The characterisation and treatment of cough in lung cancer

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD)in the Faculty of Medical and Human Sciences

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Dr Amélie Sylvia Mary Harle

School of Medicine
Institute of Inflammation and Repair

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List of Abbreviations

ACCP	American College of Chest Physicians
ACE	Angiotensin Converting Enzyme
ACM	Ambulatory Cough Monitoring
AE	Adverse Events
AMPA	α-Amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid
ARDS	Acute Respiratory Distress Syndrome
ASCO	American Society of Clinical Oncology
AST	ASpartate aminoTransferase
BAC	Bronchioalveolar Carcinoma
BAL	Bronchioalveolar Lavage
BK	Bradykinin
BK2	Bradykinin 2
BOOP	Bronchiolitis Obliterance Organising Pneumonia
BRI	Brief Reflux Inventory
CCIQ	Chronic Cough Impact Questionnaire
CF	Cystic Fibrosis
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CQLQ	Cough Quality of Life Questionnaire
CRTZ	Chemoreceptor Trigger Zone
CSD	Cough Severity Diary
CTCAEv4.0	Common Toxicity Criteria for Adverse Events version 4.0
CXR	Chest X-ray
DAD	Diffuse Alveolar Damage
DVD	Digital Versatile Disc
ECOG	Eastern Cooperative Oncology Group

EGFR	Epidermal Growth Factor Receptor
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Core 30
EP	Eosinophilic Pneumonia
ERS	European Respiratory Society
ES	Extensive Stage
FACT-L	Functional Assessment of Cancer Therapy – Lung
FEV-1	Forced Expiratory Volume in first 1 second of expiration
FEV6	Forced Expiratory Volume in first 6 seconds of expiration
FU	Follow-up
FVC	Forced Vital Capacity
Ga-67	Gadolinium 67
GB	Gigabyte
GCP	Good Clinical Practice
GEE	General Estimating Equations
GI	Gastro-Intestinal
GORD	Gastro-Oesophageal Reflux Disease
GRCS	Global Rating of Change Scale
HRCT	High Resolution Computed Tomography
IASLC	Internation Association for the Study of Lung Cancer
ICC	Intra-class Correlation Coefficient
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IQR	Inter Quartile Range
LC	Lung Cancer
LC13	Lung Cancer Module 13
LCQ	Leicester Cough Questionnaire

LCSS	Lung Cancer Symptom Scale
LDH	Lactate Dehydrogenase
LS	Limited Stage
MCLCS	Manchester Cough in Lung Cancer Scale
mGluR	Metabotrophic Glutamate Receptor
MID	Minimum Important Difference
NICE	National Institute for Clinical Excellence
NK1	Neurokinin-1
NK2	Neurokinin-2
NK3	Neurokinin-3
NKA	Neurokinin A
NMDA	N-Methyl-D-Aspartate
NRS	Numerical Rating Scale
NSCLC	Non Small Cell Lung Cancer
nTS	Nucleus Tractus Solitarius
NYHA	New York Heart Association
OCP	Oral Contraceptive Pill
OTC	Over The Counter
P2X3	P2X purinoceptor 3
PF	Pulmonary Fibrosis
PGE2	Prostaglandin E2
PPI	Proton Pump Inhibitor
PRO	Patient Reported Outcome
PS	Performance Status
QoL	Quality of Life
RAR	Rapidly Adapting Receptor
REC	Research Ethics Committee

RS	Raw Score
SAE	Serious Adverse Event
SAS	Symptom Assessment Scale
SCC	Squamous Cell Carcinoma
SCLC	Small Cell Lung Cancer
SD	Standard Difference
SDS	Symptom Distress Scale
SF36	Short Form 36 item health status questionnaire
SGRQ	St Georges Respiratory Questionnaire
SP-A	Substance P-A
SP-D	Substance P-D
SUB P	Substance P
TKI	Tyrosine Kinase Inhibitor
TRP	Treatment Related Pneumonitis
TRPA1	Transient Receptor Potential A1
TRPV1	Transient Receptor Potential Vanilloid-1
TSSD-LC	Thurston Scale of Symptom Distress in Lung Cancer
VAS	Visual Analogue Scale

Abstract

Institution
University of Manchester
Candidate
Dr Amélie Sylvia Mary Harle
Degree Title
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Cough in lung cancer (LC) is a significant unmet need. There are no evidence-based effective antitussives for its treatment and a lack of well-designed trials incorporating validated cough assessment tools and placebo controls. There is little research on its underlying mechanisms, perhaps with the assumption that it is simply ‘due to the cancer’. Therefore, we have sought to characterise cough in terms of its severity, impact on quality of life, frequency and prevalence using LC specific subjective and objective assessment tools for the first time. We have also explored its potential mechanisms and treatment. Published preclinical data show that the substance P/neurokinin-1(NK1) pathway is implicated in cough in 5 different species. This pathway is targeted by the antiemetic aprepitant in humans. Data on the use of aprepitant as a novel antitussive are presented.

To characterise cough and assess cough assessment tools in a cohort of patients with LC attending outpatient clinics, subjective and objective cough assessment tools including 24-hour ambulatory cough monitoring (ACM), were used to determine the cough severity, frequency, impact and cough- associated clinical factors in a longitudinal study.To determine cough prevalence, a cross sectional study of all patients attending thoracic oncology outpatient clinics in a single centre over a defined period were approached to determine whether they had a cough, to provide demographic and cancer related data and if applicable, to complete the Manchester Cough in Lung Cancer Scale (MCLCS) cough impact questionnaire and the cough severity visual analogue scale.To explore the role of the NK1 pathway in cough in patients with LC, a single-arm randomised placebo controlled pilot trial assessing aprepitant for the treatment of cough was conducted.

The presented data demonstrated that cough affects over half of patients with LC, representing a huge unmet clinical need. Over 2/3rds of patients felt that their cough was severe enough to warrant treatment and over 1/4 described it as painful. Patients with LC suffer from a very severe and frequent cough. Its impact is considerable, with effects on physical, psychological and social domains. The longitudinal study is the first to report that cough severity and impact is predicted by gastro-intestinal co-morbidities rather than cancer related factors. The presented data demonstrate that ACM is feasible and acceptable to patients with LC. This provides researchers with an objective endpoint for use in clinical trials. The MCLCS performs well and is valid. The cough intervention trial is the first to demonstrate that aprepitant is associated with lower subjective cough scores and cough frequency using validated cough assessment tools. No antitussive therapy study has ever shown a positive antitussive effect using both types of cough assessment tools in the LC population. This suggests that the substance P/NK1 pathway is implicated in cough in LC and identifies this as a potential new therapeutic target, providing exciting data and hope for future patients with LC.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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Dedication

This thesis is dedicated to James, Théodore, Félix. It was a team effort in so many ways and I thank you for your kindness and support. I would also like to dedicate it to Grandad. Merci d'avoir été aussi enthousiaste vis à vis ma recherche. Je suis ravie d'avoir pu la partager avec toi. Lastly, I would like to dedicate my work to Howard Raynor, an inspirational patient I cared for in 2011:"Whatever you do, do it to the best of your ability."

1. Introduction

1.1 Search Strategy

Since there was little published research directly pertaining to cough in patients with lung cancer, the search strategy was broad. Handsearching was essential for identification of studies that may have had relevant information. Studies with such information may not have had “cough” as a key word, nor key phrases such as “cough prevalence”, “cough impact” etc. Many studies would fail to have the key words or phrases in the abstract since this was not the main focus of the publication. Therefore, formal systematic review methods would have been too restrictive and may have led to significant omissions. Handsearching included key journals such as Cough, Journal of Thoracic Oncology, Lung Cancer and Supportive Care in Cancer. Authors of main studies and leaders in the field of cough and in the field of lung cancer were approached in order to determine any unpublished literature or grey literature. Conference abstracts were reviewed for key conferences. Search terms such as “cough”, “lung cancer”, “cough impact”, “cough prevalence”, “cough mechanisms”, “cough predictors”, “clinical factors”, “cough frequency”, “quality of life”, “antitussive”, “cough treatment” , “cough assessment”, “cough questionnaire”, “lung cancer symptom”, “ambulatory cough monitoring” were extensively searched. Abstracts in the English and French language were all reviewed and if there was the suggestion that relevant information may be within the main body of the article, this was also reviewed.

1.2 Overview

” Coughing at night time seems to be the worst…when I'm lying there…and it can be a prolonged bad cough. I could be sick, but I've not been. But it's that sort of feeling that you just cough and cough and cough. The cough is the worst thing. “ (a patient with lung cancer)[1]

Although cough is a common symptom associated with lung cancer, it remains poorly understood by health care professionals and researchers alike. Its impact on patients is significant yet, effective, scientifically-proven treatments are lacking. The existing published data on this troublesome symptom are often of poor quality. To date, cough has received minimal research attention. Therefore, many

questions about its prevalence, severity, impact, assessment, predictors, causes and treatment remain unanswered. Currently, thousands of patients with lung cancer live with a high symptom burden. Lung cancer is often incurable and associated with a short prognosis. Therefore optimising the quality of life of patients is of paramount importance. Effective symptomatic relief represents one of the cornerstones of supportive care for cancer patients. The American Society of Clinical Oncology (ASCO) stated in 1998:

"…it is the oncologists' responsibility to care for their patients in a continuum that extends from the moment of diagnosis throughout the course of the illness. In addition to appropriate anticancer treatment, this includes symptom control and psychosocial support during all phases of care, including those during the last phase of life " [2].

To this end, Temel et al. has sought to investigate the benefits of early palliative care input for newly diagnosed patients with advanced stage lung cancer commencing first line chemotherapy [3]. The results have been widely publicised and continue to be frequently cited by researchers and health care professionals alike since they have surprised many. Not only does the integration of palliative care at the time of diagnosis lead to better palliation of symptoms and improvements in quality of life, but it has also been shown to improve overall survival by about eight weeks. This, despite the fact that many patients randomised to early palliative care received less aggressive anticancer therapies. Sloan et al. have also shown that baseline quality of life scores at the time of lung cancer diagnosis are significant and independent predictors of survival (even when other clinical factors are adjusted for)[4]. Whilst the exact reasons for the improvement in overall survival still need to be elucidated, this emphasises the importance of recognising and treating symptoms such as cough early in the course of the disease to improve patient outcomes.

