Palliative Care and Interventional Pulmonology

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KEYWORDS

• Palliative care • Interventional pulmonology • Chronic obstructive pulmonary disease
• Lung cancer • Bronchoscopy

KEY POINTS

- Lung cancer and chronic obstructive pulmonary disease are among the leading causes of death worldwide. Unfortunately, these patients are at high risk of having unmet palliative care needs.
- Non-interventional therapies, including opioids, antibiotics, antifibrinolytics, exercises, and so forth, should be tried to palliate symptoms, such as dyspnea, cough, and hemoptysis.
- Many of these patients will be candidates for invasive pulmonary interventions with palliative intent.

INTRODUCTION

The World Health Organization defines palliative care as "an approach which improves the quality of life of patients and their families facing life-threatening illnesses, through the prevention, assessment and treatment of pain and other physical, psychosocial and spiritual problems."[1] Because pulmonary pathologies, such as lung cancer and chronic obstructive pulmonary disease (COPD), are some of the leading causes of morbidity and mortality around the world, pulmonologists are likely to encounter patients with unmet palliative care needs.[2,3] This article focuses on the symptoms and complications encountered by patients with terminal pulmonary conditions, briefly describes the non-interventional palliative strategies, and then discusses more advanced therapies available in the realm of interventional pulmonology. Most of the literature discussed here is derived from patients with lung cancer and COPD.

Malignant and Nonmalignant Pulmonary Disease Burden

Lung cancer is not only the most common cancer but also the most common cause of cancer-related deaths in the world.[4] Unfortunately, for 79% of patients, the diagnosis is made in stages III and IV.[5] At these stages, the 5-year survival is only 9.5% to 16.8%. At the same time, chronic lower respiratory tract diseases are the third leading cause of death in the United States. In fact, COPD is the only major cause of worldwide mortality, whose age-adjusted mortality is increasing.[6] Other nonmalignant pulmonary diseases, such as interstitial lung diseases (ILDs), cystic fibrosis, and pulmonary hypertension, are also associated with significant disease burden.[7]

Symptoms Encountered

The symptoms most commonly encountered by patients with lung cancer include pain, dyspnea,

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cough and restlessness.[8–10] One symptom in particular that merits special mention is the presence of terminal secretions (also known as *death rattle*). It results from the pooling of secretions at the back of the throat and airways and typically heralds the last few hours to days before death.[11] The causes of dyspnea in advanced lung cancer include parenchymal destruction, airway obstruction, pleural effusions, pulmonary embolism, superior vena cava obstruction, muscle weakness, and so forth.[4] Symptoms from nonmalignant pulmonary diseases overlap the symptoms previously described for malignant diseases. In fact, some studies suggest that the symptom burden of nonmalignant diseases may even be higher than malignant diseases.[12] Although dyspnea is the most serious symptom encountered in COPD, other symptoms include fatigue, depression, anxiety, weight loss, and insomnia.[13]

Why Palliative Care?

The goal of palliative care is to relieve the suffering experienced by the patients and their caregivers. This relief is accomplished by comprehensive assessment and management of afflictions in physical, psychosocial, existential, and spiritual domains.[3] The role of palliative care just does not end there. As Dame Cicely Saunders, father of the modern hospice movement, famously said: "How people die lives on in the memories of those who live on."[4] In line with this spirit, after patients pass away, palliative care focuses on providing support to the bereaved family.[14] Recent studies have shown that instituting palliative care is associated with greater use of symptom control medications and improved quality-of-life scores.[15]

The common practice has been of following a dichotomous approach, whereby the patients would initially get aggressive life-prolonging or curative therapies and at some point they would be transitioned to palliative care. The Center to Advance Palliative Care has countered this notion. They have advocated that palliative care is appropriate at any age and stage of a serious illness and can be provided along with curative treatment.[16] Temel and colleagues[17] reported a trial of newly diagnosed metastatic non–small cell lung cancer whereby patients were randomized to either palliative care with standard oncologic care or standard oncologic care alone. The patients in the early palliative care group had improvements in the quality-of-life and depression scores. Interestingly, these patients were less likely to receive aggressive therapies and yet their median survival was longer than patients receiving standard oncologic care alone. Other investigators have also reported improved 1-year survival with early palliative care consultation.[18] Despite these unequivocal benefits, unfortunately, trends show that palliative care is underutilized and the proportion of patients getting aggressive medical therapies toward the end of their lives is increasing.[19]

