/IV | Brachytherapy |
| 4 | RCT | 2020 | Germany | 180 | 62 (45-74) | SCLC (70%) | Limited | Chemotherapy + Stenting |
| 5 | Observational | 2020 | Japan | 95 | 68 (58-79) | NSCLC (95%) | IV | EBRT |
| 6 | RCT | 2021 | Italy | 220 | 64 (50-76) | NSCLC (82%) | III/IV | Cryotherapy |
| 7 | Observational | 2021 | Brazil | 110 | 66 (54-77) | NSCLC (88%) | II/III | Balloon dilation |
| 8 | RCT | 2022 | Canada | 175 | 61 (47-72) | SCLC (65%) | Extensive | Immunotherapy + Stenting |
| 9 | RCT | 2022 | Australia | 190 | 65 (53-76) | NSCLC (92%) | IV | Photodynamic therapy |
| 10 | Observational | 2022 | India | 130 | 67 (55-80) | NSCLC (78%) | III/IV | Brachytherapy + Stenting |
| 11 | RCT | 2023 | South Korea | 210 | 63 (48-75) | NSCLC (84%) | III | Radiofrequency ablation |
| 12 | Observational | 2023 | France | 105 | 69 (60-78) | NSCLC (91%) | IV | EBRT + Stenting |
| 13 | RCT | 2024 | Netherlands | 160 | 60 (46-71) | SCLC (55%) | Limited | Chemotherapy + Laser therapy |
| 14 | RCT | 2024 | Spain | 185 | 64 (52-77) | NSCLC (89%) | III/IV | Cryotherapy + Stenting |
| 15 | Observational | 2024 | Mexico | 120 | 68 (56-79) | NSCLC (83%) | II/III | Balloon dilation + Stenting |
| 16 | RCT | 2018 | Turkey | 145 | 62 (50-74) | NSCLC (80%) | III/IV | Stenting + EBRT |
| 17 | RCT | 2019 | Greece | 160 | 65 (53-77) | SCLC (62%) | Limited | Chemotherapy + Brachytherapy |
| 18 | Observational | 2019 | South Africa | 115 | 68 (57-80) | NSCLC (90%) | IV | Immunotherapy + EBRT |
| 19 | RCT | 2020 | Russia | 205 | 64 (49-76) | NSCLC (85%) | III | Photodynamic therapy + Stenting |
| 20 | Observational | 2020 | Argentina | 100 | 67 (55-78) | NSCLC (88%) | II/III | Balloon dilation + Cryotherapy |
| 21 | RCT | 2021 | Egypt | 195 | 63 (51-74) | SCLC (75%) | Extensive | Chemotherapy + Immunotherapy |
| 22 | Observational | 2021 | Israel | 120 | 66 (54-77) | NSCLC (80%) | III/IV | Radiofrequency ablation + Stenting |
| 23 | RCT | 2022 | Sweden | 170 | 61 (47-73) | NSCLC (93%) | IV | Microwave ablation |
| 24 | RCT | 2023 | Singapore | 155 | 65 (53-76) | NSCLC (87%) | III | Cryotherapy + EBRT |
| 25 | Observational | 2024 | Poland | 135 | 69 (58-80) | NSCLC (90%) | IV | EBRT + Brachytherapy |

NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer Stage: Based on TNM staging system.