In order to meet the huge unmet clinical need and to answer questions that have remained unanswered for too long, we have sought to characterise cough in lung cancer, using novel validated subjective and objective cough assessment tools.

1.3 The impact of cough and its assessment in lung cancer

Traditionally, in the field of oncology, the impact of symptoms such as cough has been underestimated. Physician-rated scales such as the Common Toxicity Criteria for Adverse Events have been widely used in intervention trials. Therefore, much of the published data on the symptom burden of lung cancer on patients have been derived from such trials. However, this poses three main problems.

The first is that patients enrolled on these trials may not be representative of a "real-world" lung cancer patient population since trial patients are frequently of good performance status, well enough to receive treatments such as chemotherapy and with a lower burden of symptoms than many other patient with lung cancer.

The second is that physician rated scales frequently underestimate the true impact and distress of symptoms compared to patient-reported outcome scores [5-7]. It is only more recently, that the importance of using *patient-reported outcomes* in the field of oncology research for the robust assessment of cancer-related symptoms has been recognised by many oncology researchers.

The third is that since many cancer intervention trials are not designed to assess symptom scores as their primary endpoint, the symptom data are often incompletely reported, if at all and are rarely collected longitudinally thereby failing to describe changes over time. Tishelman et al. have previously suggested that the impact that a cough has on a patient or carer differs according to the situation the patient finds themselves in, i.e.: where they are on the disease trajectory (i.e. newly diagnosed compared to palliative, end of life care), where they are on the treatment trajectory or their social circumstances[8]. In a study of 400 patients with inoperable lung cancer, cough was described as the fourth most distressing symptom in the year prior to death [9]. The distress caused by the cough was most marked one-two months prior to death [9].

Although quality of life studies often focus on the frequency or intensity of symptoms, Tishelman et al has shown that symptom distress does not necessarily equate to symptom intensity [8]. In this study, patients with lung cancer ranked nine symptoms in terms of distress and intensity using the Thurston Scale of Symptom Distress in Lung Cancer (TSSD-LC) and the Symptom Distress Scale (SDS) at several time points following diagnosis. Dyspnoea and pain were consistently ranked higher in terms of distress than intensity, whilst fatigue was consistently ranked lower in terms of distress than intensity. Cough, like dyspnoea and pain had higher reported distress than intensity scores. The next most distressing symptoms after breathlessness tended to be pain and fatigue. Tishelman et al. explain that the different emphasis placed on the distress caused by these symptoms may relate to the future implications of the symptom. For example, a patient may relate dyspnoea to death more readily than fatigue to death. Hence, it is the future implications of the symptom that may be more relevant if we are to understand its distress, rather than its intensity. For a complete assessment of the symptoms, both intensity and distress need to be measured to understand the impact that a symptom has on a patient.

1.3.1 Impact of cough in lung cancer

A study by Molassiotis et al., published in 2010, is the only known study to specifically describe the "*experience"* of cough in lung cancer patients [1]. This was a qualitative study of 26 patients who had had a cough in the past or were current sufferers. The study's aim was to characterise the impact of cough rather than the symptom intensity. It showed that cough impacted on physical, psychological and social aspects of daily living. It also impacted on caregivers. Although the study was small, it has provided researchers and health care professionals with a more comprehensive assessment of the wide-ranging impact of cough [1]. A more recent study assessing the content validity of the Pulmonary Symptom Index of the Functional Assessment of Cancer Therapy—Lung (FACT-L) in the context of patients with advanced NSCLC receiving second and third-line systemic anticancer therapy, showed that 10/15 patients ranked their cough as

“very important”, 2/15 patients ranked it as “moderately important” and only 2/15 ranked it as “not important”. Patients also had semi-structured interviews. Some explained that their cough prevented them from lying down and sleeping [10].

More recently, two studies by Iyer et al. have sought to describe the burden of symptoms in lung cancer patients, in European and US populations [11, 12]. The assessment tools used were lung cancer-specific and generic tools as well as the lung cancer symptom severity tool (LCSS) rather than comprehensive symptom-specific tools. These two studies were conducted in large real-life clinic populations and therefore increase our understanding of the burden of symptoms in the context of lung cancer even if they do not specifically measure the full impact of individual symptoms such as cough. They both showed a high burden of symptoms which had a negative impact on the quality of life of patients. Although cough was not identified as an independent predictor of lung cancer specific quality of life scores (FACT-L) in the European study, it was an independent predictor of lung cancer specific quality of life scores (FACT-L) in the US study ($\beta = -0.145$; $p = 0.001$). The discrepancy between the two studies may suggest that the FACT-L may not be sufficiently robust to reliably assess the impact of symptoms such as cough on quality of life. It may also be that the LCSS, which comprises of nine visual analogue scales to assess nine symptoms is too blunt to assess cough and therefore to identify a potential correlation between cough and QoL. Not only this but, the visual analogue scales ask for recall over the previous 24hours specifically. Interestingly, in the US study, both shortness of breath and fatigue were independent predictors of FACT-L scores. Since shortness of breath, cough and fatigue are a recognised symptom cluster of lung cancer, one might also expect cough to be an independent predictor of quality of life scores [13].

In other diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), asthma and chronic cough, cough is known to have a significant impact on the quality of life of patients [14-22]. Its impact is also known to differ according to the diagnosis, even if the magnitude of the effect of quality of life is similar across different diseases [23]. For example, COPD sufferers tend to have significant physical limitations and have less energy compared to gastro-oesophageal reflux disease (GORD) and asthma sufferers [16]. Hence, a patient

with a cough and impaired lung function due to COPD may find that the cough limits their daily activities more severely than in a patient with a cough but normal lung function (i.e. relating to GORD). Similarly, the degree of anxiety caused by a cough and hence the effect of anxiety on the QoL of patients may vary. Anxiety is known to be a factor in determining the QoL of chronic cough sufferers [24]. How QoL is affected by cough in lung cancer is not fully known. There has been very little research in this area. There is therefore a real need for lung cancer specific cough QoL research to be conducted.

Several studies assessing cancer treatments show that improving cough is associated with improved QoL [25-27]. Rarely is cough isolated in terms of QoL measurements. Studies tend to look at respiratory and other symptoms and show that the treatment measured leads to an improvement in symptoms and improvement in quality of life. However, the extent to which global QoL is affected by cough is not clear. This was highlighted by a study by in which different QoL questionnaires were used, both generic and cough specific in a chronic cough population. There was a statistically significant correlation between cough and quality of life using the cough specific quality of life tools but that this was not apparent when the generic quality of life tool was used [28].

Currently, the QoL tools that are lung cancer specific are inadequate to assess the impact that a specific symptom such as cough has on the overall QoL of a patient. There is a need for not only lung cancer specific quality of life tools to be used but also a need for the development of validated symptom specific tools to assess the impact of specific symptoms such as cough in lung cancer patients [29].

The physical impact of cough in lung cancer

In a very limited number of studies, cough has been shown to cause a variety of symptoms, including poor appetite, poor sleep, vomiting, fatigue, pain, anxiety, syncope and even incontinence [1, 30, 31] It is also significantly associated with dyspnoea [32]. Cough may also aggravate pre-existing symptoms or be associated with other symptoms, such as in the case of symptom clusters [33].

Variables	Symptoms
Cardiovascular	Arterial hypotension
	Bradyarrhythmias and tachyarrhythmias
	Dislodgement/malfunctioning of intravascular catheters
	Loss of consciousness
	Rupture of subconjunctival, nasal, and anal veins, and massive intraocular suprachoroidal haemorrhage during pars plana vitrectomy
Constitutional symptoms	Excessive sweating, anorexia, exhaustion
GI	Gastroesophageal reflux events
	Gastric haemorrhage following percutaneous endoscopic gastrostomy
	Hepatic cyst rupture
	Herniation's (*eg:* inguinal, through abdominal wall, small bowel through laparoscopic trocar site)
	Malfunction of gastrostomy button
	Mallory-Weiss tear
	Splenic rupture
Genitourinary	Inversion of bladder through urethra
	Urinary incontinence
Musculoskeletal	From asymptomatic elevations of serum creatinine phosphokinase to rupture of rectus abdominus muscles
	Diaphragmatic rupture
	Rib fractures
	Sternal wound dehiscence
Neurological	Acute cervical radiculopathy
	Cerebral air embolism
	Cerebral spinal fluid rhinorrhoea
	Cervical epidural hematoma associated with oral anticoagulation
	Cough syncope
	Dizziness
	Headache
	Malfunctioning ventriculoatrial shunts
	Seizures
	Stroke due to vertebral artery dissection
Ophthalmologic	Spontaneous compressive orbital emphysema of rhinogenic origin
	Others are listed under 'Cardiovascular'
Psychosocial	Fear of serious disease
	Lifestyle changes
	Self-consciousness
Quality of life	Decreased
Respiratory	Exacerbation of asthma
	Herniations of the lung (*e.g.*, intercostal and supraclavicular)
	Hydrothorax in peritoneal dialysis
	Laryngeal trauma (*e.g.*, laryngeal oedema and hoarseness)
	Pulmonary interstitial emphysema, with potential risk of pneumatosis intestinalis, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum, pneumothorax, subcutaneous emphysema
	Tracheobronchial trauma (*e.g.*, bronchitis and bronchial rupture)
Skin	Petechiae and purpura
	Disruption of surgical wounds

Table 1 The physical complications of cough.

Adapted from Irwin et al.[33], GI = gastro-intestinal

Pain (usually in the chest area) is often reported by patients with lung cancer who cough [1]. Cough can lead to muscle strain and fracturing of ribs and can also aggravate pain at other sites [30]. Controlling the pain associated with coughing is problematic since coughing is usually intermittent and this can heighten distress [1]. Retching and vomiting are sometimes associated with coughing. It can also interrupt sleep [1].

