ESMO Open Cancer Horizons

Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines†

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Highlights

- This ESMO Clinical Practice Guideline provides key recommendations on the management of breathlessness in patients with cancer.
- Authorship includes a multidisciplinary group of experts from different institutions and countries in Europe and worldwide.
- Key treatment recommendations are provided, including levels of evidence and grades of recommendation where applicable.
- Routine assessment of breathlessness and its impact facilitates timely interventions.
- Key non-pharmacological measures include fan, breathing retraining, mobility aids, education and pulmonary rehabilitation.
- The main pharmacological option is opioids. Supplemental oxygen, non-invasive ventilation and high flow may be considered.

INTRODUCTION

Breathlessness, dyspnoea and shortness of breath are synonymous terms to describe the 'subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'.[1 2] Chronic breathlessness syndrome was recently defined by an international consensus as breathlessness 'that persists despite optimum treatment for the underlying pathophysiology and causes disability'.[3 4] The pathophysiology and characterisation of breathlessness are described in further details in the supplemental material available at *ESMO Open* online. Breathlessness is often cited as the most distressing symptom experienced by patients with cancer.[5] A 2019 systematic review highlighted six major areas of concerns for patients living with breathlessness refractory to disease-modifying treatments, including physical, emotional, spiritual, social, control and context, unifying these under the concept of total breathlessness.[6] In addition to the significant functional limitation, breathlessness can have devastating effects on patients' quality of life (QoL) and is associated with a poor prognosis.[7]

This ESMO Clinical Practice Guideline provides an up-to-date, evidence-based approach on the assessment and management of breathlessness in patients with cancer (figure 1). Proper assessment of breathlessness involves screening and in-depth evaluation to characterise the symptom and direct management. Treatments include interventions aimed at reversing any underlying causes, non-pharmacological and pharmacological therapies to palliate breathlessness, and multimodal approaches. Although the focus of this guideline is on patients with cancer, the evidence base for breathlessness in the oncology setting is relatively limited; thus, we have included studies conducted in other patient populations, such as chronic obstructive pulmonary disease (COPD), if the findings are applicable to the oncology setting.

PREVALENCE

Breathlessness is highly prevalent, affecting between 20% and 70% of patients with cancer,[8] particularly among patients with thoracic malignancies, with advanced stages of disease, and in the last weeks of life.[9–11]

ASSESSMENT

Breathlessness is a subjective experience and thus the gold standard for breathlessness assessment is based on patient self-report.[2] Breathlessness is easily overlooked when relying only on observation of the patient at rest (such as in clinic or on the ward) where they can appear comfortable. Breathlessness is intimately related to physical and emotional exertion and patients usually avoid activity causing a vicious cycle of deconditioning. The response to 'are you short of breath' is often