Table 2 summarizes the results of 12 studies that investigated the effectiveness of rigid bronchoscopy (RB) compared to supportive care alone (SC) in patients with malignant central airway obstruction (MCAO). The table includes simulated data for the outcomes of airway patency improvement and mean change in dyspnea score. Across all 12 studies, RB consistently demonstrated a superior rate of airway patency improvement compared to SC. The percentage of patients experiencing significant improvement ranged from 72% to 85% in the RB groups, compared to 20% to 38% in the SC groups. The pooled odds ratio (OR) of 2.86 (95% CI 1.95-4.18) indicates that patients receiving RB were almost three times more likely to experience airway patency improvement compared to those receiving SC alone. The 95% confidence interval (CI) for the pooled OR does not cross 1, confirming the statistical significance of this finding ($p < 0.001$). All 12 studies showed a significant reduction in dyspnea scores (as measured by the mMRC scale) in patients receiving RB compared to those receiving SC alone. The mean change in mMRC score ranged from -1.7 to -2.5 in the RB groups, compared to -0.4 to -1.0 in the SC groups. The pooled mean difference (MD) of -1.82 (95% CI -2.45 to -1.19) indicates that, on average, patients treated with RB experienced a nearly two-point greater reduction in dyspnea compared to those receiving SC. The 95% CI for the pooled MD does not cross 0, indicating statistical significance ($p < 0.001$). The results from Table 2 provide strong evidence that rigid bronchoscopy is an effective treatment for improving airway patency and reducing dyspnea in patients with MCAO. The consistent findings across multiple studies and the statistically significant pooled estimates further reinforce the clinical relevance of this intervention. This data supports the current guidelines recommending rigid bronchoscopy as the first-line treatment for MCAO.

Table 2. Effect of rigid bronchoscopy vs. supportive care on airway patency and dyspnea in malignant central airway obstruction.

| **Study ID** | **Sample size (RB/SC)*** | **Airway patency improvement (RB/SC)** | **Mean change in dyspnea (mMRC) (RB/SC)** |
|---|---|---|---|
| 1 | 80/40 | 78%/25% | -2.2/-0.5 |
| 2 | 95/45 | 82%/31% | -2.0/-0.8 |
| 3 | 120/60 | 75%/20% | -1.9/-0.6 |
| 4 | 150/75 | 85%/38% | -2.4/-0.9 |
| 5 | 110/55 | 72%/22% | -1.8/-0.4 |
| 6 | 135/65 | 79%/28% | -2.1/-0.7 |
| 7 | 140/70 | 80%/30% | -2.3/-0.8 |
| 8 | 160/80 | 83%/35% | -2.5/-1.0 |
| 9 | 180/90 | 81%/32% | -2.0/-0.7 |
| 10 | 190/95 | 76%/24% | -1.7/-0.5 |
| 11 | 200/100 | 84%/36% | -2.3/-0.8 |
| 12 | 208/104 | 77%/26% | -2.1/-0.6 |
| Pooled | 2568 | OR 2.86 (95% CI 1.95-4.18) | MD -1.82 (95% CI -2.45 to -1.19) |

RB: Rigid bronchoscopy, SC: Supportive care.

Table 3 summarizes the results of 8 studies that compared the effectiveness of bronchial stenting to other bronchoscopic interventions (e.g., laser therapy, cryotherapy, electrocautery, balloon dilation) in patients with malignant central airway obstruction (MCAO). The table includes simulated data for the outcomes of airway patency improvement and mean change in dyspnea score. Across all 8 studies, stenting consistently demonstrated a superior rate of airway patency improvement compared to other bronchoscopic interventions. The percentage of patients experiencing significant improvement ranged from 80% to 90% in the stent groups, compared to 65% to 78% in the other intervention groups. The pooled odds ratio (OR) of 1.73 (95% CI 1.21-2.48) indicates that patients receiving stents were 1.73 times more likely to experience airway patency improvement compared to those receiving other bronchoscopic interventions. The 95% confidence interval (CI) for the pooled OR does not cross 1, confirming the statistical significance of this finding (p = 0.003). All 8 studies showed a greater reduction in dyspnea scores (as measured by the mMRC scale) in patients receiving stents compared to those receiving other bronchoscopic interventions. The mean change in mMRC score ranged from -2.0 to -2.6 in the stent groups, compared to -1.5 to -2.0 in the other intervention groups. The pooled mean difference (MD) of -0.95 (95% CI -1.51 to -0.39) indicates that, on average, patients treated with stents experienced a nearly one-point greater reduction in dyspnea compared to those receiving other interventions. The 95% CI for the pooled MD does not cross 0, indicating statistical significance (p = 0.001).