Clusters of symptoms are increasingly being recognised in patients suffering from cancer. Two recent studies have shown that cough is associated with dyspnoea and fatigue [13, 34] . It is not always apparent to patients which symptom precedes the other. Dyspnoea can cause coughing at times, but patients also report that coughing causes dyspnoea. Fatigue results directly from continuous coughing and breathlessness but it can also be caused indirectly by insomnia [1]. Not only do symptoms appear to precipitate one another, but they also exacerbate one another. The distress from these symptoms can be significant, confirming earlier research suggesting that cough, breathlessness and fatigue are the symptoms most associated with distress in patients with lung cancer [1, 9]. In lung cancer survivors, the same symptom cluster of cough, dyspnoea and fatigue has also been identified [34].

The psychological impact of cough in lung cancer

Patients living with a serious diagnosis such as lung cancer, whether it is potentially curable or incurable, are under significant emotional pressure. The additional burden from uncontrolled symptoms such as cough can sometimes significantly impact on their quality of life [4]. It is well recognised that patients who suffer from a persistent cough also frequently suffer from psychological complaints [31, 35, 36]. However, very few studies have sought to describe the psychological impact of cough on lung cancer patients specifically.

In a study by McGarvey et al. chronic coughers were shown to have a higher prevalence of psychological co-morbidity than a normal population [35]. However,

this study was limited by the small number of patients included, most of whom were female, the lack of controls and by the fact that cough-specific assessment tools were not used. Polley et al. showed that many chronic cough sufferers often feel self-conscious about their cough[23]. In Molassiotis' study, a minority expressed feelings of anger, irritability and anxiety associated with the cough [1]. This has also been shown in chronic cough sufferers and in a study of members of the general public by Everett et al, in which UK patients answering a postal survey indicated that the presence of a cough caused distress, anger, anxiety and depression[36]. In a further study in which 170 outpatients with lung cancer were enrolled in a prospective observational study, cough was found to be significantly associated with anxiety (p=0.001) in patients *and* in their carers [31].

The reasons for an association between anxiety and cough may demonstrate that for some patients, cough is a reminder of their illness or even an indication that their treatment might not be working [1]. It may also be an indication to others of illness and therefore embarrassing. A recent study showed that cancer related symptoms such as cough were related to hope (i.e.: higher burden of symptoms led to decreased hope[37]). Since this was a cross-sectional study, causality could not be attributed. However, patients with increased symptoms may lose hope since they feel that their worsening symptom indicates worsening disease. The loss of hope may also exacerbate symptoms such as cough. In chronic cough sufferers, cough has been found to be significantly associated with depression [38]. This has not been demonstrated to date in patients with lung cancer.

The social impact of cough in lung cancer

Many patients are dependent on their social interaction with close family and friends in order to cope with their diagnosis of lung cancer. Patients who are socially isolated are likely to be more vulnerable than those who have a strong social network to support them through an emotionally and physically difficult time.

In a study assessing the quality of life of patients with different respiratory illnesses, patients with chronic cough reported that their cough had a significant impact on the psychosocial aspects of their lives, compared to patients with bronchiectasis [23]. This related particularly to social embarrassment due to their cough [23]. Patients with chronic cough are known to restrict their social life due to coughing [14, 30]. The same appears to be true for patients with lung cancer. In the qualitative study by Molassiotis et al, patients with lung cancer reported that their cough had a significant impact on their social interaction [1]. Sometimes the fear of coughing in public venues or even the prospect of coughing during the night in a hotel room and disturbing other hotel guests was a cause of anxiety, limiting their outings [1]. Patients reported losing the enjoyment of food because meal times were so difficult due to the cough. Sometimes, patients even limited their use of the telephone since their cough worsened during conversation and significantly interrupted the calls [1].

The social impact of a cough may vary depending on the gender of the patient. This has previously been shown in a study of patients with chronic cough in which women were found to suffer from greater physical and social consequences of their cough in terms of their quality of life [15]. Women had a greater burden of physical symptoms such as urinary stress incontinence which caused social embarrassment. The gender differences on the impact of cough on the overall quality of life of patients with a cough remain to be determined in lung cancer. However, it is apparent that coughing can significantly limit social activities, some of which may be vital for patients to maintain quality of life and feel supported at an emotionally difficult time.

The impact of cough on carers

The effect that cough has on caregivers has been shown in the study by Molassiotis et al.[1]. Patients comment on how disturbing the cough is for their partners, whose sleep is often disrupted by the cough. Patients sleep elsewhere in order to ensure that their partners have an undisturbed night’s sleep [1]. This has also been shown in studies assessing chronic cough sufferers [14, 30]. However,

cough may impact on carers in a number of different ways. Not only is it difficult to listen to a chronic cough daily and to attempt conversation despite a disruptive cough but anxiety may also be heightened since the cough may indicate worsening disease or lack of response to cancer treatment [31]. Hence the impact of a symptom such as cough on carers is significant. Yet, the reported impact by patients and carers often differs [39]. Assessing the impact of a cough on a patient requires a patient centred approach since carers or health care professionals will have a different perspective.

1.3.2 Measuring the impact of cough

The impact of a symptom such as cough may be measured in several different ways. It may be measured in terms of global quality of life and more specifically in terms of distress due to physical, psychological and social factors, all of which may relate to quality of life. The impact can be measured on the patient, caregiver or both. Similarly, it can be reported by the patient, carer or physician, leading to different accounts of its impact. In addition, whether reported by patient or carer, a reported outcome (such as cough quality of life questionnaires) differs significantly from a measured outcome (such as in the case of cough frequency monitoring). Central to these issues is the assessment tool used. If robust clinical trials are to be designed to assess the impact of an intervention, it is crucial to have validated, comprehensive cough impact assessment tools. Similarly, in the clinical setting, robust symptom assessment tools are sometimes necessary to determine the effects of cancer and its therapy.

Several cough specific quality of life questionnaires have been developed and validated, particularly for patients with chronic cough. Some of their items are inappropriate for patients with cancer, containing statements such as “I am concerned that I have cancer”[22]. They are therefore suboptimal for use in patients with lung cancer. However, recently a new cough quality of life questionnaire has been developed for patients with lung cancer specifically: the

Manchester Cough in Lung Cancer Scale[40] (Appendix 1). To date, its use has not been reported beyond its original validation study.

In the sections below, each of the validated cough specific quality of life questionnaires will be described.

Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ) is a self-administrated 19 item questionnaire that is based on a seven point Likert scale [41]. The questionnaire was developed specifically for patients suffering from a chronic cough. Like other QoL tools, it contains a physical (eight items), psychological (seven items) and social domain (four items). It has been shown to be a valid and reproducible cough assessment tool in the English, Dutch and Chinese language.

In its original validation study, all its items correlated well with their domains[41]. There was high internal consistency for all domains and the total score. The overall LCQ score was compared in 56 patients to VAS, SF36 (Short Form 36 item health status questionnaire, a generic QOL questionnaire) and the St Georges Respiratory Questionnaire (SGRQ). Some patients (n=27) also underwent cough reflex sensitivity testing. Overall the LCQ scores showed highly significant correlations between the LCQ and other outcome measures ($p<0.001$). Spearman's correlation of LCQ with VAS = 0.72, with SF36 = 0.46, with SGRQ = 0.54). However there was poor correlation between LCQ total score and cough reflex sensitivity test scores. This questionnaire has been used extensively in chronic cough research.

Cough Specific Quality of Life Questionnaire

The Cough Specific Quality of Life Questionnaire (CQLQ) is a 28 item questionnaire, with four point Likert response scales, that has been developed in the English language and psychometrically tested in patients with acute (n=30) and chronic cough (n=154) [22]. The possible score ranges from 28 (no adverse effect of cough) to 112 (highest impact of cough possible). Factor analysis

revealed 6 item subscales: physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints and personal safety fears. There was excellent internal consistency. It had excellent test-retest reliability It also appeared to be a responsive scale.

The CQLQ remains to be validated in other respiratory conditions, including lung cancer. The study population involved in its development were predominantly white with a mean age of 54 years. Overall there were significantly more women included in the study. This gender imbalance may have influenced the overall construct of the questionnaire. However it has since been used in patients with COPD in a study comparing objective and subjective measures of cough[42]. Twenty-four patients with COPD completed the CQLQ. The scores were compared to ambulatory cough monitoring cough frequency scores. There was moderate correlation with the night-time scores ($r=0.50$, $p=0.01$ but no correlation with day-time scores ($r=0.20$, $p=0.11$). The explanation for this may rest in the fact that patients are very aware of night-time coughing. It can have a significant effect on their quality of life since coughing affects their sleep causing fatigue and mood disturbances. Despite very different objective cough scores between patients with COPD and patients with chronic cough, the impact of the cough on their quality of life appeared to be similar. This suggests that measuring a patient's quality of life in addition to objective measures of cough can complement the overall assessment of cough and its impact. Objective measures alone are likely to be insufficient to quantify the impact of cough on individual patients.

Chronic Cough Impact Questionnaire (CCIQ)

This is a cough quality of life questionnaire that has been developed in Italian for patients with chronic cough. One of the reasons for its development was that its authors felt that other cough quality of life questionnaires (such as the LCQ and CQLQ) reflected their Anglo-Saxon heritage in a way that was not transferrable to a Southern European population. Items that referred to "singing in church" or conditions such as cancer were felt to be inappropriate for Italian patients. It has never been validated in the English language.

The CCIQ comprises of 21 items shown by factor analysis to relate to 4 domains: sleep/concentration, relationship, daily life impact, and mood[43]. Overall it was shown to be a valid tool in this population with high levels of internal consistency, good reliability. It was also shown to be responsive to change. To date, it has not been compared to other subjective or objective cough assessment tools.

Manchester Cough in Lung Cancer Scale

This is a recently developed cough assessment tool which measures cough severity and quality of life for patients with lung cancer [40]. Items were generated by interviews with patients enrolled in a study characterising the experience of cough [1] and in a study of the respiratory symptom cluster: cough, breathlessness and fatigue, in patients with lung cancer [13]. A review of cough specific questionnaires such as the Leicester Cough Questionnaire (LCQ), Cough Quality of Life Questionnaire (CQOL), Chronic Cough Impact Questionnaire (CCIQ) and the Lung Cancer Cough Questionnaire [44] also led to further items being generated. A team of academics (n=25) and representative patients with lung cancer (n=18) subsequently reviewed, scored and prioritised each item to ensure that the least relevant items were removed. The wording of each item was reviewed and adapted by a team of 4 academics and 3 clinicians to ensure clarity and no overlap. The cough scale was subsequently validated by testing for internal consistency, repeatability and responsiveness. In total, 139 patients with NSCLC, SCLC and mesothelioma were recruited from 5 sites.

