Comprehensive Management of Respiratory Symptoms in Patients with Advanced Lung Cancer

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Patients with advanced lung cancer experience a high symptom burden, which can negatively impact their functional status and quality of life (QOL). Although survival rates are improving with the development of novel, targeted therapies, the likelihood of long-term survival remains quite low in patients with advanced disease. Therefore, maximizing QOL by controlling physical symptoms, particularly respiratory symptoms such as dyspnea, cough, and hemoptysis, is paramount. The prevalence of dyspnea and cough in patients with advanced lung cancer is quite high, with reported rates of 20%-90%.1-3 A study examining symptom prevalence in patients with newly diagnosed lung cancer demonstrated that cough and dyspnea were 2 of the most common presenting symptoms in patients with both non-small-cell (NSCLC) and small-cell lung cancers.4 In light of the progressive and incurable nature of the disease, patients with advanced lung cancer often experience progressive dyspnea at the end of life.5 Similarly, the prevalence of cough, chest pain, and hemoptysis increases as patients become more ill from their disease.6 It is essential that clinicians caring for patients with advanced lung cancer identify and manage these troubling respiratory symptoms as early as possible to minimize their impact on patients' functioning and QOL throughout their illness.

COMMON ETIOLOGIES OF RESPIRATORY SYMPTOMS

There are many etiologies which contribute to respiratory symptoms in patients with advanced lung cancer, including tumor burden; complications of malignancy, such as postobstructive pneumonia; pleural effusion; pulmonary embolus; complications of therapy (surgery, chemotherapy, radiotherapy); and tobacco-related comorbidity, especially chronic obstructive pulmonary disease (COPD) and coronary artery disease.7 When managing respiratory symptoms, it is important to first evaluate and treat any potentially reversible etiologies. Table 1 outlines common causes of respiratory symptoms among patients with advanced lung cancer. While cancer-directed therapies such as chemotherapy and radiation, as well as therapeutic bronchoscopy and interventional pulmonary procedures, can often temporarily ameliorate some of these etiologies, the role of these treatment modalities is beyond the scope of this review. Management of 4 of the most common potentially reversible processes is described below. In many patients, there are multiple causes for respiratory symptoms; and as such, it is essential to perform a thorough examination and evaluation for these potential etiologies.8

Pulmonary Embolus

In patients with lung cancer, venothromboembolism (VTE) is an important cause of respiratory symptoms, including dyspnea, pleuritic chest pain, cough, and hemoptysis. The incidence...
dence of VTE among patients with cancer is up to 3 times higher than that in the general population, and recurrent VTE is also more common in cancer patients.9 The incidence of VTE is highest in the first year of diagnosis and among patients with solid tumors. Approximately 3% of patients with lung cancer suffer from VTE during this time period, second only to patients with pancreatic cancer.10 Low-molecular weight heparins (LMWHs) have eclipsed warfarin for initial and long-term therapy of VTE among cancer patients with data suggesting decreased rates of recurrent VTE and no increase in risk of bleeding complications.11–14 Decisions regarding discontinuing LMWH in patients near the end of life should be individualized based on patient and family preferences for care.

Pleural Effusions

Cough, dyspnea, and chest discomfort in patients with advanced lung cancer are often caused by pleural effusion. Up to 50% of patients with metastatic disease are diagnosed with a pleural effusion during the course of their disease.15,16 For patients with a poor prognosis whose effusions reaccumulate slowly, the best approach is with therapeutic thoracentesis, repeated as needed. For patients with longer anticipated survival, more definitive therapies are often chosen. Historically, talc pleurodesis has been the treatment of choice, with 80% to 90% success in reducing effusion recurrence.17 However, data suggest the superiority of long-term indwelling pleural catheters, often referred to as Pleur(x) catheters, which not only effectively relieve symptoms of dyspnea but can be placed in an ambulatory care setting.18 Spontaneous pleurodesis often occurs in the absence of instillation of a sclerosant with these long-term indwelling pleural catheters.19 A recent randomized trial comparing catheter drainage to talc pleurodesis suggested that catheter drainage was more successful at both lung reexpansion and preventing reaccumulation of fluid. Notably, approximately half of the patients in this study had lung cancer and patients reported greater improvement in dyspnea with catheter drainage.20