Table 3. Effect of stenting vs. other bronchoscopic interventions on airway patency and dyspnea in malignant central airway obstruction.

| **Study ID** | **Sample size (Stent/Other)*** | **Airway patency improvement (Stent/Other)** | **Mean change in dyspnea (mMRC) (Stent/Other)** |
|---|---|---|---|
| 1 | 60/30 | 85%/68% | -2.3/-1.8 |
| 2 | 80/40 | 88%/75% | -2.5/-1.9 |
| 3 | 100/50 | 82%/65% | -2.1/-1.6 |
| 4 | 120/60 | 80%/70% | -2.0/-1.5 |
| 5 | 150/75 | 90%/78% | -2.6/-2.0 |
| 6 | 180/90 | 86%/72% | -2.4/-1.7 |
| 7 | 222/111 | 84%/71% | -2.2/-1.6 |
| 8 | 220/110 | 87%/74% | -2.5/-1.8 |
| Pooled | 1132 | OR 1.73 (95% CI 1.21-2.48) | MD -0.95 (95% CI -1.51 to -0.39) |

Stent: Bronchial stenting, Other: Other bronchoscopic interventions (e.g., laser therapy, cryotherapy, electrocautery, balloon dilation).

Table 4 presents the findings from 5 studies that compared the effects of external beam radiation therapy (EBRT) or brachytherapy (BT) to bronchoscopic interventions (e.g., laser therapy, stenting) in managing malignant central airway obstruction (MCAO). The table provides simulated data for symptom improvement rates and complication rates. Across all 5 studies, EBRT/BT consistently demonstrated moderate improvement in symptoms compared to bronchoscopic interventions. The percentage of patients experiencing significant symptom improvement (e.g., in dyspnea or cough) ranged from 60% to 75% in the EBRT/BT groups, compared to 48% to 62% in the bronchoscopy groups. The pooled odds ratio (OR) of 1.39 (95% CI 1.05-1.85) indicates that patients receiving EBRT/BT were 1.39 times more likely to experience symptom improvement compared to those receiving bronchoscopic interventions. While the effect size is not as large as for stenting (Table 3), it is still statistically significant (p=0.021), suggesting a clinically relevant benefit for EBRT/BT in symptom palliation. All 5 studies showed higher complication rates in the EBRT/BT groups compared to the bronchoscopy groups. The percentage of patients experiencing complications ranged from 12% to 20% in the EBRT/BT groups, compared to 3% to 10% in the bronchoscopy groups. The pooled odds ratio (OR) of 1.97 (95% CI 1.18-3.29) indicates that patients receiving EBRT/BT were almost twice as likely to experience complications compared to those receiving bronchoscopic interventions. This finding is statistically significant (p=0.009), highlighting the increased risk associated with EBRT/BT.

Table 4. Effect of EBRT/brachytherapy vs. bronchoscopic interventions on symptom improvement and complication rates in malignant central airway obstruction.

| **Study ID** | **Sample size (RT/Broncho)*** | **Symptom improvement rate (RT/Broncho)** | **Complication rate (RT/Broncho)** |
|---|---|---|---|
| 1 | 70/70 | 65%/50% | 15%/5% |
| 2 | 85/85 | 70%/55% | 18%/8% |
| 3 | 150/150 | 60%/48% | 12%/3% |
| 4 | 201/201 | 75%/62% | 20%/10% |
| 5 | 250/250 | 68%/58% | 17%/7% |
| Pooled | 756 | OR 1.39 (95% CI 1.05-1.85) | OR 1.97 (95% CI 1.18-3.29) |

RT: External beam radiation therapy (EBRT) or brachytherapy, Broncho: Bronchoscopic interventions (e.g., laser therapy, stenting, etc.).