The Manchester Cough in Lung Cancer Scale (appendix 1) now comprises of 10 items. Each item is a 5 point scale where 1 = never and 5 = all the time. All the items refer to cough “in the last week”. The items have shown high item to total correlations, a high level of stability, good internal consistency. Patients found the scale easy to complete, clear, useful and comprehensive. It therefore appears to be a valid scale. Its strength lies in the fact that it can measure several important aspects of cough. Not only does it measure the distress caused by cough but also

the impact of cough on quality of life, the psychosocial impact of cough and cough severity. Other than a pilot study assessing preliminary reliability and validity of a lung cancer specific cough assessment tool [44], this is the first lung cancer specific cough scale that has been more extensively validated to date. We present data on the use of this new cough assessment tool in other patient cohorts to provide data on its applicability in the wider setting. It may facilitate the measurement of validated endpoints in future cough intervention studies. This would greatly enhance the quality of data generated by lung cancer-related cough research in the future

Cancer specific quality of life questionnaires

Many cancer specific or lung cancer specific tools assess common symptoms related to cancer or lung cancer respectively. Of these, cough is frequently assessed. These tools tend to be health related quality of life questionnaires measuring symptom frequency, severity and impact to varying degrees. For example, the EORTC QLQ C30 questionnaire is a 30 item questionnaire that assesses cancer related quality of life. It contains no item relating to cough. However, the 13-item lung cancer module (LC13) which is to be used with the EORTC QLQ C30 in patients with lung cancer, contains one item relating to cough and one item relating to haemoptysis (Appendix 3). Both items relate to the symptom during the week prior to completion of the questionnaire. The cough item is phrased, “During the past week, how much did you cough?”. Answers are on a 4 point Likert scale 1- 4 where 1= not at all, 2= a little, 3= quite a bit and 4= very much”. This item therefore relates to frequency and severity rather than the impact of cough. The complexities of cough impact assessment fail to be addressed by a single item. The EORTC QLQ C30 + LC 13 questionnaires have never been validated for the specific assessment of cough.

Other lung cancer assessment tools such as the Functional Assessment Of Cancer Therapy-Lung (FACT-L) and the Lung Cancer Symptom Scale (LCSS) questionnaires are similar to the EORTC QLQC30+LC13 questionnaires. Their primary aim is not to measure cough and its impact but rather lung cancer related

quality of life. The LCSS is a nine item patient questionnaire and a nine item observer questionnaire. Each patient item is answered by completing a VAS. One item on the patient and observer questionnaires relates to cough. The patient cough item is “How much coughing do you have?” with the corresponding VAS marked, “None” and “As much as it could be”. The observer cough item is marked “Cough” with a corresponding scale 0-100 where 100 = none, 75 = mild, 50: moderate, 25= marked and 0= severe”. Again, like the EORTC QLQ C30, this scale has not been validated specifically to assess cough in patients with lung cancer. Whilst some assessment of cough can be made in terms of frequency and severity, its items are not designed to form a complete assessment of cough impact or cough severity on quality of life in patients with lung cancer [45]. The FACT-L questionnaire is also a lung cancer specific quality of life questionnaire rather than a cough assessment tool. It has one question relating to coughing which is answered on a four point Likert Scale[46] . Again, this item does not adequately determine the impact and severity of cough in lung cancer patients.

The EORTC QLQC30+LC13, LCSS and FACT-L questionnaires are the most widely used tools in oncology clinical trials, however, it is important to understand that these questionnaires were designed to determine lung cancer related quality of life rather than to measure cough in terms of severity and its impact on quality of life. Since many oncology clinical trials assess anticancer therapies in terms of impact on cancer symptoms and toxicity of therapy, the relative merits and limitations of generic quality of life assessment tools and symptom specific assessment tools need to be balanced.

1.3.3 Summary

Whilst the data presented above demonstrate that there is significant anecdotal evidence to show that cough has a significant impact on the quality of life of patients with lung cancer, the published literature lacks high quality studies that have used lung cancer specific cough quality of life questionnaires. No study to date has sought to investigate the clinical factors associated with cough impact

scores in the context of lung cancer. Since the advent of the newly validated Manchester Cough in Lung Cancer Scale (Appendix 1), researchers and health care professionals alike now have the opportunity to characterise the impact of cough in patients with lung cancer for the first time using a robust and comprehensive cough assessment tool that assesses the physical, psychological and social impact of cough. We present data relating to its use and further evaluation in two large, distinct cohorts of patients with lung cancer. We also present data on potential predictors of cough impact scores in patients with lung cancer. Ultimately, the hope is that this tool will be incorporated into future, well designed cough intervention trials to further the development of much needed, evidence-based effective antitussive therapies for lung cancer patients.

1.4 The severity of cough and its assessment in lung cancer

Similar to the impact of cough, much of the data on cough severity are derived from oncology intervention trials using cancer specific tools rather than cough specific tools. Therefore the published data on lung cancer related cough severity are flawed in much the same way as the data on the impact of cough. Patients enrolled on oncology intervention trials are often fitter than “real-world” patients with a lower symptom burden. Most of the published cough severity estimates are therefore likely to be underestimates of the true cough severity rates in the lung cancer population. Few trials have assessed the changes in cough severity over time and those that have tended to use scales with only one item assessing cough. These scales are often four-point Likert scales rather than 100mm visual analogue scale, thereby limiting their precision and sensitivity to change over time. Many trials have relied on the *physician*-reported scales such as the Common Terminology Criteria for Adverse Events (CTCAE) scale to assess severity (Appendix 4). Like cough impact, physician reported cough severity scores are likely to systematically underestimate cough severity scores. To date, no

comprehensive data using validated subjective and objective cough assessment tools in large cohorts of lung cancer patients have been published.

1.4.1 Severity of Cough in Lung Cancer

Despite the limitations with the current literature on the severity of cough in lung cancer, some subjective measurements of cough in the lung cancer population have been published. Most recently, the two studies by Iyer et al. have provided researchers and health care professionals with estimates of cough severity for large “real-world” lung cancer populations using lung cancer specific cough assessment tools rather than cough specific severity assessment tools [11, 12]. In the US study conducted in 450 patients with advanced stage NSCLC, the mean cough item score according to the LCSS was 48.4 (SD 29.9, n=421) for the total population (scale range 0-100mm where 0=worse cough severity). There was no significant difference between the mean cough scores whether stage IIIB or stage IV NSCLC (p= 0.148). Physician scores indicated a lower cough severity than patient cough severity scores[11]. In the European study, the mean cough LCSS score was lower (indicating a more severe cough) in the combined French and German population (mean 41.4, SD 30.9, n=837)[12]. Whether this represents a true difference between US and European populations is difficult to ascertain. The population characteristics of the patients in the US study were incompletely reported. The table of characteristics included all patients (n=1200) who had had a physician reported form completed but of these, only about 450 patients subsequently completed symptom and quality of life assessment tools. The specific population characteristics of these 450 patients were not reported separately. The patients that chose to and felt able to complete the patient reported outcome measures may significantly differ from the total study population.

In a single cancer institution study by Podnos et al. 100 newly diagnosed lung cancer patients had their case notes retrospectively reviewed following diagnosis [47]. This study sought to determine the severity of symptoms, the impact on quality of life and the health service utilisation. However, it was flawed in many

respects. The study failed to describe any symptom or quality of life assessment tools used or indeed any measure for symptom severity or quality of life in this patient group. Another flaw was the fact that this was a review of case notes rather than a clinical assessment of study participants. Despite this, some statistics were revealing. Firstly, cough was a common symptom affecting 44% patients in the study with 14% patients requiring an inpatient stay due to their cough (presumably signifying a more severe cough) but only 2% patients were referred to palliative and supportive care services. In this group at least, cough appeared to cause a significant health care burden, severe enough that it could not be managed in the community. Whilst patients may have had their symptom adequately treated by oncology physicians, it is surprising that only 2% had a formal referral to the palliative care services.

Temel et al. have investigated the feasibility of early palliative care involvement for patients with newly diagnosed lung cancer, using the FACT -L to determine the severity of lung cancer associated symptoms [48]. In 51 patients, cough was assessed on a scale of 0-4 where 0 is most symptomatic and 4 is asymptomatic. Overall, 10% patients in this study scored their cough 0-1, 54% scored it 2-3 and 34% scoring it 4 (one patient failed to answer the question). Unfortunately, the authors did not publish the symptom specific scores at three months and six months following study enrolment. However, the mean lung cancer scale scores were 19.9, 20.6 and 20.4 at baseline, three and six months respectively showing that the symptom burden did not appear to change significantly during the period of the study despite their intervention (scale range 0-28 where high score = better quality of life). The specific contribution that the cough item made to this total score is not known.

In a study by Lovgren et al., 159 inoperable patients with lung cancer were assessed at the time of diagnosis, one month after diagnosis and three months after diagnosis to determine the differences in symptom prevalence and intensity between men and women [49]. The symptom intensity was measured using the EORTC QLQ C30 + LC13 questionnaire (Appendix 3). In the LC13 module, there is one question which relates to cough (a further item relates to haemoptysis). Patients are asked to rate their cough severity according to the question: “During

the last week, how much did you cough?". This question reflects frequency, which is part of the assessment of severity but other factors such as intensity and disruptiveness also significantly contribute to the assessment of severity. In Lovgren's study, women reported an intensity of coughing of 37.7 (SD 29.6, scale 0-100 where 100=most symptomatic) at diagnosis, compared to 36.0 (SD 25.0) for men. The intensity of cough was shown to relate to the age and sex of patients (p value 0.004). Trying to compare this intensity figure with Temel's study is not possible since the assessment tools used differed.

