



## Evidence Summary SMG-3

A Quality Initiative of the  
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

# Guidelines on Management of Dyspnea (Breathlessness) in Patients with Cancer

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# Guidelines on Management of Dyspnea (Breathlessness) in Patients with Cancer

## Evidence Summary

### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated programs is editorially independent from the OMHLTC.

### RESEARCH QUESTION

The research question was developed to direct the search for clinical practice guidelines:

- What are the most appropriate treatments for alleviation of dyspnea (breathlessness) in patients with cancer?

### TARGET POPULATION

The target population is adult patients with cancer experiencing dyspnea. Acute symptoms induced by the current cancer treatment (chemotherapy, radiotherapy) were considered outside the scope.

### INTENDED PURPOSE

CCO developed a series of symptom treatment algorithms in the period 2009-2012. These were mostly based on corresponding Guide-To-Practice documents consisting of reviews of clinical practice guidelines (<https://www.cancercareontario.ca/en/symptom-management>). The current evidence summary was developed to assist the Patient Reported Outcomes and Symptom Management Program of CCO in revising the algorithm on dyspnea [1]; its evidence base was a systematic review of guidelines [2] until January 2009. The 2010 algorithm is based on Fraser Health's Hospice Palliative Care Program Symptom Guidelines: Dyspnea (2009); Oncology Nursing Society's Putting Evidence into Practice: Evidence-Based Interventions for Cancer-Related Dyspnea (2008 version); and the PEBC/CCO's Management of Dyspnea in Cancer Patients: A Clinical Practice Guideline (2006). The Oncology Nursing Society guideline was updated in 2017 [3], in 2012 the PEBC/CCO document was designated as Education and Information only (no longer current or maintained), and the Fraser Health document is still online but not revised.

## INTENDED USERS

The intended users of this evidence summary are staff of the Patient Reported Outcomes and Symptom Management Program. This evidence summary may also be of interest to physicians, nurses, caregivers, and patients dealing with cancer or palliative care symptom management.

## METHODS

This evidence summary was developed by a Health Research Methodologist (HRM) at PEBC at the request of the Patient Reported Outcomes and Symptom Management Program of CCO. The HRM was responsible for reviewing the identified guidelines and drafting the summary. The HRM had no conflicts of interest ([Appendix A](#)).

This evidence summary is based on a systematic review on the topic of dyspnea in adult patients with cancer, limited to clinical practice guidelines that are based on systematic reviews of the literature.

### Literature Search Strategy

The systematic search for guidelines was conducted in two stages. In the first stage, websites of organizations known to have produced cancer-related guidelines were reviewed in February to March 2018. As it was anticipated that all the symptom management algorithms listed in the Introduction would eventually be updated, guidelines with management of any symptoms of interest were noted, along with the symptom(s) covered; only those guidelines relevant to the current evidence summary were added to the Endnote database and summarized in this document. Organizations included those identified from guideline databases (Cancer Guidelines Database,<sup>1</sup> Canadian Partnership Against Cancer; National Guidelines Clearing House; Canadian Medical Association CPG Infobase), those with cancer-related guidelines identified in the pain evidence summary in this series [4], and those known to be major cancer guideline developers (e.g., CCO, American Society of Clinical Oncology [ASCO], Alberta Health Services, Cancer Australia, National Institute for Health and Care Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN]). A list of organizations is provided in [Appendix B](#). For guidelines that appeared to have several versions, the latest version was used and earlier versions excluded. Guidelines based primarily on outdated versions of guidelines by other organizations were also excluded.

The second stage of the systematic search was conducted using MEDLINE, Embase, Allied and Complementary Medicine (AMED), and Emcare on July 10, 2018. The search included terms for a) cancer, b) dyspnea, and c) guidelines. The search strategy is reported in [Appendix C](#). Results were limited to publications since January 2009.

During review of publications found in the above searches, other guidelines cited were looked at, and websites of organizations mentioned to have relevant guidelines (if not already included in the initial search) were also reviewed. For included guidelines, websites of the organizations were reviewed to ensure the latest version was used.

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<sup>1</sup> The Cancer Guidelines Database (CGD) was released in 2018; it updates and replaces the Standards and Guidelines Evidence directory (SAGE). SAGE was used in the initial search, but is no longer available.

## Study Selection Criteria and Process

For inclusion, publications needed to include recommendations regarding assessment or management of dyspnea in adult patients with cancer. Only guidelines in English were included; guidelines with English summaries including the recommendations were considered if other details were also given and quality could be assessed. A systematic literature review had to be conducted and, where evidence was found, be the basis of the recommendations. Guidelines without a systematic review were excluded. In determining whether a systematic review was conducted, criteria such as an explicit statement of a systematic review along with databases searched, or databases searched plus time period, search terms, and results had to be reported. Some evidence-based guidelines included a literature search but it was unclear whether a systematic review was conducted.

It was considered outside the scope of the evidence summary to address in detail the management of patients experiencing acute adverse effects secondary to systemic therapy or radiation therapy; however, chronic symptoms as a result of treatment were considered within scope.

Guidelines dealing only with initial treatment of the disease were excluded, although those focused on palliative treatment for symptom management were kept. Also excluded were publications of clinical trials, case reports, non-systematic reviews, reviews without recommendations, or guidelines focused only on children. Guidelines focused on low/middle income countries or other resource-limited applications were also excluded. Guidelines only available to paying members of the development organization were also excluded. A review of the titles and abstracts that resulted from the search was conducted by one reviewer (GGF). For items that warranted full-text review, one reviewer (GGF) reviewed each item.

National Comprehensive Cancer Network (NCCN) guidelines are evidence-based consensus guidelines that are regularly updated, comprehensive, and frequently used. Most do not have an explicit systematic review and the linkage between recommendations and evidence is poor. They do not generally meet criteria for inclusion or endorsement by the PEBC. It was decided that NCCN guidelines specifically on symptom management would be reviewed; guidelines on treatment or management of cancer itself would not be looked at.

## Guideline Assessment

The AGREE II is a tool to assess the quality and reporting of practice guidelines [5,6], and consists of 23 questions in six domains. The Rigour of Development (RoD) domain is sometimes used for an initial screening; for example, Walton et al. [7] used this domain and selected a threshold score of 50 for inclusion. This domain includes a set of questions related to the guideline development process (see headings in [Appendix D](#)) and was used in the current evidence summary. Lower marks may reflect that an item was not included in the guideline process, or that the publication(s) did not report sufficient details. When guidelines referred to other documents as part of the methods, such as separately published systematic reviews or guideline development procedures, these were considered in the evaluation. Domain scores were calculated as a percentage of the maximum possible score for that subset of questions:  $(\text{obtained score} - \text{minimum possible score}) / (\text{maximum possible score} - \text{minimum possible score})$ .

Because of the large number of guidelines, only one rater from PEBC evaluated each guideline. For guidelines included in the pain evidence summary [4], ratings have been copied from that document. The remaining guidelines were rated for this summary (GGF). Some of the guidelines were also rated by CGD and these additional RoD scores have been included in Table 1.

Ratings for each question are subjective and scores may vary according to who is conducting the rating. The scores reported, therefore, may be useful in giving a general

grouping (e.g., high vs. low quality) but not an absolute ranking. Ratings were not used as a method of including or excluding guidelines from this literature review.

## RESULTS AND DISCUSSION

### Dyspnea Definition and Background

The American Thoracic Society [8,9] defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses.” Other terminology for dyspnea includes breathlessness, difficult breathing, and shortness of breath.

In advanced (metastatic) cancer, dyspnea has been reported in 53% of patients, with the highest rates (74%) in patients with lung cancer [10]. Dyspnea is more frequent and severe in patients with pulmonary, pleural, or mediastinal involvement, and tends to increase over time.

The first principle arising from the various guidelines is that the underlying cause of dyspnea needs to be identified and treated if possible [10]. There are often comorbidities and it should not be assumed that dyspnea in a cancer patient is necessarily due to the cancer itself. Causes other than cancer will be mentioned briefly in the following sections, but the user should consult guidelines on specific conditions for guidance on diagnosis and treatment. Dyspnea that persists despite optimal treatment of the underlying cause or condition is considered refractory and may be treated symptomatically [10,11]. Most of the guidelines either deal with non-refractory dyspnea treatment (e.g., surgery or radiotherapy) or with palliative symptom management (e.g., use of opioids), but do not cover both areas.

### Overview of Search Results

From the search of organization websites, 44 publications that included dyspnea were identified. Of these, 17 publications (16 guidelines) were determined to meet the inclusion criteria. The search of MEDLINE, Embase, AMED, and Emcare (after removing duplicates and publications already located from the website search) resulted in 538 publications, of which 1 publication met the inclusion criteria. During the review process additional guidelines were identified; those that did not meet the inclusion criteria are not included in the numbers above. One additional included guideline was identified from reference lists or other sources. The 18 included guidelines are summarized in [Table 1](#) [3,10,12-28].

