Therapeutics in Malignant Central Airway Obstruction
Activity Overview
This is a digital CME will discuss the interventional pulmonary approach to malignant central airway obstruction, including cold and hot as well as mechanical therapies.

Target Audience
This activity is intended for primary care, pulmonologists, thoracic surgeons, and oncologists.

Instructions to Receive Credit
To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.
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Nathaniel Ivanick, MD, has indicated no real or apparent conflicts.

The peer reviewers and activity planners have no financial relationships to disclose.
Upon completion, participants should be able to:

• Compare and contrast available therapeutic modalities for patients with MCAO based on the latest clinical safety and efficacy data

• Describe the impact of available treatment modalities for patients with MCAO on future patient metrics, including quality of life
Therapeutics in Malignant Central Airway Obstruction

Nathaniel Ivanick, MD
Interventional Pulmonology
Department of Thoracic Surgery
1. Definition and Etiology
2. Symptoms
3. Therapeutic Approach
4. Outcomes and Rationale
Malignant Central Airway Obstruction

• Obstruction to airflow to trachea or mainstem bronchi
• Most (>90%) are malignant
• 20-30% of Lung Cancer will develop complications of CAO during course of disease
• Untreated survival 1-2 months, however this data is over 26 years old

Ernst A et al. AJRCCM (2004)
Macha HN et al. (1994) Chest
### Differential of Malignant Central Airway Obstruction (mCAO)

<table>
<thead>
<tr>
<th>Airway Involved</th>
<th>Trachea</th>
<th>Bronchi</th>
<th>Trachea/Bronchi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell, adenoid cystic carcinoma, metastases</td>
<td>Squamous cell, carcinoid, Mucoepidermoid (MEC)</td>
<td>Metastases</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion Distribution</th>
<th>Focal</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell, adenoid cystic, carcinoid, MEC</td>
<td>Adenoid cystic vs metastases vs Non-malignant</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Suggests Malignant</th>
<th>Suggests Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal, history of malignancy, irregular margins, mediastinal invasion</td>
<td>Diffuse, multifocal, circumferential, near complete involvement of airway, multiple equal sized nodules</td>
<td></td>
</tr>
</tbody>
</table>

*Stevic, R et al. Journal of Thoracic Disease (2016)*
Types of Malignant Central Airway Obstruction

Ed P. Jain, A.C. Mehta p 144
Symptoms of Central Airway Obstruction: Symptoms

- Symptoms of cough, hemoptysis, dyspnea
- Often mistaken for other airway disorders, particularly if slow in development
- Symptoms with exertion when lumen reduced to around 8 mm in diameter or 50%
- Symptoms at rest 5 mm or 25% the original diameter
- Stridor usually present at narrowing of 5 mm or less
- Focal wheezing significant clue
- Post-obstructive pneumonia, sepsis, substantial downstream atelectasis often noted

Flow Volume Loops in Airway Obstruction

Therapeutic Considerations

- Speed of action required
- Type of Obstruction
- Temporizing measures

*Therapeutic Bronchoscopy for Central Airway Obstruction Chapter. S. Hadique, eds A. Mehta, P. Jain. 2013*
Therapeutic Modalities: Speed Considerations

• Severe (>80%) obstruction to the trachea or mainstem bronchi is often life threatening and involves rapid therapeutic relief, if possible

• Obstruction under 50% may allow for a less rapid approach

Therapeutic Bronchoscopy for Central Airway Obstruction
Chapter. S. Hadique, eds A. Mehta, P. Jain. 2013
Speed and Safety Considerations

- Hot therapies (Laser, APC, Electrocautery) have immediate effect, but cannot be used if FiO2 is over 40% due to risk of airway fire.
- Mechanical therapies (can be used at any FiO2, but bleeding must be considered).
- Delayed/Cold therapies (PDT, Cryoprobe) may have delayed effect (1-2 weeks) but can be used if FiO2 cannot be reduced.