Underutilization of Palliative Care

There are multiple reasons behind the underutilization of palliative care. Firstly, significant knowledge gaps exist when determining the most potent and cost-effective palliative care interventions. Aslakson and colleagues[20] determined key areas that should be the subject of future research to address these knowledge gaps. Secondly, even though the availability of palliative care has increased over the last few years, significant disparities still exist globally.[21] Even within developed countries, comprehensive palliative care teams are less likely to be available in safety-net hospitals. As a result, ethnic minorities, immigrants, and underprivileged patients face greater barriers to seeking palliative care. Thirdly, often times, no distinction is made between palliative care on the one hand and hospice and end-of-life (EOL) care on the other.[22] Although hospice care is generally reserved for patients in their last 6 months of life, palliative care is appropriate at any stage of a serious illness.[23] Given this confusion in terminology, patients are likely to have misconceptions that by opting for palliative care, they will be deprived of other potential disease-modifying therapies. It needs to be emphasized to the patients that although palliative care is an indispensable component of high-quality EOL care, it should not be limited to just the EOL.[3] Fourthly, patients and at times even physicians tend to think that palliative care is only appropriate for patients with cancer. Brown and colleagues[24] reported that among the patients dying in the intensive care unit, patients with COPD and ILD received fewer elements of palliative care as compared with the patients with lung cancer. Other investigators have also reported discrepancies in palliative care involvement and EOL care discussions in patients with COPD. Palliative care should be embraced for all patients with life-threatening illnesses, regardless of their cancer status.[7]

Some of the aforementioned issues can be addressed by increasing awareness regarding the role and scope of palliative care among primary care physicians, pulmonologists, and oncologists, so that they may, in turn, be more open to having this discussion with their patients. Investigators have also looked at other innovative strategies to enhance the delivery of palliative care. One such strategy is to increase the availability of palliative

care in the outpatient setting. Skorstengaard and colleagues[25] found that for most of the terminally ill patients, home was the preferred place of care and the preferred place of death. Care at home can be maximized by making the elements of palliative care available in the ambulatory setting. Follwell and colleagues[26] reported significant improvements in pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, dyspnea, insomnia, and constipation among patients with metastatic cancer enrolled in an outpatient palliative care clinic.

NON-INTERVENTIONAL PALLIATIVE THERAPIES

Several non-interventional strategies can be used in terminally ill patients with pulmonary diseases. Dyspnea is the most commonly encountered symptom in lung cancer, COPD, ILDs, and so forth. Opioids are the backbone for the management of dyspnea without a reversible cause.[27,28] In COPD, long-acting bronchodilators are effective even in patients nearing the end of their lives.[29] Investigators have also reported success with the use of nonpharmacologic therapies, such as upright positioning, cool-air fans, breathing/relaxation exercises, and reassurance.[30] Similarly, use of walking aids, neuroelectrical muscle stimulation, and chest wall vibration therapies have also been shown to improve dyspnea.[7] Robust evidence is lacking regarding the use of benzodiazepines in these situations, especially given their potential adverse effects. However, they can still be tried as second- or third-line agents.[31,32] Similarly, the use of noninvasive ventilation in terminally ill patients with COPD is controversial.[6]

Cough is the second most commonly encountered symptom in patients receiving palliative care for pulmonary disorders. For cough productive of purulent sputum, antibiotics may be used. Expectoration of mucus can be augmented by using mucolytic agents, such as nebulized hypertonic saline, bromhexine, n-acetyl cysteine, and guaifenesin. In patients with dry cough and those who are too feeble to cough, the goal is to suppress the cough with opioids and nebulized anesthetics such as lidocaine.[4] In patients with COPD, smoking cessation should be encouraged, in addition to humidified air and stopping protussive medications.[33] Palliation of hemoptysis may be attempted with antifibrinolytics, such as tranexamic acid. In severe cases, radiation therapy can be used.

