폐암 환자에서 발생하는 호흡기계 증상 관리

강원대학교병원 호흡기내과 홍윤기

Introduction

폐암 환자에서 발생하는 호흡기계 증상 관리

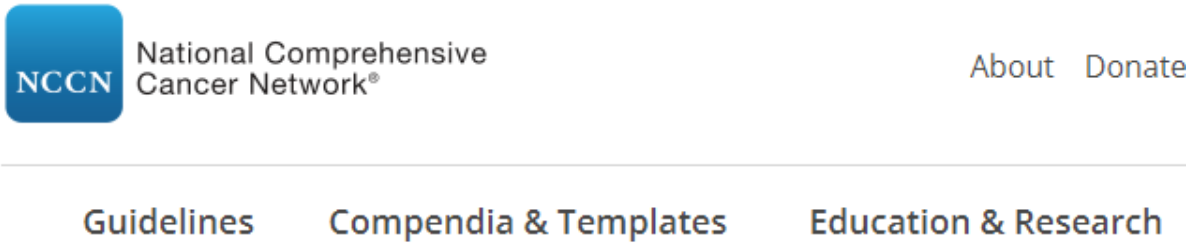
Pain ✗

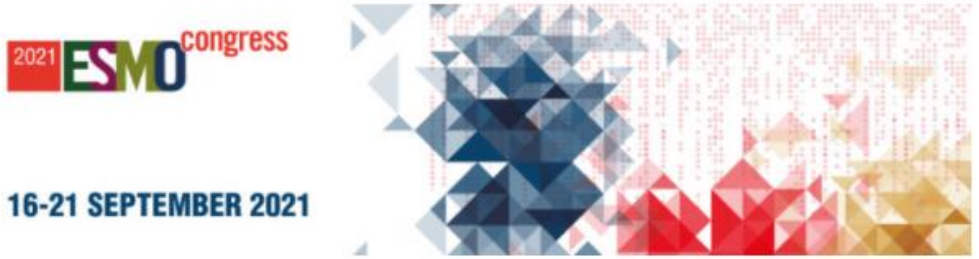
Anticancer treatments ✗
(Toxicities d/t I-O…)

Underlying disease ✗
(COPD …)

Introduction

폐암 환자(





Introduction

폐암 환자에서 발생하는 호흡기계 증상 관리

*** Palliative care : 기침, 호흡곤란 ….**

Little high quality of reference

Experience in clinical practice

Introduction

- Symptom clusters in advanced patients with lung cancer

- Symptomatic treatments in patients with lung cancer

  - Cough

  - Breathlessness

Symptoms in patients with advanced lung cancer

- fatigue (~ 100%)
- dyspnea or cough (~ 84%)
- depression (~ 83%)
- pain (~ 58%)

Hofman M, et al. Oncologist 2007

Walling AM, et al. J Pain Symptom Manage 2015

Table 2
Respiratory Symptom Items—Analysis of the Participants' Responses

Variables	Mean (SD)	Asymptomatic (%) Score 4	Symptomatic (%) Score 0–3		
			All	Moderate (2–3)	Severe (0–1)
Respiratory symptoms					
Shortness of breath	2.91 (1.16)	51 (39.8%)	77 (60.2%)	62 (48.4%)	15 (11.7%)
Coughing	2.54 (1.32)	38 (29.7%)	90 (70.3%)	63 (49.2%)	27 (21.1%)
Tightness in the chest	2.81 (1.24)	50 (39.1%)	78 (60.9%)	56 (43.7%)	22 (17.2%)
Breathing difficulty	2.27 (1.33)	28 (21.9%)	100 (78.1%)	59 (46.1%)	41 (32.0%)

Lou VW, et al. J Pain Symptom Manage 2017

Symptom clusters in lung cancer

- physical symptoms : pain, breathlessness, cough, fatigue, nausea, vomiting …
- psychological problems : depression, anxiety, impaired concentration…

- Respiratory symptoms played a central role in patients' symptom experiences across the entire period

- Respiratory symptoms also commonly co-occurred

- a discreet **'respiratory distress' symptom cluster** (Molassiotis A, et al. Lung Cancer. 2011)

  (cough, breathlessness and fatigue

  -> co-occur and influence each other.)

Management for symptom clusters in lung cancer

the Respiratory Distress Symptom Intervention (RDSI)

- Controlled breathing techniques
- Cough easing techniques
- Acupressure
- Information pack

(i) intervention group receiving usual care and RDSI

(ii) control group receiving usual care only

Yorke J, et al. Support Care Cancer. 2015

Table 3 Analysis of respiratory symptom cluster outcomes: mean change scores from baseline to week 4 and baseline to week 12

	Mean (SD) difference (week 4–baseline)		Mean (SD) difference (week 12–baseline)	
	Control	RDSI	Control	RDSI
Breathlessness—NRS				
Average breathlessness	−0.38 (2.21)	−0.06 (1.55)	−0.75 (2.33)	−0.17 (2.00)
Worst breathlessness	−0.38 (2.55)	−0.45 (2.06)	−0.56 (2.7)	−0.34 (2.59)
Relief breathlessness	−0.55 (3.27)	0.41 (3.16)	−0.38 (3.34)	0.68 (3.5)
Distress breathlessness	0.03 (2.26)	−0.63 (1.9)	−0.88 (2.9)	−1.07 (2.07)
Ability to cope	0.81 (2.74)	0.5 (2.62)	0.5 (2.97)	1.03 (2.63)
Unpleasant	0.13 (2.97)	−0.27 (2.23)	−0.25 (3.09)	−0.07 (2.39)
Dyspnoea−12	−2.13 (7.41)	−2.98 (7.46)	−1.52 (8.31)	−3.04 (7.78)
Cough—MCLC	−1.00 (6.33)	−1.69 (5.91)	−2.26 (8.84)	−0.86 (7.02)
Fatigue—FACIT	−2.44 (9.19)	−1.45 (9.5)	−1.28 (9.47)	−1.64 10.01)
Lung Cancer Symptom Scale	−17.83 (132.79)	−27.68 (129.54)	−21.90 (121.71)	7.48 (118.88)
HADS				
Anxiety scale	0.06 (2.85)	0.31 (3.08)	−0.06 (3.10)	0.81 (2.75)
Depression scale	0.58 (2.66)	0.64 (2.39)	1.22 (3.97)	0.70 (3.14)
EQ-5D Score	0.02 (0.29)	0.06 (0.23)	−0.05 (0.33)	0.06 (0.28)
EQ-5D Health State Today (VAS)	−3.30 (18.94)	0.40 (24.14)	−4.50 (21.03)	−2.20 (2.53)

NRS numerical rating scale, *MCLC* Manchester Cough in Lung Cancer Scale, *HADS* Hospital Anxiety and Depression Scale, *EQ-5D* Euro-Qual, *VAS* visual analogue scale, *RDSI* Respiratory Distress Symptom Intervention

Yorke J, et al. Support Care Cancer. 2015

Symptom clusters in lung cancer

- Respiratory symptoms -> a reduced quality of life
- sleep quality and respiratory symptoms are associated with each other.

- 128 patients with advanced (stage III or IV) lung cancer

Table 6
Correlation Among Respiratory Symptoms, Sleep Disturbance, and Quality of Life

Variables	1	2	3	4	5	6	7
1. Respiratory symptoms	1						
2. Global PSQI	−0.40[a]	1					
3. Physical well-being	0.43[a]	−0.49[a]	1				
4. Social well-being	0.18[b]	−0.09	0.37[a]	1			
5. Emotional well-being	0.46[a]	−0.52[a]	0.71[a]	0.42[a]	1		
6. Functional well-being	0.41[a]	−0.58[a]	0.72[a]	0.50[a]	0.73[a]	1	
7. FACT-G	0.46[a]	−0.53[a]	0.87[a]	0.64[a]	0.87[a]	0.90[a]	1

PSQI = Pittsburgh Sleep Quality Index; FACT-G = Functional Assessment of Cancer Therapy–General.
[a] $P < 0.01$.
[b] $P < 0.05$.