*Therapeutic Bronchoscopy for Central Airway Obstruction Chapter. S. Hadique, eds A. Mehta, P. Jain. 2013*
Temporizing Measures

- Heliox—variable percentages 60-80%
- Low density gas
- Laminar vs Turbulent Airflow
- Reduce work of breathing
- Positive pressure ventilation
- Highly trained bronchoscopy staff, capable of responding to airway hemorrhage, hypoxia is crucial

- Feller-Kopman D (2002) Up to Date
Types of central airway obstruction: (a) endoluminal, (b) extrinsic, (c) mixed endoluminal and extrinsic

Therapeutic Modalities: APC

**Pro**
- Low depth of penetration (0.5 to 2 mm)
- Excellent for hemostasis
- Can treat lesions lateral to probe

**Con**
- Low depth of penetration
- Can’t use if ET 02 >40% for risk of airway fire
- Caution with stents
- Risk of cerebral air embolism
- Caution with Pacer/ICD

*Ernst A et al. AJRCCM (2004)*
Therapeutic Modalities: Electrocautery

- Electrical current generates heat which causes tissue destruction
- Lower cost, ease of use, wide availability
- Modalities include snare, knife, blunt probe, hot forceps
- Retrospective review of 94 patients
- 71% with symptomatic improvement

Wahidi et al. (2011) Journal Thoracic Oncology
Therapeutic Modalities: Corecath

- Contact method
- Debulking, coagulation, evacuation of smoke
- Allows for more precise cuts
- Penetration depth 0.9 mm

Video Courtesy of Dr. Ganesh Krishna, Interventional Pulmonology. El Camino Hospital, Mountain View CA
Therapeutic Modalities: Cryoprobe

- Joule Thomson effect (N\(_2\)O)
- Fast Freeze, Slow thaw most effective
- Ice crystal formation, desiccation, destructive to intracellular organelles
- Cartilage has little water, thus minimal collateral damage
- 2 types of Ablation
- Apply probe, activate x30 seconds, allow thaw, repeat 2-3 times
- Cryoprobe put in contact with tissue, activated for 3-7 seconds and pulled *en bloc*

*Diaz-Jimenez JP and Mezalek RT. Cryotherapy Chapter. Interventions in Pulmonary Medicine, eds J.P. Diaz-Jimenez and A.N. Rodriguez.*
Therapeutic Modalities: Balloon Bronchoplasty

- Balloon catheter with 2 or 3 cm length inflated to supra-atmospheric pressures to dilate airways
- Water/lohexol injection may be used
- Expanded diameter held for up to 3 minutes
- Risks: Airway rupture, major bleeding

*Hautman, H et al. (2001) Chest*
Considerations

1. Benign versus malignant
2. Anatomy
3. Duration of airway collapse
4. Need to customize
5. “Jailing”
6. Future therapy (Chemo/Radiation)
7. Migration

Stent Placement During Therapeutic Bronchoscopy

Fluoroscopy Image Courtesy Nathaniel Ivanick, M.D. RPCCC 2019
Outcomes and Rationale: Questions to Consider

• Expectations post therapeutic bronchoscopy
• Pulmonary Function Tests
• Exercise Capacity
• Quality of Life Improvement
• Ventilation Liberation
• Survival Advantage
• Beneficial or Futile

Therapeutic Bronchoscopy for Central Airway Obstruction Chapter. S. Hadique, eds A. Mehta, P. Jain. 2013
Rationale and Outcomes: PFT’s

Prospective Multicenter study of nitinol airway stent
34 patients with malignant CAO
19/34 had life threatening stenosis, with immediate improvement in 82%
Remaining 16 had PFT’s prior to and after procedure
All stents were tracheobronchial stent system

Miyazawa T et al. Chest 2000
Outcomes and Rationale: PFT’s

### PFT’s

**Table 4—Pulmonary Function Tests Obtained in 16 Patients Before and After Implantation of the Ultraflex Stent**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, L</td>
<td>1.97 ± 0.54</td>
<td>2.46 ± 0.60†</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.40 ± 0.51</td>
<td>1.74 ± 0.52§</td>
</tr>
<tr>
<td>PEF, L/s</td>
<td>2.9 ± 1.4</td>
<td>3.6 ± 1.2†</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD.