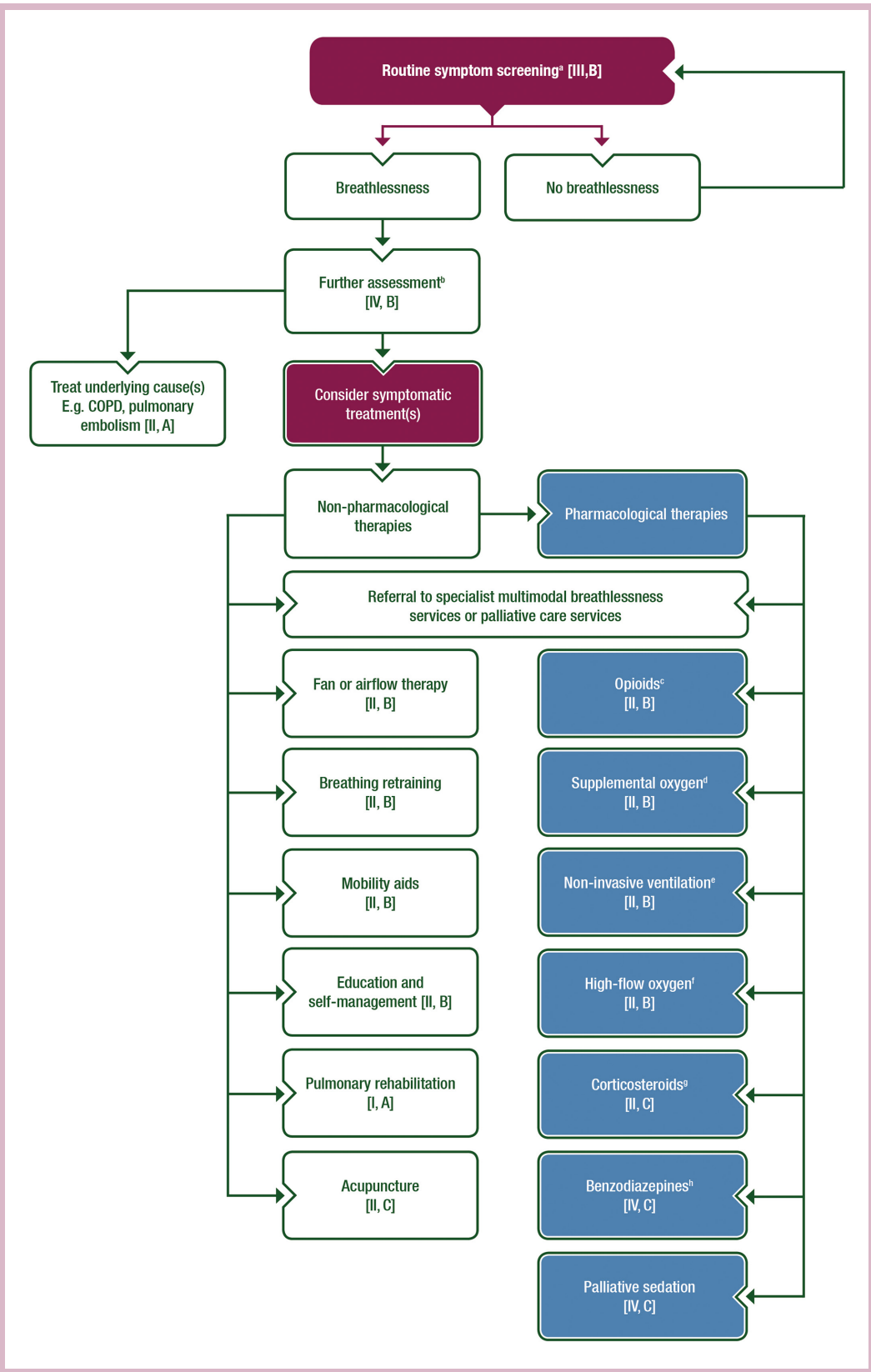

Figure 1 Management of breathlessness in cancer patients in outpatient or inpatient settings [a]Breathlessness intensity and functional impact. [b]Assessment for causes, severity, episodic nature, emotional and functional impact and caregiver support. [c]If favourable benefit–risk ratio. [d]If SpO_2 <90%, however, palliative oxygen is not recommended in patients with resting SpO_2 ≥90% [II, D]. [e]If hypercapnic respiratory failure. [f]If hypoxaemic respiratory failure. [g]If other therapies have failed. [h]Especially for anxiety and after trial of other agents.COPD, chronic pulmonary obstructive disease; SpO_2, peripheral oxygen saturation.

therefore 'no', rendering the breathlessness 'invisible'.[12] Enquiry should include the activities that the patient has reduced or given up because of breathlessness.

Commonly used objective physiological measures only have a weak association with subjective sensations of breathlessness.[13] However, in patients unable to self-report breathlessness, vital signs are useful to indicate breathlessness distress as well as underlying pathology.[14] In general, lung function tests correlate poorly with the symptom of breathlessness and relatively normal values do not obviate enquiry about breathlessness.

The multi-faceted experience of breathlessness represents another challenge. There is no one tool which captures the full experience of breathlessness. Screening for breathlessness should include an assessment of intensity with unidimensional tools (eg, Numerical Rating Scale (NRS)), and functional impact (eg, modified Medical Research Council Breathlessness Scale). Patients with a positive screen would require further assessment for potential causes, pattern and severity of breathlessness (perception), distress due to breathlessness (emotional response), functional impairment, and impact on social, family, financial and spiritual domains. Patients with episodic breathlessness should be asked about the average frequency and duration of episodes, the intensity of these episodes and potential triggers.

Over 40 patient-reported outcomes for breathlessness were identified in the 2007–2008 reviews.[15–18] Many of these questionnaires have multiple questions and are designed more for research. A rapid review (Medline database; search terms relating to breathlessness/dyspnoea and neoplasms/cancer/malignancy and measurement/patient-reported outcome measures; date limits 2009–2019; single reviewer) failed to show a more recent systematic review of breathlessness measurement tools usable in cancer. The recommendations therefore are unchanged: breathlessness assessment should include a unidimensional measure of severity, a measure of multidimensional functional impact and patient interview. Details of assessments can be found in supplemental material available at *ESMO Open* online.

Recommendations

- Patient-reported outcomes are the gold standard for assessment of breathlessness. Physiological assessments may complement but not replace patient reports (III, B*).
- All patients should be screened for breathlessness routinely at all inpatient and outpatient clinical encounters (III, B*).
- Routine screening for breathlessness should include a unidimensional scale of choice and activities that patients have stopped or reduced because of breathlessness (III, B*).
- Patients identified as having chronic breathlessness should have a fuller assessment which includes potential causes, pattern and severity of breathlessness, distress due to breathlessness and functional impairment (IV, B*).
- For patients with episodic breathlessness, clinicians should ask about the intensity, frequency, duration and impact of these episodes along with potential triggers (IV, B*).

MANAGEMENT

Treat the underlying cause

Breathlessness may be related to cancer progression, cancer therapies and/or acute complications such as infections or pulmonary embolism. Pre-existing comorbidities such as COPD and heart failure may also contribute to breathlessness. One of the key strategies in the management of breathlessness is to identify and treat any potential underlying cause(s).[19] However, breathlessness is often not the primary outcome in randomised clinical trials (RCTs) evaluating interventions to treat any underlying causes, and validated patient-reported outcomes are rarely used to assess breathlessness as a secondary outcome. In clinical trials, the Common Toxicity Criteria are often used to assess breathlessness instead of patient-reported outcomes. A detailed review is beyond the scope of this guideline. Table 1 includes management strategies for selected conditions, with further explanations provided in supplemental material section 'Treatment of underlying causes' available at *ESMO Open* online.