Lou VW, et al. J Pain Symptom Manage. 2017

Symptom clusters in lung cancer

Table 7
Multiple Regression Results for Predictors of Quality of Life

	Unstandardized Coefficients		Standardized Coefficients	
Predictors	*B*	SE	*β*	*t* (*P*)
Step 1				
(Constant)	12.69	9.01		
Age	0.39	0.12	0.21	3.23 (0.002)
Loss of appetite	6.28	1.03	0.45	6.11 (<0.001)
Weight loss	4.03	1.11	0.26	3.62 (<0.001)
Unclear thinking	3.34	1.32	0.17	2.53 (0.013)
Step 2				
Respiratory symptoms	0.98	0.31	0.20	3.12 (0.002)
Sleep disturbance	−1.04	0.26	−0.27	−4.01 (<0.001)

Respiratory symptoms -> sleep disturbance -> poor quality of life

Lou VW, et al. J Pain Symptom Manage. 2017

Patterns of Symptom Management Medication Receipt at End-of-Life Among Medicare Beneficiaries with Lung Cancer

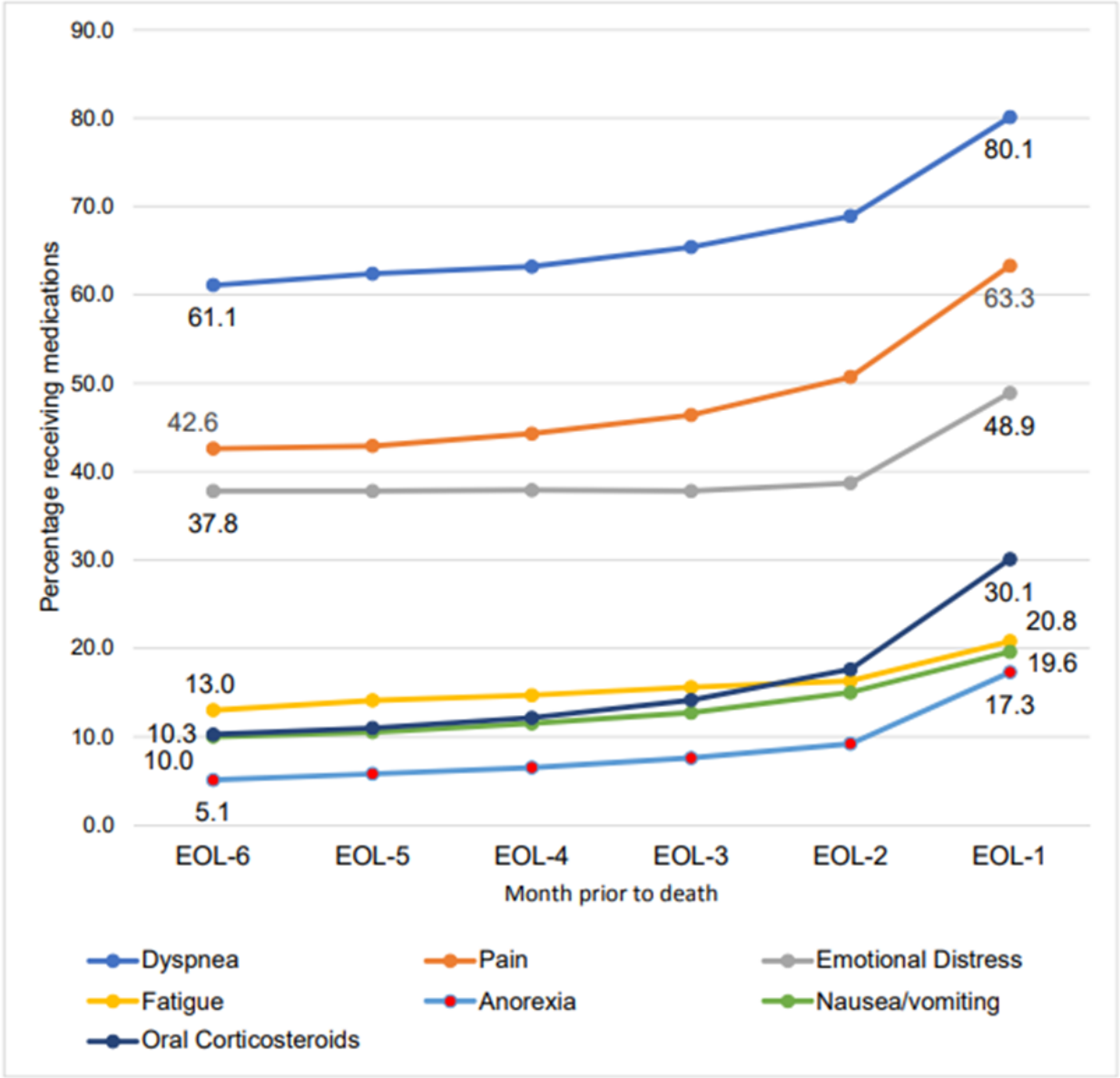
Maureen Saphire, PharmD[1*]; Elizabeth Prsic, MD[2*]; Maureen E. Canavan, PhD, MPH[3]; Shiyi Wang, MD, PhD[3-5]; Carolyn J. Presley, MD, MHS[1,3]; Amy J. Davidoff, PhD, MS.[3-5]

- diagnosed at age ≥67 years with lung cancer between 1/1/2008 and 12/31/2013.

- pain (opioids, non-opioid analgesics, and adjuvants);
- emotional distress (antidepressants, anxiolytics/sedatives, and antipsychotics);
- fatigue (transfusions, erythropoietin stimulating agents, or methylphenidate);
- dyspnea (inhaled bronchodilators or corticosteroids, diuretics, oral COPD or asthma, and secretion management);
- anorexia (appetite stimulants);
- nausea/vomiting (serotonin (5-HT3) antagonists, neurokinin 1 antagonists, prochlorperazine/promethazine, cannabinoid, and metoclopramide).

Saphire ML, et al. J Pain Symptom Manage. 2020

Figure 1. Trends in receipt of palliative symptom management medications by category during the 6-month end-of-life (EOL) period.



Saphire ML, et al. J Pain Symptom Manage. 2020

Table 2. Medications received for symptom management during EOL-1 among lung cancer patients in the outpatient setting (N=16,246)

		Claim Type					
Symptom	**Medication**	**Part A or B**		**Part D**		**Any**	
		N	%	N	%	N	%
Dyspnea	Any	1489	9.2	11278	69.5	11475	70.7
	Inhaled bronchodilators or corticosteroids	1477	9.1	5717	35.2	6394	39.4
	Diuretics			5215	32.1	5215	32.1
	Oral COPD/Asthma			974	6.0	974	6.0
	Secretion Management	17	0.1	118	0.7	134	0.8

Table 3. Monthly proportion of use of palliative care and concurrent cancer directed therapy, overall and 6 months prior to death (N=14,343)

		Month prior to death						
Symptom	Medication	EOL-6	EOL-5	EOL-4	EOL-3	EOL-2	EOL-1	Change (EOL-6 to EOL-1)
Dyspnea	Any	61.1	62.4	63.2	65.4	68.9	80.1	19
	Inhaled bronchodilators or corticosteroids	29.7	30.0	30.3	30.8	31.9	39.9	10.2
	Diuretics	18.1	18.3	18.9	19.6	20.2	32.2	14.1
	Oral COPD/Asthma	3.9	3.9	4.1	4.4	4.4	6.1	2.2
	Secretion Management	0.2	0.1	0.1	0.1	0.2	0.7	0.6