INTERVENTIONAL THERAPIES

If palliation cannot be achieved with the previously mentioned conservative measures, pulmonologists may be able to offer interventional therapies. Disease processes for which pulmonologists routinely offer palliative procedures include malignant pleural effusions (MPEs), airway obstruction, hemoptysis, and bronchopleural fistulas (BPFs).

Malignant Pleural Effusions

MPE is defined as the accumulation of a significant amount of exudate in the pleural space, accompanied by the presence of malignant cells or tumor tissue.[34] The most common route of spread of the tumor to the pleura is hematogenous, although it can also spread through direct extension or lymphatic route.[35] MPE accumulates as a result of increased fluid leakage from hyperpermeable blood vessels and impaired lymphatic drainage.[36] The major causes of MPEs are lung cancer in men and breast cancer in women. These two cancers account for 50% to 65% of all MPEs.[37] The disease burden of MPEs is enormous; 150,000 people develop MPEs in the United States each year.[38] MPE typically heralds advanced incurable cancer. The mean survival with MPE is 4 to 6 months.[39] Therefore, at this stage emphasis should be on palliation and symptom control rather than pursuing aggressive treatments.

On computed tomography (CT) scan, the presence of pleural thickening and nodularity along with the absence of air-bronchograms and septations should raise the suspicion for MPE.[40,41] PET-CT has an 81% sensitivity and 74% specificity for the detection of MPE; therefore, its routine use for diagnosing MPEs is not recommended. Ultrasound-guided thoracentesis is generally the first step toward confirming the diagnosis in suspected cases of MPE. It not only provides the fluid for cytologic examination but also provides useful information, such as the degree of symptom improvement with fluid removal, the rate of reaccumulation, and whether a trapped lung is present. The mean diagnostic yield of one cytologic examination is 60%. Therefore, thoracentesis may need to be performed 2 to 3 times to increase the sensitivity.[42] Thoracentesis is a safe procedure with rates of pneumothorax and chest tube insertion of 2.5% and 0.8%, respectively.[43] If the diagnosis cannot be established, a pleural biopsy may have to be pursued.[44] Medical thoracoscopy has a sensitivity of 91% and specificity of 100% for the diagnosis of MPE.

Even though earlier definitive therapies minimize the risk of complications associated with MPEs, many MPEs will not recur after the first thoracentesis. Therefore, it is reasonable to wait and watch after the first drainage. If the MPE recurs, available

options include indwelling pleural catheters (IPCs), chest tubes with pleurodesis, and surgical pleurodesis. Among these options, IPCs are most commonly offered by the interventional pulmonologists and have the strongest literature backing them.

Walker and colleagues[45] reported a prospective cohort study that compared 4 different modalities for the treatment of MPEs: IPC versus video-assisted thoracic surgery (VATS) and IPC versus chest tube and talc slurry versus VATS and talc poudrage. All options were equally effective in relieving patients' dyspnea and other symptoms; however, IPCs were associated with the least amount of discomfort and time in the hospital. The Second Therapeutic Intervention in Malignant Effusion Trial (TIME2) was an unblinded randomized controlled trial comparing IPC with chest tube and talc pleurodesis for MPE. IPC was associated with better symptom control at 6 months. IPC was also associated with shorter hospitalization and a decreased need for repeat procedures.[46] The Australasian Malignant Pleural Effusion (AMPLE) Trial was a multicenter trial comparing IPC with talc slurry pleurodesis for the management of MPE. A total of 144 patients were enrolled, and the total duration of follow-up was 1 year. The total hospitalization days were significantly lower in the IPC group compared with the pleurodesis group, with a mean reduction in hospitalization of 3.7 days per patient. No significant differences in mortality or adverse event rates were noted between the two groups. The investigators concluded that IPC use can save 555,000 hospital days over pleurodesis, without significantly affecting complication rates or mortality.[47]