Non-pharmacological symptomatic interventions

Several non-pharmacological interventions offer first-line treatment options for the management of breathlessness and complement use of pharmacological interventions in advanced disease. Although studies of sole interventions are lacking in cancer, direct evidence exists in chronic respiratory disease, and the interventions below are core components in most studies of multimodal services (see the 'Multimodal interventions section').[20]

Fan or airflow

Using a hand-held fan to increase airflow towards the face represents a simple intervention that patients can use to self-manage their breathlessness. Although there is a paucity of studies on the use of a fan in patients with hypoxaemia and it is unclear if a fan would provide additional benefit in patients already on supplemental oxygen (ie, delivering airflow), the guideline panel supports the use of a fan irrespective of the patient's oxygen saturation given its potential benefit and lack of harm. The fan is a cheap, easily-obtained, light, portable and non-stigmatising piece of equipment.[21] Plausible mechanisms of action include cooling nasal receptors and moderating afferent signals to the respiratory centre, and increasing self-efficacy, particularly around unexpected episodes of breathlessness that patients can find difficult to manage.[22]

A recent review summarised 10 studies of fan therapy (median duration 5 min) in 344 patients (159 with cancer). Six studies reported a statistically significant improvement in breathlessness whereas four did not.

Table 1 Management strategies of selected conditions contributing to breathlessness

Condition	Management strategies
Anaemia (symptomatic)	Consider transfusion if haemoglobin <70–80 g/L to keep haemoglobin above 70–80 g/L
Asthma/COPD exacerbation	Medical optimisation
Cachexia	Consider referral to palliative care, dietician and/or physical therapy
Central airway obstruction	For proximal lesions, consider endobronchial interventions, such as bronchoscopy with mechanical debridement, tumour ablation and airway stent placement For distal lesions, consider radiotherapy
Cytotoxic chemotherapy-induced pulmonary toxicities	Withhold treatment and consider corticosteroids
Immunotherapy-induced pulmonary toxicities	Withhold treatment and consider corticosteroids
Heart failure exacerbation	Medical optimisation
Lymphangitic carcinomatosis	Treatment of underlying malignancy. Consider corticosteroids (anecdotal)
Malignant ascites	Paracentesis with or without indwelling catheter
Malignant pleural effusions	For patients with a short-life expectancy (<3 months), consider simple thoracentesis For patients with longer life expectancy, consider tunnelled pleural catheter or chemical pleurodesis; both are reasonable options
Malignant pericardial effusion/tamponade	Pericardiocentesis, pericardiectomy with or without pericardial window
Metabolic acidosis	Identify and treat the underlying cause
Pneumonia	Anti-infective agents
Pulmonary embolism	Anticoagulation
Radiation-induced pneumonitis or fibrosis	Consider corticosteroids
Superior vena cava syndrome	Treatment of underlying malignancy. Consider corticosteroids (anecdotal)
Tumour embolism	Treatment of underlying malignancy

COPD, chronic obstructive pulmonary disease.

Some non-significant findings may relate to underpowered study designs; however, no meta-analysis was undertaken to increase statistical power. The authors concluded limited experimental evidence of efficacy, calling for larger trials in more diverse populations and settings.[23]

A secondary multimethod analysis of qualitative interview data explored benefits of a hand-held fan as perceived by patients with breathlessness (n=133, n=21 with cancer) and their carers (n=72). Most patients with usable data (91/111) perceived some or substantial benefit, described in terms of shorter recovery time, especially after physical activity. Negative perceptions of a few patients included dislike of the cooling sensation and embarrassment in public.[21] An exploratory review of uncontrolled pre-to-post measures in 16 studies (n=929) where airflow was used either as an intervention (eg, fan) or comparator (eg, as a sham in an oxygen trial), found hand-held fan at rest, airflow via nasal cannula at rest and airflow during exercise all led to reductions in breathlessness intensity.[24]

Breathing retraining

Altered breathing patterns, including increased respiratory rate, apical breathing, excessive accessory muscle recruitment and/or dynamic hyperinflation, can reduce efficiency of ventilation, increase work of breathing and cause or exacerbate breathlessness.[25] Breathing retraining techniques aim to improve a patient's control over their breathing to counter these changes. Common techniques include pursed-lip breathing, to produce pressure to support the airways and improve expiratory flow; diaphragmatic breathing, to reduce accessory muscle use, and breathing control or timed breathing, which aims to normalise respiratory rate. Individual breathing patterns and pathophysiology should be considered in their selection.[26]

A review of 16 trials in COPD (n=1233) found breathing retraining over 4–15 weeks improved functional exercise capacity, though effects on breathlessness and health-related QoL were inconsistent.[25] Widespread use as a stand-alone intervention was not recommended. A large trial (n=655) in patients with incompletely controlled asthma of a self-guided breathing retraining intervention, delivered either face-to-face or as a digital audio–visual programme plus printed booklet, improved QoL over 12 months.[27] A single acute trial in patients (n=63) with lung cancer (n=32), COPD and asthma, who were breathless at rest, found 20 min mindful breathing control reduced breathlessness within 5 min. A follow-on effect was not studied.[28]

Mobility aids

Mobility aids help to improve both breathlessness and mobility through an increased ventilatory capacity and/or reduced metabolic cost.[29 30] Despite the absence of studies in patients

with cancer, several randomised crossover studies in breathless patients with COPD demonstrate that use of a rollator improves self-paced walking distance in both indoor[31 32] and outdoor environments,[33] especially in patients severely limited by breathlessness including those using ambulatory oxygen.[34] Using a modern 'draisine' (bicycle without pedals) improved indoor walking distance further still, with the same metabolic requirements and breathlessness scores,[35] but in outdoor environments with obstacles it had a detrimental effect on mobility compared with unaided walking.[33] All the above studies have been conducted over a short time period and prolonged satisfaction and benefit should not be assumed. If mobility aids are prescribed, a subsequent review is recommended.