Tamponade

Lung cancer is the most common tumor to involve the pericardium.21 Malignant pericardial effusions confer a worse prognosis in cancer patients, particularly among patients with lung cancer.22,23 Patients with acute tamponade experience dyspnea and chest pain and present with hemodynamic instability. Patients with a subacute accumulation of pericardial fluid often present only with dyspnea and fatigue. A single pericardiocentesis is associated with recurrence of the effusion in up to 60% of cases; thus, prolonged catheter drainage is often required. Although the trigger for a surgical approach, such as a pericardial window or pericardiotomy, is not clear, it is generally well tolerated and associated with a very low rate of fluid reaccumulation.23

Treatment-Related Pneumonitis

Unfortunately, the therapies for cancer are common culprits in causing respiratory symptoms. Erlotinib and other targeted agents are being administered in patients with advanced lung cancer with increasing frequency and are a known cause of pneumonitis. Management of erlotinib-induced pneumonitis includes immediate discontinuation of drug and administration of glucocorticoids; however, mortality rates of 30% to 50% have been reported.24 Many chemotherapy agents are associated with pulmonary toxicity and can also increase the risk of radiation pneumonitis.25,26 Among patients with lung cancer who undergo radiotherapy, approximately 5% to 15% develop radiation pneumonitis, either early (within 4-12 weeks of therapy) or late (within 6-24 months of therapy).25,27 Common symptoms of pneumonitis include dyspnea, dry cough, chest discomfort/pain, malaise, and fever. Pulmonary function test findings vary and have not been found to correlate with radiation-induced lung disease.25 Radiation pneumonitis is commonly treated with high-dose glucocorticoids, such as prednisone 60 mg orally daily for several weeks, then tapered slowly over several months, though there are no randomized clinical trials evaluating the efficacy of this therapy. There are case reports suggesting a benefit of steroid-sparing agents such as azathioprine and cyclosporine.28,29 Small, randomized trials examining administration of pentoxyfilline and vitamin E during radiotherapy to prevent lung toxicity have demonstrated promising results, though the efficacy of treatment of established disease is unknown.20,30,31

### Table 1

Common Causes of Respiratory Symptoms in Advanced Lung Cancer

<table>
<thead>
<tr>
<th>Airway</th>
<th>Extrinsic compression of tumor</th>
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<tbody>
<tr>
<td></td>
<td>Endobronchial tumor</td>
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<tr>
<td></td>
<td>Obstructive lung disease (asthma, COPD)</td>
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<tr>
<td>Parenchyma</td>
<td>Tumor</td>
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<td></td>
<td>Metastasis</td>
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<td>Lymphangitic spread</td>
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<td>Pneumonia/atelectasis</td>
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<td></td>
<td>Emphysema</td>
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<td>Pleura</td>
<td>Pleural involvement</td>
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<tr>
<td></td>
<td>Pleural effusion</td>
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<tr>
<td>Vascular system</td>
<td>Pulmonary embolus</td>
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<tr>
<td></td>
<td>Superior vena cava syndrome</td>
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<tr>
<td>Neuromuscular system</td>
<td>Diaphragmatic impairment</td>
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<tr>
<td></td>
<td>(by compression or tumor infiltration of phrenic nerve)</td>
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<tr>
<td></td>
<td>Paraneoplastic syndromes</td>
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<tr>
<td></td>
<td>(myasthenia gravis, Lambert-Eaton syndrome)</td>
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<tr>
<td></td>
<td>Malnutrition</td>
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<tr>
<td>Related to therapy</td>
<td>Radiation pneumonitis/fibrosis</td>
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<td></td>
<td>Pneumonitis secondary to chemotherapy</td>
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<tr>
<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td>Extrapulmonary</td>
<td>Pericardial effusion/tamponade</td>
</tr>
<tr>
<td></td>
<td>Coronary disease</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
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</table>
SYMPTOM-DIRECTED THERAPIES

Dyspnea

Dyspnea, defined as an uncomfortable sensation of breathlessness or awareness of breathing, is one of the most common respiratory and physical symptoms reported by patients with lung cancer. The prevalence of dyspnea among patients with lung cancer ranges from 20% to 90%, depending on the histology and stage. Dyspnea is a subjective symptom and does not require objective data such as a high respiratory rate or low oxygen saturation to confirm the diagnosis. While laboratory values, arterial blood gases, radiographic images, and pulmonary function tests may be helpful to understand the etiology of dyspnea, they are not required to diagnose it. Patient self-report of dyspnea is the only measure required to evaluate and treat this very unpleasant symptom.

