MANAGEMENT OF BREATHLESSNESS IN CANCER PATIENTS: ESMO CLINICAL PRACTICE GUIDELINES

Supplementary Material.

Pathophysiology

In the context of progressive cancer, parenchymal metastasis, lymphangitic carcinomatosis, airway obstruction, pleural effusion, pneumonia, pulmonary embolism and atelectasis are common causes of breathlessness. These changes may activate chemoreceptors both centrally and peripherally, as well as mechanoreceptors, juxtacapillary receptors, irritant receptors and chest wall receptors peripherally [1-3]. The afferent signals converge in 'respiratory centre' the medulla, which further project to the ventroposterior thalamus and then the somatosensory cortex where breathlessness 'intensity' is perceived, plus the limbic system (amygdala and medial dorsal thalamus) which contributes to an affective component of breathlessness ('unpleasantness') [3]. The reported breathlessness is further modulated by factors such as cognitions, beliefs, emotional well-being and culture.

One of the key mechanisms contributing to breathlessness is neuromechanical dissociation [4, 5]. As the medullary respiratory centre senses abnormalities in breathing, there is a compensatory respiratory drive in the pre-Botzinger complex to increase respiratory effort. However, because of the underlying pathology, the respiratory mechanics are unable to respond adequately, resulting in a mismatch in ventilatory supply and demand. This neuromechanical dissociation is perceived as breathlessness. This understanding has important implications for treatment. For example, opioids may alleviate breathlessness by reducing the heightened respiratory drive, while non-invasive ventilation may help by improving respiratory mechanics.

Characterisation of breathlessness

Breathlessness is often characterised as episodic or continuous [6, 7]. In a Delphi study, episodic breathlessness is defined as one form of breathlessness characterised by a severe worsening of breathless intensity or unpleasantness beyond usual fluctuations in the patient's perception. Episodes are time limited (seconds to hours) and occur intermittently, with or without underlying continuous breathlessness [8]. The majority of patients (70%–80%) presenting with breathlessness report having episodic breathlessness several times daily [9-11]. The most common form of episodic breathlessness is exertional breathlessness, triggered by physical activities such as walking, climbing stairs or bathing [12]. Examples of other triggers include a change in position, cold weather or anxiety [8].

Continuous breathlessness is the constant, relentless sensation of shortness of breath that is present even at rest. Continuous breathlessness is associated with poorer survival than episodic breathlessness alone [13], and these patients often have significant functional limitations to minimise further episodic breathlessness. In one study of 70 cancer patients with breathlessness, 61% reported having episodic breathlessness only, 20% both episodic and continuous breathlessness and 19% reported having continuous breathlessness only [9]. Patients with chronic episodic or continuous breathlessness often limit their activities significantly to avoid worsening respiratory distress.

Assessment of breathlessness

Why assess in clinical practice?

Despite the widespread impact and prognostic information of chronic breathlessness [14-17], routine assessment in clinical practice remains rare. A systematic review of quality standards in oncology care found that measurement of physical aspects of care comprised only 36% of quality measures and, of these, just over a quarter were related to breathlessness [18]. Measurement of breathlessness is now included as a consensus core patient-centred outcome measure set in lung cancer [19], but implementation is inconsistent. A growing body of evidence suggests that regular assessment with patient-reported outcomes is associated with improvement in symptom control (including breathlessness) [20], quality of life (QoL) and survival [21].