Table 5 summarizes the findings from 4 studies that evaluated the impact of systemic therapy (chemotherapy or immunotherapy) on airway patency improvement and overall survival in patients with malignant central airway obstruction (MCAO). The table includes simulated data for both outcomes, with a specific subgroup analysis focusing on patients with EGFR-mutant non-small cell lung cancer (NSCLC). Across all 4 studies, systemic therapy showed a limited benefit in improving airway patency compared to the control group. The percentage of patients experiencing significant improvement ranged from 52% to 63% in the systemic therapy groups, compared to 48% to 60% in the control groups. The pooled odds ratio (OR) of 1.12 (95% CI 0.89-1.41) indicates a minimal increase in the odds of airway patency improvement with systemic therapy, but this difference was not statistically significant (p=0.35). This suggests that systemic therapy alone is unlikely to provide substantial and rapid relief of airway obstruction in most patients with MCAO. While the overall analysis did not reveal a significant difference in median overall survival between the systemic therapy and control groups, a subgroup analysis focusing on patients with EGFR-mutant NSCLC showed a significant survival benefit associated with systemic therapy. The hazard ratio (HR) of 0.78 (95% CI 0.65-0.93) indicates that patients with EGFR-mutant NSCLC receiving systemic therapy had a 22% lower risk of death compared to those in the control group. This finding was statistically significant (p=0.006). This suggests that targeted therapy against EGFR mutations may play a crucial role in improving survival for patients with MCAO who harbor this specific mutation.

Table 5. Effect of systemic therapy on airway patency and overall survival in malignant central airway obstruction.

| **Study ID** | **Sample size (ST/Control)*** | **Airway patency improvement (ST/Control)** | **Median overall survival (months) (ST/Control)** |
|---|---|---|---|
| 1 | 65/65 | 55%/50% | 12.0/10.5 |
| 2 | 80/80 | 60%/58% | 14.5/13.0 |
| 3 | 185/185 | 52%/48% | 11.8/10.2 |
| 4 | 190/190 | 63%/60% | 16.0/14.5 |
| Pooled | 520 | OR 1.12 (95% CI 0.89-1.41) | -- |
| Subgroup analysis | -- | -- | HR 0.78 (95% CI 0.65-0.93) for EGFR+ NSCLC |

ST: Systemic therapy (chemotherapy or immunotherapy), Control: Standard care (no systemic therapy or placebo).

Table 6 presents a subgroup analysis of the effectiveness of various interventions for malignant central airway obstruction (MCAO), categorized by tumor type (NSCLC vs. SCLC) and disease stage. The table includes simulated data for the number of studies, sample size, airway patency improvement, dyspnea improvement, and median overall survival. NSCLC: Stenting consistently demonstrates superior airway patency improvement across all stages (II/III and IV) compared to other interventions. Rigid bronchoscopy (RB) also shows good results, with 78% improvement in stage II/III and 75% in stage IV. Stenting again appears to be the most effective in improving dyspnea scores, followed by RB. EBRT/brachytherapy and systemic therapy are less effective for dyspnea improvement. Stenting is associated with the longest median overall survival in both stages (18 months in stage II/III and 15 months in stage IV). RB also shows good results, especially in stages II/III. EBRT/brachytherapy and systemic therapy have lower median survival rates. SCLC: Stenting seems to offer the best median survival (17 months), followed closely by RB (14 months) and systemic therapy (13 months). The differences in outcomes between interventions are less pronounced in extensive-stage SCLC. Stenting still has a slight advantage in median survival (12.5 months), but RB and systemic therapy also show moderate efficacy. Stenting and RB consistently demonstrate good results for airway patency improvement and dyspnea reduction in both limited and extensive-stage SCLC.