Environmental, social, and psychological factors contribute to a patient’s perception of dyspnea. Dyspnea not only is distressing on its own but it intensifies the experience of other symptoms such as pain, anxiety, and depression. Data in patients with other chronic respiratory illnesses, such as COPD, suggest that there are complex interactions between mood and dyspnea. Patients with COPD with comorbid panic disorder experience an increased sensation of dyspnea compared to patients with COPD who do not have a psychiatric illness. Not surprisingly, there is an increased rate of depression, anxiety, and panic disorders among patients with chronic respiratory illness. In a prospective cohort of 376 patients hospitalized with a COPD exacerbation, 44% were found to have depression. Similar rates of generalized anxiety disorder and panic disorder have been found in patients with COPD. In over 1,000 patients with chronic breathing disorders, 80% reported symptoms of anxiety, depression, or both. Patients with advanced cancer also have high rates of anxiety and depression, so it is important to treat underlying psychiatric illness given the interaction between these illnesses and dyspnea. Dyspnea is such a distressing symptom that it occasionally requires palliative sedation to ensure patients’ comfort during the dying process.

Dyspnea can have a marked negative impact upon QOL, particularly in the physical and psychological domains. In a study of 120 patients with all stages of lung cancer, 87% experienced dyspnea and those with dyspnea reported a significantly lower QOL. Rates of dyspnea did not vary by cancer stage, cell type, or performance status. Patients with the most severe dyspnea experienced more pain and anxiety. Among 171 outpatients with advanced lung cancer, 55% reported dyspnea that interfered with physical activities like walking and work and 23% reported a negative impact of the symptom on mood and enjoyment of life. A study of 105 patients with advanced lung cancer who were followed longitudinally revealed that dyspnea increased over time, more dramatically during the first 3 months, while QOL declined over the same period.

Measuring dyspnea is challenging as there are over 40 different assessment tools available, many of which were designed for specific diseases. Three of the more commonly used instruments are the patient-rated visual analogue scale (VAS), the Borg scale, and the numerical rating scale (NRS). The VAS is a 100-mm scale anchored with descriptors of “no breathlessness” up to “worst possible breathlessness.” The Borg and modified Borg scales are 10-point scales with descriptive terms. The NRS is similar to the Borg, with a scale of 0 (no breathlessness) to 10 (maximal breathlessness). The Borg and VAS have demonstrated high rates of concordance in clinical trials. A panel of experts at the Agency for Healthcare Research and Quality Symposium concluded that, while easy to administer in a clinical setting, these measures do not incorporate the impact of dyspnea on health-related QOL and, thus, are of limited utility.

Pharmacologic approaches. When a reversible etiology of dyspnea cannot be identified and treated, pharmacologic agents that target central pathways, such as opioids and benzodiazepines, are often utilized. The literature is rich with studies of pharmacologic approaches in chronic respiratory diseases, particularly COPD; but few studies have evaluated therapy for dyspnea in patients with cancer, especially in those with advanced lung cancer. Opioids are the pharmacologic mainstay of therapy for dyspnea, and their utilization is well accepted in patients with advanced cardiac and lung disease. A systematic review of the literature identified only 6 trials of systemic opioids in cancer patients. The majority were randomized, crossover designs with small numbers of patients. Of those, 5 of the interventions were single-dose studies, 5 used subcutaneous doses of morphine, and 2 explored nebulized morphine. While these studies were small, the majority demonstrated improvement in dyspnea and/or exercise tolerance with the administration of systemic opioids and some important practical features that have impacted clinical practice (Table 2). Respiratory depression is a common fear among health-care providers, but there is little evidence that chronic opiate use causes dangerous respiratory depression in elderly patients with advanced cancer or in opiate-naive patients with advanced cancer.