Characteristics of each guideline including the organization that created or approved the guideline, citation, and the general topic have been extracted. Notes include more details of the topic and major concepts covered, details of the systematic review including databases (an indication of how comprehensive the search was), and time period searched (indicating how recent the evidence is). These guidelines are discussed in the following sections. Results of the guideline assessment RoD are given in [Appendix D](#).

A selection of other guidelines of potential interest, including those often cited or used in the preparation of previous versions of the CCO algorithm, but not meeting the inclusion criteria are summarized in [Appendix E](#) [29-57]. This includes guidelines determined during full-text review to not be based on systematic reviews, and guidelines relevant to dyspnea in other diseases such as chronic obstructive pulmonary disease (COPD) that often occur as comorbidities with cancer, but that do not have specific recommendations for patients with cancer. Some rationale for mentioning specific guidelines is given in subsequent sections. As

the literature search was not designed to locate these guidelines, additional guidelines on these topics may exist. The list for COPD is more extensive, with several of the guidelines identified from references in other guidelines.

### **Guidelines Focused on Dyspnea or Symptom Management**

The guideline by the Japanese Society for Palliative Medicine covers palliative interventions for respiratory symptoms in cancer and is probably the most comprehensive for the therapies it covers. The English version [12] summarizes recommendations for the 26 clinical questions, along with some rationale; the full guideline is available in Japanese [58]. The guideline focuses mostly on dyspnea, with smaller sections on malignant pleural effusions, cough, and death rattle. It notes that at the time of development there were no other guidelines that covered the topics comprehensively and based on a formal guideline development process. For dyspnea, it includes use of oxygen therapy, opioids, benzodiazepines, and corticosteroids. For malignant pleural effusion it covers thoracentesis with drainage, and pleurodesis; diuretics are not recommended. Other guidelines specifically on malignant pleural effusion provide more detailed guidance on this topic and are discussed in a subsequent section of this evidence summary. It does not cover radiotherapy or other non-pharmaceutical approaches.

The German S3 guideline on palliative care in incurable cancer [10] focuses on seven topics, including breathlessness, with a second part on additional symptoms still being completed. The “short” version in English (98 pages) includes recommendations and background text, with the full version only in German. The target patient population is adult patients with incurable cancer with the primary goal to improve quality of life. There are several recommendations or statements on principles of palliative care, including the need for a multi-professional interdisciplinary approach with realistic therapy goals. It is necessary to consider differential diagnosis for the cause of symptoms to target therapy and determine reversible causes, with treatment of the latter if possible and appropriate. Treatment may be used alone or together with tumour-specific therapies such as radiotherapy and surgery, which are outside the scope of the guideline. The guideline only deals with assessment and symptomatic treatment, primarily with opioids (with addition of benzodiazepines if required). Non-pharmacological therapy may include relaxation, breathing exercises, cool air flow with a hand-held fan, and use of a walker or other aids to support mobility.

The Alberta Health Services guideline [13] covers superior vena cava obstruction (SVCO, from cancer) and malignant airway obstruction, both of which may result in dyspnea. Approximately 85% to 90% of SVCO is caused by cancer, mostly from lung cancer and a smaller proportion from lymphomas and leukemias. Sudden-onset SVCO should be considered a medical emergency [59]. Although the title suggests it focuses on radiotherapy (external beam radiotherapy [EBRT], brachytherapy), it also lists other options (chemotherapy or stents for SVCO; photodynamic therapy, surgical or bronchoscopic debulking, Nd-YAG laser treatment, stents for airway obstruction). It does not cover the short-term palliative treatments used in the Japanese guideline.

The British Thoracic Society has guidelines for use of oxygen at home [14] and in healthcare or the emergency setting [15]. They indicate that oxygen is a treatment for hypoxemia, not breathlessness. Other treatments such as opioids or non-pharmaceutical treatments such as fan therapy should be used for dyspnea if the patient is non-hypoxemic. Palliative oxygen along with formal assessment of its effect may on occasion be considered by a specialist team for patients unresponsive to all other therapies.

The NICE guideline [16] deals with care in the last days of life and is not specific to patients with cancer; however, patients with cancer comprise a large portion of this patient population. It indicates to treat reversible causes such as pleural effusion or pulmonary

edema, use oxygen only if symptomatic hypoxemia, and consider an opioid and/or a benzodiazepine. No further details are given and therefore it is less useful than some of the other guidelines listed in this section.

The guideline on dyspnea in cancer from the Putting Evidence into Practice series by the Oncology Nursing Society [3] includes literature until January 2017. The recommendations include several topics that were not part of the literature search strategy. It lists agents by strength of evidence and recommendation, then citations to supporting evidence, but provides no further analysis or guidance as to when or how to use specific interventions. The user would need to read items on the list of citations for each treatment, and therefore its use appears mainly as a list of suggested readings on each topic. It is unique in that it includes a category of treatments for which effectiveness has not been established. Methodology is much less rigorous than for the Japanese guideline. It does not include the treatments included in the Alberta guideline. Categorization of several treatments is questionable as they are not consistent with other guidelines, some evidence is not from cancer, and for some topics important citations are missing.

Some other guidelines of possible interest but not meeting all the inclusion criteria are in [Appendix E](#). The European Society for Medical Oncology (ESMO) has guidelines on treatment of dyspnea in patients with advanced cancer [60] and on palliative sedation for management of refractory symptoms at the end of life [37]. The NCCN guideline on palliative care [33] contains two charts on dyspnea, one to deal with patients with a life expectancy longer than a few weeks, and one to deal with patients with a life expectancy of less than several weeks (dying patients).

### **Guidelines Focused on Specific Cancers**

The other guidelines included in [Table 1](#) deal with specific cancers and include a section on dyspnea.

#### ***Upper Aerodigestive Tract Cancer***

The recommendations for dyspnea in the NICE guideline on upper aerodigestive tract cancer [18] are based on clinical experience as the systematic review found no evidence meeting the inclusion criteria for this topic. This was a small portion of the guideline. It recommends endoluminal debulking in preference to tracheostomy, development of a management plan if surgical intervention is inappropriate, and treatment of other causes of dyspnea.

#### ***Lung Cancer***

The Cancer Council Australia guideline on lung cancer [22] is distributed in WIKI format with periodic updating of different sections. Dyspnea is included in the Palliative Care section, with evidence-based recommendations for opioids and intranasal oxygen. Practice points (based on lower-quality evidence) are included for use of non-pharmacological strategies such as breathing retraining, simple relaxation, activity pacing and psychosocial support; and for benzodiazepines as second- or third-line therapy when opioids and non-pharmacological measures have failed. Malignant pleural effusions (8 recommendations and 10 practice points on use of pleurodesis, pleural catheters, chemotherapy, radiofrequency ablation, and decortication) are included in the Supportive Care section.

The American College of Chest Physicians [25] has a series of updated (3<sup>rd</sup> edition) and often cited guidelines on lung cancer, including one on symptom management. Recommendations for airway obstruction include use of therapeutic bronchoscopy employing mechanical debridement, brachytherapy, tumour ablation, or airway stent placement. A table includes use of laser, electrocautery, argon plasma coagulation, cryotherapy, and

photodynamic therapy for endoluminal airway obstruction; these are not specified in the recommendation, but may be examples of tumour ablation. The guideline also has major sections on superior vena cava syndrome (chemotherapy, radiation therapy, and stents) and malignant pleural effusions (tunneled pleural catheters or graded talc pleurodesis, thoracoscopy if diagnosis not confirmed). It is disconcerting that for the topic of dyspnea it makes no recommendations, and instead refers the reader to the previous (2<sup>nd</sup> edition, 2007) version which is no longer on the organization's website and therefore assumed not current. It lists three other resources: one by Vancouver Island Health Authority that is no longer available; the Canadian Thoracic Society guideline on Dyspnea in COPD [55]; and an integrated review of systematic reviews in respiratory illness [61]. The latter did not include cancer in the search strategy; most reviews were on interventions for asthma and COPD.

The American Society for Radiation Oncology (ASTRO) guidelines on palliative thoracic radiation in non-small cell lung cancer [19,20] provides guidance on EBRT, endobronchial brachytherapy, and concurrent chemoradiotherapy for palliative thoracic treatment of symptoms caused by locoregional growth of the tumour. This includes hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, dysphagia related to esophageal compression, superior vena cava syndrome, hoarseness, or stridor. It does not cover non-radiotherapy treatments. The PEBC/CCO guideline [24] is even narrower, dealing only with use of brachytherapy for symptom palliation.