Education and self-management

For patients receiving curative treatment, education is often framed around enhancing recovery and returning to a healthy lifestyle. In advanced cancer, where deterioration is expected, it can be framed around making the most of the present and staying independent for as long as possible. Patients should be assured that being breathless is itself not dangerous, and that breathlessness is a normal exertional response that settles with rest. Even following incremental exercise to a symptom-limited maximum, breathlessness in people with lung cancer typically recovers within a few minutes.[36] Advice on positions to aid recovery following exertion, or during an episode of breathlessness, can be useful.[37] A 'forward-lean' position may reduce accessory muscle work, improving diaphragm function and ventilatory capacity.[38] Relaxed sitting (with hands or elbows rested on thighs) or standing (using a wall as support) and high side lying (supporting head and chest) are frequently recommended within breathlessness services.[20]

Activity pacing (balancing rest and activity) education teaches patients to moderate activity behaviour and to avoid extremes of rest or activity for optimising the use of available energy. A change in routine is often required to avoid 'boom or bust' situations where patients push themselves too much and then need a prolonged period of recovery. Study of activity pacing as a standalone intervention for breathlessness is lacking, but evidence from its use in cancer-related fatigue[39] and/or pain[40] is generally applicable. Distraction using music or visualisation has been tested in small studies. An uncontrolled study (n=53) found guided imagery with theta music reduced breathlessness in patients with advanced cancer,[41] and a retrospective analysis reported positive responses to music therapy sessions in a palliative care setting.[42] In COPD, auditory distraction with music improved the effect of exercise training on functional exercise performance, but was inconsistent in its short-term effect on exercise testing and in reducing breathlessness at rest.[43] Bredin *et al* found a nurse-led clinic combining these educational strategies with psychological support improved breathlessness, performance status and emotional state over 8 weeks in people with lung cancer.[44]

Pulmonary rehabilitation

A rehabilitation approach incorporating exercise should be considered for most patients with chronic breathlessness to reduce the impact of the symptom on physical function. Breathlessness tends to lead towards reduced physical activity, which in turn precipitates a downward spiral of deconditioning. Rehabilitation helps to counter this downward spiral by improving the physical condition of patients, by exposing them to being breathless while staying in control.

As the spiral of deconditioning involves physical inactivity, an approach that targets lower limb function and mobility is generally helpful. Breathlessness can also limit upper limb activities, for example, cooking and shopping, as the muscles around the shoulder have a dual role for breathing and stability. By improving physical capacity, the relative level of ventilatory demand for a fixed activity becomes lower, and perceived exertion is reduced. Following exercise training, the anxiety related to breathlessness is also reduced allowing patients to improve functional performance.[45]

Both pulmonary and cardiac rehabilitation have a strong evidence of effectiveness in improving breathlessness, functional exercise capacity and health-related QoL.[46] Though most evidence for pulmonary rehabilitation relates to COPD, consistent effects are found across other respiratory diseases, including lung cancer.[47] However, the efficacy of pulmonary rehabilitation in patients with advanced cancer is unclear, especially when these patients may be too weak to participate in exercise sessions. Referral and uptake to these programmes should be encouraged. The availability of cancer rehabilitation programmes is relatively low, but with accumulating evidence of the effect on symptom burden, fitness and QoL[48] and exercise recommendations in national treatment guidelines,[49 50] this should improve.

Programmes typically incorporate a combination of aerobic and resistance training, plus tailored education. In general, supervised training leads to a greater exercise workload and response[47]; however, home-based unsupervised training is also beneficial if completed regularly. Mind–body movement therapies (eg, yoga, tai chi and qigong) may be preferred by some patients, and when compared with conventional training modalities, outcomes related to breathlessness are similar.[51] Low-intensity resistance training using novel approaches, for example, neuromuscular muscle stimulation[52] or partitioned training, may be suited to patients where exertional breathlessness is severely limiting.[53] The low ventilatory demand of these modalities allows the severely breathless patient to exercise to help counteract the deconditioning associated with physical inactivity.

Complementary therapies

A few, mostly small RCTs have examined the role of acupressure or acupuncture in patients with cancer and reported short-term benefit on breathlessness.[54–56] One open-label trial involving 152 patients with lung cancer compared prolonged acupuncture (with indwelling studs) with morphine or a combination of both and found similar reduction on breathlessness but fewer side-effects in the acupuncture group.[55] A recent systematic review

of 12 clinical trials involving 190 patients with cancer and 347 patients with COPD found overall benefit from acupuncture on breathlessness severity.[57] Additional therapies, including aromatherapy massage, hypnotherapy, meditation, reflexology and reiki, may provide limited short-term benefit.[58] Further high-quality studies are needed to examine the risks and benefits of acupuncture and other complementary therapies in the long term, especially in patients with cancer.

Pharmacological symptomatic interventions

Recommendations on the pharmacological management were informed by searches in Medline using the terms (dyspnea/dyspnoea/breathlessness) and cancer and, in turn, the treatment of interest: (opioid/morphine/fentanyl), benzodiazepine, steroid, oxygen, high-flow oxygen, or (non-invasive/non invasive/NIV), antidepressant and cannabinoid. In addition, reference lists of major papers and systematic reviews were hand searched.