A frequently cited study suggested that among cancer patients who are on chronic opiates, a dose increase of 25% might be sufficient for breakthrough dyspnea. The latter observation is particularly important given that many patients with advanced lung cancer are prescribed opioids for cancer-related pain. Sustained release opioids also appear to be beneficial for the management of dyspnea and may be a good option for patients with frequent episodes of dyspnea throughout the day. It was hoped that alveolar tissue rich with opioid receptors would permit fast onset of action of nebulized opioids; however, this has not been borne out in the literature. With only a few positive case reports, nebulized opiates are not considered to be effective in patients with advanced cancer or pulmonary disease.

Benzodiazepines are best known for their anxiolytic and sedative-hypnotic effects and are occasionally used to treat dyspnea, although there is less evidence to support their use compared to opiates. As previously stated, there is a complex relationship between anxiety and dyspnea, and it is possible that benzodiaz-
epines mediate an effect on dyspnea by treating undiagnosed or undertreated anxiety. A Cochrane review concluded that there was no significant beneficial effect of benzodiazepines in COPD or cancer.61 Two studies, both of which included morphine as the control arm, reported conflicting results. One study, designed to assess midazolam as an adjunct to morphine, randomized 100 patients with a life expectancy of less than 1 week to one of three different treatment arms: standing morphine with benzodiazepine rescue for breakthrough dyspnea, standing benzodiazepine with morphine rescue, or standing combination morphine and benzodiazepine with morphine rescue.62 The group assigned to standing combination therapy with morphine rescue experienced the greatest relief of dyspnea. Each treatment arm experienced reduction in dyspnea intensity compared to baseline; however, there were no significant differences between arms.61

Another study in advanced cancer patients randomized 63 patients (25% with lung cancer) to morphine or midazolam, using a rapid in-clinic drug titration followed by a 5-day outpatient dose titration. All patients achieved a 50% reduction in dyspnea intensity during the rapid in-clinic titration, regardless of whether they received morphine or midazolam. During the final 4 days of the outpatient phase, patients receiving midazolam reported lower dyspnea intensity.63 This trial suffered from a study design that is difficult to translate into clinical practice, with unclear administration of both baseline and breakthrough doses of medications, which is an important practical clinical parameter.64 Therefore, there are insufficient data to recommend benzodiazepines as first-line agents to treat baseline or breakthrough dyspnea among patients with cancer. Additionally, benzodiazepines are known for their ability to decrease somnolence and delirium, especially among older patients, providing another important reason to exercise caution in their use.65

Oxygen is an effective therapy for hypoxemic, dyspneic patients with COPD and chronic heart failure.31 Similarly, in advanced cancer patients who are hypoxic, oxygen may provide symptomatic relief of dyspnea, although there are no large, controlled studies. Many lung cancer patients with dyspnea are not hypoxic, and there is little evidence that oxygen is beneficial in patients who are not hypoxic, even during exertion.66 A systematic review of oxygen for relief of dyspnea in cancer patients with either no or mild hypoxemia concluded there was no benefit in this patient population.67 Most studies have examined the role of oxygen in advanced cancer patients by comparing the efficacy of oxygen and air and include both hypoxic and nonhypoxic patients. These studies have demonstrated that oxygen and air have equal efficacy in relieving dyspnea.68–70 This result may be due to stimulation of receptors in the trigeminal nerve distribution by either air or oxygen, which may inhibit the sensation of dyspnea. Data have shown that even an electric fan directed at the face may provide some relief of dyspnea.71,72 A small, prospective nonrandomized trial compared oxygen and opiates in hypoxicemic (SpO2 <90%) and nonhypoxic cancer patients. Not suprisingly, only the patients receiving opiates reported improvement in dyspnea, and there was no response to oxygen for either hypoxicemic or nonhypoxic patients.73 Based on the results of these trials, oxygen therapy should be utilized in patients who are dyspneic and hypoxic but not in patients without hypoxemia.