One study has sought to describe the severity of symptoms following thoracotomy for patients with lung cancer [50]. Ninety-four patients were followed up at one month, two months and four months post surgery. Several symptoms were assessed, including cough. Co-morbid conditions were present in 77% of the study population. The frequency and severity of this symptom was determined using the LCSS. This study showed that the cough severity scores at one, two and four months were 24.7, 27.3 and 23.3 respectively. In this publication, the authors explained that a higher score indicated a more severe symptom. This is in contrast to the usual scoring of the LCSS where a lower score indicates more severe symptoms. However, there appeared to be no statistically significant difference in the severity of the cough with time. At one month, co-morbid conditions including depression explained 54% of the variance in cough severity. In total 36%, 38% and 30% patients rated the severity of their cough >25mm at one, two and four months post thoracotomy. The differences were not statistically significant. This study did not seek to analyse symptoms prior to surgery. Cough was shown to be more severe in patients who were smokers. Interestingly, the most severe symptoms at four months post thoracotomy were dyspnoea, fatigue and cough: the same symptom cluster described by Molassiotis et al[13]. No surgical quality assurance was conducted across the participating centres. Differing levels of care may have biased the results. There were also more women in this study than men, which may have increased the reported severity of symptoms. Despite these limitations, this study has used a validated tool to determine the severity of cough in a specific lung cancer population.

A similar study by Win et al. conducted in the UK, followed 101 lung cancer patients up at one,three and six months post thoracotomy[51] . In this study, the EORTC QLQ C30 + LC 13 questionnaire was used. It showed that cough was the most frequent symptom at baseline. Immediately post operatively, its severity declined but it subsequently increased again to preoperative levels by six months. The authors explain that this may relate to postoperative pain. Opioids used to control this, may also control the patients' cough. As the postoperative pain improves, the use of opioids reduces causing the cough to worsen again. However, it may also be that as the lung tissue healed, it may have fibrosed leading to cough. Equally, habits such as smoking may have been temporarily halted around the time of surgery but subsequently restarted following surgical recovery.

Several small studies have sought to investigate the use of cough interventions (both pharmacological and non-pharmacological) in the context of lung cancer. These studies are limited by the fact that the cough assessment tools to determine severity and hence response to therapy are usually inadequate. There is little uniformity of the cough assessment tools used in the different studies. They tend to be unvalidated subjective tools. The populations included in these studies are often single arm, heterogeneous, small and from single centres. Due to the limitations of these studies, it is difficult to draw any conclusions regarding the severity of cough in lung cancer.

1.4.2 Measuring Cough Severity

Defining the severity of a symptom such as cough is difficult in much the same way that measuring cough impact is challenging. Critical to the measure of severity is the assessment tool used. Whilst there is little debate about the fact that trials assessing cough should use validated cough-specific assessment tools, there is still much debate regarding which cough assessment tool is best [52]. Since different cough assessment tools are used in different studies, it is often extremely difficult if not impossible to compare results across studies. Very few

studies to date, have sought to define the severity of cough in patients with lung cancer specifically. Most of the data available regarding cough in this patient group are derived from generic quality of life questionnaires that have an item or two that relate to cough specifically. They are therefore inadequate to fully assess cough severity. Although the afore mentioned Manchester Cough in Lung Cancer Scale (Appendix 1) has an item relating to cough severity, other cough severity tools may provide a more comprehensive assessment of cough severity.

In patients with chronic cough, a descriptive analysis of cough severity was conducted using patient focus groups [53]. The aim was to characterise the cough so that a cough severity tool could be developed in the future. Vernon et al. found that three domains are of particular importance when defining cough severity [53]. These are frequency, intensity and disruptiveness. These can be measured quantitatively (particularly frequency and intensity) and qualitatively (particularly disruptiveness). Therefore a cough severity assessment tool needs to incorporate both quantitative and qualitative aspects in order to form a complete assessment of severity, or different severity assessment tools (both subjective and objective) are likely to be necessary in order to fully determine the severity of a symptom such as cough [52, 54].

Visual Analogue Scale

The visual analogue scale (VAS) (Appendix 2) has been widely used in studies assessing cough. It is represented by a 100mm line where the start of the line is defined as “no cough” and the end of the line is defined as “worst cough”. Patients are asked to show the severity of their cough by marking the line at the point which they feel most represents the severity of the cough. It is simple and easy to use. However, variation in the scale exists since different wordings exist for the start and end of the line. There is no standardised wording. A VAS scale with the question, “How has cough affected me?” is different to “How severe is your cough?”. Although both relate to severity of cough, it may be that the values across both scales are not equal. No cough studies to date have sought to quantify the differences between VAS scales and their wording. Similarly, a VAS

scale asking the patient to recall the severity of their cough over the last 24 hours or the last week may perform very differently. Recall can be influenced by factors such as mood, vigilance and cough intensity. These factors complicate the interpretation of VAS scores since they are likely to vary significantly during the course of conditions such as lung cancer.

However, in a study assessing COPD, the VAS has been shown to be a reliable measure of cough over a two week period [55]. In this study, the intra-class correlation coefficient (ICC) was 0.87 for cough. Similar results were confirmed in a study of patients with Idiopathic Pulmonary Fibrosis (IPF) [56]. VAS scores have also been shown to be responsive measures of cough. In studies assessing interventions such as tonsillectomy and inhaled steroid use in patients with chronic cough, VAS scores were shown to be highly responsive to the interventions [57, 58]. It is thought that VAS is probably the most responsive of the subjective cough severity assessment tools [41]. Despite its uses as a reliable and responsive measure for cough in certain disease groups, the VAS has not been formally validated in patients with chronic cough. However, VAS scores have been shown to correlate well with other subjective measures of cough such as the LCQ[41]. This does suggest validity of the VAS tool in this group of patients. To date, no studies have sought to determine the validity of the VAS in the context of lung cancer.

In conditions such as idiopathic pulmonary fibrosis (IPF), VAS scores have been shown to strongly correlate to objective measures of cough severity such as Ambulatory Cough Monitoring (ACM)[56].This may be explained by the fact that in a patient who has pre-existing respiratory compromise as a result of severe COPD or IPF, the effects of coughing are much more significant than in a patient with normal respiratory function. Hence, these patients are very aware of their coughs and have perceptions of their cough severity that correlate extremely well with objective measures [59]. Moderate correlations (0.38, p=0.007 and 0.45, p=0.002) between the VAS score and objective cough counting has been shown in patients with conditions such as chronic cough and asthma respectively [59, 60]. The relationship between objective and subjective measures of cough (such as VAS)

has yet to be studied in patients with lung cancer. It may be that strong correlations exist between subjective and objective cough measures in lung cancer patients since many suffer from significant dyspnoea and may therefore be very aware of their cough.

Cough Severity Diary

A sevenitem cough severity assessment tool (the Cough Severity Diary, CSD) has been developed by Vernon et al [61]. This is a tool that has seven 11-point scales ranging from scores of 0 to 10 that assess severity in terms of disruptiveness (two items), frequency (three items) and intensity (two items). Vernon et al. asked patients to complete the CSD as well as several other cough assessment tools and generic symptom and quality of life questionnaires. The aim of the study was to determine the preliminary measurement characteristics of the scale. In a group of 39 patients with chronic cough and subacute cough, it was found to be a reliable, reproducible and valid tool.

Whilst this is only a single study in small sample of patients with chronic cough and sub acute cough, the statistical analysis and development of this tool is robust. Further studies in other disease groups, particularly lung cancer patients, are required in order to further validate this newly developed cough severity tool.

Manchester Cough in Lung Cancer Scale

The Manchester Cough in Lung Cancer Scale (Appendix 1) has already been described in the section “The Impact of Cough”. It measures cough frequency, distress, cough quality of life and severity. There are three items relating to physical aspects of the cough (whether it interferes with breathing, sleep and whether it is productive), two items relating to severity, four items relating to psychosocial aspects and one item relating to the distress caused by the cough.

Lung Cancer Cough Questionnaire

Chernecky et al. published a study in 2004 that sought to validate a lung cancer specific cough questionnaire and a lung cancer specific wheezing questionnaire [44]. In total, 31 patients participated in this study. The study was limited by the fact that the questionnaire development was not robust. Item generation for the questionnaire was conducted by three professionals by reviewing the literature but the exact process by which items were generated or rejected was not described. Patients do not appear to have been involved in this process. Once the questionnaire was developed, the questionnaire validation study only included women with NSCLC. No population characteristics were reported in the publication but a statement was made about the fact that all stages of NSCLC were eligible for the study. Only 39% patients reported a cough in the week prior to completion of the cough assessment tool. In view of the small numbers included in the study and the low prevalence of cough in the study population, full validation of this tool was not possible. However, the tool did show good test-retest reliability, good internal consistency and percent agreement. To date, further validation studies of this tool have not been published.

Cancer specific symptom questionnaires

These cough assessment tools have already been described in the section “The Impact of Cough”. They are lung cancer quality of life questionnaires rather than cough quality of life questionnaires. As a result, they assess several symptoms that relate to lung cancer rather than cough specifically. They assess both the severity and the impact of cough. They have one or two items that relate to cough severity but as stated earlier, Vernon suggests the need to determine severity in terms of frequency, intensity and disruptiveness [61]. They are therefore inadequate tools to fully determine the severity of cough.

Ambulatory Cough Monitoring (ACM)

Traditionally, cough has been assessed using subjective assessment tools. However, over the last few years, there has been increasing interest in the objective measurement of cough through the use of 24 hour ambulatory recordings since acoustic monitoring studies have shown that patient recorded cough events are significantly lower than ambulatory cough monitoring cough frequency [42, 60, 62, 63]. It is not known whether this reflects a true difference between different subject groups or between the methods used to quantify cough. It may be that subjective and objective assessments provide complimentary data. Therefore, both the European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP) have issued guidelines on 24 hour ambulatory cough monitoring (ACM) [52, 54]. The ACCP recommend its use to objectively assess cough in patients undergoing therapy for their cough. The ERS discusses its potential merits and describes ACM as a new and exciting area of research in the assessment of cough. However, the interpretation of such recordings is far from straightforward. The inherent complexities of ACM include determining physiological coughing from pathological coughing, differentiating cough related sounds from other sounds and understanding which values of cough can act as markers of frequency/severity. These matters are a source of great debate.