While an IPC allows the patients to intermittently drain the pleural fluid at home, it also affords the possibility of achieving pleurodesis, at which time the IPC can be removed. Pleurodesis is reported in 45.6% cases. Trapped lung, a longer interval between MPE onset and insertion of the IPC, fluid glucose less than 60 mg/dL, pH less than 7.20, and lactate dehydrogenase greater than 700 IU/L decrease the chances of pleurodesis.[48,49] Multiple cost-effectiveness analyses have also shown IPCs to be more cost-effective than other modalities.[50,51]

The potential complications of IPC include empyema, pneumothorax requiring chest tube insertion, and cellulitis, reported in 2.8%, 5.9%, and 3.4% cases, respectively.[52] In another trial, 4.9% patients developed IPC-related pleural space infections; 94% of these infections were controlled with antibiotics. Only 1 out of 1021 patients died of an IPC-related infection.[53] Fourteen percent of patients with MPE and IPC will develop loculations. Although fibrinolytic drugs may be instilled to break up the loculations, there is no consensus for the management of these patients.[54] Catheter tract metastasis is another potential complication, typically presenting as nodules or masses at the catheter insertion site or along its tract. In one study, they were reported in 1.9% of the cases.[46] However, these show a good response to radiation therapy.[55] Mild pain following catheter insertion is common; severe pain necessitating catheter removal is only reported in 0.6% cases.[56]

Airway Obstruction

About one-third of patients with lung cancer develop central airway obstruction.[57] The resulting dyspnea, hemoptysis, secretions, and recurrent pneumonia are a major cause of morbidity and reduced quality of life. Unfortunately, only one-fifth of these patients' disease will be amenable to curative surgery, with the reset requiring some form of palliative intervention.[58] Airway obstruction can be caused by an endobronchial tumor or by external compression from esophageal cancer, lymphoma, metastasis, and so forth. No uniform guidelines exist for the management of airway obstruction, and the choice of intervention depends on the patient characteristics and local expertise.

Mechanical tumor debulking can be achieved with the beveled edge of the rigid bronchoscope. However, most of the times, mechanical debulking has to be coupled with stenting and additional ablative therapies to increase the efficacy and reduce the risk of bleeding.[59] These additional ablative therapies include electrocautery, laser, argon plasma coagulation (APC), and cryotherapy.

Silicon stents are the most commonly used stents. They come in various sizes and shapes, with multiple brands available. The Studded Dumon stent (manufactured by Novatech, France) is the most widely inserted silicon stent.[60] The studs on their surface are designed to embed in the airway walls and resist migration. There is a component of barium in the silicon stents that makes them visible on radiographs. Silicon stents are relatively cheaper and can be easily repositioned. However, they can only be inserted with a rigid bronchoscope under general anesthesia and have high rates of migration. Self-expandable metallic stents, on the other hand, can be inserted with a flexible bronchoscope and have a low risk of migration. Their main disadvantages are a higher cost and difficulty in removing or repositioning them.[61] The rate of granulation tissue formation is also higher on metallic stents. Hybrid stents were created with multiple materials. The idea is to incorporate the best of both worlds. Metallic struts

in hybrid stents provide the strength to counter compression, whereas the silicon covering makes granulation tissue formation and tumor overgrowth less likely.[62,63] Their biggest drawback is their cost. Like metallic stents, they are also hard to reposition and retrieve. Furukawa and colleagues[64] reported their experience with 58 stents in 40 patients with lung cancer. Statistically significant improvements in the performance status and Hugh-Jones classification scores were noted. Sixteen patients experienced complications, including hemoptysis (8 patients), retention of secretions (3 patients), restenosis (2 patients), tracheoesophageal fistulas (2 patients), and migration (1 patient).

Additional ablative therapies can be used with either flexible or rigid bronchoscopes. Ablative therapies may or may not be used in conjunction with stent placement. Electrocautery uses electricity to generate heat, which leads to tissue ablation.[65] In terms of the laser, the thermal effect of the Nd:YAG laser is most commonly used in interventional pulmonology.[66] Boxem and colleagues[67] performed a retrospective comparative review of the Nd:YAG laser and electrocautery for symptomatic airway obstruction. Symptomatic improvement was noted in 70% of the cases, and the efficacy of the laser and electrocautery was similar; however, electrocautery was noted to be much cheaper. However, the laser has the fastest onset of action, making it the preferred modality in life-threatening critical obstructions.[59] APC is a method of noncontact electrocoagulation that uses ionized argon gas.[68] Morice and colleagues[69] reported their experience with APC for airway obstruction and hemoptysis. In the group of patients with airway obstruction, an overall decrease in mean obstruction size to 18.4 $\pm$ 22.1% was noted. All patients, except one, reported symptomatic improvement.