Saphire ML, et al. J Pain Symptom Manage. 2020

폐암 환자에서 발생하는 호흡기계 증상 관리

- Cough

- Breathlessness

Symptomatic treatments of cough

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for cough in cancer (Review)

Molassiotis A, Bailey C, Caress A, Tan JY

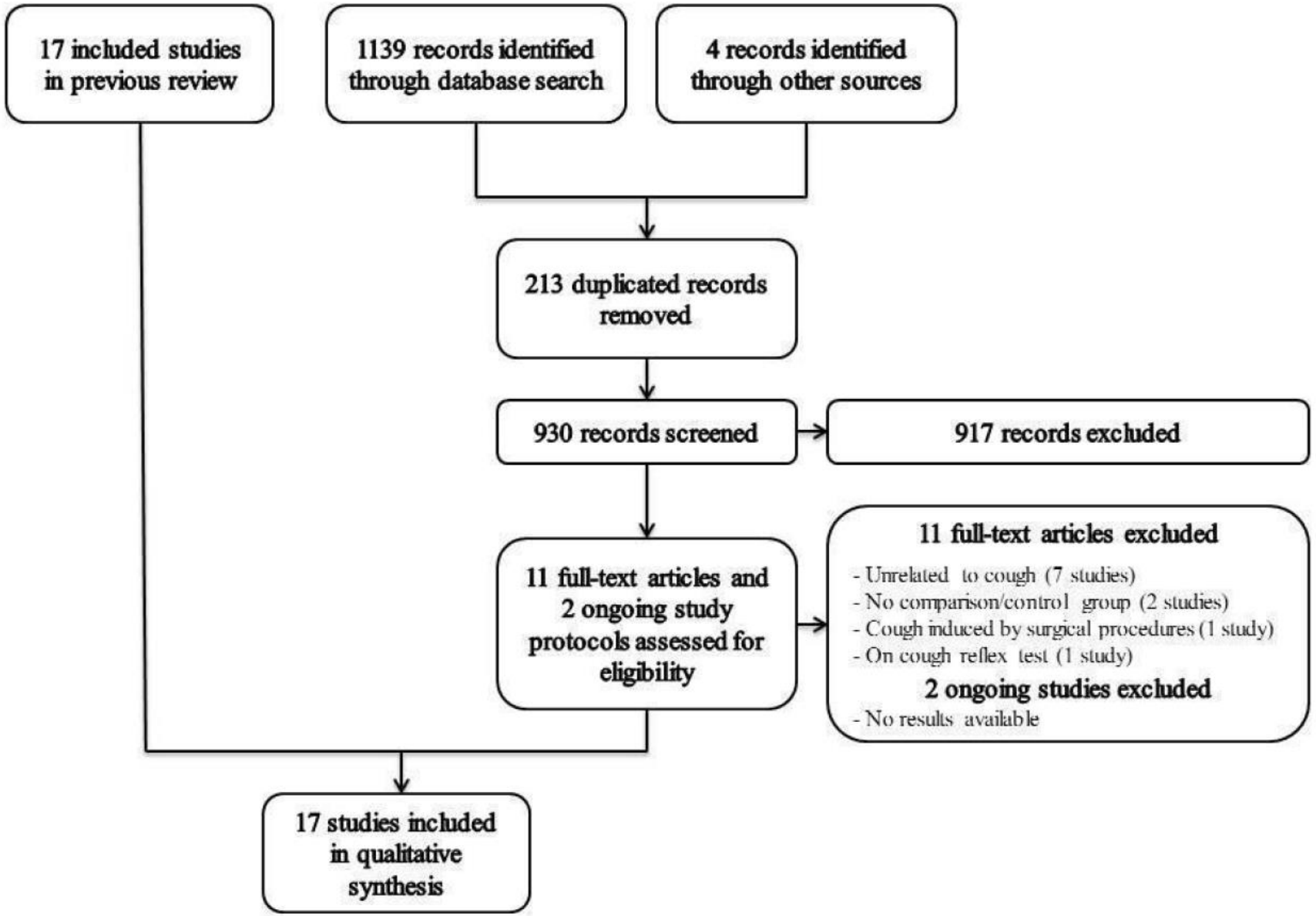
[Evidence-Based Medicine]

CHEST

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer

CHEST Guideline and Expert Panel Report

Alex Molassiotis, RN, PhD; Jaclyn A. Smith, MBChB, PhD; Peter Mazzone, MD, MPH; Fiona Blackhall, MD, PhD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel



Cochrane Library
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Interventions for cough in cancer (Review)

Molassiotis A, Bailey C, Caress A, Tan JY

Molassiotis A, et al. Cochrane Database Syst Rev. 2015

Intervention of cough

A. Brachytherapy, laser therapy and photodynamic therapy

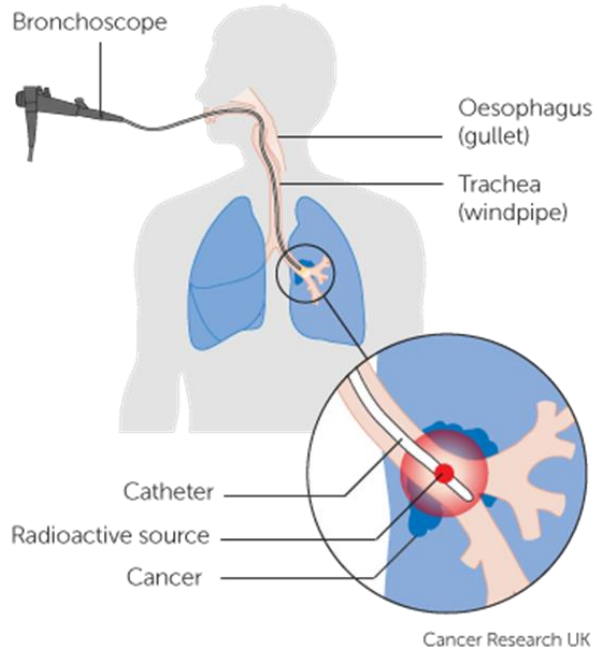
- laser resection vs **laser resection plus brachytherapy**
  (Canak 2006)

- **Photodynamic therapy**
  (Diaz-Jimenez 1999)

- **Endobronchial brachytherapy**

: a variety of doses and distances from the tumour
(Mallick 2006) (Muto 2000) (Nori 1993) (Ofiara 1997) (Speiser 1993) (Tredaniel 1994)

no standard dose of brachytherapy, similar outcomes for cough.
--> the lowest dose should be preferred



Molassiotis A, et al. Cochrane Database Syst Rev. 2015

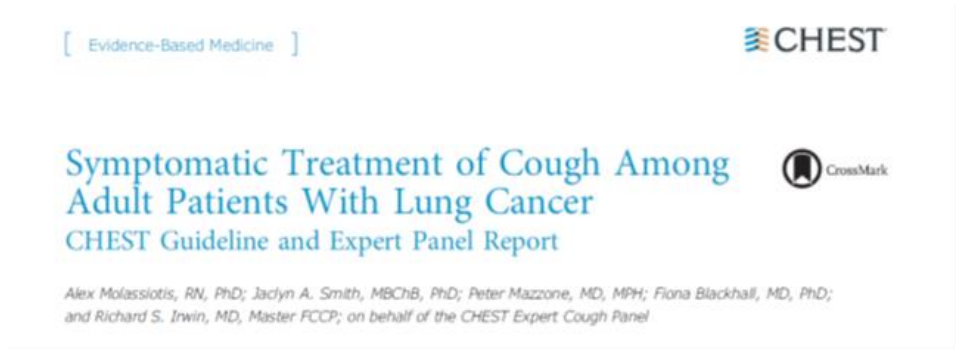
Intervention of cough

B. Pharmacological treatments

- hydropropizine and oxadiazol (Boselli 1972)
- butamirate citrate linctus (Charpin 1990)
- a mixture of codeine with phenyltoloxamine and dihydrocodeine (Dotti 1970)
- Two different Chinese herbal preparations (Koichiro 2002; Tao 2003)
- morphine and codeine (Kleibel 1982)
- levodropropizine and dihydrocodeine (Luporini 1998)
- sodium cromoglycate (Moroni 1996)
- dihydrocodeine (Tansini 1971)