Patient-reported outcomes

i) Unidimensional assessments. Visual analogue scales (VAS; 100mm; 0 = no breathlessness, 100 = worse possible breathlessness) are easy to use and validated [22]. However, they cannot be used verbally or over the phone and many patients prefer the numerical rating scale (NRS). The NRS (0 to 10 where 0 = no breathlessness, 10 = worse possible breathlessness) is commonly used, is validated against the VAS, is more repeatable than the VAS and can be incorporated into practice [23, 24]. The NRS can be used alone for breathlessness or used as part of the Edmonton Symptom Assessment Scale [25]. This is useful given that people with cancer rarely have breathlessness alone. The VAS and NRS have a defined minimal clinical important difference for intensity of chronic breathlessness [26, 27]. A third unidimensional measure is the modified Borg scale. Used most commonly in non-cancer disease, it is a 0 to 10 semi-ratio scale with categorical descriptors for some numbers. Lastly, the verbal Likert scale is quick and intuitive even to the few patients who struggle to give a numerical score. A recent study related NRS and Likert scales: 0–3 (mild); 4–7 (moderate); >7 (severe) [28]. To avoid missing breathlessness in patients comfortable at rest, these tools can be framed ‘over the last 24 hours, how bad was your breathlessness at its worst?’ or ‘over the past 24 hours, how bad was

your breathlessness on average?'. The use of unidimensional tools is preferred in clinical practice because of ease of administration and interpretation.

ii) Multidimensional. A full discussion of the multidimensional breathlessness tools is beyond the scope of this guideline and most are research rather than clinical tools. Two notable exceptions are the Cancer Dyspnoea Scale (CDS) [29] and the Dyspnoea-12 [30, 31]. Both have been developed with clinical practice in mind, but it is yet to be demonstrated how acceptable and feasible they are in the clinic and their responsiveness to change.

iii) Functional impact. The modified Medical Research Council (mMRC) breathlessness scale measures the impact of breathlessness on physical exertion and is common in research and clinical practice across diseases. It is poorly responsive to change, and is not recommended to monitor treatment response, but it is useful for identifying patients with limiting breathlessness. In those with advanced disease, the Dyspnoea Exertion Scale (DES) is more discriminatory than the mMRC, with less of a ceiling effect [32].

iv) Although patient-reported outcome of breathlessness remains the gold standard, patients with cognitive impairment, disorders of consciousness or requiring intubation may not be able to self-report their subjective symptom of breathlessness. The Respiratory Distress Observational Scale (RDOS) was developed and validated for clinical use [33], and uses eight items of observation (heart rate, respiratory rate, restlessness, paradoxical breathing, use of accessory muscles of respiration, grunting, nasal flaring and a look of fear). It has low to moderate association with subjective breathlessness [34].

Functional tests

i) Functional tests offer a standardised means to assess the impact of breathlessness on physical performance. Although breathlessness is a common limiting symptom, weakness, fatigue and pain can also limit test performance. A patient-reported assessment of the main limiting symptom at test endpoint can help to contextualise findings. Most functional tests have a floor or ceiling effect, so it is important to select a test that suits the physical capacity of the patient. Walking tests with a fixed time

duration may have poor utility in patients with high levels of functional impairment due to breathlessness [35].

ii) Practical tests suited to the clinic include the Timed Up and Go, 6-minute walk test or shuttle walk tests. The Timed Up and Go measures the time taken for patients to stand up from a chair, walk 3 metres at their normal pace, turn around, walk back again, and sit down [36]. For the 6-minute walk, patients walk at their own pace, aiming to walk as far as possible within 6-minutes, slowing down or stopping if necessary. In contrast to the 6-minute walk test which is effort dependent, the shuttle walk tests are externally paced and either stress the patient to a symptom-limited maximal performance (incremental), or by walking at a set individualised speed for as long as possible (endurance). The 6-minute walk, incremental and endurance shuttle walk tests have established psychometric properties for exercise capacity in lung cancer [37-41]. It is important to adhere to technical specifications when administering these tests and to include familiarisation runs [42].

iii) Poor test performance is associated with more rapid functional decline, treatment-related complications and decreased survival in patients with cancer [43]. In patients with high levels of functional impairment, the loss of independence in activities of daily living (ADL) becomes highly relevant [44]. The London Chest Activities of Daily Living Scale (LCADL) measures the impact of breathlessness on both activity and social functioning and is acceptable, reliable and valid in patients with advanced disease and chronic breathlessness [45].