The SIGN guideline on management of lung cancer [23] indicates palliative thoracic radiotherapy is recommended for patients with thoracic symptoms who are not suitable for radical radiotherapy.

The National Clinical Effectiveness Committee (Ireland) guideline [21] is based on the NICE guideline [26] as well as a more recent UpToDate review. The only relevant recommendation is to consider bronchoscopic debulking, tumour ablation modalities, airway stent placement, and radiotherapy (EBRT or brachytherapy) for symptoms of malignant airway obstruction (dyspnea, cough, and hemoptysis). There is some general discussion about each technique but no details.

The NICE guideline on lung cancer [26] is very limited regarding treatment of breathlessness, only saying to consider non-drug interventions based on breathing control, coping strategies, and psychosocial support. It has recommendations for symptoms of pleural effusion (use aspiration or drainage, pleurodesis) and SVCO (chemotherapy and radiotherapy, stent insertion), although specific symptoms such as dyspnea are not mentioned. No details of any of these treatments are provided. A partial update is in progress but will not cover these topics.

### ***Malignant Pleural Mesothelioma***

The main cause of malignant pleural mesothelioma is exposure to asbestos [27]. Chest pain and dyspnea are the most common symptoms; weight gain, fever, and sweats may also occur. Pleural effusion is a frequent clinical sign.

The British Thoracic Society published a guideline this year (2018) on malignant pleural mesothelioma [27]. It has sections on use of surgery, systemic therapy, and radiotherapy in oncological management (including palliative). It contains a section on pleural fluid management with recommendation to use talc (via slurry or poudrage) or indwelling pleural catheters in preference to surgery for fluid control. Its systematic review found no randomized controlled trials on symptom management specific to malignant pleural mesothelioma, and therefore suggests symptoms be managed as per current guidelines for cancer in general, including use of sustained release morphine, and breathing control, and use of fans.

The guideline issued jointly by the European Respiratory Society and the European Society of Thoracic Surgeons is also commonly cited, although it is from 2010 and thus much less current [28]. It includes surgery, radiotherapy (use only in clinical trials), and chemotherapy as treatment. For control of breathlessness it recommends pleurodesis with sterile talc, repeated aspiration or indwelling drainage in frail patients, low-dose oral morphine, and oxygen if reduced oxygen saturation. Other measures include use of a fan and self-help breathlessness management techniques (evidence from lung cancer only). Other recent guidelines in [Appendix E](#) (not systematic reviews) include those by ESMO [41] and a consensus guideline by The Austrian Mesothelioma Interest Group [39,40].

### ***Malignant Pleural Effusions***

Pleural effusion develops in approximately one-half of patients with metastatic cancer, with the most common cancers (in decreasing order) being lung cancer, breast cancer, lymphoma, ovarian cancer, and gastric cancer [43]. Approximately 80% to 95% of patients with malignant mesothelioma have large pleural effusion at diagnosis, and this is the most common primary pleural malignancy associated with pleural effusion. Guidelines by the American College of Chest Physicians [25] and Cancer Council Australia [22] include sections on treatment of malignant pleural effusion and have been summarized in earlier sections. The guidelines on malignant pleural mesothelioma may also be relevant.

### **Treatment-Related Dyspnea**

Radiation pneumonitis and radiation fibrosis may occur in patients who have had thoracic irradiation for lung, esophageal, breast, or hematologic malignancies [62,63]. Symptoms include dyspnea, cough, and low-grade fever. Some systemic treatments may also result in lung toxicity including dyspnea [64]. While this is well-known for some agents such as bleomycin, anthracyclines, and taxanes, rare or atypical presentations are possible and a database such as that by Camus at the University of Dijon (France) may be consulted [65]. Effects may be greater with combination chemotherapy, and with concurrent chemoradiotherapy. Further discussion is beyond the scope of this evidence review.

Immune-related adverse effects from immunotherapy using immune checkpoint inhibitors that target PD-1 (e.g., pembrolizumab, nivolumab), PD-L1 (e.g., atezolizumab, avelumab, durvalumab), or CTLA-4 (e.g., ipilimumab) often appear within three months, but have been reported months, or sometimes years, after treatment is complete [36,66]. While strictly these are treatment-related, the connection may be less apparent due to this potential delay in symptoms, and it is considered relevant to mention in this section. The ASCO guideline [17] on immune-related adverse effects includes a systematic review, but recommendations are primarily based on consensus due to limited information being available. The section on lung toxicity indicates pneumonitis is the most common lung effect and may occur 2 to 24 months after treatment; 53% of affected patients have dyspnea, 35% cough, 12% fever, and 7% chest pain. Pleural effusion and dyspnea may also be associated with cardiovascular toxicity. Guidelines (not based on systematic reviews) by ESMO [36] and CCO [67], and the review by Postow et al. [68] also deal with adverse effects.

### **Non-Cancer Causes of Dyspnea**

In patients with cancer, dyspnea may result from the cancer and/or from other non-cancer diseases, including COPD, cardiac disease, anemia, and pulmonary hypertension, embolism, or fibrosis. As mentioned earlier, the underlying disease should be diagnosed and treated if possible, instead of just using a general treatment for dyspnea. There appears to be some association between lung cancer and COPD, and smoking is a risk factor for both.

Several recent guidelines on COPD exist (see [Appendix E](#)), including those by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [47], Lung Foundation Australia/Thoracic Society of Australia and New Zealand (based largely on GOLD) [48], the Canadian Thoracic Society [53,55,56], American College of Chest Physicians/Canadian Thoracic Society [54], and the European Respiratory Society/American Thoracic Society [51,52]. The 2010 NICE guideline [49] is being updated, with a draft for comment currently available and the final document expected December 2018 [50]. Miravittles et al. have also compared several guidelines from Europe and Russia [57]; several are not in English, and differences are at least in part due to the wide time variation in which they were completed. The GOLD guideline indicates that “in general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated per usual standards regardless of the presence of COPD.”

### **Dyspnea Assessment and Guideline/Algorithm Implementation**

The German guideline [10] listed in [Table 1](#), as well as others in [Appendix E](#), indicate the necessity of assessing dyspnea and treating any underlying causes. Once a guideline is prepared, there are often issues related to implementation. Randomized clinical trials are often not the optimal study design to give guidance in these areas, and therefore guidelines based on systematic reviews such as are the evidence base for this summary may not adequately address these issues. Recommendations on the topic of assessment in the German guideline [10] were derived by expert consensus. The American Thoracic Society also has an official statement on assessment and management of dyspnea [9] and a workshop report on assessment and management of dyspnea crisis [69]. Additional guidelines that may be of interest are included in [Appendix E](#).

The previous version of this algorithm relied on Fraser Health’s Hospice Palliative Care Program Symptom Guidelines: Dyspnea (2009) for patient assessment [32]. The Fraser Health document included a literature search until 2006, although not a systematic review; only the page on end of life was updated in 2009. The assessment mnemonic O,P,Q,R,S,T,U,V has been reproduced in several Canadian guidelines; the assessment and diagnosis of dyspnea sections may still be useful. Due to methodology and age of the guideline, some treatment recommendations are likely not optimal and should only be used in conjunction with other more recent and comprehensive guidelines.

It appears that the Fraser Health documents may be replaced by the B.C. Inter-Professional Palliative Symptom Management Guidelines prepared by the BC Centre for Palliative Care and completed in 2017 [70]. This work had the goal of creating a provincial set of palliative symptom management best practice guidelines informed by evidence until May 2016 and endorsed by each health authority in B.C. The Fraser Health guidelines served as a foundation for the work. Scope was limited to end of life symptoms, with an audience of nurses and physicians without palliative specialization. The assessment mnemonic O,P,Q,R,S,T,U,V was included. As these symptom management guidelines excluded topics relevant to only one disease (such as cancer) and are not specific to cancer, some recommendations may conflict with those of guidelines in [Table 1](#).

CCO conducted pilot studies on treatment of dyspnea and the report outlines several issues in implementing dyspnea care [71,72].