Hemoptysis

Malignancy is responsible for 30% of the cases of hemoptysis; conversely, hemoptysis complicates 30% of lung cancer cases. 10% of these hemoptysis episodes can be classified as massive.[70] These episodes of massive hemoptysis are life-threatening emergencies and can be fatal in 50% to 85% of the cases without emergent intervention.[71] Bronchoscopists play an important role in localizing the bleeding and offering interventions. Bronchoscopy can localize bleeding in 90% of the cases.[72] In these cases, tamponade can be achieved by tightly wedging the scope in the affected segment and instilling cold saline and vasoconstrictors.[73]

Despite the aforementioned interventions, many patients will continue to bleed; in these cases, additional bronchoscopic interventions may be warranted. Valipour and colleagues[74] reported success in achieving topical hemostatic tamponade with oxidized regenerated cellulose (ORC) mesh. Hemostasis was achieved in 98% of the cases. Importantly, ORC mesh was absorbed in all patients without a foreign-body reaction. Morice and colleagues[69] reported their experience of APC in 31 patients with hemoptysis and 25 patients with both hemoptysis and obstruction. APC controlled bleeding in all patients. No procedural complications were noted. Similar success with the use of APC for hemoptysis was also reported by Crosta and colleagues.[68] The Nd:YAG laser has also been used for achieving hemostasis with a reported success rate of 60%.[75] If bronchoscopic interventions fail, patients should be referred for bronchial artery embolization, which typically falls in the realm of interventional radiology.[76]

Bronchopleural Fistulas

BPFs represent persistent communications between airways and pleural space. They can develop as a surgical complication or in patients with lung cancer, emphysema, fibrosis, or infections. In these cases of advanced pulmonary diseases, BPFs can be a major cause of morbidity and mortality. Traditionally the treatment of BPF includes prolonged chest tube drainage, pleurodesis, or surgical correction.[77] These treatments are cumbersome; in the case of surgical correction, some patients may be too frail to be good candidates.

Although strong evidence is lacking, the Food and Drug Administration approved the use of endobronchial valves for the treatment of BPFs as humanitarian use devices in 2008.[78] Firstly the segmental location of BPF is determined. Endobronchial valves are then placed using a flexible delivery catheter through a bronchoscope parked at the orifice of the affected segment. The valves have a one-way mechanism preventing air entry into the affected segment while allowing for the expulsion of air and mucus. Over time this causes atelectasis of the affected segment. Endobronchial valves are associated with minimal complications; however, their cost can be prohibitive.[79] If they are successful and a lasting resolution of the air leak has been achieved, the valves can be removed in 6 weeks.[80] Investigators have also studied endobronchial valves for endobronchial lung volume reduction in select cases of emphysema. However, this application is not recommended in the sickest patients and falls outside the realm of palliative care.[81] Endobronchial Watanabe Spigots are small silicone fillers, which have

also been studied for BPFs. However, their use has not caught on outside of Japan.[79]

SUMMARY

Lung cancer and COPD are among the leading causes of death worldwide. Unfortunately, these patients are at a high risk of having unmet palliative care needs. Although non-interventional therapies, including opioids, antibiotics, antifibrinolytics, exercises, and so forth, should be tried to palliate symptoms, such as dyspnea, cough, and hemoptysis, many of these patients will be candidates for invasive pulmonary interventions with palliative intent. MPE, airway obstruction, hemoptysis, and BPF are the most common problems for which interventional pulmonologists can offer palliative procedures. With the ongoing advances in interventional pulmonology, its scope in the palliative care arena is likely going to increase. Future research also needs to focus on understanding and overcoming barriers that lead to underutilization of palliative care along the spectrum of advanced pulmonary disorders.