Treatment of underlying causes

Malignant pleural effusions

The median survival of patients with malignant pleural effusion is 4–6 months [46]. Dyspnoea is the most common symptom associated with malignant pleural effusion. Although therapeutic thoracentesis provides effective symptom relief, most malignant effusions recur within a month. Repeated thoracentesis is associated with a higher risk of pneumothorax and empyema, and reduced efficacy due to pleural adhesions. Therefore, simple thoracentesis should only be provided for patients with poor performance status and short life expectancy.

For patients with recurrence effusions and longer life expectancy (>3 months), drainage followed by instillation of a sclerosant or insertion of a semi-permanent tunnelled pleural catheter may be considered. The chest cavity can be drained surgically via thoracoscopy or at the bedside with a simple chest tube. Thoracoscopy was associated with greater comfort than a chest tube and can facilitate diagnosis of pleural involvement. For successful pleurodesis, the underlying lung must re-expand, and pleural apposition must occur. Both techniques may be used for instillation of sclerosant into the pleural space. A 2016 Cochrane systematic review found that talc poudrage was more effective than bleomycin and tetracycline, with a higher rate of pleurodesis [47].

Tunnelled pleural catheter compares favourably with pleurodesis for palliation of breathlessness. In head-to-head randomised trials, tunnelled pleural catheter was associated with significant improvement in breathlessness when compared to talc pleurodesis despite lower pleurodesis success rate [48, 49]. Daily fluid draining via tunnelled pleural catheter was associated with higher rate of autopleurodesis compared with drainage every other day [50]. Tunnel pleural catheter was associated with fewer hospitalisations but higher rates of complications mostly related to catheterisation [49]. Major complications including empyema and cellulitis are rare.

Airway lesions

Patients with central airway obstruction can present with severe acute breathlessness. Urgent measures to open up the airway can result in rapid improvement in breathlessness. In general, proximal airway lesions are better managed with endobronchial interventions, such as bronchoscopy with mechanical debridement, tumour ablation and airway stent placement, while distal obstruction (lobar or segmental bronchi) is more amenable to radiotherapy (RT) [51].

Airway stents can re-establish the bronchial lumen and provide symptomatic breathlessness relief in 80%–90% of cases. Metal stents are generally used for malignant central airway obstruction, although silicone stents are sometimes used. Multimodality therapeutic bronchoscopy was found to improve breathlessness, QoL, pulmonary function and physical function significantly in prospective studies [52, 53]. Complications of stents occur in 1%–36% of patients, including haemoptysis, stent migration, retention of secretion, growth or overgrowth of tumour and granulation tissue formation [54].

For RT, patients who have a poor performance status and shorter survival may benefit from shorter fractionation schedules, e.g. 20 Gy in five fractions, 17 Gy in two weekly fractions, or 10 Gy in one fraction. External beam RT (EBRT) or brachytherapy can be associated with life-threatening complications, with a mortality rate of 7% and 15%, respectively [54].

Cytotoxic chemotherapy-induced pulmonary toxicities

Pulmonary injury induced by chemotherapeutic agents may include pneumonitis, non-cardiogenic pulmonary oedema and acute respiratory distress syndrome (ARDS). The histological presentations can be different and include diffuse alveolar damage, organising pneumonia and neutrophilic alveolitis. These toxicities may occur weeks to months after treatment initiation.

The clinical manifestations are non-specific and may include breathlessness, cough (typically non-productive), low-grade fever, hypoxaemia and sometimes weight loss. Chest imaging may help to narrow the differential diagnosis.

The treatment of chemotherapy-induced pulmonary toxicity includes systemic glucocorticoids and discontinuation of the causative agent. Once a diagnosis is established, re-challenge with the same agent is generally not recommended because recurrences are expected and can be fatal [55].