Molassiotis A, et al. Cochrane Database Syst Rev. 2015

Symptomatic treatment of cough in patients wit lung cancer


[Evidence-Based Medicine]

CHEST

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer

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- CHEST assessed the existing guidelines and an updated Cochrane systematic review

2. The American College of Chest Physicians. Palliative care in lung cancer : ACCP evidence-based clinical practice guidelines (2nd edition). 2007
3. Clinical expert guidelines for the management of cough in lung cancer : report of a UK task group on cough. Cough. 2010
4. Management of chronic cough in patients receiving palliative care : review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland. Palliat Med. 2012

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in

1. In adult patients with cough associated with lung cancer that persists despite cancer treatment, we suggest, as a first step, that a comprehensive assessment according to a published, evidence-based management guideline be undertaken to identify any co-existing causes linked with cough and initiate treatment accordingly (Ungraded, Consensus Based Statement).

TABLE 2] Causes of Cough Among Patients With Cancer[a]

Pleural disease-effusion, tumor
Lung parenchyma infiltration
Major airway or endobronchial tumor
Cough after radiation or after chemotherapy
COPD; chronic bronchitis
Bronchiectasis
Pericardial effusion
Upper airway cough syndrome due to a variety of rhinosinus conditions
Gastroesophageal reflux disease
Asthma
Lymphangitis carcinomatosis
Chest infection
Microembolism
Tracheoesophageal fistula
Vocal cord paralysis
Congestive heart failure
Postinfectious cough
Eosinophilic bronchitis
Angiotensin-converting enzyme inhibitor

[a]Reviewed in Tse.[20]

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

2. In adult patients with lung cancer experiencing cough despite anticancer treatment, we suggest cough suppression exercises as alternative or additional to pharmacological therapy where such services are available (Grade 2C).

- **Cough suppression exercises**

- identifying cough triggers, cough suppression techniques (ie, pursed lip breathing, swallowing, sipping water), improvements in laryngeal and vocal hygiene and hydration, breathing exercises, and counseling

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

3. In adult patients with cough due to localized endobronchial disease for whom surgery, chemotherapy, or external beam radiation are not indicated, we suggest the use of endobronchial brachytherapy where such specialist facilities are available and in suitable patients (Grade 2C).

- When brachytherapy is indicated but not locally available, patients should be transferred to a facility where it is available.

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

4. In adult patients with lung cancer who require a pharmacological approach for the treatment of cough, we suggest an initial trial with demulcents such as butamirate linctus (syrup) or simple linctus (syrup) or glycerol-based linctus (syrup) where available (Grade 2C).

- There was one double-blind randomized trial

  butamirate citrate linctus (Sinecod syrup)

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

Dextromethorphan		
코타민(cotamin)SYR	대원제약	chlorpheniramine maleate 20 mg, dextromethorphan hydrobromide 150 mg, guaifenesin 400 mg, phenylephrine hydrochloride 75 mg/100 mL/SYR
코푸 에스 (cough s) SYR	유한양행	dextromethorphan hydrobromide 7.5 mg, dl-methylephedrine hydrochloride 13.125 mg, chlorpheniramine maleate 1.5 mg, ammonium chloride 0.1 g/10 mL/SYR
화이투벤 큐노즈 (whituben q nose) SC	알피코프	acetaminophen 180 mg, dextromethorphan hydrobromide hydrate 8 mg, dl-methylephedrine hydrochloride 12.5 mg, pseudoephedrine hydrochloride 15 mg, triprolidine hydrochloride 0.66 mg/SC
화이투벤 큐 (whituben q) SC	알피코프	
화이투벤 큐코프 (whituben q cough) SC	알피코프	

SMART 일차진료매뉴얼 2판(근거편) Vol.1
Part 04. 호흡기 - Chapter 01. 호흡기 진료를 위한 기초 - Topic 02. 호흡기에 흔히 사용되는 약물 - Subtopic 02-1. 진해제

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

5. In adult patients with lung cancer experiencing cough that does not respond to demulcents, we suggest pharmacological management using an opiate-derivative titrated to an acceptable side-effect profile (Grade 2C).

- Pholcodine or hydrocodone (where available) or dihydrocodeine or morphine
- Codeine is less preferred, because of its greater side effect
- Morphine should be used if the cough is not suppressed by other opioids

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

5. In adult patients with lung cancer experiencing cough that does not
suggest pharmacolo
opiate-derivative titr
profile (Grade 2C).

ffect

- Pholcodine or **hydrocodone** (whe
- Codeine is less preferred, because
- Morphine should be used if the cc

or **morphine**

r opioids

약학정보원

Molassiotis A, et al. Chest. 2017

Medication	Dosage
Simple linctus	5 mL tid or qid
Dextromethorphan	10-15 mg tid or qid (10-30 mg in some publications, maximum dose of 120 mg/d)
Codeine	30-60 mg qid
Pholcodine	10 mL qid
Morphine (Oramorph)	5 mg (single-dose trial of Oramorph; if effective 5-10 mg slow-release morphine bid)
Diamorphine	5-10 mg subcutaneously/24 hrs
Methadone linctus	Single dose 2 mg (2 mL of 1 mg/mL solution)
Dihydrocodeine[b]	10 mg tid
Hydrocodone	5 mg bid
Inhaled cromoglycate	10 mg qid
Levodropropizine[b]	75 mg tid
Moguisteine[b]	100-200 mg tid
Levocloperastine[b]	20 mg tid
Nebulized lidocaine[c]	5 mL of 0.2 tid
Nebulized bupivacaine[c]	5 mL of 0.25% tid
Benzonatate[b]	100-200 mg qid
Prednisolone	30 mg daily for 2 wk

[a]Adapted from Molassiotis et al.[13]

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

6. In adult patients with lung cancer experiencing opioid-resistant cough, we suggest a peripherally-acting antitussive (where available), such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate (Grade 2C).

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

levo-cloperastine fendizoate			
프리비투스(프리비투스) supp	대원	8 mL	• 1일 3회 1회 5 mL 복용
levodropropizine			
레보투스(levotuss) SYR	현대약품	6 mg/mL/SYR	• 1회 60 mg 1일 3회
레보투스(levotuss) T	현대약품	60 mg/T	
드로피진(dropizin) T	코오롱제약	60 mg/T	
드로피진(dropizin) SYR	코오롱제약	6 mg/mL/SYR	
레보텍(levotec) C	일화	60 mg/C	

Symptomatic treatment of cough in patients wit lung cancer

7. In adult patients with lung cancer experiencing opioid-resistant cough {that does not respond to peripheral antitussives} we suggest a trial with local anesthetics, including nebulized lidocaine/ bupivacaine or benzonatate (Ungraded, Consensus Based Statement).

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

8. In adult patients with intractable cough due to lung cancer in whom surgery, chemotherapy, external beam radiation, brachytherapy and the previously mentioned nonpharmacological and pharmacological approaches are ineffective or not indicated, we suggest that clinicians consider performing N-of-1 randomized controlled trials to determine if any of the following drugs might be of benefit in controlling cough because none have been definitively shown to be effective nor devoid of side effects: diazepam, gabapentin, carbamazepine, baclofen, amitriptyline, thalidomide (Ungraded, Consensus Based Statement).