Opioids

Among the various pharmacological options for breathlessness, opioids have been studied the most. However, existing randomised trials were generally small and only a handful had specifically focused on patients with cancer. Although opioids appear to have a pharmacological effect on breathlessness, the overall evidence is low and there is much uncertainty how they should be used in clinical practice.[59–62]

Efficacy of systemic opioids on chronic breathlessness was shown in the latest Cochrane report from 2016 of 12 RCTs (198 participants of whom 41 (21%) had cancer).[59 61] There is no clear evidence to support use of nebulised opioids.[61] Compared with placebo, systemic opioids decreased breathlessness intensity by a pooled mean of 0.8 points on a 0–10 NRS,[59] which represents between a small and a moderate effect size.[63 64] Assuming a moderate effect size represents clinically meaningful improvement, this value is just below this level and suggests that only a proportion of patients derived an improvement. Several methodological issues may have impacted the study findings. For instance, the trials were mostly small, cross-over trials (11 out of 12) with short follow-up.[59 61] When the cross-over design was taken into account in the statistical analysis, the precision around the findings improved.[59]

Opioid-naïve patients

A multicentre parallel group RCT (<20% with cancer) reported that neither 20 mg/day of sustained-release morphine nor 5 mg every 8 hours of extended-release (ER) oxycodone improved the primary outcome of intensity of 'breathless now', compared with placebo over 7 days.[65 66] However, several methodological limitations complicate its interpretation: 'rescue' immediate-release morphine (MIR) was available for all patients with higher usage in the placebo groups; early termination of the oxycodone group; difficulties with enrolment; opioid dosing; and not all patients were opioid-naïve. While the best evidence for opioids is in people with COPD, a pooled data study showed no predictive association of underlying disease,[61] although younger patients and patients with more severe breathlessness were more likely to gain benefit.[67] Given methodological limitations in existing studies, further research is needed to examine the efficacy of opioids and optimal administration in opioid-naïve patients.

There are no head-to-head comparisons of immediate-release (IR) and ER formulations for breathlessness. The Therapeutic Goods Administration has extended the licence for one ER formulation of oral morphine (morphine sulfate pentahydrate) to include chronic breathlessness in Australia. A dose range of 10–30 mg per 24 hours is licensed, with an explicit statement that additional morphine sulfate IR doses should not be given for breathlessness but may be needed for concurrent pain.[68]

Opioid-tolerant patients

There are few RCTs to inform use of opioids for treatment of breathlessness in patients with cancer taking regular opioids for pain. A cross-over, placebo-controlled trial found that a single dose of subcutaneous morphine given at 50% higher than the scheduled 4-hourly dose resulted in a significant reduction of breathlessness consistently over the first hour compared with placebo among patients with cancer.[69] In a second dose-comparison study, patients with persistent breathlessness were given a dose of MIR at 25% or 50% more than their usual 4-hourly dose.[70] There was no difference in the improvement of breathlessness between the two groups. Preliminary data from a small randomised trial comparing fentanyl buccal tablet with morphine sulfate for treatment of episodic breathlessness suggested that fentanyl had a faster onset and provided greater relief.[71] Several small placebo-controlled trials have examined the use of prophylactic fentanyl given prior to exertion in opioid-tolerant patients with cancer and reported a benefit (discussed below).[72–74] Taken together, the available evidence signals that opioids have a positive effect on breathlessness among opioid-tolerant individuals, giving justification for further studies to examine these findings in confirmatory trials and to determine the optimal dose and timing of opioids for breathlessness.

Prophylactic use of opioids prior to exertion among opioid-tolerant patients

Because breathlessness predictably increases with exertion, the use of IR opioids prior to activity (or indeed, the use of sustained-release opioid) may potentially reduce this distressing symptom and thereby maximise activity level.[75] Rapid-onset fentanyl formulations may be appealing for this purpose given their fast onset of action and ease of administration. To date, only a handful of small RCTs have examined the use of opioids in patients with cancer for prophylaxis. Small double-blind, placebo-controlled studies of subcutaneous fentanyl,[72] fentanyl pectin nasal spray[73] and fentanyl buccal tablet[74] showed within-arm improved breathlessness and/or exercise

capacity; however, these studies were not powered for between-arm comparisons. Recently, a dose-finding study suggested the use of higher proportional dose of fentanyl sublingual spray (35%–45% of morphine equivalent daily dose (MEDD)) conferred a clinical benefit in contrast to a lower dose (15%–25% of MEDD) in the prophylactic setting.[76] Outside of the cancer setting, two randomised trials also suggested that nebulised fentanyl may improve dyspnoea during exercise.[77 78] Importantly, the long-term use of rapid-onset fentanyl has not been examined systematically and the risk of addiction with these agents needs to be further investigated. Limited use of prophylactic opioids should only be considered among patients with severe functional impairment and/or distress related to specific activities causing breathlessness and when the benefits likely outweigh potential risks. Larger pragmatic studies are needed to examine how opioids could be used on a prophylactic basis to improve episodic breathlessness.