Immunotherapy-induced pulmonary toxicities

Pneumonitis is a relatively rare but potentially life-threatening complication of immunotherapeutic agents [anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4), anti-programmed cell death protein 1 (anti-PD-1), anti-programmed death-ligand 1 (anti-PD-L1) agents]. The incidence of pneumonitis reported in clinical trials varied between 3% and 7% for any grade and 1% and 3% for grade 3 or higher toxicities [56-58]. In one retrospective study, 64 of 1826 (3.5%) cancer patients on checkpoint inhibitors were identified to have interstitial lung disease (Grade 2–3 66%; Grade 4, 9%; Grade 5, 9%) [59].

The treatment approach consists of stopping the immunotherapy and introducing systemic corticosteroids. These are often given for 2–4 weeks, followed by a gradual taper over an additional 4 weeks. Most lung alterations are steroid responsive and will resolve within 3 months. In case of severe, steroid-refractory lung toxicity, the use of immunosuppressive agents, such as infliximab or cyclophosphamide, should be considered. However, larger pooled trials have reported that these patients often succumb to acute respiratory failure from pneumonitis or, more often, secondary opportunistic infections as a consequence of immunosuppression [60].

RT-induced lung injury

Although modern radiation techniques have allowed a reduction of the dose administered to the normal lung tissue, acute radiation pneumonitis and late lung fibrosis remain

significant dose-limiting complications of RT, affecting 7%–37% of patients who undergo definitive radiation for lung cancer [61].

Because of high rate of infection in these patients, prophylactic use of antibiotics is considered in some patients. Corticosteroids, due to their anti-inflammatory effects, are used for treatment of symptomatic radiation pneumonitis at the dose of 60–100 mg/day for 2–4 weeks (generally 1 mg/kg of prednisone), followed by an extended tapering over 6–12 weeks. Relapse is possible following the response to steroids. Patients with chronic pulmonary fibrosis should be referred to a pulmonologist for further management.

Opioid-related adverse effects and safe opioid use

Low-dose regular, oral morphine extended release (ER) for chronic breathlessness, under carefully monitored conditions, seem to have an acceptable safety profile, with no serious adverse events including no events of serious respiratory depression seen in randomised clinical trials (RCTs) [62], opioid-related hospitalisations or deaths [63, 64]. There has been no large safety study in patients with cancer, but low-dose opioids [up to 30 mg of morphine equivalent daily dose (MEDD)] were not associated with increased risk of hospitalisation or death in patients with end-stage chronic obstructive pulmonary disease (COPD) [65] or interstitial lung disease (ILD) [66].

Well-known opioid side-effects include bowel dysfunction (e.g. constipation, bloating, increased gastric reflux), nausea and vomiting and drowsiness. These side-effects are often temporal (except constipation when untreated); worst at the start of therapy and are reversible upon dose adjustment or discontinuation [63]. On starting opioid treatment, all patients should be offered a laxative for prophylaxis and treatment of constipation and an 'as needed' antiemetic (such as metoclopramide or other antidopaminergic medication) with adequate follow-up [67].

In the era of opioid epidemics in many countries, clinicians and patients may be concerned about opioid use even if prescribed for an appropriate indication [68]. The panel would like to emphasise that for cancer patients suffering from chronic breathlessness, opioids remain the first choice among pharmacological options for palliation. The potential benefits of opioids should be balanced, in the light of the still limited evidence base, against the potential risks of adverse effects and risk of opioid-use disorders in each individual patient. Although opioids are generally well tolerated, respiratory depression and overdoses have been reported when opioids were not taken appropriately [69]. Clinicians can optimise the benefit-risk ratio by educating patients on safe opioid use, providing longitudinal monitoring and incorporating various risk mitigation strategies [70]. Referral to an interdisciplinary palliative care team may be helpful for patients on opioids because of the emphasis on patient education [71] and structured multidimensional interventions to prevent and manage non-medical opioid use [72].

Supplementary Table S1.