Molassiotis A, et al. Chest. 2017

Symptomatic treatment of cough in patients wit lung cancer

[Thoracic Oncology Original Research]

CHEST

Aprepitant for Cough Suppression in Advanced Lung Cancer

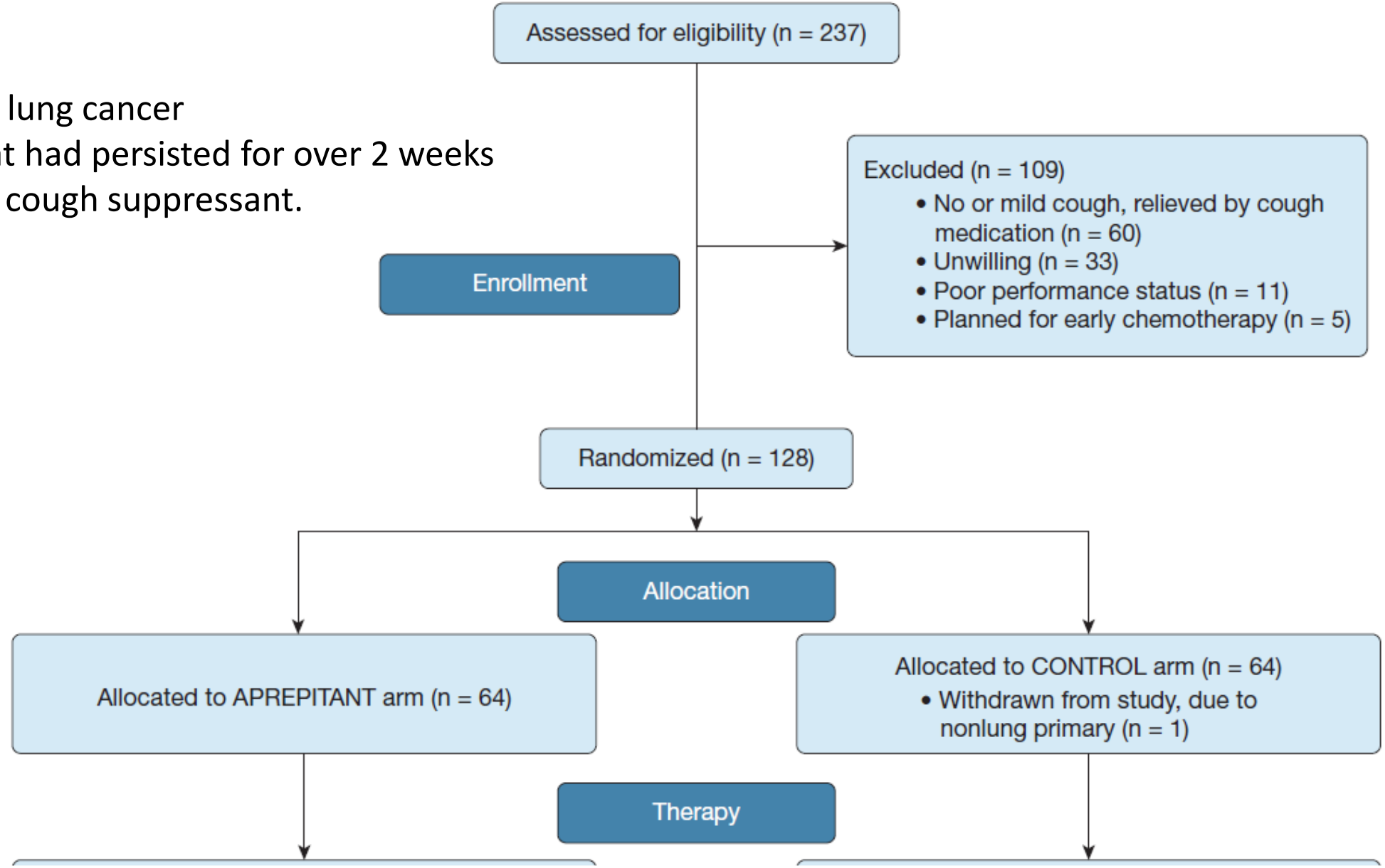
A Randomized Trial

Vanita Noronha, DM; Atanu Bhattacharjee, PhD; Vijay M. Patil, DM; Amit Joshi, DM; Nandini Menon, DNB; Srushti Shah, PDCR; Sadhana Kannan, MSc; Sadaf A. Mukadam, MTech; Kamesh Maske, MBA; Sandeep Ishi, DM; and Kumar Prabhash, DM

- Aprepitant is a neurokinin-1 inhibitor approved for the treatment of chemotherapy-induced nausea and vomiting.
- Via blockade of the effects of substance P
- Substance P has also been implicated in the cough reflex

Noronha V, et al. Chest. 2020

- advanced lung cancer
- cough that had persisted for over 2 weeks
  despite a cough suppressant.



Noronha V, et al. Chest. 2020

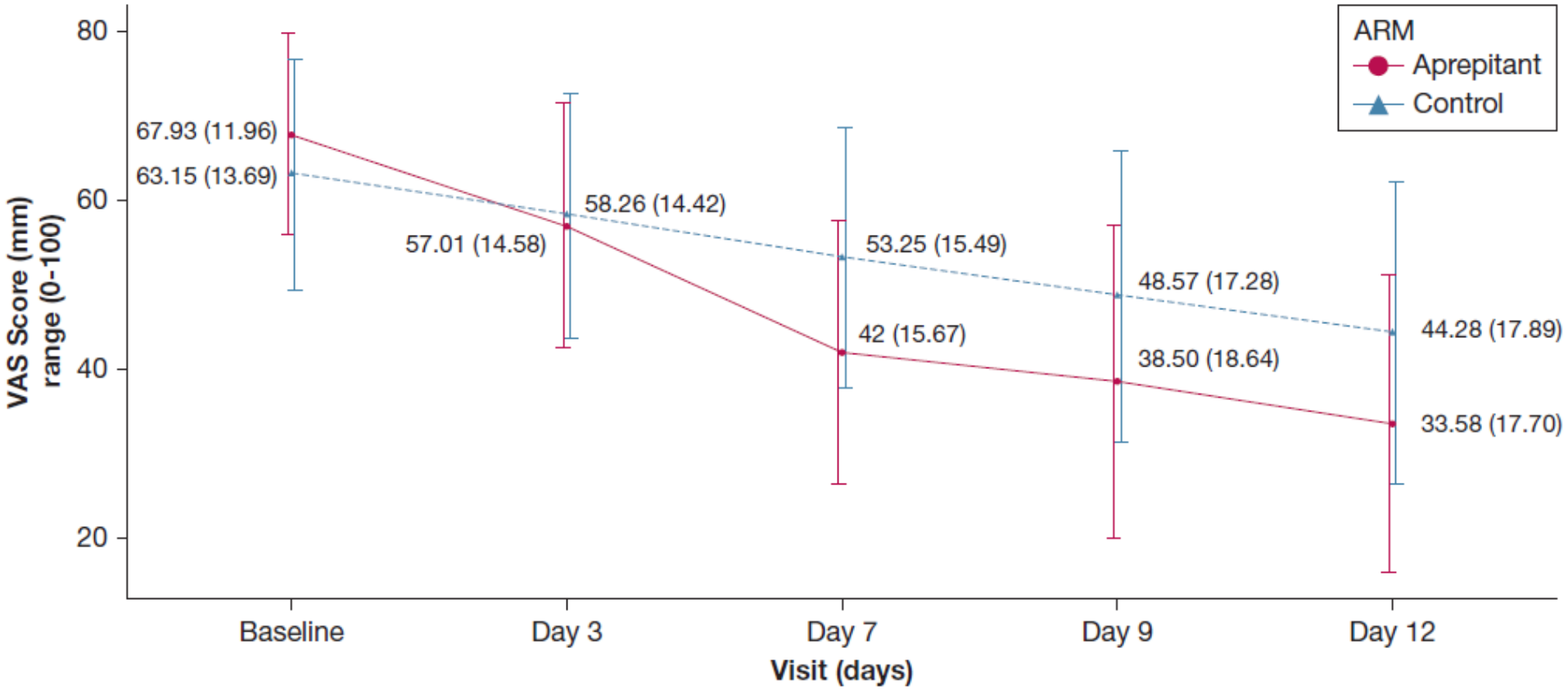


Figure 2 – *Mean Visual Analog Scale (VAS) scores at baseline and at time points 3, 7, 9, and 12 days of patients in the aprepitant arm and the control arm. Values provided at each time point represent mean VAS scores (in mm), followed by the SD in parentheses. Scores gradually decreased in both arms from baseline to days 3, 7, 9, and 12, but the magnitude of improvement was greater in the aprepitant arm compared with the control arm.*