Several units of measure for cough severity exist in the literature. They include 1) explosive cough sounds (the number of cough sounds), 2) cough seconds (the number of seconds/hour containing at least one explosive cough sound), 3) cough breaths (the number of breaths containing at least one explosive cough sound) and 4) cough epochs (the number of continuous coughing episodes without a two second pause). It is not known which of these measures represents the severity of cough more accurately [52]. Attempts to quantify the intensity and disruptiveness of cough from ACM recordings are also underway. Intensity may be measured by determining the values such as the peak intensity of the cough (or airflow during the cough) and the overall energy released by coughing [52]. The pattern of coughing may be significant to determine the disruptiveness or impact of cough.

Infrequent severe coughing bouts that lead to retching or vomiting may be more limiting than a frequent cough that has no associated symptoms. The pattern may also indicate different mechanical purposes and hence suggest different interventions that may be of use to limit the cough. The acoustic properties of cough may indicate bronchoconstriction or the presence of secretions [52]. For effective treatments to be determined for the cough, these properties will need to be taken into account.

Ambulatory cough monitoring has been performed and validated in several disease groups including COPD, cystic fibrosis, asthma and chronic cough. Good correlations have been shown in idiopathic pulmonary fibrosis between VAS and ACM scores [56]. In a paper by Faruqi et al., 25 patients with chronic cough underwent 24 hour ACM, VAS, LCQ, and Symptom Assessment Scale (SAS) assessments twice, eight weeks apart [59]. It showed that there were moderate to strong correlations across the scores, subjective and objective. Scores were strongly correlated between the two visits ((r = 0.6–0.9, p < 0.01). Cough counts correlated well with subjective assessments (r = 0.4–0.6, p < 0.01). There was strong correlation between each of the subjective forms of assessment (r = 0.6, p < 0.01). In asthma, there appears to be weak correlation between subjective cough rate scores (Numerical Rating Scale and VAS) and objective cough rates measured by ACM although moderate correlation between objective cough measures (overall time spent coughing) and the LCQ scores [60].The reason for differences in correlation between objective and subjective cough scores across different diseases such as asthma may relate to differences in recall, the intensity of the cough, the underlying pulmonary function and the mood of the patient. Each disease population will have different characteristics that influence the relationship between subjective assessment tool scores and objective measurements of cough.

If ACM is to be used in lung cancer, clinically meaningful differences in cough severity will need to be determined. In a study by Kelsall et al., 62 patients with chronic cough were assessed with ACM twice (about a month apart), with and without oesophageal impedance/pH monitoring catheter [64]. Anecdotally, patients in prior studies who had undergone pH monitoring reported an improvement in

cough severity with the catheter in situ. The aim of this study was therefore to determine whether the pH catheter did reduce cough severity objectively and if it did, to determine a clinically meaningful difference in cough severity and whether the subjective assessment of cough severity correlated with changes in objective cough frequency. The patients undergoing pH monitoring did indeed show a reduction in objective cough frequency (7.2 coughs/hour 95%CI 5.4-9.5 vs. 15.4 coughs/hours 95% CI 12.3-19.3, p<0.001)). This equated to a median 33.3% reduction in objective cough frequency. Although cough scores (numerical rating scale,NRS) did not change with the pH catheter, the VAS scores did reduce significantly in 72% patients in the presence of the pH catheter, with a mean improvement of 9.5mm over the 24hour period (0<0.001). This may relate to the fact that the NRS assesses both intensity and disruptiveness. It may not measure both linearly. Higher scores may indicate greater disruptiveness but not necessarily greater intensity. Of note, the VAS scores were not found to correlate with the objective measurements of cough frequency. This shows that although patients perceive an improvement in their cough, the degree of change in the VAS does not correlate with the degree of change in the objective cough frequency. A “Global Rate of Change” score may correlate more closely with changes an objective cough counts. This remains to be investigated. However, this is the first study that has suggested an improvement in objective cough frequency that is perceived clinically in patients with chronic cough. This value may differ across different diseases, including lung cancer.

Despite the fact that ACM has been previously validated in other disease groups, its use in patients with lung cancer has never yet been reported. The acoustic properties of cough sounds vary according to the disease and have yet to be determined in lung cancer [56]. The objective quantification of cough may not only allow for a more complete assessment of cough severity to be made but also offer an objective endpoint in intervention studies to monitor response to therapy. ACM also offers the opportunity to monitor the diurnal variation of cough in lung cancer in a way that other cough assessment tools do not.

In conclusion, the additional measures that are provided by ACM may prove invaluable to understand the full impact, severity, intensity and identify potential

treatments of cough in individuals. It is therefore important to validate ACM in patients with lung cancer and aim to use objective measurements of cough as well as subjective measures of cough if we are to better characterise and assess cough in lung cancer following an antitussive intervention. However, there remain unanswered questions in terms of the ideal cough severity measure to use, the clinically relevant difference in cough severity that should be targeted by cough intervention studies using ACM and the role of other measures that can be derived from ACM to determine the intensity of cough.

1.4.3 Summary

There is a need to determine the severity of cough affecting patients with lung cancer using validated and robust cough assessment tools. It is likely that the lung cancer literature underestimates the true severity of cough because it has traditionally used tools that are not specific to the assessment of cough. This may explain the lack of research attention on this troublesome symptom. In isolation, a cough severity score may not sufficiently describe the full impact on a patient. The first available data on the comprehensive assessment of cough in patients with lung cancer using both subjective and objective cough specific assessment tools to measure its severity and impact are presented. These tools assess the three important domains of cough severity: intensity, disruptiveness and frequency.

1.5 The prevalence of cough in lung cancer and its measurement

Quoted cough prevalence rates in patients with lung cancer vary significantly in the literature. Few published studies are of longitudinal design and therefore there are little data to inform researchers and health care professionals about the changes in the presence of cough over time. Cough is also a symptom that may be present for normal physiological reasons rather than necessarily as a result of a

pathological process. A normal physiological cough may be reported by some patients with lung cancer. Defining cough accurately may therefore be difficult. Direct cross-study comparison is problematic since the study populations differ, the cancer interventions differ, there are differences related to the time point on the treatment trajectory, and a wide variety of research methodologies employed to determine specific symptoms (i.e. patient reported vs. physician reported symptoms). Validated cough assessment tools are rarely, if ever used. Moreover, even comparison across trials that use the same tool, such as the EORTC QLQ-C30 questionnaire, are hindered because no specified time points on the disease trajectory are stated in many studies.

1.5.1 The prevalence of cough in lung cancer

However, despite these limitations, cough is often reported as the most common symptom of lung cancer [65]. Kvale et al. suggests a cough prevalence of >65% patients with lung cancer, with >25% having a productive cough [66]. In Table 2 below, larger studies assessing cough prevalence in lung cancer are described.

Study	Population	No	Method	Time assessed	Cough prevalence	Cough tool used	Comment
Walling [67] 2014	CANCORS Study population US	2411	Cross-sectional	Within weeks of diagnosis	81.5% (early stage) 84.1% (advanced stage)	EORTC QLQ C30+LC13	Moderate to severe cough was reported by 39.6% of early stage patients vs 44.5% late stage patients.
Iyer[12] 2013	Stage IIIB/IV NSCLC On chemotherapy France and Germany	837	Cross sectional	At time seen by physician for 1st line, 2nd line or 3rd line treatment	93% reported a cough	Patient rated LCSS	Very high cough prevalence - did this include patients reporting normal physiological cough?
Iyer[11] 2013	Stage IIIB/IV NSCLC On chemotherapy US	450	Cross sectional	At time seen by physician for 1st line, 2nd line or 3rd line treatment	64.8% patients reported a persistent cough	physician rated observer LCSS and patient rated LCSS	Receiving 1st, 2nd or 3rd line chemotherapy Observer LCSS cough severity scores lower than patient rated LCSS cough severity scores
Buccheri[68] 2004	Lung cancer patients Single centre Italy	1277	Retrospective analysis of lung cancer database (data collected prospectively)	At diagnosis and then f/u until death	50% over course of study At diagnosis: SCC 18.4% Adeno19.2% SCLC 13.2%	None described	No prevalence for patients with large cell NSCLC or unidentified histological subtype. Represented 344 patients in total
Hernandez[69] 2006	Lung cancer patients Multicentre Spain	1189	Prospective observational study	At diagnosis	31.5% at diagnosis for all lung cancer	None described	Wide differences in cough prevalence at different sites at diagnosis. Cause not clear. Similar ages, stages and types of cancer across the centres with widest differences in prevalence?relates to geography/environmental factors High proportion of men: 1064/1189 patients

Study	Population	No	Method	Time assessed	Cough prevalence	Cough tool used	Comment
Lee[70] 1997	Lung cancer patients Multicentre Korea	3794	Retrospective analysis Of case notes and physician interviews	At diagnosis	57.2% at diagnosis At diagnosis 3 subtypes associated with highest cough frequency: SSC 2.7% SCLC 63.4% BAC 51.2%	None described	Statistically significant differences in cough prevalence between histological subtypes - Higher cough prevalence for SCC and NSCLC may be due to higher proportion of central tumours in these subtypes - BAC causes significant mucous production and this may explain high cough prevalence
Martins[71] 1999	Lung cancer patients Single centre Brazil	1565	Review of prospectively collected data in lung cancer database	At diagnosis	84% at diagnosis	None described	Very high cough prevalence? Related to high numbers of stage III/IV patients (86%)
Hopwood[72] 1995	Lung cancer patients entering LU12 (SCLC) + LU13 (NSCLC) MRC trials UK	650	Prospective collection of data at trial entry	Pre treatment at trial entry	87% at trial entry SCLC (18% severe) 80% at trial entry NSCLC (20% severe)	Rotterdam Symptom Checklist	Despite significant differences between stage of disease, histology, and PS, no significant differences between cough prevalence in both studies. Study enrolment over 20 years ago.

Table 2 Published studies reporting the prevalence of cough in lung cancer populations

This shows a wide range of quoted cough prevalence figures. This may be explained by heterogenous patient populations and different methods of cough assessments between studies.