Choice of opioid

The panel would like to emphasise that there are significant limitations among existing clinical trials on opioids, particularly for people with cancer, which contribute to variable interpretation of these studies. When formulating treatment recommendations, the panel carefully weighed the risks and benefits of opioid therapy based on all available literature, while recognising significant variations in practices across regions. In a patient with severe, debilitating chronic breathlessness at rest or provoked by minimal exertion despite non-pharmacological management, treatment with ER morphine provides the smoothest steady-state where the effect size appears to be greatest, at least in COPD studies. A starting dose in an opioid-naïve patient could be between 5 and 15 mg of ER morphine two times a day,[79] although the doses may need to be lower for selected populations (eg, renal failure). Titration should be tailored to the individual starting with the lowest possible dose. A placebo-controlled dose titration RCT in COPD is expected in 2021.[80] Similar to pain,[81] a rescue dose or IR morphine of about 1/6 of the patient's total daily morphine dose may be considered, if needed. Most research evidence pertains to doses equivalent to 10–30 mg oral morphine per day,[59 61 82 83] and it is unknown if higher doses give further benefit; data are awaited.

Most evidence, including the adequately powered trials, relates to morphine and to people with non-malignant disease. There is emerging evidence for fentanyl and adequately powered trials would be useful to inform use in people with poor renal function, or where different pharmacokinetic profiles may be helpful. Theoretically, opioids given at equianalgesic doses are expected to provide similar levels of benefits on breathlessness; however, some patients may respond better to selected opioids. More research is needed to investigate this. All patients starting opioids should be offered prophylaxis for constipation with laxatives and, as needed, antiemetics. For further discussion of opioid-related adverse effects and principles of safe opioid use see supplemental material available at *ESMO Open* online.

Benzodiazepines

Benzodiazepines are frequently used for the relief of breathlessness in clinical practice, especially when breathlessness is associated with symptoms of anxiety or panic. However, there is currently insufficient evidence from clinical trials to support the use of benzodiazepines for the relief of breathlessness, either in malignant or non-malignant disease.[84] The Cochrane systematic review of Simon *et al* included eight small RCTs, most of them with a unclear risk of bias, that tested the effect of benzodiazepines for the relief of breathlessness in adult patients with advanced disease, out of which 66 had COPD and 148 patients had cancer.[84] Only one trial showed a significant reduction of breathlessness intensity in patients receiving midazolam in comparison with the morphine group, which is conflicting with the result of a second study by the same research team.[85 86] The other seven studies included in the review did not demonstrate any significant difference for benzodiazepines compared with placebo or morphine. Two additional RCTs have been identified both without any significant effect of benzodiazepines for the relief of breathlessness intensity.[87 88]

The most common side-effects of benzodiazepines were drowsiness and somnolence, which were significantly more frequent compared with placebo but less frequent compared with morphine.[84] Patients with cancer having breathlessness are at high risk of delirium, and the use of benzodiazepines may compound this concern.

It has been hypothesised that benzodiazepines may improve the coping capacity or reduce the unpleasantness related to breathlessness by a better coping of anxiety. However, the studies cited above measured intensity of breathlessness alone. There is a need for well-conducted and adequately powered studies measuring predictors and symptoms associated with breathlessness that may be modulated by benzodiazepines.

In the last days of life, some patients may continue to experience severe breathlessness despite maximising all other palliative measures within the limited time frame. In these unique situations, palliative sedation may be considered to alleviate suffering. Benzodiazepines such as midazolam infusion and/or lorazepam may be titrated carefully to reduce consciousness as little as possible while maximising comfort.[89 90] This should only be considered a treatment of last resort and only after careful discussion with patients/families. When given to patients with only days of life expectancy, palliative sedation has not been associated with shorter survival.[91 92]

Corticosteroids

The efficacy of systematic steroids for the relief of cancer-related breathlessness was investigated in a systematic review of two RCTs.[93] The first RCT, a placebo-controlled, double-blind pilot trial, tested the effect of

dexamethasone among 41 patients with cancer on the reduction of breathlessness intensity 'now' as the primary outcome (NRS 0–10, subscale of the Edmonton Symptom Assessment System (ESAS), Modified Dyspnoea Borg Scale).[94] Between-group differences were not statistically significant, although there was a significant within-arm reduction of breathlessness intensity at day 4 in the dexamethasone group of 1.9 on ESAS (95% CI 3.3 to 0.5; p=0.01), whereas the placebo group showed a non-significant reduction of 0.7 (95% CI 2.1 to 0.6; p=0.38). The authors concluded that dexamethasone may provide rapid relief from breathlessness. A larger confirmatory randomised trial is currently under way to examine the effect of dexamethasone on breathlessness in patients with cancer (clinicaltrials.gov NCT03367156).

Several randomised trials have examined breathlessness as a secondary outcome and reported some improvement.[95 96]

There are no published data regarding inhaled corticosteroids in patients with cancer, and although commonly used in people with asthma and COPD, the very different pathophysiological characteristics of the underlying disease would make application of indirect evidence questionable. From clinical experience and biological rationale, the use of steroids for breathlessness due to lymphangitis carcinomatosis or tumour-induced respiratory obstruction may have positive effects, although evidence is insufficient.[97]