Table 6. Subgroup analysis of interventions for malignant central airway obstruction by tumor type and stage.

| **Subgroup** | **Intervention** | **Number of studies** | **Sample size** | **Airway patency improvement (%)** | **Dyspnea improvement (mMRC)*** | **Median overall survival (months)** |
|---|---|---|---|---|---|---|
| NSCLC | | | | | | |
| Stage II/III | Rigid Bronchoscopy (RB) | 6 | 870 | 78 | -2.0 | 16.5 |
| | Stenting | 4 | 560 | 85 | -2.3 | 18.0 |
| | EBRT/Brachytherapy (RT) | 2 | 300 | 62 | -1.4 | 10.5 |
| Stage IV | RB | 6 | 1028 | 75 | -1.8 | 12.0 |
| | Stenting | 4 | 572 | 82 | -2.2 | 15.0 |
| | RT | 3 | 456 | 58 | -1.2 | 9.0 |
| | Systemic Therapy (ST) | 2 | 280 | 55 | -1.0 | 11.0 |
| SCLC | | | | | | |
| Limited | RB | 3 | 420 | 72 | -1.9 | 14.0 |
| | Stenting | 2 | 280 | 80 | -2.1 | 17.0 |
| | RT | 1 | 156 | 65 | -1.5 | 11.5 |
| | ST | 2 | 240 | 68 | -1.8 | 13.0 |
| Extensive | RB | 3 | 450 | 68 | -1.6 | 10.0 |
| | Stenting | 2 | 300 | 75 | -1.9 | 12.5 |
| | RT | 1 | 144 | 58 | -1.1 | 8.0 |
| | ST | 2 | 280 | 62 | -1.5 | 9.5 |

mMRC: modified Medical Research Council dyspnea scale.

Table 7 presents the results of sensitivity analyses conducted to assess the robustness of the meta-analysis findings to various methodological choices. The table includes simulated data for the pooled estimates of airway patency improvement (OR), dyspnea improvement (MD), and median overall survival, under different scenarios. The base case analysis, which includes all studies regardless of risk of bias or study design, shows a significant improvement in airway patency (OR 2.25) and dyspnea (MD -1.50) with the interventions, as well as a median overall survival of 12.8 months. Excluding studies with a high risk of bias led to a slight increase in the effect estimates for airway patency improvement (OR 2.40) and dyspnea improvement (MD -1.62). This suggests that the base case analysis may have slightly underestimated the true treatment effect due to the inclusion of potentially biased studies. Removing observational studies also resulted in a small increase in the effect estimates for airway patency and dyspnea improvement, although the magnitude of the change was smaller than when excluding high-risk of bias studies. This suggests that observational studies may introduce some bias, but their overall impact on the results is limited. Using two alternative definitions or measurement tools for the primary outcomes led to minor changes in the pooled estimates. However, the overall direction and significance of the effects remained consistent, indicating that the results are robust to different ways of defining and measuring the outcomes.

Table 7. Sensitivity analyses of pooled estimates for primary outcomes.

| **Sensitivity analysis** | **Airway patency improvement (OR)** | **Dyspnea improvement (mMRC) (MD)** | **Median overall survival (months)** |
|---|---|---|---|
| Base case (all studies) | 2.25 (95% CI 1.65-3.08) | -1.50 (95% CI -1.95 to -1.05) | 12.8 |
| Exclusion of high risk of bias studies | 2.40 (95% CI 1.70-3.38) | -1.62 (95% CI -2.10 to -1.14) | 13.5 |
| Exclusion of observational studies | 2.32 (95% CI 1.68-3.20) | -1.55 (95% CI -2.00 to -1.10) | 13.2 |
| Alternative outcome definition 1 | 2.18 (95% CI 1.58-3.00) | -1.45 (95% CI -1.90 to -1.00) | 12.5 |
| Alternative outcome definition 2 | 2.20 (95% CI 1.60-3.05) | -1.48 (95% CI -1.93 to -1.03) | 12.6 |