The Visual Analog Scale (VAS; range, 0 to 100 mm)
- one end labeled “No cough” [0 mm]
- the other end labeled “Worst cough ever” [100 mm];

Noronha V, et al. Chest. 2020

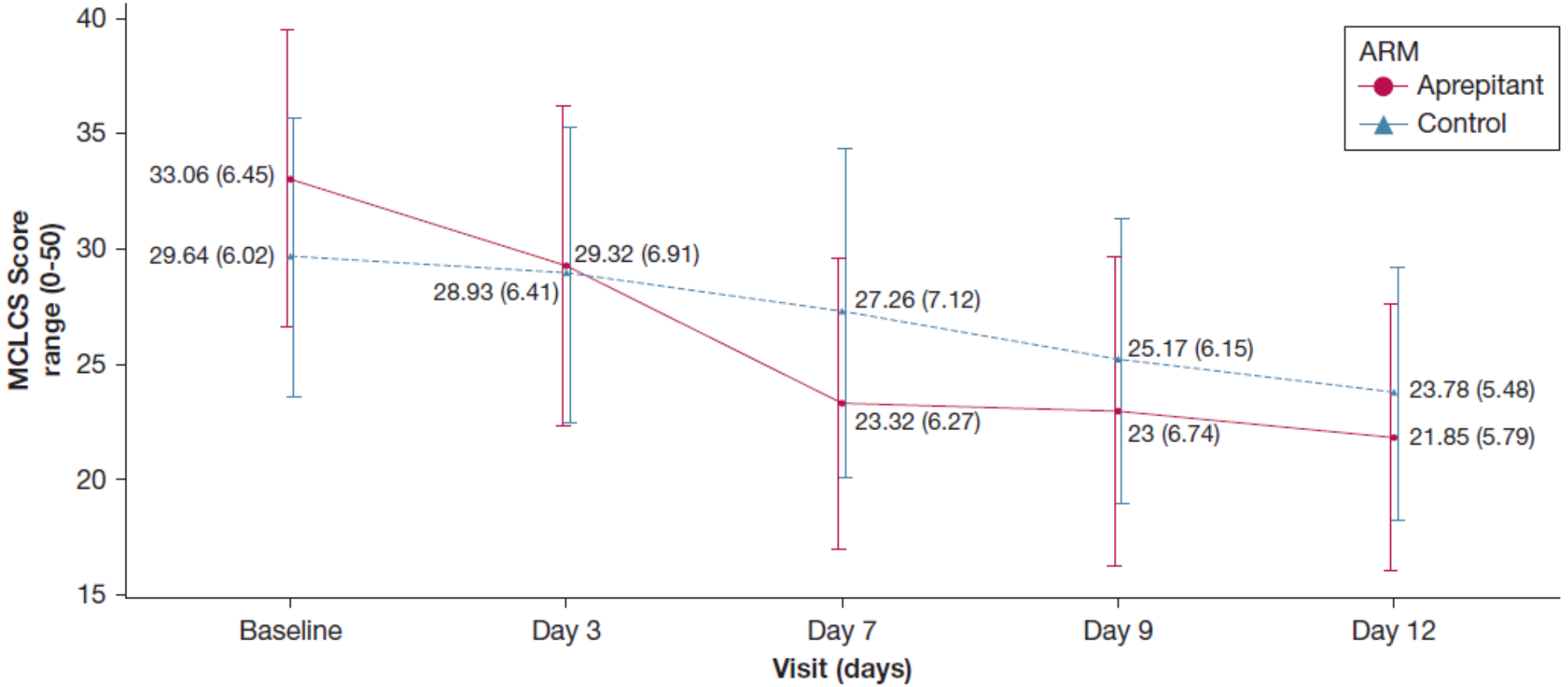


Figure 3 – *Mean Manchester Cough in Lung Cancer Scale (MCLCS) scores at baseline and at time points 3, 7, 9, and 12 of patients in the aprepitant arm and the control arm. Values provided at each time point indicate mean MCLCS scores, followed by the SD in parentheses. These values gradually decreased in both arms from baseline to days 3, 7, 9, and 12, but the magnitude of improvement was greater in the aprepitant arm compared with the control arm.*

The Manchester Cough in Lung Cancer Scale (MCLCS, score range, 10-50)
; describe the patient's cough experience in the preceding week
- a questionnaire consisting of 10 questions
- each, scored as 1 [never] to 5 [all the time];

Noronha V, et al. Chest. 2020

Symptomatic treatment of cough in patients wit lung cancer

- 다른 기침 원인 (COPD, IPF..) or endobronchial tumor
- Cough suppression exercises

Linctus (syrup) -> hydrocodone -> levodropropizine -> Aprepitant

morphine
codeine

levocloperastine

Noronha V, et al. Chest. 2020

Management of breathlessness in patients with lung cancer

- **Breathlessness - dyspnea - shortness of breath**

-> ‘subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity’.

- The gold standard for breathlessness assessment is based on **patient self-report**

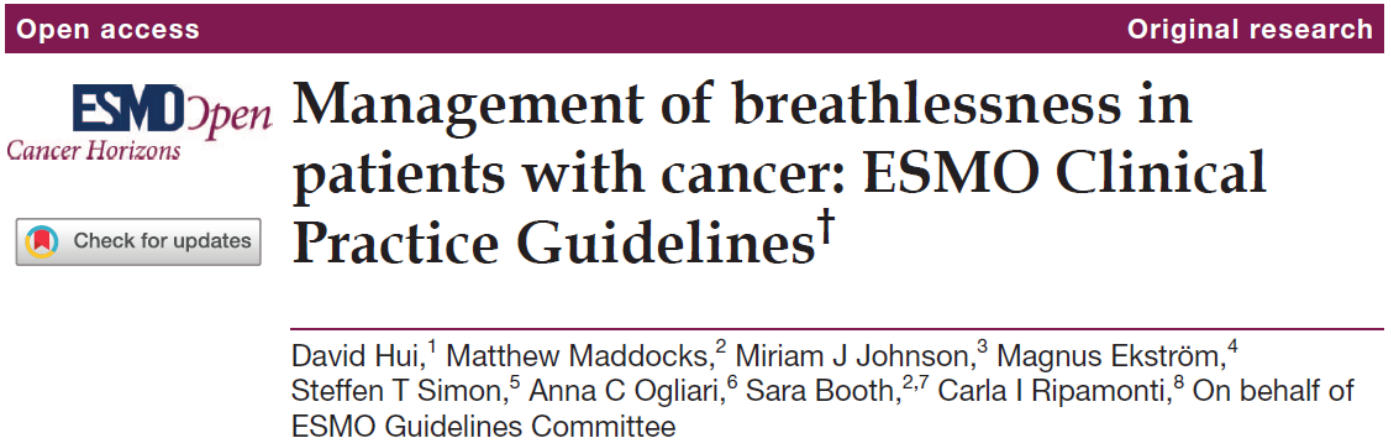
  : commonly used objective physiological measures & lung function tests

  -> a weak association with subjective sensations

(Hui D, et al. *J Palliat Med* 2013)

(Campbell ML, et al. *J Palliat Med* 2010)

Management of breathlessness in patients with lung cancer



- the evidence base is relatively limited
- Include studies conducted in other patient populations (COPD..)