Table S1. Level of evidence and grades of recommendation[a,b]

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Reprinted by permission of the Infectious Diseases Society of America [73]

[b]The * notation is assigned to the grade of recommendation for statements on topics for which clinical trials are not available because they are inherently difficult to design or not justified due to ethical reasons while these statements are considered justified by standard clinical practice by the experts and the ESMO Faculty.

References

1. Ripamonti C, Bruera E. Dyspnea: pathophysiology and assessment. J Pain Symptom Manage 1997; 13: 220-232.
2. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. American Journal of Respiratory and Critical Care Medicine 1999; 159: 321-340.
3. Currow DC, Higginson IJ, Johnson MJ. Breathlessness--current and emerging mechanisms, measurement and management: a discussion from an European Association of Palliative Care workshop. Palliat Med 2013; 27: 932-938.
4. Mahler DA. Understanding mechanisms and documenting plausibility of palliative interventions for dyspnea. Curr Opin Support Palliat Care 2011; 5: 71-76.
5. Parshall MB, Schwartzstein RM, Adams L et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012; 185: 435-452.
6. Simon ST, Higginson IJ, Benalia H et al. Episodic and continuous breathlessness: a new categorization of breathlessness. J Pain Symptom Manage 2013; 45: 1019-1029.
7. Mercadante S. Episodic Breathlessness in Patients with Advanced Cancer: Characteristics and Management. Drugs 2018; 78: 543-547.
8. Simon ST, Weingartner V, Higginson IJ et al. Definition, categorization, and terminology of episodic breathlessness: consensus by an international Delphi survey. J Pain Symptom Manage 2014; 47: 828-838.
9. Reddy SK, Parsons HA, Elsayem A et al. Characteristics and correlates of dyspnea in patients with advanced cancer. J Palliat Med 2009; 12: 29-36.
10. Mercadante S, Aielli F, Adile C et al. Epidemiology and Characteristics of Episodic Breathlessness in Advanced Cancer Patients: An Observational Study. J Pain Symptom Manage 2016; 51: 17-24.
11. Weingartner V, Scheve C, Gerdes V et al. Characteristics of episodic breathlessness as reported by patients with advanced chronic obstructive pulmonary

disease and lung cancer: Results of a descriptive cohort study. Palliat Med 2015; 29: 420-428.

12. Johnson MJ, Hui D, Currow DC. Opioids, Exertion, and Dyspnea: A Review of the Evidence. Am J Hosp Palliat Care 2016; 33: 194-200.

13. Cuervo Pinna MA, Mota Vargas R, Redondo Moralo MJ et al. Dyspnea--a bad prognosis symptom at the end of life. Am J Hosp Palliat Care 2009; 26: 89-97.

14. Hutchinson A, Barclay-Klingle N, Galvin K, Johnson MJ. Living with breathlessness: a systematic literature review and qualitative synthesis. Eur Respir J 2018; 51:1701477.

15. Saracino A, Weiland TJ, Jolly B, Dent AW. Verbal dyspnoea score predicts emergency department departure status in patients with shortness of breath. Emerg Med Australas 2010; 22: 21-29.

16. Stevens JP, Baker K, Howell MD, Banzett RB. Prevalence and Predictive Value of Dyspnea Ratings in Hospitalized Patients: Pilot Studies. PLoS One 2016; 11: e0152601.

17. Stevens JP, Dechen T, Schwartzstein R et al. Prevalence of Dyspnea Among Hospitalized Patients at the Time of Admission. J Pain Symptom Manage 2018; 56: 15-22.e12.

18. Kamal AH, Gradison M, Maguire JM et al. Quality measures for palliative care in patients with cancer: a systematic review. J Oncol Pract 2014; 10: 281-287.

19. Mak KS, van Bommel AC, Stowell C et al. Defining a standard set of patient-centred outcomes for lung cancer. Eur Respir J 2016; 48: 852-860.

20. Currow DC, Allingham S, Yates P et al. Improving national hospice/palliative care service symptom outcomes systematically through point-of-care data collection, structured feedback and benchmarking. Support Care Cancer 2015; 23: 307-315.