†p < 0.05.

‡p < 0.01.

§p < 0.001.

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Miyazawa T et al. Chest 2000

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**Obstruction over Time**

![Graph showing obstruction over time](image-url)
Outcomes and Rationale: PFT’s

- Prospective cohort of 37 patients with malignant central airway obstruction of any cause (65% NSCLC, also metastatic disease)
- Measured 6 minute walk test distance, spirometry, dyspnea specific quality of life, overall quality of life at baseline, 30 days, 90 days and 180 days
- 92% successful bronchoscopy (patent airway lumen >50%)

Oviatt PL et al. J Thorac Oncol 2011
Outcomes and Rationale: PFT’s and 6 MWT

<table>
<thead>
<tr>
<th>Measure</th>
<th>Day 0, Mean (SD)</th>
<th>Day 30 Mean, Change (95% CI)</th>
<th>Day 90 Mean, Change (95% CI)</th>
<th>Day 180 Mean, Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT (m)*</td>
<td>195.7 (161.2)</td>
<td>295.4, +99.7 (33.2–166.2)</td>
<td>319.2, +123.6 (44.0–203.1)</td>
<td>318.0, +122.3 (47.8–196.8)</td>
</tr>
<tr>
<td>EORTC QLQ-C30*</td>
<td>33.3 (23.6)</td>
<td>42.5, +9.2 (–5.7 to 24.1)</td>
<td>52.6, +19.3 (6.9–31.6)</td>
<td>55.0, +21.7 (4.5–38.9)</td>
</tr>
<tr>
<td>C30 Dyspnea scale*</td>
<td>84.3 (21.8)</td>
<td>44.3, –39.9 (–58.4 to –21.4)</td>
<td>36.0, –48.3 (–73.2 to –23.4)</td>
<td>49.9, –34.4 (–56.5 to –12.3)</td>
</tr>
<tr>
<td>LC13 Dyspnea scale*</td>
<td>61.3 (22.0)</td>
<td>33.1, –28.2 (–43.5 to –12.9)</td>
<td>32.0, –29.3 (–44.9 to –13.6)</td>
<td>35.6, –25.7 (–41.2 to –10.3)</td>
</tr>
<tr>
<td>FEV1 (litres)*</td>
<td>1.283 (0.450)</td>
<td>1.731, +0.448 (0.203–0.692)</td>
<td>1.888, +0.605 (0.339–0.870)</td>
<td>1.752, +0.469 (0.214–0.724)</td>
</tr>
<tr>
<td>FVC (litres)*</td>
<td>2.20 (0.785)</td>
<td>2.618, +0.416 (0.130–0.702)</td>
<td>2.802, +0.600 (0.273–0.928)</td>
<td>2.548, +0.346 (0.014–0.678)</td>
</tr>
<tr>
<td>MRC Dyspnea*</td>
<td>3.88 (1.00)</td>
<td>3.17, –0.709 (–1.436 to 0.018)</td>
<td>2.71, –1.17 (–1.83 to –0.51)</td>
<td>2.80, –1.08 (–1.86 to –0.30)</td>
</tr>
<tr>
<td>Resting Borg*</td>
<td>2.13 (2.32)</td>
<td>0.82, –1.32 (–2.41 to –0.23)</td>
<td>0.89, –1.24 (–2.19 to –0.30)</td>
<td>0.42, –1.71 (–2.57 to –0.86)</td>
</tr>
<tr>
<td>6MWT Borg*</td>
<td>3.92 (1.92)</td>
<td>2.58, –1.34 (–2.61 to –0.06)</td>
<td>2.22, –1.70 (–2.86 to –0.55)</td>
<td>2.85, –1.07 (–2.41 to 0.26)</td>
</tr>
</tbody>
</table>

Higher scores for European Organization for Research and Treatment of Cancer (EORTC) main module (QLQ-C30) equate to improved quality of life, while higher scores for dyspnea (C30 and lung cancer module [LC13]) equate to increased (worsened) symptoms.