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Assessment

►► **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*).

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Management of breathlessness

- Treat the underlying cause

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.

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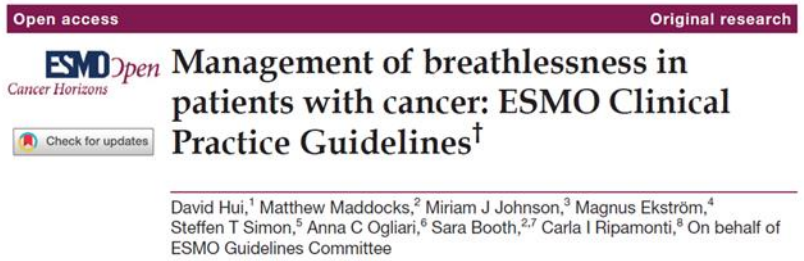
Management of breathlessness
- Non-pharmacological symptomatic interventions

- Fan or airflow
- Breathing retraining
- Mobility aids
- Education and self-management
- Pulmonary rehabilitation
- Complementary therapies



Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Fan or airflow

- a hand-held fan

- supports the use of a fan
  irrespective of the patient's oxygen saturation
  given its potential benefit and lack of harm.

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Review Article

Fan Therapy for the Treatment of Dyspnea in Adults: A Systematic Review

Yu Qian, MD, Yuan Wu, MD, Aline Rozman de Moraes, MD, Xue Yi, MD, Yimin Geng, MS, Seyedeh Dibaj, PhD, Diane Liu, MS, Jane Naberhuis, PhD, and Eduardo Bruera, MD

Table 1
Characteristics of Included Studies

Study (Reference)	*N*	Setting	Study Design	Blinding	Cancer-Related Dyspnea *n* (%)	COPD-Related Dyspnea *n* (%)	Age, yrs Mean (SD)	Fan The Durati minu
Bausewein 2010[19]	70	Hospital	RCT	Single blind	25 (36)	45 (64)	66 (9)	NR
Booth 2016[13]	31	Hospital/hospice	Single cohort	Open label	12 (39)	7 (23)	75 (11)	5
Galbraith 2010[6]	50	Hospital	RCT	Single blind	11 (22)	26 (52)	71 (33–90)	5
Johnson 2016[14]	49	Clinic/hospice	RCT	Open label	13 (27)	23 (47)	68 (12)[a]	NR
Kako 2018a[15]	9	Hospital	RCT	Single blind	7 (78)	2 (22)	77 (9)	5
Kako 2018b[16]	40	Hospital	RCT	Single blind	40 (100)	0 (0)	71 (8)[c]	5
Marchetti 2015[18]	10	Clinic	RCT	Single blind	0 (0)	10 (100)	62 (6)	NR
O'Driscoll 2011[11]	34	Hospital/clinic	RCT	Single blind	0 (0)	34 (100)	67 (9)	NR
Puspawati 2017[17]	21	Hospital	RCT	Single blind	21 (100)	0 (0)	54 (9)	5
Wong 2017[12]	30	Hospital	RCT	Single blind	30 (100)	0 (0)	NR	5
Total	344	—	—	—	159 (46)	147 (43)	—	—

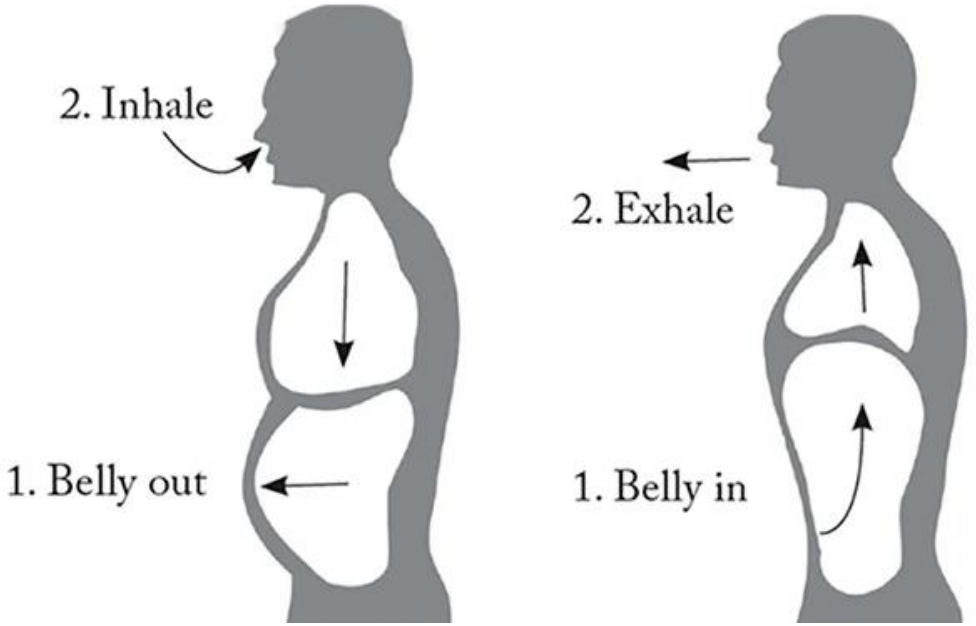
Summary of Study Findings

Study (Reference) and Intervention	Absolute Change in Dyspnea Mean (SD/Range)	*P*-value	Conclusion
Bausewein 2010[19]			
Fan	−0.6 (2.1)[a]	0.9	The effectiveness of a fan at relieving dyspnea could not be established
A placebo wristband	−0.8 (2.67)[a]		
Booth 2016[13]			
Fan	−1.04[b]	N/A	50% of patients with dyspnea at rest experienced relief using a handheld fan
Galbraith 2010[6]			
Fan to face	−7 (1.5 to 14.5)[c]	0.003	A handheld fan to the face reduced dyspnea
Fan to leg	−1.5 (−2 to 7)[c]		
Johnson 2016[14]			
Fan	−6 (2)[b]	0.853	Confirmed the feasibility of a definitive multisite trial to study the use of a handheld fan as part of the self-management of chronic dyspnea
No intervention	−5 (4)[b]		
Kako 2018a[15]			
No fan	0[b]	0.02	A fan to the face resulted in relief of dyspnea
Fan to leg	0[b]		
Fan to face	−0.7[b]		
Kako 2018b[16]			
Fan to face	−1.35 (−1.85 to −0.84)[b]	0.001	A fan to the face was effective at alleviating dyspnea in terminally ill cancer patients
Fan to leg	−0.1 (−0.53 to 0.33)[b]		
Marchetti 2015[18]			
Fan to face	5 (0–10)[a]	0.03	A fan to the face improved exercise performance in patients with COPD
Fan to leg	6.5 (0–10)[a]		
O'Driscoll 2011[11]			
Room air	5.1 (1.7)[a]	N/A	A fan had no apparent physical or placebo effect
Electric fan	5.1 (1.7)[a]		
Air mask	5.3 (1.6)[a]		
Oxygen mask	5.1 (1.7)[a]		
Puspawati 2017[17]			
Fan with diaphragmatic breath exercise	−1.21 (0.56)[a]	0.003	A handheld fan decreased dyspnea in non-hypoxemic, dyspneic lung cancer patients
Diaphragmatic breathing exercise	−0.69 (0.46)[a]		
Wong 2017[12]			
Fan	−1.53[b]	0.01	Fan therapy was effective at alleviating dyspnea in Chinese patients with advanced cancer
Accompanied by caregivers with no fan	−0.13[b]		

COPD = chronic obstructive pulmonary disease; N/A = not applicable.
[a]Modified Borg Scale/Borg Scale.