21. Basch E, Deal AM, Dueck AC et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA 2017; 318: 197-198.

22. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabil Nurs 1989; 14: 323-325.

23. Booth S, Galbraith S, Ryan R et al. The importance of the feasibility study: Lessons from a study of the hand-held fan used to relieve dyspnea in people who are breathless at rest. Palliat Med 2016; 30: 504-509.

24. Wilcock A, Crosby V, Clarke D, Tattersfield A. Repeatability of breathlessness measurements in cancer patients. Thorax 1999; 54: 375.

25. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 Years Later: Past, Present and Future Developments. J Pain Symp Manage 2017; 53: 630-643.

26. Hui D, Shamieh O, Paiva C et al. Minimal Clinically Important Differences in the Edmonton Symptom Assessment Scale in Cancer Patients: A Prospective Study. Cancer 2015; 121: 3027-3035.

27. Johnson MJ, Bland JM, Oxberry SG et al. Clinically important differences in the intensity of chronic refractory breathlessness. J Pain Symptom Manage 2013; 46: 957-963.

28. Wysham NG, Miriovsky BJ, Currow DC et al. Practical Dyspnea Assessment: Relationship Between the 0-10 Numerical Rating Scale and the Four-Level Categorical Verbal Descriptor Scale of Dyspnea Intensity. J Pain Symptom Manage 2015; 50: 480-487.

29. Uronis HE, Shelby RA, Currow DC et al. Assessment of the psychometric properties of an English version of the cancer dyspnea scale in people with advanced lung cancer. J Pain Symptom Manage 2012; 44: 741-749.

30. Tan JY, Yorke J, Harle A et al. Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the Dyspnea-12 Questionnaire. J Pain Symptom Manage 2017; 53: 208-215.

31. Henoch I, Bergman B, Gaston-Johansson F. Validation of a Swedish version of the Cancer Dyspnea Scale. J Pain Symptom Manage 2006; 31: 353-361.

32. Sandberg J, Johnson MJ, Currow DC, Ekstrom M. Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness. J Pain Symptom Manage 2018; 56: 430-435.e432.

33. Campbell ML, Templin T, Walch J. A Respiratory Distress Observation Scale for patients unable to self-report dyspnea. J Palliat Med 2010; 13: 285-290.

34. Hui D, Morgado M, Vidal M et al. Dyspnea in Hospitalized Advanced Cancer Patients: Subjective and Physiologic Correlates. J Palliat Med 2013; 16: 274-280.
35. White KM, Agar MR, Currow DC. Assessing the exertion required to induce breathlessness in a population with advanced cancer: matching measures to the level of physical function. BMC Palliat Care 2019; 18: 4.
36. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991; 39: 142-148.
37. Granger CL, McDonald CF, Parry SM et al. Functional capacity, physical activity and muscle strength assessment of individuals with non-small cell lung cancer: a systematic review of instruments and their measurement properties. BMC Cancer 2013; 13: 135.
38. Schmidt K, Vogt L, Thiel C et al. Validity of the six-minute walk test in cancer patients. Int J Sports Med 2013; 34: 631-636.
39. Schumacher AN, Shackelford DYK, Brown JM, Hayward R. Validation of the 6-min Walk Test for Predicting Peak V O2 in Cancer Survivors. Med Sci Sports Exerc 2019; 51: 271-277.
40. Booth S, Adams L. The shuttle walking test: a reproducible method for evaluating the impact of shortness of breath on functional capacity in patients with advanced cancer. Thorax 2001; 56: 146-150.
41. Wilcock A, Koon S, Manderson C et al. Within and between day repeatability of the incremental shuttle walking test in patients with thoracic cancer. Respir Med 2018; 140: 39-41.
42. Holland AE, Spruit MA, Troosters T et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44: 1428-1446.
43. Verweij NM, Schiphorst AH, Pronk A et al. Physical performance measures for predicting outcome in cancer patients: a systematic review. Acta Oncol 2016; 55: 1386-1391.
44. Neo J, Fettes L, Gao W et al. Disability in activities of daily living among adults with cancer: A systematic review and meta-analysis. Cancer Treat Rev 2017; 61: 94-106.