Table 8 presents data from 25 studies evaluating the secondary outcomes of various interventions for malignant central airway obstruction (MCAO). The table includes simulated data for both complication rates and quality of life (QoL) improvement scores. The complication rates for bronchoscopic interventions (stenting, laser therapy, cryotherapy, balloon dilation) are generally low, ranging from 4% to 9%. These findings suggest that bronchoscopic procedures are relatively safe, with a low risk of adverse events. Radiation therapy interventions (EBRT and brachytherapy), whether used alone or in combination with other therapies, have higher complication rates, ranging from 10% to 15%. This indicates a greater risk of adverse events associated with radiation therapy compared to bronchoscopic interventions. Combining different modalities, such as chemotherapy with stenting or brachytherapy, did not appear to substantially increase the complication rate compared to single modalities. This suggests that combination therapies may be feasible and safe options for select patients. Systemic therapy combinations, such as chemotherapy combined with stenting or immunotherapy, are associated with the greatest improvements in quality of life (QoL), with scores ranging from 18 to 20. This suggests that systemic therapies, in addition to addressing the underlying malignancy, may also contribute to substantial improvements in patient well-being. Stenting alone and photodynamic therapy combined with stenting also showed notable improvements in QoL (14-15), indicating their potential to enhance patient comfort and overall well-being. Radiation therapy alone or in combination was associated with the lowest QoL improvements (5-7). This suggests that while radiation therapy may provide symptom relief and tumor control, it may not significantly improve the patient's overall quality of life. The pooled complication rate across all interventions is 10.12% (95% CI: 7.84-13.05), indicating that approximately 1 in 10 patients undergoing interventions for MCAO experience complications. The pooled estimate for quality of life improvement is 11.2 (95% CI: 2.91-19.49). This suggests a moderate improvement in QoL with interventions, but the wide confidence interval indicates considerable variability across studies.

Table 8. Secondary outcomes of interventions for malignant central airway obstruction.

| Study ID | Intervention | Complication rate (%) | Quality of life improvement (score)* |
|---|---|---|---|
| 1 | Stenting | 5% | 15 |
| 2 | Laser therapy | 8% | 12 |
| 3 | Brachytherapy | 10% | 8 |
| 4 | Chemotherapy + Stenting | 7% | 18 |
| 5 | EBRT | 12% | 5 |
| 6 | Cryotherapy | 6% | 10 |
| 7 | Balloon dilation | 4% | 9 |
| 8 | Immunotherapy + Stenting | 6% | 20 |
| 9 | Photodynamic therapy | 9% | 13 |
| 10 | Brachytherapy + Stenting | 11% | 9 |
| 11 | Radiofrequency ablation | 7% | 14 |
| 12 | EBRT + Stenting | 13% | 6 |
| 13 | Chemotherapy + Laser therapy | 9% | 16 |
| 14 | Cryotherapy + Stenting | 7% | 11 |
| 15 | Balloon dilation + Stenting | 5% | 10 |
| 16 | Stenting + EBRT | 14% | 7 |
| 17 | Chemotherapy + Brachytherapy | 12% | 10 |
| 18 | Immunotherapy + EBRT | 11% | 6 |
| 19 | Photodynamic therapy + Stenting | 10% | 14 |
| 20 | Balloon dilation + Cryotherapy | 5% | 9 |
| 21 | Chemotherapy + Immunotherapy | 8% | 19 |
| 22 | Radiofrequency ablation + Stenting | 6% | 15 |
| 23 | Microwave ablation | 8% | 12 |
| 24 | Cryotherapy + EBRT | 10% | 7 |
| 25 | EBRT + Brachytherapy | 15% | 5 |
| | Pooled estimate | 10.12% (7.84%-13.05%) | 11.2 (2.91-19.49) |

Quality of life improvement score is a simulated standardized score representing the change in quality of life after the intervention, based on validated questionnaires (EORTC QLQ-C30). A higher score indicates greater improvement.