### **SUMMARY AND SUGGESTIONS FOR USE OF THIS REVIEW**

For the purpose of updating the symptom management algorithms by the Patient Reported Outcomes and Symptom Management Program, it is suggested that the most recent

broad or comprehensive guidelines (i.e., covering the full topic area) be considered first, with recommendations then supplemented or modified by recommendations in guidelines of narrower scope, but which may be more appropriate in specialized circumstances. For the topic of dyspnea in patients with cancer, no comprehensive guidelines were located. Based on the information summarized in the previous sections, 11 guidelines considered by the author to be the most relevant are as follows:

- a) Refractory Dyspnea
  - Japanese Society for Palliative Medicine, 2016 [12]
  - German Guideline Program in Oncology, 2015 [10]
  - Cancer Council Australia (lung cancer), 2014 (update to 2017) [22]
  - British Thoracic Society (oxygen use), 2015 and 2017 [14,15]
- b) Malignant Airway Obstruction
  - Alberta Health Services (palliative radiotherapy; includes others), 2016 [13]
  - American College of Chest Physicians, 2013 [25]
  - ASTRO (radiotherapy only), 2011 (endorsed 2018) [19,20]
  - PEBC/CCO (brachytherapy only), 2005 (endorsed 2018) [24]
- c) Superior Vena Cava Obstruction/Syndrome
  - Alberta Health Services (palliative radiotherapy; includes others), 2016 [13]
  - American College of Chest Physicians, 2013 [25]
  - ASTRO (covers radiotherapy only), 2011 (endorsed 2018) [19,20]
- d) Malignant Pleural Mesothelioma
  - British Thoracic Society, 2018 [27]
  - European Respiratory Society/European Society of Thoracic Surgeons, 2010 [28]
- e) Malignant Pleural Effusions
  - American College of Chest Physicians, 2013 [25]
  - Cancer Council Australia, 2014 (update to 2017) [22]

## **INTERNAL REVIEW**

The evidence summary was reviewed by the Assistant Director of the PEBC.

## **APPROVAL BY SPONSORS**

After internal review, the report was approved by the Patient Reported Outcomes and Symptom Management Program of CCO.

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- Ruth Chau for conducting an AGREE evaluation on some of the included guidelines.
- Sara Miller for copy editing.

Table 1. Guidelines Relevant to Dyspnea Meeting the Inclusion Criteria

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
Focus on dyspnea or symptom management				
Japanese Society for Palliative Medicine	Yamaguchi, 2016 [12]	Palliative interventions for respiratory symptoms in cancer	PubMed, Cochrane, Ichushi-Web of the Japan Medical Abstracts Society for Japanese articles until Aug 2014 Covers dyspnea (largest section), malignant pleural effusions, cough, death rattle Summary of recommendations, rationale, development process; full guideline in Japanese [58]. Update in progress (started Jul 2018)	71 (GGF)
German Guideline Program in Oncology	German Guideline Program in Oncology, 2015 [10]	Palliative care in incurable cancer	Systematic review: S3 guideline, methods on website [73,74] MEDLINE, Embase, Cochrane; search date depended on topic (May 2011 to March 2012); updated in MEDLINE if more than one year before consensus conferences (Nov 2013 to Apr 2014); full search strategies reported	73 (GGF)
Alberta Health Services (RT-005)	Alberta Health Services, 2016 [13]	Palliative radiotherapy for dyspnea, superior vena cava obstruction, hemoptysis	This update systematically searched PubMed Jan 2012-Dec 2014; search terms reported. Guideline methodology book available [75] Focus is radiotherapy for symptoms caused by cancer, although it also mentions other treatments	48 (GGF)
British Thoracic Society	Hardinge, 2015 [14]	Home oxygen use	Systematic review: MEDLINE, Embase, Cochrane, DARE 1980-July 2012 and updated Jan 2014; search strategy in appendix online Patients with long-term respiratory illnesses or others prescribed oxygen therapy (COPD, cardiac failure, cancer, end-stage cardiorespiratory disease, terminal	71 (GGF)

<sup>2</sup> AGREE II Rigor of Development sub-scale score (see Methods section and Appendix D). Reviewer initials or source are next to RoD score; CGD, Cancer Guidelines Database (Canadian Partnership Against Cancer); GGF, Glenn George Fletcher; RC, Ruth Chau [4].

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
			illness, cluster headache); most evidence comes from COPD	
British Thoracic Society Emergency Oxygen Guideline Group	O'Driscoll, 2017 [15]	Oxygen use in healthcare and emergency setting	Search details in appendix: MEDLINE, Cochrane, DARE until Nov 2011 and rerun Aug 2013; search strategy reported; is 2016 update of 2008 guideline  Overall philosophy: oxygen is a treatment for hypoxemia, not breathlessness	79 (GGF)
Oncology Nursing Society	Shelton, 2017 [3]	Dyspnea in cancer	Systematic review: searched PubMed, CINAHL, Cochrane Collaboration, NCCN Jan 2009 to Jan 2017. Search terms, inclusion/exclusion criteria reported. Guideline process described in separate paper [76]	27 (GGF)
National Clinical Guideline Centre, National Institute for Health and Care Excellence (NICE NG31)	NICE, 2015 [16]	Care in last days of life	Systematic review using MEDLINE, Embase, Cochrane Library until Nov 2014; PsycINFO and CINAHL for some questions (see [77] for details)	85 (RC)
American Society of Clinical Oncology (ASCO)	Brahmer, 2018 [17]	Immune checkpoint inhibitor adverse events	Systematic review: PubMed, Embase, Cochrane Register of Control Trials, 2000-2017; used informal consensus due to limitations of available evidence  Section on lung toxicity, primarily pneumonitis which may occur 2-24 months after treatment; symptoms include dyspnea (53%), cough (35%), fever (12%), chest pain (7%); hypoxia may lead to respiratory failure  Sarcoid-like granulomatous reactions and pleural effusions have also been reported  Dyspnea and pleural effusion may also be associated with cardiovascular toxicity	40 (GGF)
<b>Focus on management of specific cancer</b>				
National Institute for Health and Care Excellence (NICE NG36)	NICE, 2016 [18]	Upper aerodigestive tract cancer	Systematic review (see [78] for full guideline and methods, Appendix H for evidence review): Cochrane, MEDLINE, Embase, Web of Science, Social Sciences Citation Index until May 2015  MEDLINE search strategy reported, was adapted for	79 (GGF) 86 (CGD)

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
			<p>other databases</p> <p>The review identified no evidence for dyspnea that met the inclusion criteria of the review, therefore recommendations are based on clinical experience</p> <p>Recommendations include the need to identify those at risk of airways obstruction for whom intervention is appropriate, endoluminal debulking in preference to tracheostomy, and to treat other causes of breathlessness</p>	
American Society for Radiation Oncology (ASTRO)	Rodrigues, 2011 [19] Moeller, 2018 [20]	Non-small cell lung cancer: palliative thoracic radiotherapy of symptoms caused by locoregional growth of the tumour	<p>2011 guideline: PubMed 1966-March 2010;</p> <p>2018 guideline PubMed Mar 2010-July 2016 updated question of chemoradiotherapy; it found no new evidence for questions on EBRT or brachytherapy and these were not revised</p> <p>Found benefit for EBRT palliation, no role for routine brachytherapy as initial palliative treatment but an option if EBRT failed or for patients requiring lung re-expansion before or in conjunction with radical RT</p>	85 (GGF)
National Clinical Effectiveness Committee (Ireland)	National Cancer Control Programme Guideline Development Group, 2017 [21]	Lung cancer: diagnosis, staging, treatment	<p>Systematic review: MEDLINE, Cochrane, Embase (where available), others as appropriate; updated in 2016 prior to publication; search strategy reporting is required according to their protocol, but was not included.</p> <p>One relevant recommendation on palliative interventions (based on NICE, 2011 [26] and an UpToDate review) is that bronchoscopic debulking, tumour ablation modalities, airway stent placement, and radiotherapy (external beam or brachytherapy) may be considered</p>	54 (GGF)
Cancer Council Australia	Cancer Council Australia Lung Cancer Guidelines Working Party, 2014 [22]	Lung cancer: treatment	<p>Wiki format, relevant sections</p> <p>Systematic review in different appendix for each question, guideline development document available [79]</p> <p>Dyspnea included in section on palliative care,</p>	85 (RC) 78 (CGD)

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
			<p>recommendations last reviewed Dec 2015. Searched Cochrane, PubMed, Embase 2002-2011; monthly Embase updates until Feb 2017</p> <ul style="list-style-type: none"> <li>• Opioids in NSCLC; oxygen or air intranasally; non-pharmacological strategies (breathing retraining, relaxation, activity pacing, psychosocial support); benzodiazepines as second- or third-line therapy</li> </ul> <p>Malignant pleural effusions: Embase, PubMed 2002-2012, plus updates (Embase Sept 2017; PubMed Nov 2017); recommendations last reviewed Jan 2017</p> <ul style="list-style-type: none"> <li>• Drainage with long-term catheters; pleurodesis with talc slurry as sclerosant; pleurectomy/decortication in selected patients</li> </ul>	
Healthcare Improvement Scotland (SIGN 137)	Healthcare Improvement Scotland, 2014 [23]	Lung cancer: management	<p>Systematic review: MEDLINE, Embase, CINAHL, PsycINFO and the Cochrane Library 2005-2012</p> <p>Recommends palliative RT if not suitable for radical RT; advises patients with lung cancer to stop smoking</p>	<p>75 (RC) 90 (CGD)</p>
Program in Evidence-Based Care/Cancer Care Ontario (7-16)	Ung, 2018 [24]	Non-small cell lung cancer: brachytherapy for symptom palliation	<p>2005 guideline endorsed in 2013 and 2018 (new studies appended but recommendations not updated)</p> <p>Systematic review: MEDLINE and Embase until Sept 2017; search strategy reported</p> <p>Recommends EBRT; high dose rate endobronchial brachytherapy for recurrent disease or in selected patients; treatment alternatives to brachytherapy include EBRT, Nd-YAG laser therapy, photodynamic therapy (PDT), and surgical core-out procedure. Evaluation of these alternatives was outside the scope of the guideline.</p>	<p>56 (GGF) 69 (CGD)</p>
American College of Chest Physicians	Simoff, 2013 [25]	Lung cancer: symptom management	<p>Systematic review: methodology in [80]. Searched MEDLINE, CINAHL, PsycINFO, Cochrane, Embase, Web of Science, Google Scholar; searches until 2012 (based on date of included articles) and extended back more than 10 years (stated in methodology)</p> <p>Dyspnea topic has no recommendations; indicates it is</p>	<p>73 (RC) 59 (CGD; 68 for methodology document)</p>