REFERENCES

1. Palliative care n.d. Available at: http://www.who.int/hiv/topics/palliative/PalliativeCare/en/. Accessed June 13, 2017.
2. CDC: Leading causes of death n.d. Available at: http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed September 4, 2016.
3. Akgün KM. Palliative and end-of-life care for patients with malignancy. Clin Chest Med 2017;38:363–76.
4. Lim RBL. End-of-life care in patients with advanced lung cancer. Ther Adv Respir Dis 2016;10(5):455–67.
5. Surveillance, Epidemiology, and End Results Program n.d. Available at: http://seer.cancer.gov/. Accessed September 3, 2016.
6. Lilly EJ, Senderovich H. Palliative care in chronic obstructive pulmonary disease. J Crit Care 2016;35:150–4.
7. Boland J, Martin J, Wells AU, et al. Palliative care for people with non-malignant lung disease: summary of current evidence and future direction. Palliat Med 2013;27:811–6.
8. Ellershaw J, Smith C, Overill S, et al. Care of the dying: setting standards for symptom control in the last 48 hours of life. J Pain Symptom Manage 2001;21:12–7.
9. Stone P, Rees E, Hardy JR. End of life care in patients with malignant disease. Eur J Cancer 2001;37:1070–5.
10. Kvale PA, Selecky PA, Prakash UBS, American College of Chest Physicians. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:368S–403S.
11. Morita T, Ichiki T, Tsunoda J, et al. A prospective study on the dying process in terminally ill cancer patients. Am J Hosp Palliat Care 1998;15:217–22.
12. Diaz-Lobato S, Smyth D, Curtis JR. Improving palliative care for patients with COPD. Eur Respir J 2015;46:596–8.
13. Disler RT, Currow DC, Phillips JL, et al. Interventions to support a palliative care approach in patients with chronic obstructive pulmonary disease: an integrative review. Int J Nurs Stud 2012;49:1443–58.
14. Rome RB, Luminais HH, Bourgeois DA, et al. The role of palliative care at the end of life. Ochsner J 2011;11:348–52.
15. Hui D, Li Z, Chisholm GB, et al. Changes in medication profile among patients with advanced cancer admitted to an acute palliative care unit. Support Care Cancer 2015;23:427–32.
16. Palliative care related definition n.d. Available at: https://media.capc.org/filer_public/68/bc/68bc93c7-14ad-4741-9830-8691729618d0/capc_press-kit.pdf. Accessed June 4, 2017.
17. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–42.
18. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 2015;33:1438–45.
19. Earle CC, Neville BA, Landrum MB, et al. Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol 2004;22:315–21.
20. Aslakson RA, Reinke LF, Cox C, et al. Developing a research agenda for integrating palliative care into critical care and pulmonary practice to improve patient and family outcomes. J Palliat Med 2017;20:329–43.
21. Are M, McIntyre A, Reddy S. Global disparities in cancer pain management and palliative care. J Surg Oncol 2017;115:637–41.
22. Parikh RB, Kirch RA, Smith TJ, et al. Early specialty palliative care — translating data in oncology into practice. N Engl J Med 2013;369:2347–51.
23. National Hospice and Palliative Care Organization. National Hospice and Palliative Care Organization n.d. Available at: http://www.nhpco.org/. Accessed September 3, 2016.
24. Brown CE, Engelberg RA, Nielsen EL, et al. Palliative care for patients dying in the intensive care unit with chronic lung disease compared with metastatic cancer. Ann Am Thorac Soc 2016;13:684–9.
25. Skorstengaard MH, Neergaard MA, Andreassen P, et al. Preferred place of care and death in terminally ill patients with lung and heart disease compared to cancer patients. J Palliat Med 2017;20(11):1217–24.
26. Follwell M, Burman D, Le LW, et al. Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. J Clin Oncol 2009;27:206–13.