Supplemental oxygen

The benefit of supplemental oxygen for relief of breathlessness (palliative oxygen therapy) and for improving physical capacity and activity in daily life has not been established.[98–100] While supplemental oxygen is indicated in patients with chronic severe hypoxaemia (partial pressure of oxygen (PaO_2) <7.4 kPa or peripheral oxygen saturation (SpO_2) <89% at rest) to prolong life,[101] oxygen has not been consistently shown to relieve breathlessness in the palliative setting in patients with mild or no hypoxaemia in advanced disease[98 99] including cancer.[100] Recent guidelines from the British Thoracic Society and the National Guideline for Palliative Care in patients with non-curative cancer in Germany state that palliative oxygen therapy is not indicated in patients with SpO_2 ≥92%, and that other treatments should be considered first, such as treatment of underlying causes, exercise-based rehabilitation, a hand-held fan and opioids.[101] In the largest double-blind RCT to date by Abernethy *et al* of patients with advanced disease (n=239; 16% with cancer) with no or mild hypoxaemia (PaO_2 >7.3 kPa, corresponding to a SpO_2 >88%), there was no difference in breathlessness between supplemental oxygen and room air over 7 days.[98]

However, in patients with chronic breathlessness despite other evidence-based treatments, a trial of supplemental oxygen could be justified,[101] based on indirect data that supplemental oxygen can improve exercise capacity and breathlessness observed during exercise testing in the laboratory for patients with COPD and interstitial lung disease.[99 102] Individualised information and shared decision-making with patients and caregivers are important.[101 103] If tried, supplemental oxygen should be re-evaluated within a few days and discontinued if the patient perceives no benefit.[60 98] Based on RCT data[98] and clinical experience, a cut-off for defining clinically relevant hypoxaemia as SpO_2 <90% is recommended.

High-flow oxygen therapy can deliver up to 60 L/min of humidified and heated oxygen via nasal canulae. To date, only one cross-over RCT study has specifically evaluated its effect on breathlessness in hospitalised patients with cancer in the palliative care setting.[104] This randomised trial found that high-flow oxygen and bilevel positive airway pressure (BiPAP) were both similarly effective in reducing breathlessness. More research is needed to examine its impact on breathlessness, particularly in the home setting.

Non-invasive ventilation

Non-invasive ventilation (NIV) may improve both oxygenation and hypoventilation, while supporting chest wall muscles. In a randomised trial of 200 patients with advanced solid tumours, NIV decreased breathlessness compared with supplemental oxygen, especially in patients with hypercapnia. NIV was associated with lower use of rescue opioid and had an acceptable tolerance and safety profile.[105] Another RCT reported that BiPAP reduced breathlessness by 3.2 (95% CI 1.3 to 5.1) points on a 0–10 NRS.[104] However, some patients could not tolerate the positive pressure and there are multiple contraindications to NIV.

Antidepressants

Depression and anxiety are associated with increased breathlessness.[106 107] Five RCTs (n=336) and three case studies (n=19) investigated antidepressants (nortriptyline, paroxetine, citalopram, sertraline, protriptyline) to relieve breathlessness mostly in patients with COPD.[108–114] The largest randomised trial (n=223) tested sertraline against placebo in patients with chronic breathlessness, of whom around 20% had cancer.[109] None of the RCTs reported any significant improvement in breathlessness with antidepressants. The three case studies reported breathlessness relief by citalopram, sertraline or mirtazapine.[112 113 115] A preliminary trial of mirtazapine shows promise, although further investigation is needed.[116]

Cannabinoids

Few studies of cannabinoids for the relief of breathlessness have been published, evaluating small samples of healthy participants or patients with COPD, with no effect observed.[117 118] A broader clinical experience and adequately powered clinical trials are missing.

Multimodal interventions

Recognition that breathlessness is a multidimensional construct leads to development of multimodal interventions that include both non-pharmacological and

pharmacological treatments. Specialist palliative care teams, because of their interdisciplinary nature and symptom management expertise, may be particularly suited to manage breathlessness.[119 120]

A systematic review of holistic breathlessness services for patients with advanced cancer and non-cancer diagnoses identified 37 articles across 18 different services. Most comprised 4–6 contacts over 4–6 weeks. Commonly used interventions included the hand-held fan, breathing techniques, psychological support and relaxation techniques, although there was significant variation in the structure and processes for these services. Meta-analyses of randomised trials demonstrated reductions in NRS distress due to breathlessness (n=324; NRS mean difference (MD) −2.30, 95% CI −4.43 to −0.16, p=0.03) and Hospital Anxiety and Depression Scale (HADS) depression scores (n=408, MD −1.67, 95% CI −2.52 to −0.81, p<0.001) compared with usual care. Statistically non-significant effects were observed for Chronic Respiratory Questionnaire mastery (n=259, MD 0.23, 95% CI −0.10 to 0.55, p=0.17) and HADS anxiety scores (n=552, MD −1.59, 95% CI −3.22 to 0.05, p=0.06).[20] An analysis of pooled individual datasets (n=259) found outcomes of reduced mastery and distress were influenced by baseline scores for these variables, but not by patient diagnosis, lung function or health status. Therefore stratifying patients by levels of mastery and/or distress due to breathlessness appears appropriate for research and clinical services.[121] In a meta-synthesis of qualitative interviews (n=216), patients and carers accessing breathlessness services valued tailored education, self-management interventions and expert staff providing person-centred, dignified care.[20] These components should be integrated into clinical practice.

Taken together, there is good evidence to support the use of multimodal breathlessness services. However, the availability of these services remains limited. In the absence of such dedicated services, there is good evidence to support that palliative care teams can improve patient and caregiver outcomes.[122–125] Thus, a timely referral is recommended.