*p < 0.05 overall.
†p < 0.05 compared with day 0.
NS, non-statistically significant.

Oviatt PL et al. J Thorac Oncol 2011
Outcomes and Rationale: PFT’s

• Prospective study measuring impact of therapeutic bronchoscopy for central airway obstruction on: Pulmonary Function Tests (Spirometry), dyspnea and quality of life.

• Only 9 stents used in malignant CAO

Mahmood K et al. Respiration 2015
### Table 4. Rigid bronchoscopy outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>p value for difference in mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, l</td>
<td>1.4 ± 0.60</td>
<td>1.8 ± 0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>47.8 ± 19.43</td>
<td>60.7 ± 20.39</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC, l</td>
<td>2.2 ± 0.91</td>
<td>2.7 ± 0.80</td>
<td>0.009</td>
</tr>
<tr>
<td>FVC%</td>
<td>57.8 ± 21.08</td>
<td>68.8 ± 17.53</td>
<td>0.006</td>
</tr>
<tr>
<td>PEF, l/min</td>
<td>3.6 ± 1.92</td>
<td>4.4 ± 1.92</td>
<td>0.05</td>
</tr>
<tr>
<td>PEF%</td>
<td>48.7 ± 22.44</td>
<td>59.3 ± 22.91</td>
<td>0.03</td>
</tr>
<tr>
<td>SOBQ</td>
<td>55.8 ± 30.1</td>
<td>37.9 ± 27.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>37.5 ± 28.40</td>
<td>49.4 ± 29.90</td>
<td>0.04</td>
</tr>
<tr>
<td>Role Limitations – Physical Health</td>
<td>7.5 ± 23.81</td>
<td>29.3 ± 39.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role Limitations – Emotional Health</td>
<td>67.9 ± 44.80</td>
<td>75.7 ± 37.41</td>
<td>0.34</td>
</tr>
<tr>
<td>Energy/Fatigue</td>
<td>40.7 ± 26.93</td>
<td>51.5 ± 21.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>73.8 ± 21.52</td>
<td>77.7 ± 15.31</td>
<td>0.29</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>54.2 ± 36.44</td>
<td>65.6 ± 26.65</td>
<td>0.07</td>
</tr>
<tr>
<td>Pain</td>
<td>74.6 ± 29.19</td>
<td>76.4 ± 24.90</td>
<td>0.73</td>
</tr>
<tr>
<td>General Health</td>
<td>47.3 ± 21.20</td>
<td>51.5 ± 22.87</td>
<td>0.33</td>
</tr>
</tbody>
</table>

PEF = Peak expiratory flow.

Mahmood K et al. Respiration 2015
Fig. 4. Change in SF-36 domains after bronchoscopic intervention.
PF = Physical Functioning; RL PH = Role Limitations – Physical Health; RL EM = Role Limitations – Emotional Health; EF = Energy/Fatigue; EWB = Emotional Well-Being; SF = Social Functioning; PN = Pain; GH = General Health. * Statistically significant change.

Mahmood K et al. Respiration 2015
Take Away Points:

1. Associated with a clinically and statistically meaningful improvement in Spirometry (350-480 ml). This benefit is maintained over time
2. Associated with improvement in 6 MWT distance (~100 meters) Oviatt et al. This benefit is maintained over time
3. Associated with improvement in a variety of quality of life, physical health and dyspnea scores
4. Associated with improvement in airway patency, maintained over time

_Mahmood K et al. Respiration 2015_
_Oviatt PL et al. J Thorac Oncol 2011_
_Miyazawa T et al. Chest 2000_
Outcomes and Rationale: Ventilation Liberation

- Retrospective Review of ICU admissions and emergent therapeutic rigid bronchoscopy
- 3/11 with immediate discontinuation of mechanical ventilation post bronchoscopy
- 8/15 patients transferred immediately out of ICU following bronchoscopy
- Patients with benign central airway obstruction fared better overall
- Life expectancy after therapeutic bronchoscopy ranged from 2 to 363 days