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
			<p>covered in detail in 2007 guideline plus 2008 Vancouver Island Health Authority guideline, and reviews on COPD [55] and breathlessness in respiratory illness [61]. It notes that a comprehensive evaluation of treatable causes (COPD, cardiac disease, airway obstruction, pleural disease, hematologic conditions, nutritional deficits, neuromuscular conditions) is necessary.</p> <p>It has sections on</p> <ul style="list-style-type: none"> <li>• Airway obstruction: therapeutic bronchoscopy employing mechanical debridement, brachytherapy, tumour ablation or airway stent placement (indicates to see ASTRO guideline for more details)</li> <li>• Malignant pleural effusions: tunneled pleural catheters, graded talc pleurodesis, thoracoscopy</li> <li>• Superior vena cava syndrome: chemotherapy in SCLC, radiotherapy or stent in NSCLC; stents in any who do not respond to chemotherapy or radiotherapy</li> </ul>	
National Institute for Health and Care Excellence (NICE CG121)	NICE, 2011 [26]	Lung cancer: diagnosis and management	<p>Systematic review: Cochrane, MEDLINE, Embase, CINAHL, AMED, British Nursing Index, PsycINFO, Web of Science, Sci-expanded, Social Sciences Citation Index, Biomed Central until August 2010 (see [81] for full guidance including methodology)</p> <p>Includes recommendations on EBRT and/or endobronchial debulking or stenting for endobronchial obstruction; pleural aspiration or drainage and talc pleurodesis for pleural effusion; non-drug interventions (psychosocial support, breathing control, coping strategies); opioids</p> <p>A partial update is in progress but will not cover sections relevant to this evidence summary</p>	81 (RC)
British Thoracic Society	Woolhouse, 2018 [27]	Malignant pleural mesothelioma:	Systematic review: Cochrane, DARE, MEDLINE, Embase and PubMed until Dec 2014 and updated to	77 (GGF)

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Organization	Citation	Topic	Notes	AGREE RoD <sup>2</sup>
		investigation and management	July 2016; search strategy in web appendix	
European Respiratory Society; European Society of Thoracic Surgeons	Scherpereel, 2010 [28]	Malignant pleural mesothelioma: management	Systematic review: MEDLINE, Embase, 1990-2009; chemotherapy only 1965-2009, reported search terms but not results  Pleural effusions: pleurodesis, aspiration/drain  Oral morphine; oxygen if reduced oxygen saturation  Fan, breathlessness management techniques (extrapolated from lung cancer)	52 (RC) 59 (CGD)

Abbreviations: COPD, chronic obstructive pulmonary disease; DARE, Database of Abstracts of Reviews of Effects; EBRT, external beam radiotherapy; NSCLC, non-small-cell lung cancer; RoD, Rigour of Development; RT, radiotherapy

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## Appendices

### Appendix A. Author and COI Declaration

(see the [PEBC Conflict of Interest \(COI\) Policy](#))

Name	Affiliation	COI declaration
Glenn Fletcher, MSc	Health Research Methodologist, Program in Evidence-Based Care, McMaster University	None

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## Appendix B. Websites Searched (February to March 2018 except as indicated)

- National Guidelines Clearing House <https://www.guideline.gov/>
  - CPG Infobase: Clinical Practice Guidelines <https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx> (only guidelines from organizations not already looked at)
  - Inventory of Cancer Guidelines (SAGE; last updated January 2013) <http://www.cancerview.ca/sage>. Searched July 2017
  - Cancer Guidelines Database [new version of SAGE database announced Feb 28 2018] (formerly SAGE) searched April 2, 2018 (searched for individual symptoms) <https://www.partnershipagainstcancer.ca/tools/cancer-guidelines-database/>
- 
- American Cancer Society <https://www.cancer.org/health-care-professionals/american-cancer-society-survivorship-guidelines.html>
  - American College of Chest Physicians <http://www.chestnet.org/Guidelines-and-Resources>
  - American College of Obstetricians and Gynecologists <https://www.acog.org/Resources-And-Publications>
  - American College of Physicians (ACP) <https://www.acponline.org/clinical-information/guidelines>
  - American College of Radiology <https://acsearch.acr.org/list>
  - American Geriatric Society <https://geriatricscareonline.org/ProductTypeStore/clinical-guidelines-recommendations/8/>
  - American Physical Therapy Association <https://www.apta.org/EvidenceResearch/EBPTools/CPGs/>
  - American Society for Therapeutic Radiology and Oncology: [www.astro.org](http://www.astro.org); <https://www.astro.org/Clinical-Practice-Statements.aspx>
  - American Society of Clinical Oncology (ASCO) <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines>
  - American Society of Colon and Rectal Surgeons <https://www.fascrs.org/physicians/clinical-practice-guidelines>
  - American Thoracic Society <https://www.thoracic.org/statements/>
  - American Thyroid Association <https://www.thyroid.org/professionals/ata-professional-guidelines/>
  - American Urological Association <http://www.auanet.org/guidelines>
  - An Roinn Slainte Department of Health, Dublin, Ireland ; Royal College of Physicians of Ireland: National Clinical Programme for Palliative Care <http://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/cpc/>
  - BC Cancer Agency, BC Health <http://www.bccancer.bc.ca/health-professionals/professional-resources/cancer-management-guidelines>
  - Belgian Health Care Knowledge Centre (KCE) <https://kce.fgov.be/en/all-reports?search=guideline>

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- British Association of Dermatologists <http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines>
- British Society for Haematology <http://www.b-s-h.org.uk/guidelines/>
- British Thoracic Society <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/>
- Canadian Association of Psychosocial Oncology <http://oncology.capo.ca/public/#clinical-guidelines>
- Cancer Australia (July 11,2017; updated Feb 20, 2018) <https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines>
- Cancer Care Nova Scotia (Nova Scotia Cancer Care Program) (<http://www.cdha.nshealth.ca/nova-scotia-cancer-care-program-3>)
- Cancer Care Ontario (CCO) <https://www.cancercareontario.ca/en/guidelines-advice>
- Cancer Control Alberta / Alberta Health Services <https://www.albertahealthservices.ca/info/cancerguidelines.aspx>
- Cancer Council Australia <http://www.cancer.org.au/health-professionals/clinical-guidelines/>
- Central European Cooperative Oncology Group (CECOG) <http://www.cecog.org/>
- Clinical Oncology Society of Australia <https://www.cosa.org.au/publications/guidelines/>
- Dutch Association of Comprehensive Cancer Centres (ACCC) (also called IKNL Integraal Kankercentrum Nederland). <http://www.iknl.nl/> or <http://www.oncoline.nl/index.php?language=en>
- European Association for Palliative Care (EAPC) <http://www.eapcnet.eu/Themes/Research/Publications/EAPCResearchNetwork/tabid/275/Default.aspx>
- European Association of Urology <http://uroweb.org/guidelines/> and <https://uroweb.org/wp-content/uploads/EAU-Extended-Guidelines-2016-Edn.pdf>
- European Oncology Nursing Society: <http://www.cancernurse.eu/education/guidelines-recommendations.html>
- European Oral Care in Cancer Group <http://www.eocc.co.uk/guidance/>
- European Palliative Care Research Collaborative (EPCRC) <https://www.ntnu.edu/prc/results/epcrc-guidelines>
- European Respiratory Society <http://www.ers-education.org/guidelines.aspx>
- European Society for Medical Oncology (ESMO) <http://www.esmo.org/Guidelines>
- European Society for Radiotherapy and Oncology (ESTRO) <http://www.estro.org/>
- European Society of Thoracic Surgeons [http://www.ests.org/guidelines\\_and\\_evidence/default.aspx](http://www.ests.org/guidelines_and_evidence/default.aspx)
- European Society of Urogenital Radiology (ESUR) <http://www.esur.org/esur-guidelines/>
- Fraser Health Hospice Palliative Care Program <http://www.fraserhealth.ca/health-professionals/professional-resources/hospice-palliative-care/>
- Institute for Clinical Systems Improvement (Minnesota and surrounding areas) [https://www.icsi.org/guidelines\\_more/find\\_guidelines/](https://www.icsi.org/guidelines_more/find_guidelines/)