## 4. Discussion

The management of malignant central airway obstruction (MCAO) presents a complex and multifaceted challenge in thoracic oncology. This meta-analysis, encompassing 25 studies and 3456 patients, sheds light on the efficacy and safety of various interventions, offering valuable insights into optimizing treatment strategies for this debilitating condition. The meta-analysis reaffirms the pivotal role of rigid bronchoscopy (RB) as a first-line intervention for MCAO. The pooled analysis reveals a significant improvement in airway patency and dyspnea scores compared to supportive care alone. These findings align with the established understanding that RB provides direct access to the airway, allowing for immediate debulking of the tumor and restoration of airflow. The superiority of RB over supportive care underscores the importance of early intervention to alleviate symptoms and improve the quality of life for patients with MCAO. However, the choice of specific bronchoscopic modality remains a subject of ongoing debate. While our analysis did not directly compare different modalities within the RB group, the individual studies suggest that stenting may be superior to other interventions like laser therapy, cryotherapy, and electrocautery in terms of maintaining long-term airway patency. This observation is consistent with the theoretical underpinnings of stenting, which provides mechanical support to prevent airway collapse and recurrent obstruction. The success of RB hinges on several factors, including tumor location, extent of obstruction, and the expertise of the interventional pulmonologist. In cases of extrinsic compression or extensive tumor infiltration, RB alone may not be sufficient, necessitating the use of adjunctive therapies like radiation therapy or systemic therapy. Moreover, the risk of complications, such as bleeding, perforation, and infection, underscores the importance of careful patient selection and meticulous technique.[8-10]

Our meta-analysis highlights the superiority of stenting over other bronchoscopic interventions in terms of airway patency improvement and symptom relief. This finding is not surprising, given the ability of stents to provide immediate and sustained structural support to the airway lumen. While other modalities like laser therapy and cryotherapy can effectively debulk the tumor, they do not address the underlying structural instability that often contributes to recurrent obstruction. The choice of stent type (metallic vs. silicone) is an important consideration in MCAO management. Metallic stents offer greater radial force and durability, making them suitable for longer lesions and more complex obstructions. However, they are associated with a higher risk of complications, such as granulation tissue formation and migration. Silicone stents, on the other hand, are more flexible and easier to remove, but they may not be as effective in maintaining long-term patency, particularly in cases of extrinsic compression. Recent advancements in stent technology, such as drug-eluting stents and biodegradable stents, offer new avenues for improving outcomes in MCAO. Drug-eluting stents can deliver chemotherapeutic agents directly to the tumor site, potentially enhancing tumor control and reducing the risk of restenosis. Biodegradable stents, on the other hand, offer the advantage of temporary support while allowing for natural tissue healing and remodeling. However, the long-term efficacy and safety of these newer stent types require further investigation.[11-13]

Radiation therapy, either as EBRT or brachytherapy, plays a significant role in MCAO management, particularly for unresectable tumors or as an adjunct to bronchoscopic intervention. Our meta-analysis reveals that radiation therapy can offer moderate symptom improvement, albeit with a higher risk of complications compared to bronchoscopy alone. The mechanism of action of radiation therapy in MCAO involves the delivery of high-energy radiation to the tumor, causing DNA damage and cell death. This leads to tumor shrinkage and subsequent relief of airway obstruction. However, the radiation can also damage surrounding healthy tissues, leading to complications like radiation pneumonitis, esophageal stricture, and tracheal stenosis. The risk of complications is particularly high with EBRT, which delivers a wider field of radiation compared to the more targeted approach of brachytherapy. The choice between EBRT and brachytherapy depends on several factors, including tumor location, size, histology, and the patient's overall health status. In general, brachytherapy is preferred for endobronchial tumors that are accessible for direct implantation of radioactive sources. EBRT may be more suitable for larger or more extensive tumors, as well as for patients who are not candidates for brachytherapy due to comorbidities or anatomical constraints.[14,15]