27. Abernethy AP, Currow DC, Frith P, et al. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003;327:523–8.
28. Jennings A-L, Davies AN, Higgins JPT, et al. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57:939–44.
29. Pantilat SZ, O'Riordan DL, Dibble SL, et al. Longitudinal assessment of symptom severity among hospitalized elders diagnosed with cancer, heart failure, and chronic obstructive pulmonary disease. J Hosp Med 2012;7:567–72.
30. Bourke S, Peel E. Palliative care of chronic progressive lung disease. Clin Med (Lond) 2014;14:325.
31. Currow D, Johnson M, White P, et al. Evidence-based intervention for chronic refractory breathlessness: practical therapies that make a difference. Br J Gen Pract 2013;63:609–10.
32. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev 2010;(10):CD007354.
33. Louie K, Bertolino M, Fainsinger R. Management of intractable cough. J Palliat Care 1992;8:46–8.
34. Psallidas I, Kalomenidis I, Porcel JM, et al. Malignant pleural effusion: from bench to bedside. Eur Respir Rev 2016;25:189–98.
35. Meyer PC. Metastatic carcinoma of the pleura. Thorax 1966;21:437–43.
36. Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. Am J Respir Crit Care Med 2012;186:487–92.
37. Mongardon N, Pinton-Gonnet C, Szekely B, et al. Assessment of chronic pain after thoracotomy: a 1-year prevalence study. Clin J Pain 2011;27:677–81.
38. Thomas R, Francis R, Davies HE, et al. Interventional therapies for malignant pleural effusions: the present and the future. Respirology 2014;19:809–22.
39. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: analysis of primary data. Chest 2000;117:87–95.
40. Bugalho A, Ferreira D, Dias SS, et al. The diagnostic value of transthoracic ultrasonographic features in predicting malignancy in undiagnosed pleural effusions: a prospective observational study. Respiration 2014;87:270–8.
41. Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax 2009;64:139–43.
42. Hooper C, Lee YCG, Maskell N, BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010. Thorax 2010;65(Suppl 2):ii4–17.
43. Jones PW, Moyers JP, Rogers JT, et al. Ultrasound-guided thoracentesis: is it a safer method? Chest 2003;123:418–23.
44. Henderson DW, Reid G, Kao SC, et al. Challenges and controversies in the diagnosis of mesothelioma: part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers. J Clin Pathol 2013;66:847–53.
45. Walker S, Zubrinic M, Massey C, et al. A prospective study of patient-centred outcomes in the management of malignant pleural effusions. Int J Palliat Nurs 2016;22:351–8.
46. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012;307:2383–9.
47. Lee YCG, Fysh ETH, Thomas R, et al. Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis. PLEURAL DISEASE: CLINICAL STUDIES. San Francisco (CA): American Thoracic Society; 2016. Available at: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A7812. Accessed December 1, 2017.
48. Wong WM, Tam TC, Wong MK, et al. Managing malignant pleural effusion with an indwelling pleural catheter: factors associated with spontaneous pleurodesis. Hong Kong Med J 2016;22:334–40.
49. Martínez-Moragón E, Aparicio J, Sanchis J, et al. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. Respiration 1998;65:108–13.
50. Olden AM, Holloway R. Treatment of malignant pleural effusion: PleuRx catheter or talc pleurodesis? A cost-effectiveness analysis. J Palliat Med 2010;13:59–65.
51. Puri V, Pyrdeck TL, Crabtree TD, et al. Treatment of malignant pleural effusion: a cost-effectiveness analysis. Ann Thorac Surg 2012;94:374–9 [discussion: 379–80].
52. Van Meter MEM, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med 2011;26:70–6.
53. Fysh ETH, Tremblay A, Feller-Kopman D, et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest 2013;144:1597–602.
54. Thomas R, Piccolo F, Miller D, et al. Intrapleural fibrinolysis for the treatment of indwelling pleural catheter-related symptomatic loculations: a multicenter observational study. Chest 2015;148:746–51.
55. Thomas R, Budgeon CA, Kuok YJ, et al. Catheter tract metastasis associated with indwelling pleural catheters. Chest 2014;146:557–62.
56. Lui MMS, Thomas R, Lee YCG. Complications of indwelling pleural catheter use and their management. BMJ Open Respir Res 2016;3:e000123.