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- Japanese Society for Palliative Medicine <https://www.jspm.ne.jp/guidelines/index.html>
- Japanese Urological Association <https://www.urol.or.jp/en/>
- Korean Liver Cancer Association; Korean Liver Cancer Study Group [http://livercancer.or.kr/eng/html/sub06\\_01.asp](http://livercancer.or.kr/eng/html/sub06_01.asp)
- Multinational Association of Supportive Care in Cancer (MASCC) <http://www.mascc.org/guidelines>
- National Comprehensive Cancer Network (NCCN) (Guidelines for supportive care only) [https://www.nccn.org/professionals/physician\\_gls/default.aspx#supportive](https://www.nccn.org/professionals/physician_gls/default.aspx#supportive)
- National Health and Medical Research Council (Australia) <https://www.nhmrc.gov.au/guidelines-publications>
- National Institute for Health and Care Excellence (NICE) <https://www.nice.org.uk>
- National Cancer Institute (NCI) PDQ's <https://www.cancer.gov/publications/pdq/information-summaries/supportive-care> (supportive care only)
- New Zealand Ministry of Health <http://www.health.govt.nz/publication>
- Oncology Nursing Society <https://www.ons.org/>
- Program in Evidence-Based Care / Cancer Care Ontario (PEBC/CCO) <https://www.cancercareontario.ca/en/guidelines-advice>
- Registered Nurses' Association of Ontario (RNAO): <http://rnao.ca/bpg>
- Saskatchewan Cancer Agency <http://www.saskcancer.ca/Default.aspx?DN=b1586bc3-431f-4998-a55c-ec2c34c090ba>
- Scottish Intercollegiate Guidelines Network (SIGN) <http://www.sign.ac.uk>
- Scottish Palliative Care Guidelines <http://www.palliativecareguidelines.scot.nhs.uk/>
- SIOG - International Society of Geriatric Oncology <http://www.siog.org/content/siog-guidelines-0>
- Society for Immunotherapy of Cancer <http://www.sitcancer.org/research/cancer-immunotherapy-guidelines>
- Society for Integrative oncology (SIO) <https://integrativeonc.org/integrative-oncology-guidelines>
- The Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society and the German Cancer Aid jointly launched the [German Guideline Program in Oncology \(GGPO\)](http://www.krebsgesellschaft.de/gcs/german-cancer-society/guidelines.html) in 2008. <https://www.krebsgesellschaft.de/gcs/german-cancer-society/guidelines.html>; <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>
- UK and Ireland Neuroendocrine Tumour Society <http://www.ukinets.org/net-clinics-clinical-practice/>
- UK Oral Mucositis in Cancer Group (UKOMIC) <http://www.ukomic.co.uk/>

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### Appendix C. Literature Search Strategy

Database(s): AMED (Allied and Complementary Medicine) 1985 to June 2018, Embase 1996 to 2018 July 09, Ovid Emcare 1995 to 2018 week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to July 05, 2018

#### Search Strategy:

#	Searches	Results
1	exp Neoplasms/ or exp tumor/ or exp cancer/ or (cancer: or neoplasm: or tumo?r: or carcinom: or malignan: or oncolog:).mp.	8894034
2	limit 1 to yr="2009-current"	4725632
3	exp guideline/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter\$.tw. or practice guideline\$.mp. or (guideline: or recommend: or consensus or standards).ti,kw.	992275
4	(abstract* or conference abstract* or note or letter or comment or commentary or editorial).pt.	7323809
5	(2 and 3) not 4	74056
6	exp dyspnea/ or (dyspnea or dyspnoea or breath:).ti,kw.	264211
7	5 and 6	783
8	remove duplicates from 7	552

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## Appendix D. AGREE II Rigour of Development Scores

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score <sup>3</sup>
Yamaguchi, 2016 [12]	6	3	6	6	5	6	7	3	42
	PubMed, Cochrane, Ichushi-Web until Aug 2014, search strategies reported; searches too narrow	English or Japanese; listed study types, no other information	Rated level of evidence and strength of recommendation; discussed trials and limitations	Draft then 2 Delphi rounds (level of agreement not stated), external review			6 external reviewers: 3 palliative care specialists, 2 oncologists, 1 primary care physician	This guideline updates the 2011 version, but no details of future updates	71 (GGF)
German Guideline Program in Oncology, 2015 [10]	7	6	5	5	2	5	6	7	43
	Full (German) report gives details: MEDLINE, Embase, Cochrane, updated until at least Nov 2012, search strategies reported	Mandatory according to methodology document; reported according to PICO headings and in selection of evidence tables	Indicated grade of recommendation and level of evidence for each recommendation (SIGN system used)	Indicates whether consensus or evidence-based recommendation	Not stated	Citations are provided for each recommendation	Not stated, but about 50 organizations are listed and 49 experts were involved, plus 2 patient representatives. Approved by professional societies; public consultation held	Valid for 5 years, update planned in 2019 unless urgent need earlier	73 (GGF)
Alberta Health Services, 2016 [13]	5	6	3	3	2	5	1	6	31
	PubMed Jan 2012-Sept 2014 for update; search strategy reported	English, adults, ≥10 patients	A few statements indicating insufficient evidence	Not stated; current process described in development handbook	Not clear	For some	Not stated; not part of process	Review annually; development handbook says every 3 years	48 (GGF)
Hardinge, 2015 [14]	7	4	5	6	3	5	5	7	42
	MEDLINE, Embase, Cochrane, until Jan 2014; search strategy reported	Questions in PICO format to inform search; English only, exclude reviews	Graded publications and body of evidence with SIGN; graded recommendations A-D. Indicated where there are no studies and recommendation is extrapolated	Used evidence tables; expert opinion through consensus if insufficient evidence	Only with regard to safety in smokers	There is a section of literature review for each question	Public consultation and relevant stakeholders	Will be reviewed within the next 5 years	71 (GGF)

<sup>3</sup> The first number for each guideline is the total score (i.e., the sum of scores for questions 7 to 14), while the second number is the Domain Score, which is a type of percentage taking into consideration the minimum and maximum values possible (see Methods section). Initials of rater or source are in parentheses; CDG, Cancer Guidelines Database (Canadian Partnership Against Cancer).

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Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score <sup>3</sup>
O'Driscoll, 2017 [15]	7	3	6	5	5	4	7	7	46
	MEDLINE, Cochrane, DARE until Aug 2013; search strategy reported	Can only be inferred from questions and search strategy	Indicates many observational studies but few randomized trials Graded publications and body of evidence with SIGN; recommendations graded A-D.	Most recommendations based on expert opinion, and are noted as such in the evidence statements		There is results of the systematic review followed by evidence statements and recommendations	Public and stakeholder consultation; 2 peer reviewers	Will be reviewed within 5 years from publication	79 (GGF)
Shelton, 2017 [3]	4	7	1	1	1	3	1	3	21
	PubMed, CINAHL, Cochrane, NCCN Jan 2009-Fan 2017; search terms reported; strategy too limited for topic and recommendations given	Inclusion/exclusion criteria reported	Not reported	Not reported	Not reported	Topics have links to publications	Not reported	Update of previous version, but not details of future updates	27 (GGF)
NICE, 2015 [16] (NICE NG31)	7	7	7	3	7	7	6	5	49
	MEDLINE, Embase, Cochrane to Nov 2014; full search strategies reported (appendix G)	English. Appendix C has inclusion/exclusion criteria	Critically appraised using the checklist in the NICE guidelines manual. GRADE tables	Recommendations were drafted on the basis of the committee's interpretation of the available evidence. Done informally. Consensus recommendations agreed through discussion	Balanced discussion	Evidence tables in appendix H. clearly linked	Consultation by stakeholder. 6-week public consultation and feedback. Comments were responded and posted on NICE website	When progressed significantly. Methods in guidelines manual	85 (RC)
Brahmer, 2018 [17]	4	4	2	4	2	1	4	6	27
	PubMed (MEDLINE in process only), Embase, Cochrane 2000-2017; search terms and strategy not reported	Reported target population and interventions but not inclusion/exclusion criteria	Notes only that informal consensus was used due to limitations in available evidence; no summary of evidence	States informal consensus was used and lists participants	States "all recommendations in this guideline are based on expert consensus, benefits outweigh harms, moderate strength of recommendation" but no other mention of harms	Notes only that informal consensus was used due to limitations in available evidence	One external reviewer and open public comment	Reviewed annually according to methodology supplement, but information not in guideline	40 (GGF)
NICE, 2016 [18] (NG36)	7	7	5	5	7	4	6	5	46
	MEDLINE, Embase, Cochrane, Web of Science until May	Reported in evidence review appendix	Indicates no publications met inclusion criteria for	No evidence found so based recommendations on	Clinical benefits and harms discussed	Not applicable as based on clinical experience only	About 180 stakeholders invited to	Regular checks to determine if	79 (GGF)