Breathing retraining

- pursed-lip breathing
- diaphragmatic breathing



Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Mobility aids

- A rollator

- A modern ‘draisine’ (bicycle without pedals)

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Education and self-management

►► **Educate and inform patients on strategies including activity pacing, relieving positions and distraction techniques to encourage self-management (II, B).**

- Patients should be assured that being breathless is itself not dangerous

- Even following incremental exercise to a symptom-limited maximum, breathlessness in people with lung cancer typically recovers within a few minutes

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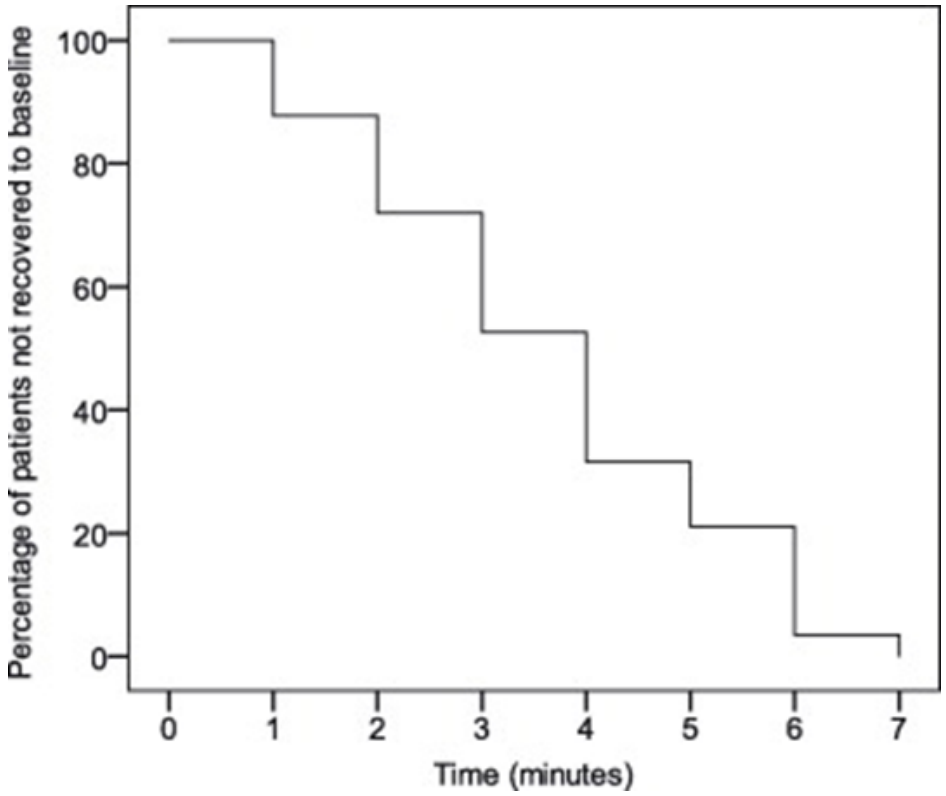
Education and self-management



Time to recovery from exercise-induced breathlessness in patients with thoracic cancer (n = 57).

(Maddocks M, et al. Lung Cancer 2012)

Pulmonary rehabilitation

►► **Refer patients to available exercise-based rehabilitation programmes**

- Both pulmonary and cardiac rehabilitation have a strong evidence of effectiveness in improving breathlessness, functional exercise capacity and health-related QoL

- However, the efficacy of pulmonary rehabilitation in patients with advanced cancer is unclear,

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Complementary therapies

►► Consider a therapeutic trial of acupressure or acupuncture according to patient preference (II, C).

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Review Article

Acupuncture for Breathlessness in Advanced Diseases: A Systematic Review and Meta-analysis

Philipp von Trott, MD, MSc, Shiao Li Oei, PhD, and Christina Ramsenthaler, MSc, PhD
King's College London (P.v.T., C.R.), Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, London, UK; Havelhoehe Hospital (P.v.T.), Berlin; and Research Institute Havelhoehe (S.L.O.), Berlin, Germany

190 patients with cancer and 347 patients with COPD found overall benefit from acupuncture on breathlessness severity

Management of breathlessness
- **Pharmacological symptomatic interventions**

- Opioids
- Benzodiazepines
- Corticosteroids
- Supplemental oxygen
- Non-invasive ventilation
- Antidepressants
- Cannabinoids


Open access Original research

ESMO Open Cancer Horizons

Check for updates

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

David Hui,[1] Matthew Maddocks,[2] Miriam J Johnson,[3] Magnus Ekström,[4] Steffen T Simon,[5] Anna C Ogliari,[6] Sara Booth,[2,7] Carla I Ripamonti,[8] On behalf of ESMO Guidelines Committee

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Pharmacological symptomatic interventions

1. Opioids

►► **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).

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Pharmacological symptomatic interventions

1. Opioids

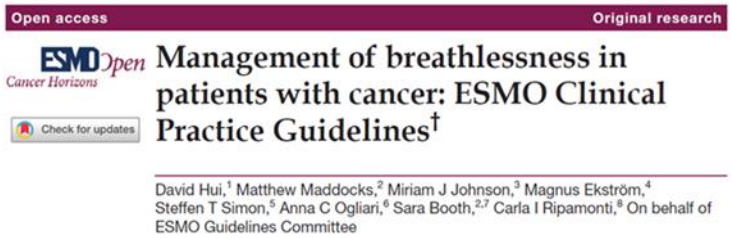
- There is no clear evidence to support use of nebulized opioids.

(Barnes H, et al. Cochrane Database Syst Rev 2016)

- There are no head-to-head comparisons of immediate-release (IR) and extended-release (ER) formulations for breathlessness.

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness
- Pharmacological symptomatic interventions
1. Opioids – prophylactic use prior to exertion



- IR opioids or sustained-release opioids prior to activity

- Subcutaneous fentanyl (Hui D, et al. *J Pain Symptom Manage* 2014)
- Fentanylpectin nasal spray (Hui D, et al. *J Pain Symptom Manage* 2016)
- Fentanyl buccal tablet (Hui D, et al. *J Pain Symptom Manage* 2017)
- Fentanyl sublingual spray (Hui D, et al. *J Pain Symptom Manage* 2019)

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Pharmacological symptomatic interventions

2. Benzodiazepines

►► Benzodiazepines **<u>may be used with caution</u>** in patients with cancer for the relief of breathlessness <u>with associated anxiety</u> if opioids are not effective (V, C).

or panic

risk of delirium

►► **In the last days of life**, benzodiazepines may be considered for palliative sedation in patients with refractory breathlessness despite other treatments (IV, C).

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Pharmacological symptomatic interventions

3. Corticosteroids

►► Corticosteroids may be considered for palliation of cancer-related breathlessness refractory to other treatments (II, C).

- Reviewed for 2 RCTs (Haywood A, et al. Cochrane Database Syst Rev 2019)

  (dexamethasone)

- A larger confirmatory randomised trial (clinicaltrials. gov NCT03367156)

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Management of breathlessness

- Pharmacological symptomatic interventions

4. Supplemental oxygen

►► 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).

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020

Management of breathlessness

- Pharmacological symptomatic interventions

5. Antidepressants and Cannabinoids

Symptom clusters

- Depression and anxiety are associated with increased breathlessness

►► 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).

Hui D, et al. ESMO Clinical Practice Guidelines. ESMO Open. 2020