SCC = Squamous cell carcinoma, SCLC = Small Cell Lung Cancer, NSCLC = Non Small Cell Lung Cancer, BAC = Bronchioalveolar Carcinoma, PS = performance status, EORTC QLQ C30+LC13=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire + Lung Cancer 13 module, LCSS = Lung Cancer Symptom Scale

Despite the lack of high level evidence in the published literature, it is thought that cough prevalence changes throughout the course of lung cancer, affecting patients more commonly in the latter stages of the illness [9]. In the sections below, the changing prevalence of cough at different stages of lung cancer will be discussed.

Pre diagnosis

Some large scale epidemiological studies have sought to identify symptoms that lead to the diagnosis of lung cancer being made. The studies assessing cough prevalence pre lung cancer diagnosis are summarised in Table 3. These studies show that cough is a common symptom in patients who develop lung cancer. However, cough is also a common symptom in the general population. Identifying cases with a cough that relates to lung cancer rather than other conditions is key. How much of this cough reflects common co-morbidities that are associated with lung cancer (such as COPD) and how much represents cough that reflects the lung cancer pathological process is unknown. Further work in this area is necessary in order to answer this more fully.

Study	Population	No.	Method	Time cough assessed	Cough prevalence	Cough tool used	Comment
Frostad[73] **2008**	General public cohort Norway	17 760	Prospective cohort study to determine risk of developing lung cancer	Until development of lung cancer, over a 30 year period	59% patients who subsequently developed lung cancer reported a cough	MRC UK respiratory Q	
Mansson[74] **1999**	General public from specific town using cancer registry Sweden	229	Retrospective analysis of case notes	Prior to development of LC	33% patients who developed lung cancer reported a cough as their initial symptom	None described	Retrospective review of case notes subject to symptom reporting bias

Study	Population	No.	Method	Time cough assessed	Cough prevalence	Cough tool used	Comment
Hamilton[75] **2005**	Lung cancer cases Controls matched for age, sex and GP surgery UK	247 lung cancer cases 1235 controls	Case control study	Prior to development of lung cancer	65% lung cancer patients had had a cough prior to lung cancer diagnosis	None described	Review of GP case notes – GP symptom recording probably varies according to what GP feels is the cause, i.e.: more likely to record cough if lung cancer suspected
Kubik[76] **2002**	Women only Lung cancer cases Controls matched for age, sex and area Single centre Czech	269 lung cancer cases 1079 controls	Case control study	Prior to development of lung cancer	33% lung cancer cases had a cough (≥3months duration) compared to 13.9% controls	Study-specific questionnaire	Prevalence of "chronic cough" ≥3/12 duration may be different to prevalence of "cough"

Table 3 Published studies reporting the prevalence of cough in general populations prior to the diagnosis of lung cancer

This shows a wide range of quoted cough prevalence figures. This may be explained by heterogeneous patient populations and different methods of cough assessments between studies.

SCC = Squamous cell carcinoma, SCLC = Small Cell Lung Cancer, NSCLC = Non Small Cell Lung Cancer, BAC = Bronchioalveolar Carcinoma, PS = performance status

In relation to time point before death

A few studies have investigated the change in symptom prevalence throughout the course of lung cancer. Skaug et al. reported that a total of 28% patients had a cough in the terminal phase of their illness [77]. There were no significant predictors of cough such as age, performance status, tumour stage or histology identified. In a study of 400 patients with newly diagnosed inoperable lung cancer, the cough prevalence ranged from 67% to 81% in different patient groups[9] . The differences across the groups were not statistically significant but there was a trend to higher cough prevalence in patients closer to death. A further study investigated carer reported symptoms in 449 patients with lung cancer in their final year of life [78]. Cough was present in 56% patients. Forty percent suffered from a cough in the final week of life. This is lower than one might expect but may relate to the changing emphasis placed on certain symptoms at different time points of an illness such as lung cancer [8]. The reported symptom prevalence may change depending on the person reporting the symptom. It is already recognised that doctors tend to under-report symptoms of lung cancer compared to patients [79].

Whether or not cough prevalence changes in relation to time point before death remains to be fully clarified. The data presented above do not adequately answer this question. Validated cough assessment tools need to be used prospectively in a well-defined lung cancer population at specific time points in the disease trajectory in order for higher quality data to be available.

In lung cancer survivors

Few studies have investigated the symptom burden following treatment and probable cure of lung cancer. Sarna et al. conducted a cross-sectional

survey of 147 patients with lung cancer, five-year minimum survivors of NSCLC[80]. The majority had undergone a lobectomy. In total, 25% patients reported a cough. A recently published systematic review of health-related quality of life after surgery in patients with non-small cell lung cancer that included the Sarna study, showed that cough was a very common symptom, with some studies reporting a prevalence of over 90% in patients two years following thoracic surgery[81]. However, a large prospective study of 447 long term lung cancer survivors assessed patient symptom burden within three years of curative treatment and after five years of curative treatment. Overall, over a third of patients (35%) reported a significant decline in their overall quality of life over time. Of these patients, 42% reported a cough (using the LCSS patient rated scale). Interestingly, even those who had reported an improvement in their symptoms over time (n=67) had similar rates of symptom burden suggesting that these patients had probably adapted to their symptoms [82]. In these patients, cough was the symptom associated with the greatest deterioration and hence suggests specific adaptation to cough.

It is not surprising that many lung cancer survivors suffer from cough. Confounding factors such as COPD, smoking and asthma are often co-exist in patients with lung cancer and may cause cough. However, it is also possible that the treatment that patients with lung cancer have received may have caused a cough. Cough is a well recognised complication of surgery, radiotherapy, chemotherapy and even the newer targeted agents such as erlotinib [83] [84]. As treatments for lung cancer improve, the late effects of therapy are likely to become increasingly relevant. Late-effects specific to particular regimens and the mechanisms that underlie these late effects need to be better understood if adequate treatments for their symptoms are to be developed in the years ahead.

1.5.2 Measuring cough prevalence

There is no standardised validated question to determine the prevalence of cough in patients with lung cancer, nor indeed in patients with other respiratory conditions. However, several validated lung cancer specific symptom scales have items relating to cough such as the LCSS and EORTC LC-13 questionnaires. These are often items relating to symptom severity rather than to the presence of a symptom. An approach that is often taken by researchers is that a patient who responds “not at all” to Item 31 of the EORTC QLQ C30+LC13 questionnaire “During the last week, how often have you coughed?” implies that there is no cough. However, this is a presumption since some patients may tick “not at all” meaning that their cough was never very frequent over that week rather than their cough was absent. These subtle differences in interpretation by patients may lead to the misinterpretation of trial results. Therefore, current subjective lung cancer symptom assessment tools do not provide us with a robust means of assessing the presence of a symptom. In this context, objective measures of cough such as ambulatory cough monitoring may be useful. However, since cough is a normal physiological process, what cough frequency value equates to a pathological cough relating to lung cancer? Objective cough counts do not currently distinguish between cough relating to normal physiology, co-morbidities, acute infections nor lung cancer specifically. It may be that with time, as the measurable components of cough are better understood such as flow rates, volumes, frequency patterns and amplitudes, it may be possible to distinguish a cough caused by lung cancer as opposed to one caused by COPD. However, until such data are available, a pragmatic approach might be to ask patients with lung cancer whether or not they have a cough. The prevalence figure derived from such a question is likely to include physiological cough, cough due to co-morbidities as well as cough relating to lung cancer specifically. However, provided that the approach taken and

the question asked are clearly defined in the research methodology, those assessing its results can interpret the value with greater clarity than is currently possible from much of the published literature.

1.5.3 Summary

Although cough is a common symptom in lung cancer; its prevalence varies widely between studies. This may be explained by the differing methodologies and patient groups used in these trials, with different comorbidities and environmental factors. There is a need for the consistent reporting of the method used to determine symptom prevalence in studies researching cough for results to be interpretable and to enable cross study comparisons to be made. There is also a need to define the time-points on the disease and treatment trajectories at the time of the cough assessment in order for the patient population to be clearly identified. The longitudinal assessment of cough is also warranted if we are to better understand its variation and predictors as lung cancer progresses. Ambulatory cough monitoring and other objective measures of cough may enable researchers in the future to define a cough relating to lung cancer specifically and therefore to provide a more precise estimate of its prevalence but there remain many unanswered questions before this may become possible. In the interim, a pragmatic approach and a predefined question may be an acceptable method to determine cough prevalence in a population of patients with lung cancer. Data on the prevalence of cough in a population with lung cancer using a defined question will be presented.

1.6 The pathophysiology, mechanisms and potential predictors of cough in lung cancer

In order for effective evidence-based treatments to be developed, potential therapeutic targets have to be identified. To date, little research has been conducted on the pathophysiology of cough and none, specifically in relation to cough due to lung cancer. Therefore, this aspect of cough research needs to be addressed to lead to the future development of effective antitussive therapies for patients with lung cancer.

1.6.1 The cough reflex

Most of the data currently available regarding the pathophysiological processes underlying cough relate to animal models, almost exclusively guinea pigs. Other rodents such as mice and rat are not thought to cough and hence are not used in preclinical cough studies.

The cough reflex protects the airways by forcibly removing obstructive or harmful substances. This brainstem-mediated reflex is activated by afferent vagal sensory nerves, located in the extra pulmonary airways. Their bodies lie in the jugular and nodose ganglia whilst their terminals are located within the larynx, trachea and bronchi. They are activated by mechanical and/or chemical stimuli. The afferents all synapse in the brainstem nucleus tractus solitarius (nTS) in the brainstem, from where second order neurones project to the medullary respiratory pattern generator to initiate a motor cough response [85, 86].