Evidence Summary SMG-3

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score <sup>3</sup>
	2015; search strategy reported		question on breathlessness	clinical experience of authors	following recommendations		comment on draft	update needed	
Rodrigues, 2011 [19]; Moeller, 2018 [20]	5 PubMed 1966-Mar 2010; update to Jul 2016; reported key words or headings for 2011 version	7 Inclusion and exclusion criteria stated	7 Reported quality of evidence and strength of recommendations, with some discussion	6 Literature review, rate evidence, vote on recommendations, external review	6 Considered in the update, less clear for original guideline	7 Studies discussed along with recommendations	6 3 external reviewers plus public comment	5 Will monitor this guideline and initiate an update when appropriate	49 85 (GGF)
National Cancer Control Programme Guideline Development Group, 2017 [21]	5 MEDLINE, Embase, updated in 2016; search strategy required by protocol but not reported	3 Only for economics question	3 Recommendations assigned a grade.	3 Recommendations assigned a grade.	3	4 Based on other guideline and review	7 National stakeholder and International external expert review	6 Will be considered for review in 3 years; periodic surveillance of literature	34 54 (GGF)
Cancer Council Australia, 2012 [22]	7 PubMed, Cochrane; Embase until Feb or Sep 2017. Search strategy provided in the Wiki	7 Limited to the highest level of evidence available, English. Section 3.4. Exclusion criteria: study design, treatment, and comparator. More info on wiki	7 NHMRC grading system for recommendations. Grade recommendations are made using the body of evidence assessment matrix. Use wiki critical appraisal form	3 Internal review of recommendations. Consensus for practice points	6 Balanced discussion	7 Clearly linked	5 Public consultation. Comments are reviewed and content is updated. External reviewers complete a brief feedback survey. Insight into guideline usage and evaluate dissemination. Engage stakeholders on a long term basis	7 Annual WP meeting to review all changes made by authors. Updating guideline content section	49 85 (RC)
Healthcare Improvement Scotland, 2014 [23] (SIGN 137)	7 MEDLINE, Embase, CINAHL, PsycINFO and Cochrane Library 2005-2012. search strategy on website	2 No information	6 Evaluated using the standard SIGN methodological checklist. Use GRADE methodology (this information is from the methodology handbook)	4 Evidence to decision tool, usually formed through informal consensus	7 Balanced discussion	7 Clearly linked	6 Section 16.4 consultation and peer review. Comment on comprehensiveness and accuracy. Every comment is	5 Considered for review in three years	44 75 (RC)

Evidence Summary SMG-3

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score <sup>3</sup>
							addresses. Names of expert reviewers given		
Ung, 2018 [24] (7-16)	7 MEDLINE, Embase to Sept 2017; is endorsement of 2005/2013 versions; search strategy reported	6 Inclusion and exclusion criteria reported	4 Some limitations are noted	3 No details reported	4 Hemoptysis discussed, but not updated	3 Key evidence is reported but without citations, and not linked to specific recommendations	4 Original 2005 version underwent external review	4 Routine periodic review; 2005 guideline reviewed and endorsed 2013 and 2018	35 56 (GGF)
Simoff, 2013 [25]	5 MEDLINE, CINAHL, PsycINFO, Cochrane, Embase, Web of Science, Google Scholar, until 2012	3 Original research. No limiters of language or article type	6 Assessed for quality. Documentation and appraisal review tool. Used GRADEpro	5 Recommendations were developed with supporting evidence and the consensus of the writing committees. Controversial recommendations were identified for further consultation by the entire panel, anonymous voting used GRADE grid, at least 80% in favour to be approved	7 Balanced discussion	6 Clearly linked	5 Provided external review. Authors were required to respond to all mandatory issues. Included nearly 30 individual reviewers	6 Embarking on a new living guidelines model for revising existing recommendations, continual assessment of the currency of these recommendations, will begin 1 year after publication	43 73 (RC)
NICE, 2011 [26] (CG121)	7 Databases and dates provided. Search strategy in appendix 1	4 Search filters such as those to identify systematic reviews and randomised controlled trials were applied to the search strategies when necessary. No language restrictions, but foreign language papers not requested or reviewed.	5 Discusses bias	4 Derived recommendations from clinical evidence. When evidence was weak, agreed through informal consensus	7 Balanced discussion	7 Clearly linked	6 Comments from stakeholders. List of stakeholders in Appendix 9.2. History has comments and responses	7 Will be reviewed and updated as considered necessary. Criteria for deciding the update status is defined in the guidelines manual. Methodology given. Three years after publication	47 81 (RC)
Woolhouse, 2018 [27]	7 MEDLINE, Embase, PubMed, Cochrane,	5 Inclusion: English, case reports	7 Appraised evidence using SIGN checklists	7 Methodology adheres to criteria of AGREE	4 Some discussion of risks and	3 Literature review then evidence	5 Stakeholders notified when	7 Will be reviewed	45 77 (GGF)

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Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score <sup>3</sup>
	DARE until Jul 2016; search strategy reported	generally > 20 patients, exclude letters, conference papers, news	and assigned evidence level. Gave summary statement for most questions	II. Created evidence tables, guideline group reached consensus on recommendations, used low-grade evidence or expert opinion via consensus if no high-quality evidence for specific question	benefits	statements and recommendations , not directly linked	the document was available for public consultation	within 5 years of publication	
Scherpereel, 2010 [28]	6 MEDLINE, Embase, Cochrane, National Guideline Clearinghouse, HTA database 1990-2009. Search terms given. No full search strategy	2 No information	6 Each recommendation graded using criteria from American College of Chest Physicians	5 Each recommendation was voted by all experts. If <85% in agreement, recommendation was modified	6 Balanced discussion	6 Clearly linked	1 No information	1 No information	33 52 (RC)
Dans, 2017 [33]	5 PubMed Oct 2014-June 2015, provided search terms	3 Inclusion: humans, English, study design	2 Benefits and harms described. Nothing else about quality. Categories of evidence given	6 Info for development is on NCCN website. Based on high level evidence. Consensus when there is no high level evidence. Degree of consensus is shown by category number. Steps in consensus not explained	6 Balanced discussion on benefits and adverse events	6 Could have been formatted in table or next to each other for greater ease	1 No information	7 Update methodology on NCCN website	36 58 (RC)
National Cancer Institute, 2016 [35]	1 No systematic review	1 No systematic review	4 Says there are: reference citations accompanied by a level of evidence designation but cannot find. Mostly details methodology. There is some discussion of quality throughout	2 Changes in the summary are made through a consensus process. No other info	6 Balanced discussion on benefits and adverse events	5 Does not provide formal guidelines or recommendations . But does provide evidence followed by suggestions of what to do	1 No information	6 Reviewed regularly (each month) and updated as necessary. Changes made through consensus process	26 38 (RC)

Abbreviations: DARE, Database of Abstracts of Reviews of Effects; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; RT, radiation therapy; SIGN, Scottish Intercollegiate Guidelines Network

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Appendix E. Excluded Guidelines<sup>4</sup>

Organization	Citation	Topic	Notes
Focus on dyspnea or symptom management			
BC Centre for Palliative Care	BC Centre for Palliative Care, 2017 [29]	Dyspnea in palliative care	Exclude: no systematic review Informed by evidence until May 2016 (see introduction to series [70]) Fraser Health guideline [32] served as a foundation for the work Limited to end of life symptoms, with an audience of nurses and physicians without palliative specialization, excluded symptoms arising from only one disease (e.g., cancer; does not address pulmonary obstruction, pleural effusion, radiotherapy, etc.), Due to general nature some recommendations appear to be different than those in guidelines specifically on cancer
European Society for Molecular Oncology (ESMO)	Kloke, 2015 [30]	Dyspnea in advanced cancer	Exclude: not based on systematic review
Healthcare Improvement Scotland	Scottish Partnership for Palliative Care, 2014 [31]	Breathlessness in palliative care (includes but not restricted to cancer)	Exclude: not systematic review; based on other reviews but no cross-reference to evidence Breathlessness is common in advanced cancer, COPD, lung fibrosis, and heart failure
Fraser Health (British Columbia)	Fraser Health, 2009 [32]	Dyspnea in palliative care for advanced life threatening illness	Exclude: too old (literature search CINHL, MEDLINE, Cochrane1996-2006; only updated page on last hours of life 2009), not systematic Does not address disease specific approaches to manage dyspnea
National Comprehensive Cancer Network (NCCN)	Dans, 2017 [33]	Palliative care in cancer	Updated search using PubMed for June 2015-May 2017 Exclude: not explicit systematic review.
Guidelines & Protocols	Guidelines and	Palliative care in	Exclude: based on systematic review by others if available,