Outcomes and Rationale: Ventilation Liberation

• Retrospective review of 8 patients on mechanical ventilation for central airway obstruction (6 malignant, 2 benign)
• Prior to procedure, variable duration of mechanical ventilation: 2 to 52 days
• Post procedure, duration of wean prior to extubation was 2 to 11 days
• Only 3/6 with lung based malignancy, also melanoma, sarcoma, and non-Hodgkin’s lymphoma causing extrinsic compression
• Only 1 patient could not be liberated from mechanical ventilation, and was made comfort care

### Table 2—Time on Ventilator and Comparison of Arterial Blood Gases Before and After Stenting

<table>
<thead>
<tr>
<th>Patient</th>
<th>Days on Ventilation Before Stenting</th>
<th>Days on Ventilation After Stenting</th>
<th>Before Stent</th>
<th>After Stent*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$F_{iO_2}$</td>
<td>$PO_2$</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>7</td>
<td>0.35</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>6</td>
<td>0.50</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>5†</td>
<td>0.50</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>11</td>
<td>0.40</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>11</td>
<td>0.40</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>91</td>
<td>‡§†</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0.60</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0.30</td>
<td>94</td>
</tr>
</tbody>
</table>

*Values obtained within 48 h of stent placement.

†$F_{iO_2}$ = fraction of inspired oxygen; $a/A$ = arteriolar-alveolar gradient.

‡Expired.

§Weaned from full mechanical ventilation to continuous positive airway pressure, eventually required only nocturnal ventilation; NA = not available.

Outcomes and Rationale: Ventilation Liberation

Take Away Points:

1. Therapeutic Bronchoscopy has variable success rates for those who have malignant central airway obstruction requiring mechanical ventilation.
2. Patients with benign central airway obstruction demonstrate a more consistent benefit to therapeutic bronchoscopy in their ability to liberate from the vent/ICU.
3. Stent placement in malignant central airway obstruction may offer a chance at ventilator liberation and transfer out of the ICU.
4. Management and decisions regarding care should be individualized and consider future treatment options, medical comorbidities, patient and family wishes and concomitant acute medical issues.

Outcomes and Rationale: Survival

- Malignant CAO perceived as having a worse prognosis compared to disease of same stage without obstruction.
- Retrospective review to assess whether survival is lower in treated malignant CAO compared to those without.
- 144 patients with advanced inoperable NSCLC.
- CAO (52) treated with therapeutic bronchoscopy + Chemo +/- Radiotherapy.
- 92 patients without CAO treated with chemotherapy.
- No significant difference in survival.

Outcomes and Rationale: Survival Benefit?

- Retrospective review of 50 patients with advanced lung cancer and symptomatic CAO
- No control group
- Assumed baseline survival compared to historical controls
- Symptom improvement in all, theoretical survival increase in intermediate

Razi S.S. et al. (2010) *Annals Thoracic Surgery*
• Tracheobronchial stenting in terminal care of patients with CAO:
• 14 patients with “imminent suffocation” due to major obstruction: due to esophageal cancer, NSCLC referred for stent insertion.
• Length of survival after stent insertion: 11 weeks. 2 patients died within 1 week in hospital
• Remaining 12 patients, stent insertion worthwhile in 7, no judgement in 4, futile in 1. Performed in Amsterdam. Euthanasia was an alternative that could be considered.
• Still considered stent insertion worthwhile in 58% of patients.

Vonk-Noordegraaf et al. Chest 2001
Outcomes and Rationale: Survival and Futility

Take-Away Points:

1. Data on Survival Benefit limited by lack of a control group
2. Patients with moderate functional status do better than those with poor functional status, although most will gain symptomatic benefit
3. Malignant central airway obstruction has been viewed as a very poor prognosis when compared to an identical stage of disease without obstruction
4. Therapeutic bronchoscopy, when used in a multi-modality approach can result in equivalent survival to those with identical stage of disease without obstruction
5. Prospective studies are needed to offer further insight

Vonk-Noordegraaf et al. Chest 2001
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