The impact of breathlessness on caregivers

There is now a substantial body of data demonstrating that carers of someone suffering from chronic breathlessness experience profound anxiety, isolation, exhaustion and poor sleep. This is heightened when they witness their loved ones having an episode of breathlessness[126 127] and feel powerless to help them. It is also clear that they can become exhausted from the extra physical work and psychological support they need to give to their loved one. There are no comparable controlled data to guide clinical teams on the most effective interventions for carers' stress—although recognition and acknowledgement seem to be useful first steps.[119]

The onset of breathlessness in cancer tends to be over a much shorter period than in other illnesses, giving less time for the patient and carer to adjust to a new reality. It also progresses more quickly (in spite of recent advances in treatment). There are some data to suggest that unscheduled use of clinical services may often be related to carer as well as patient anxiety about seemingly inexplicable breathlessness.

The psychological and physical effects of the stress of caring for a family member with a serious illness like cancer are becoming recognised.[128] Given the significant impact on caregivers, patient and carer may benefit from a joint assessment to examine the impact of breathlessness on their lives. A structured needs-assessment tool such as the Carer Needs Assessment Tool may be helpful.

Psychoeducational interventions may help them manage episodes of breathlessness, exploring what happens at these times with development of a 'ritual' for crises. Where possible these interventions should be delivered as part of a complex interdisciplinary intervention. The best evidence for impact is when they are part of a specialist breathlessness service.[119 120] The limited research to date suggests that these interventions may help reduce anxiety and distress in both patient and carer and mitigate the stress and health impact of long-term caring.[129]

Recommendations

Treat the underlying cause

- Clinicians should identify and treat any potentially reversible condition(s) contributing to breathlessness (II, A*).

Non-pharmacological symptomatic interventions

- Consider use of a hand-held fan directed to the face and inform patients of the potential mechanisms and benefit. This may be useful alone in people without hypoxaemia, or as an adjunct to those requiring oxygen supplementation for hypoxaemia (II, B).
- Advise patients on relevant breathing retraining techniques and/or refer to specialist services such as a physiotherapist (II, B).
- Consider a trial of a mobility aid to assess possible impact on breathing during ambulation and functional activities (II, B).
- Educate and inform patients on strategies including activity pacing, relieving positions and distraction techniques to encourage self-management (II, B).
- Refer patients to available exercise-based rehabilitation programmes, including pulmonary or cardiac rehabilitation for patients with comorbid chronic lung or heart disease (I, A).
- Provide individualised advice on aerobic and resistance exercises, suitable to the patient's functional status and degree of limiting breathlessness (II, B).
- Consider a therapeutic trial of acupressure or acupuncture according to patient preference (II, C).

Pharmacological symptomatic interventions

- Regular, oral, low-dose morphine is the first-line pharmacological treatment for severe chronic

breathlessness, which persists despite non-pharmacological measures (II, B).
- In opioid-naïve patients, a starting daily dose of scheduled morphine 10–30 mg over 24 hours can be used, with individual titration depending on the patient's symptoms (II, B).
- In opioid-tolerant patients, an increase in the baseline dose of opioid by 25%–50% may be considered (V, C).
- In opioid-tolerant patients with severe exertional breathlessness associated with defined triggering situations leading to significant functional impairment and/or distress despite standard treatments, consider prophylactic use of opioids prior to the episodes. Patients should use prophylactic doses sparingly (e.g. ≤2×/day) and only with close monitoring given that the long-term safety risk is not known (II, C).
- All patients starting opioids should be offered prophylaxis for constipation with laxatives and, as needed, antiemetics (I, A).
- Patients on opioids for breathlessness should be educated on safe opioid use and monitored longitudinally with various risk mitigation strategies (III, A*).
- Because of significant risk of sedation and delirium, benzodiazepines should not be used for breathlessness as first-line pharmacological therapy (III, D).
- Benzodiazepines may be used with caution in patients with cancer for the relief of breathlessness with associated anxiety if opioids are not effective (V, C).
- In the last days of life, benzodiazepines may be considered for palliative sedation in patients with refractory breathlessness despite other treatments (IV, C).
- Corticosteroids may be considered for palliation of cancer-related breathlessness refractory to other treatments (II, C).
- Palliative oxygen is not recommended in patients with resting SpO_2 ≥90% (II, D).
- High-flow oxygen therapy may be considered in selected patients for treatment of breathlessness, especially if they have hypoxaemic respiratory failure (II, B).
- A therapeutic trial for NIV can be considered in patients with cancer with severe chronic breathlessness, especially in patients with acute hypercapnic respiratory failure (II, B).
- Sertraline is not recommended for chronic breathlessness (II, D).
- The use of other antidepressants for breathlessness should only be limited to the clinical trials context at this time (V, C).
- The use of cannabinoids for chronic breathlessness is not recommended given the insufficient evidence and potential adverse event profile (IV, D).

Multimodal interventions

- Patients with cancer with chronic breathlessness should be referred to specialist multimodal breathlessness services if available (I, A).
- Timely referral to palliative care services should be considered in centres in which holistic breathlessness services are not available (II, B).

The impact of breathlessness on caregivers

- The oncology team should routinely assess the psychological status, information needs, and support network for carer(s) of breathless individuals with cancer (III, B*).
- A properly implemented caregiver needs-assessment tool may be helpful (II, B).
- Consider making referrals to specialist breathlessness services for patients suffering from breathlessness and their carers (I, A).

METHODOLOGY

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in online supplemental table S1), available at *ESMO Open* online.[130] 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.

Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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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.

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