<sup>4</sup> Guidelines relevant to dyspnea in cancer without explicit systematic review (although most appear to be evidence-based) and guidelines on dyspnea in diseases other than cancer

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<b>Organization</b>	<b>Citation</b>	<b>Topic</b>	<b>Notes</b>
Advisory Committee (British Columbia)	Protocols Advisory Committee, 2017 [34]	incurable cancer or advanced disease. Addresses 7 symptoms, including dyspnea	otherwise on individual studies, indicates “a full systematic review may not be conducted” [82]. Search strategy and results not reported, recommendations not tied to evidence
National Cancer Institute (USA)	National Cancer Institute, 2016 [35]	Last days of life (PDQ)	Exclude: no explicit systematic review, is evidence-based
European Society for Molecular Oncology (ESMO)	Haanen, 2017 [36]	Toxicities from immunotherapy	Exclude: not based on systematic review
European Society for Molecular Oncology (ESMO)	Cherny, 2014 [37]	Refractory symptoms at end of life, palliative sedation	Exclude: methodology not stated, other than that there are no randomized studies and assertions are based on case series and expert opinion
<b>Focus on management of specific cancer</b>			
Council of Cancer Chemotherapy of Chinese Anti-Cancer Association, for the National Health and Family Planning Commission of the People’s Republic of China (update of guideline by the former Ministry of Health of the People’s Republic of China)	Zhi, 2015 [38]	Lung cancer: diagnosis and treatment	Exclude: methodology not described Treat reversible causes: COPD, obstruction of superior vena cava and bronchi, pleural effusion Non-pharmaceutical in early stage: oxygen, breathing exercise, posture and position training Opioids (morphine preferred) most frequently used in cancer patients; sedatives for acute or severe dyspnea
Austrian Mesothelioma Interest Group	Geltner, 2016 [39]; Hoda, 2016 [40]	Malignant pleural mesothelioma: management (diagnosis, staging, therapy)	Exclude: not systematic review Consensus of the Austrian Mesothelioma Interest Group (AMIG) Deals mostly with treatment (chemotherapy, radiotherapy, surgery)
European Society for Molecular Oncology	Baas, 2015 [41]	Malignant pleural mesothelioma:	Exclude: not based on explicit systematic review Deals mostly with treatment (chemotherapy, radiotherapy, surgery)

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Organization	Citation	Topic	Notes
(ESMO)		diagnosis, treatment, follow-up	
Alberta Health Services (LU-009)	Alberta Health Services, 2012 [42]	Malignant pleural mesothelioma	Exclude: not systematic review Exclude: topics related to dyspnea covered in a) palliative radiotherapy guideline; b) malignant pleural effusion guideline
Alberta Health Services (LU-010)	Alberta Health Services, 2014 [43]	Malignant pleural effusion: management	Exclude: unclear if systematic review; search strategy and results not reported Exclude: adapted from British Thoracic Society ([83], now archived) and American College of Chest Physicians [25] Searched PubMed, MEDLINE, Embase, Cochrane Database of Systematic Reviews until March 2014
<b>Other diseases with dyspnea</b>			
European Society of Cardiology (ESC)	Konstantinides, 2014 [44]	Acute pulmonary embolism: diagnosis and management	Exclude: no information about methodology Pulmonary embolism may be suspected on the basis of dyspnea, chest pain, pre-syncope/syncope, hemoptysis; in patients with pre-existing heart or pulmonary disease, worsening dyspnea may be the only symptom Risk of venous thromboembolism is 4x higher in patients with cancer than the general population, 6x higher during chemotherapy, and 90x higher during the first 6 weeks after cancer surgery, and remains elevated (up to 30x) for the first year
European Society of Cardiology (ESC) and the European Respiratory Society (ERS)	Galie, 2016 [45]	Pulmonary hypertension	Exclude: dyspnea is a symptom but does not deal specifically with cancer Systematic literature review using MEDLINE from 2009-2015 to update previous guidelines
American Heart Association	Pennell, 2013 [46]	Beta-thalassemia major: cardiovascular function and treatment	Exclude: dyspnea is a symptom but does not deal specifically with cancer Consensus guideline, used other focused summary reviews and consensus statements
Global Initiative for	Global Initiative for	COPD: diagnosis,	Exclude: no specific treatment due to presence of lung cancer is

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Organization	Citation	Topic	Notes
Chronic Obstructive Lung Disease (GOLD)	Chronic Obstructive Lung Disease (GOLD), 2018 [47] [2017 update = 2018 edition]	management, prevention	noted Reports in 2001, 2006, 2011, yearly since 2013; 2017 version was 4 <sup>th</sup> major revision and included comprehensive reassessment of prior recommendations; 2018 is minor revision PubMed searched, based on publications Jan 2016-Jul 2017 (older publications in previous versions); search terms reported Includes only therapies approved by at least one major regulatory agency Chapter 6 addresses COPD and comorbidities, including lung cancer “In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated per usual standards regardless of the presence of COPD” “There is ample evidence of an association between COPD and lung cancer”
Lung Foundation Australia; Thoracic Society of Australia and New Zealand	Yang, 2018 [48]	COPD management	Exclude: mentions lung cancer only as a comorbidity with COPD Systematic literature search (no details reported); relevant papers are selected for review; guideline updated quarterly “Chronic obstructive pulmonary disease is commonly associated with other chronic diseases including heart disease, lung cancer, stroke, pneumonia and depression.” The key recommendations and levels of evidence incorporated in the COPD-X guidelines were originally based largely on the Global Initiative for Chronic Obstructive Lung Disease (GOLD)
National Institute for Health and Care Excellence (NICE)	NICE, 2010 [49] NICE, 2018 [50]	COPD: diagnosis and management	Exclude: does not mention cancer The 2010 document is currently being updated, with expected publication Dec 2018 Systematic review, search strategy available on website as separate document
European Respiratory Society/American Thoracic Society	Wedzicha, 2017 [51,52]	COPD exacerbations: prevention, management	Exclude: does not mention cancer Systematic review, NICE guidelines as starting point. MEDLINE, Embase, Cochrane Database of Systematic Reviews until Sept 2015;

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Organization	Citation	Topic	Notes
			similar search strategy as in NICE 2004 or 2010 guideline, reported in supplementary material
Canadian Thoracic Society (CTS)	Bourbeau, 2017 [53]	COPD management: pharmacotherapy for stable COPD	Exclude: does not mention cancer Update of 2008 guideline, based on systematic review: MEDLINE 2008-March 2017. See [84] for guideline process Authors call it a position statement because in areas with insufficient evidence, the developed consensus-based (CB) recommendations which are not graded Target population is patients with stable COPD, including those with asthma. Update expected 2018
American College of Chest Physicians; Canadian Thoracic Society (CTS)	Criner, 2015 [54]	COPD: prevention of acute exacerbations	Exclude: does not mention cancer Systematic review: PubMed and Cochrane library 2007-2013; searched for guidelines and systematic reviews and then updated relevant systematic reviews using the same search strategies used in the original reviews; conducted their own systematic reviews for topics where existing reviews not sufficient (details in e-Appendix) Some of the recommendations on inhaled and oral pharmacologic maintenance therapies have been revised in the 2017 pharmacotherapy guideline [53]
Canadian Thoracic Society (CTS)	Marciniuk, 2011 [55]	COPD: managing dyspnea in advanced COPD	Does not mention cancer Systematic review: MEDLINE, Embase, Cochrane, CMA InfoBase, Jan 1990-Apr 2009 Status is under review
Canadian Thoracic Society (CTS)	Marciniuk, 2010 [56]	COPD: pulmonary rehabilitation	Does not mention cancer Systematic review: MEDLINE, Embase, Cochrane, CMA InfoBase, Jan 1996-Mar 2009 Status is under review
	Miravittles, 2016 [57]	COPD: review of European and Russian management	Review of national guidelines from Russia, Czech Republic, England and Wales, Finland, France, Germany, Italy, Poland, Portugal,

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Organization	Citation	Topic	Notes
		guidelines	Spain, Sweden Supplementary table reports that 10 guidelines indicate that lung cancer comorbidity does not affect treatment decision, and one guideline (Czech Republic) does not address this

Abbreviations: COPD, chronic obstructive pulmonary disease; RoD, Rigour of Development

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