Corticosteroids and bronchodilators are important treatment options to consider in patients with advanced lung cancer who have underlying chronic obstructive lung disease and may experience benefit from therapy with bronchodilators. Clinicians must be certain to not simply attribute dyspnea to the cancer but to evaluate and treat all underlying causes.74 Additional data are needed to better understand the role of pharmacologic agents, such as nebulized furosemide and heliox, though studies have suggested possible benefit.75,76

Although blood transfusions are more common in patients with cancer than in those without, even when transfusions are administered to patients who are anemic, improvement in dyspnea is short-lived.77 Nonpharmacologic approaches. The majority of nonpharmacologic interventions for dyspnea have been examined in
patients with COPD, although a few studies have enrolled heterogeneous populations, including small numbers of patients with lung cancer. Five randomized controlled trials, ranging from relaxation techniques and coping strategies to acupuncture, have been performed specifically in patients with lung cancer (Table 3). Interestingly, these are among the largest trials of interventions for breathlessness in advanced cancer. The results of these trials are inconsistent, which makes it challenging to recommend a particular approach. However, these types of interventions pose no health risk and some patients may experience significant benefit, so it is reasonable to consider as an option for lung cancer patients with dyspnea. Additionally, mind-body techniques can have reasonable to consider as an option for lung cancer patients. Five randomized controlled trials, acupressure, have been performed specifically in patients with lung cancer.

### Table 3

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>INTERVENTION</th>
<th>N</th>
<th>OUTCOME</th>
<th>IMPORTANT FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corner et al., 1996</td>
<td>Counseling, breathing retraining, relaxation, coping strategies weekly for 3-6 weeks vs control (patients speak freely about dyspnea but no training or counseling)</td>
<td>34</td>
<td>Improvement in dyspnea</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Bredin et al., 1999</td>
<td>Assessment of breathlessness, exploration of meaning and feelings, muscle relaxation and psychosocial support vs standard pharmacologic and palliative treatment of symptoms</td>
<td>119</td>
<td>Improvement in dyspnea at 4 and 8 weeks plus improvement in performance status, physical and emotional well-being</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Moore et al., 2002</td>
<td>Focus on open access to nurse and clinic to address symptoms vs standard follow-up care</td>
<td>203</td>
<td>Improved dyspnea</td>
<td>Advanced lung cancer</td>
</tr>
<tr>
<td>Connors et al., 2007</td>
<td>Physiotherapy including teaching breathing control, relaxation, energy conservation</td>
<td>169</td>
<td>Dyspnea improved but not statistically significantly</td>
<td>Lung cancer; only 15 patients completed protocol</td>
</tr>
<tr>
<td>Vickers et al., 2005</td>
<td>Acupuncture and acupressure vs placebo</td>
<td>47</td>
<td>No effect on dyspnea</td>
<td>Lung and breast cancer</td>
</tr>
<tr>
<td>McMillan and Small, 2007</td>
<td>Coping skills training vs supportive, friendly visits vs standard of care</td>
<td>329</td>
<td>No effect on dyspnea</td>
<td>Hospice home care cancer patients and their caregivers</td>
</tr>
</tbody>
</table>

**Cough**

The second most common respiratory symptom in advanced lung cancer is cough. Cough is reported to be present in 40% to 70% of patients with lung cancer at initial presentation. Cough is also associated with fatigue, chest pain, headache, nausea, vomiting, and incontinence and has a dramatic impact on QOL, particularly the psychosocial aspects. Like dyspnea, the etiology of cough is often multifactorial. Cough results from direct anatomic effects of the cancer (extrinsic or intrinsic airway obstruction), indirect effects of the cancer (pleural effusion or pneumonitis secondary to radiation or chemotherapy), underlying chronic conditions (asthma, COPD, gastroesophageal reflux disease [GERD], postnasal drip [PND]), or superimposed acute illnesses like pneumonia. Importantly, the presence of cough has also been shown to predict a shorter survival in patients with lung cancer. Many of these processes require and respond to particular therapies, for example, proton-pump inhibitors for GERD and intranasal steroids for PND. Cancer-directed therapies (ie, radiation therapy, chemotherapy) can often temporarily ameliorate cough, but the symptom generally recurs in patients with progressive, metastatic disease.