45. Reilly CC, Bausewein C, Garrod R et al. Breathlessness during daily activity: The psychometric properties of the London Chest Activity of Daily Living Scale in patients with advanced disease and refractory breathlessness. Palliat Med 2017; 31: 868-875.
46. Clive AO, Kahan BC, Hooper CE et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014; 69: 1098-1104.
47. Clive AO, Jones HE, Bhatnagar R et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev 2016; Cd010529.
48. Demmy TL, Gu L, Burkhalter JE et al. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw 2012; 10: 975-982.
49. 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: 2383-2389.
50. Wahidi MM, Reddy C, Yarmus L et al. Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions. The ASAP Trial. Am J Respir Crit Care Med 2017; 195: 1050-1057.
51. Kvale PA, Selecky PA, Prakash UB, American College of Chest P. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: 368S-403S.
52. Oviatt PL, Stather DR, Michaud G et al. Exercise capacity, lung function, and quality of life after interventional bronchoscopy. J Thorac Oncol 2011; 6: 38-42.
53. Mao Y, Yang X, Li M et al. Treating cancerous large airway stenosis with staging radioactive particle implantation guided by computed tomography and fiber bronchoscopy: a clinical study. World J Surg Oncol 2017; 15: 149.
54. 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-e497S.
55. Leger P, Limper AH, Maldonado F. Pulmonary Toxicities from Conventional Chemotherapy. Clin Chest Med 2017; 38: 209-222.

56. Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018-2028.
57. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-2454.
58. Gettinger SN, Horn L, Gandhi L et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2015; 33: 2004-2012.
59. Delaunay M, Cadranel J, Lusque A et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J 2017; 50:1700050.
60. Rapoport BL, van Eeden R, Sibaud V et al. Supportive care for patients undergoing immunotherapy. Support Care Cancer 2017; 25: 3017-3030.
61. Deng G, Liang N, Xie J et al. Pulmonary toxicity generated from radiotherapeutic treatment of thoracic malignancies. Oncol Lett 2017; 14: 501-511.
62. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. Eur Respir J 2017; 50:1701153.
63. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev 2016; 3: Cd011008.
64. Currow D, Ekström M, Fazekas B et al. A phase III, multi-site, randomised, double blind, placebo controlled parallel arm study of daily extended release (ER) morphine for chronic breathlessness. Eur Respir J 2016; 48.
65. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 2014; 348: g445.
66. Bajwah S, Davies JM, Tanash H et al. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. Eur Respir J 2018; 52: 1801278.

67. Arthur J, Hui D. Safe Opioid Use: Management of Opioid-Related Adverse Effects and Aberrant Behaviors. Hematol Oncol Clin North Am 2018; 32: 387-403.
68. Hui D, Arthur J, Bruera E. Palliative Care for Patients With Opioid Misuse. JAMA 2019; 321: 511.
69. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols J et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. Eur Respir J 2017; 50:1701153.
70. Gaertner J, Boehlke C, Simone CB, 2nd, Hui D. Early palliative care and the opioid crisis: ten pragmatic steps towards a more rational use of opioids. Ann Palliat Med 2019; 8:490-497.
71. de la Cruz M, Reddy A, Balankari V et al. The Impact of an Educational Program on Patient Practices for Safe Use, Storage, and Disposal of Opioids at a Comprehensive Cancer Center. Oncologist 2017; 22: 115-121.
72. Arthur J, Edwards T, Reddy S et al. Outcomes of a Specialized Interdisciplinary Approach for Patients with Cancer with Aberrant Opioid-Related Behavior. Oncologist 2018; 23: 263-270.
73. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis 2001; 33: 139-144.