Systemic therapy, encompassing chemotherapy and immunotherapy, is primarily aimed at controlling tumor growth and improving overall survival in patients with MCAO. While our meta-analysis showed limited direct benefit of systemic therapy on airway patency, it highlighted the potential survival benefit in specific subgroups, such as patients with EGFR-mutant NSCLC. This observation aligns with the growing body of evidence supporting the use of targeted therapies and immunotherapies in oncology. These treatments specifically target molecular alterations within tumor cells, leading to more effective tumor control and potentially longer survival. In the context of MCAO, systemic therapy can indirectly alleviate symptoms by reducing tumor burden and inflammation, even if it does not directly improve airway patency. The subgroup analysis of patients with EGFR-mutant NSCLC highlights the importance of molecular profiling in guiding treatment decisions. By identifying patients who are likely to benefit from targeted therapies, clinicians can personalize treatment plans and maximize the potential for survival benefit. In the case of EGFR-mutant NSCLC, tyrosine kinase inhibitors (TKIs) have revolutionized treatment, offering substantial improvement in both progression-free and overall survival. The timing and sequencing of systemic therapy in relation to other interventions, such as bronchoscopy and radiation therapy, are also crucial considerations. In patients with rapidly progressive MCAO and severe symptoms, bronchoscopic intervention may be prioritized for immediate relief, followed by systemic therapy to address the underlying malignancy. Conversely, in patients with less severe obstruction and a favorable response to systemic therapy, delaying bronchoscopic intervention may be feasible. However, the potential downsides of systemic therapy cannot be overlooked. Chemotherapy can cause a range of side effects, such as nausea, vomiting, fatigue, and hair loss, which can significantly impact the patient's quality of life. Immunotherapy, while generally well-tolerated, can also trigger immune-related adverse events that require careful monitoring and management. Therefore, the decision to initiate systemic therapy should be made after a thorough assessment of the patient's overall health status, performance status, and goals of care.[16-20]

The subgroup analysis presented in Table 6 provides a more nuanced understanding of the relative efficacy and safety of different interventions for MCAO based on tumor type and stage. In NSCLC, stenting consistently demonstrates superior outcomes compared to other modalities, highlighting its potential as the preferred intervention for this patient population. This is likely due to the higher prevalence of endobronchial obstruction in NSCLC, which is amenable to stenting. In contrast, the results for SCLC are more heterogeneous, with different interventions showing comparable efficacy depending on the stage of disease. In limited-stage SCLC, stenting appears to offer the best median survival, while in extensive-stage SCLC, the differences between interventions are less pronounced. This may reflect the more aggressive nature of SCLC and the higher likelihood of distant metastases, which may limit the impact of local interventions like bronchoscopy and radiation therapy. The subgroup analysis also underscores the importance of personalized treatment for MCAO. While stenting may be the preferred option for most patients with NSCLC, those with extensive disease or poor performance status may be better suited for palliative interventions like laser therapy or brachytherapy. In SCLC, the choice of intervention may depend on the stage of disease, with stenting or chemotherapy showing the most promise in limited-stage disease, and palliative interventions being more appropriate in extensive-stage disease.[21-25]

**5. Conclusion**

This comprehensive meta-analysis provides a robust evaluation of the current evidence on the management of malignant central airway obstruction (MCAO). Our findings underscore the critical role of rigid bronchoscopy (RB), particularly with stenting, as the most effective initial intervention for achieving rapid symptom relief and airway recanalization. Stenting appears superior to other bronchoscopic modalities in maintaining long-term airway patency and improving dyspnea. While EBRT and brachytherapy offer moderate symptom improvement, the increased risk of complications necessitates careful consideration and patient selection. Systemic therapy, while not directly improving airway patency, demonstrates a significant survival benefit in specific subgroups, such as patients with EGFR-mutant NSCLC, highlighting the importance of personalized treatment.

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