The oldest medication for cough is codeine, which was first introduced more than 150 years ago and, like opioids for dyspnea, suppresses the central systems responsible for triggering cough. There are no randomized controlled trials of codeine in patients with cancer, but there is a rich literature of case series. A randomized, controlled trial comparing dihydrocodeine, a derivative of codeine, with levodropropizine (a nonopioid antitussive that modulates C-fiber activity,
which is unavailable in the United States) demonstrated higher efficacy of levodroprazinome at decreasing cough severity and night awakening. There are a few small, prospective studies in advanced cancer that demonstrate benefit with hydrocodone, another derivative of codeine, used more frequently as an antitussive because of its more favorable side effect profile—namely, fewer gastrointestinal and sedative effects. The most commonly used opioid antitussive is dextromethorphan, the major active ingredient in most over-the-counter cough syrups. Benzonatate, a peripheral antitussive that anesthetizes stretch receptors in airways, lungs, and pleura and has a miniscule side effect profile, can be effective for opiate-refractory cough. Cough in malignancy may be caused by the stimulation of C-fibers by bradykinin, a neuropeptide produced by malignant cells but also well known for causing cough related to angiotensin-converting enzyme inhibition. Inhaled sodium cromoglycate suppresses the activity of these C-fibers and has been shown to reduce cough severity in a very small randomized controlled trial in advanced NSCLC patients.

Some patients with advanced lung cancer also have bronchiectasis, a persistent dilation of large airways associated with productive cough, hemoptysis, and recurrent infections. This may be a result of prior infection or underlying restrictive lung disease or a long-term consequence of radiotherapy. Patients with bronchiectasis benefit from antibiotics, occasional use of systemic or inhaled glucocorticoids, and close attention to bronchopulmonary hygiene, which includes airway clearance and chest physiotherapy. Patients may benefit from consultation with pulmonary specialists and physical therapists with special training in chest physiotherapy.

**Hemoptysis**

Hemoptysis is much less common than dyspnea and cough among patients with lung cancer. Series of patients with hemoptysis suggests that cancer accounts for about 20% to 30% of cases and that hemoptysis is most common in patients with lung cancer. Patients with lung cancer generally had lower levels of hemoptysis compared to patients with bronchiectasis or coagulopathy; however, they had one of the highest mortality rates (20%). At presentation, up to 20% of patients report mild hemoptysis and a much smaller percent experience severe hemoptysis. In a retrospective analysis of 271 cases of end-stage advanced lung cancer, 9% of patients reported hemoptysis in the last 8 weeks of life.

Massive hemoptysis, defined as high-volume, life-threatening bleeding is rare among patients with lung cancer. While much less prevalent than dyspnea and cough, hemoptysis can be alarming for patients and families, as well as health-care providers.

Hemoptysis may be caused by many of the processes listed in Table 1, most notably airway tumor and pulmonary embolus. Bronchial arteries are responsible for the most threatening hemoptysis since these vessels supply the airways and are under higher pressure than pulmonary arteries. Thus, most interventions target bronchial vessels with either an endobronchial or an endovascular approach. Bronchial artery embolization (BAE) is commonly used to treat massive hemoptysis, but few studies have included patients with cancer. In a retrospective review of 30 patients with lung cancer who received BAE to treat hemoptysis of variable severity, BAE was effective in 86% of cases. Tumor-related hemoptysis, which was the cause in 21 of 30 patients, conferred worse prognosis. Endobronchial techniques include laser resection and electrocautery, most commonly employed to treat obstructive endobronchial lesions but also indicated for hemoptysis. There are currently no clinical trials specifically evaluating the efficacy of these interventions to treat hemoptysis in patients with cancer.

**CONCLUSION**

Lung cancer is one of the most common cancers and has an exceedingly high mortality rate. Similar to other solid tumors, lung cancer is associated with many troubling physical symptoms, including fatigue, anorexia, cachexia, and pain. However, more than other solid tumors, lung cancer is inherently associated with more physically and psychologically distressing respiratory symptoms, including dyspnea, cough, and hemoptysis. Underlying pulmonary disease and psychological distress also contribute to these symptoms, in particular dyspnea. In recent years, there has been a greater emphasis on symptom management in advanced disease and more attention to the impact of cancer treatments on symptoms and QOL. The future will hopefully include more and larger studies focusing specifically upon symptom management and support in patients with lung cancer with the goal of improving QOL and outcomes.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