57. Santos RS, Raftopoulos Y, Keenan RJ, et al. Bronchoscopic palliation of primary lung cancer: single or multimodality therapy? Surg Endosc 2004;18:931–6.
58. Kazi AA, Flowers WJ, Barrett JM, et al. Ethical issues in laryngology: tracheal stenting as palliative care. Laryngoscope 2014;124:1663–7.
59. Guibert N, Mhanna L, Droneau S, et al. Techniques of endoscopic airway tumor treatment. J Thorac Dis 2016;8:3343–60.
60. Dumon JF. A dedicated tracheobronchial stent. Chest 1990;97:328–32.
61. Marchese R, Poidomani G, Paglino G, et al. Fully covered self-expandable metal stent in tracheobronchial disorders: clinical experience. Respiration 2015;89:49–56.
62. Bolliger CT, Breitenbuecher A, Brutsche M, et al. Use of studded Polyflex stents in patients with neoplastic obstructions of the central airways. Respiration 2004;71:83–7.
63. Freitag L, Eicker R, Linz B, et al. Theoretical and experimental basis for the development of a dynamic airway stent. Eur Respir J 1994;7:2038–45.
64. Furukawa K, Ishida J, Yamaguchi G, et al. The role of airway stent placement in the management of tracheobronchial stenosis caused by inoperable advanced lung cancer. Surg Today 2010;40:315–20.
65. Mahmood K, Wahidi MM. Ablative therapies for central airway obstruction. Semin Respir Crit Care Med 2014;35:681–92.
66. Khemasuwan D, Mehta AC, Wang K-P. Past, present, and future of endobronchial laser photoresection. J Thorac Dis 2015;7:S380–8.
67. Boxem Tv, Muller M, Venmans B, et al. Nd-YAG laser vs bronchoscopic electrocautery for palliation of symptomatic airway obstruction: a cost-effectiveness study. Chest 1999;116:1108–12.
68. Crosta C, Spaggiari L, De Stefano A, et al. Endoscopic argon plasma coagulation for palliative treatment of malignant airway obstructions: early results in 47 cases. Lung Cancer 2001;33:75–80.
69. Morice RC, Ece T, Ece F, et al. Endobronchial argon plasma coagulation for treatment of hemoptysis and neoplastic airway obstruction. Chest 2001;119:781–7.
70. Masuda E, Sista AK, Pua BB, et al. Palliative procedures in lung cancer. Semin Intervent Radiol 2013;30:199–205.
71. Wang GR, Ensor JE, Gupta S, et al. Bronchial artery embolization for the management of hemoptysis in oncology patients: utility and prognostic factors. J Vasc Interv Radiol 2009;20:722–9.
72. Ong T-H, Eng P. Massive hemoptysis requiring intensive care. Intensive Care Med 2003;29:317–20.
73. Conlan AA, Hurwitz SS. Management of massive haemoptysis with the rigid bronchoscope and cold saline lavage. Thorax 1980;35:901–4.
74. Valipour A, Kreuzer A, Koller H, et al. Bronchoscopy-guided topical hemostatic tamponade therapy for the management of life-threatening hemoptysis. Chest 2005;127:2113–8.
75. Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e455S–497.
76. Mal H, Rullon I, Mellot F, et al. Immediate and long-term results of bronchial artery embolization for life-threatening hemoptysis. Chest 1999;115:996–1001.
77. Gillespie CT, Sterman DH, Cerfolio RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. Ann Thorac Surg 2011;91:270–3.
78. Humanitarian device exemption (HDE) n.d. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H060002. Accessed June 24, 2017.
79. Hance JM, Martin JT, Mullett TW. Endobronchial valves in the treatment of persistent air leaks. Ann Thorac Surg 2015;100:1780–5 [discussion: 1785–6].
80. Gaspard D, Bartter T, Boujaoude Z, et al. Endobronchial valves for bronchopleural fistula: pitfalls and principles. Ther Adv Respir Dis 2017;11:3–8.
81. Slebos D-J, Shah PL, Herth FJF, et al. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. Respiration 2017;93:138–50.