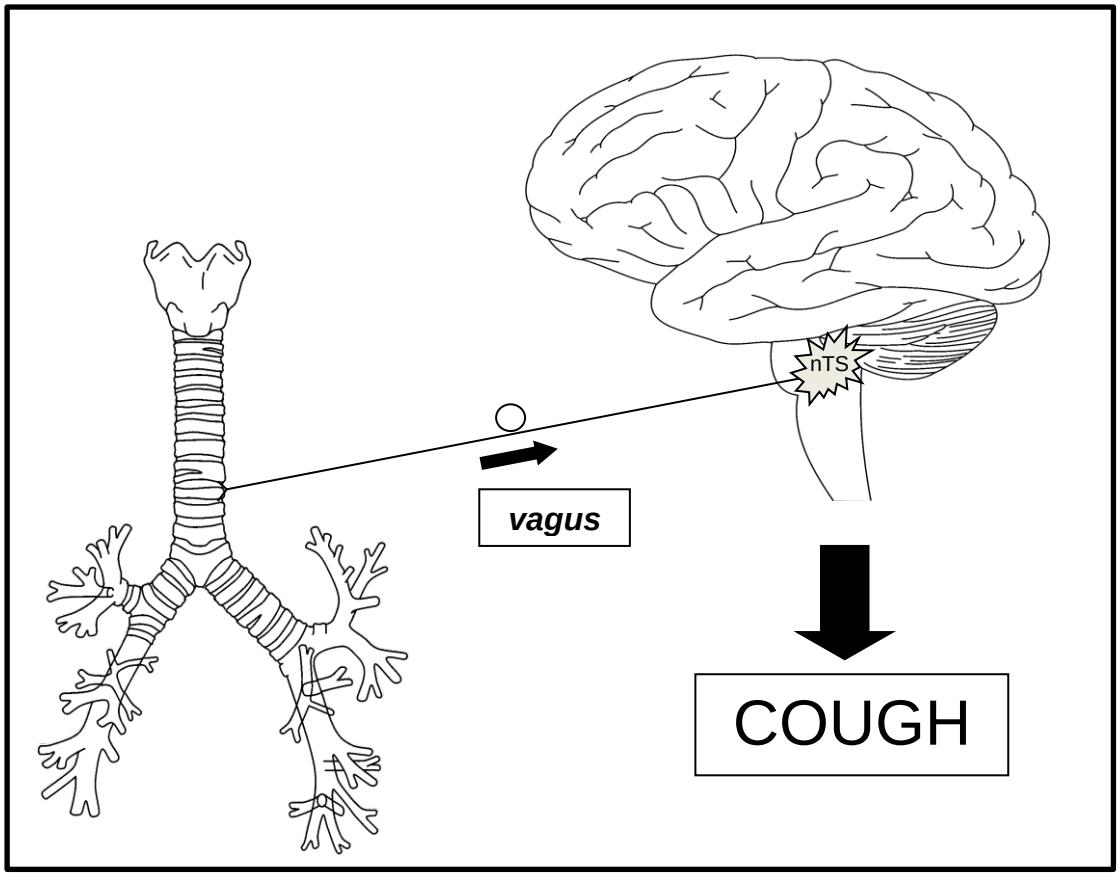


Figure 1 The cough reflex

This is a brainstem-mediated reflex activated by afferent vagal sensory nerves, located in the extra pulmonary airways.The afferents all synapse in the brainstem nucleus tractus solitarius (nTS) in the brainstem, from where second order neurones project to the medullary respiratory pattern generator to initiate a motor cough response.

There are two main types of afferent nerve fibres involved in the initiation of cough: the Aδ-fibres and C-fibres. They differ in terms of conduction velocity, physiochemical sensitivity and their anatomical location [87-89].

Aδ-Fibres

Aδ-fibres tend to be myelinated fibres located in the large airways, with lower levels found in the small airways. They are often referred to as “cough receptors”. This location shows their principal function as airway protectors. Various mechanical and chemical irritants lead to their activation and subsequent elicitation of cough [90]. The Aδ fibres can be divided into three main subtypes. These include Rapidly Adapting Receptor (RAR)-like, nociceptive and polymodal Aδ-fibres[91]. The RAR-like Aδ-fibres respond to mechanical stimuli rather than chemical stimuli. Nociceptive Aδ fibres respond to chemical stimuli (such as bradykinin and capsaicin) whilst polymodal Aδ fibres are responsive to both mechanical stimuli and acid (but not bradykinin and capsaicin). Both RAR-like and polymodal Aδ-fibres originate in the nodose ganglia whilst nociceptive Aδ-fibres originate in the jugular ganglia [85]. As a result of studies investigating the afferent cough fibres in guinea pigs, it has been shown that the fibres critical for the initiation of the cough reflex are capsaicin-insensitive fibres (polymodal and RAR-like). Their cell bodies are located in the nodose ganglia and are responsive to punctate mechanical stimuli and to acid in the trachea [90]. The proton-evoked activation of the Aδ-fibres probably relates to the gating of acid-sensitive ion channels.

C-fibres

C-fibres tend to be unmyelinated fibres located in the peripheral airways. Like Aδ-fibres, C-fibres respond to both mechanical and chemical stimuli [85]. However, C-fibres have a higher threshold for mechanical stimuli and

lung stretch. The chemical stimuli that activate cough by stimulating C-fibres include capsaicin, bradykinin, acrolein, cinnamaldehyde and citric acid. It is known that in certain species, C-fibre activation leads to the peripheral release of neuropeptides such as neurokinin A and substance P via an axon reflex which causes bronchoconstriction and inflammation. However, human airways contain very few substance P-containing nerve fibres so there is currently little evidence to support the hypothesis that C-fibres mediate cough initiation in this way in humans[92]. Human airways (in normal individuals) rarely contract in response to capsaicin compared to those of guinea pigs [93]. It may be that in normal individuals, capsaicin leads to activation of the C-fibres via the TRPV1 (transient receptor potential vanilloid-1) receptors whilst acrolein and cinnamaldehyde may lead to the activation of C-fibres via the transient receptor potential A1 (TRPA1)receptors. These chemical stimuli have been shown to evoke coughing in animals and in humans [94, 95] [96] [97] [98]. This is in contrast to the Aδ-fibres regulating cough which are insensitive to agonists of either TRPV1 or TRPA1 but are exquisitely sensitive to protons and punctate mechanical stimulation [95, 98].

C-fibres in the proximal airways are responsible for promoting cough, but those in the intra-pulmonary (peripheral) airways tend to be inhibitory. If peripheral C fibres are damaged and interrupted by pathology such as a tumour, there may be loss of inhibition and hence cough generation. Animal models have suggested that bradykinin and capsaicin evoked cough is regulated by C-fibres that arise from the jugular ganglia [99].

Other fibres

Afferent nerves innervating the nasal mucosa and oesophagus can have direct or indirect inputs to the nTS, thus providing the anatomic basis required for the association of upper airways diseases and GORD with cough [100].

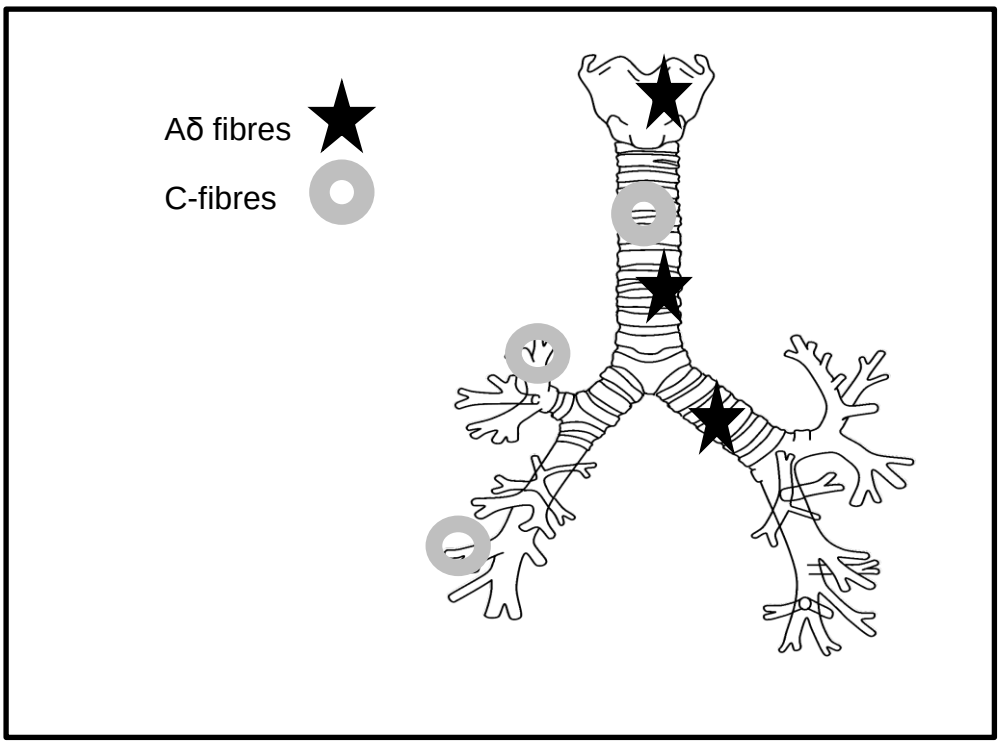


Figure 2 The anatomical location of the Aδ and C-fibre receptors

This shows that Aδ fibres are located in the larger airways and the C-fibre receptors are located in the peripheral and central airways.

Central Integration of the Cough Reflex

The cough receptor terminals have been shown to be present in a discreet area of the nTS[101]. Antitussives microinjected into the brainstem have led to therapeutic effects only by injecting specific locations [101, 102].

Glutamate and substance P have a significant role in the central integration of cough[103]. Glutamate exerts its effects via NMDA and non NMDA receptors [103] whilst substance P exerts its effects mainly at the NK1 receptor but also at the NK2 and NK3 receptors. Hence NMDA receptor and NK receptor antagonists exert central antitussive effects. Most studies have been in animals [101, 102, 104-107]. More recent studies of NK antagonists in humans have been disappointing [108, 109]. The agents tested do not cross the blood-brain barrier and therefore only exert their action on peripheral receptors. This may explain their lack of efficacy. The centrally-acting NK1 receptor antagonist aprepitant has yet to be tested as an antitussive. It may prove to be more effective.

The initial cough stimulus first synapses at the 2nd order neurone in the nTS. This synapse location is strategically important since complex local circuits, central and peripheral signals meet to modify the sensory information and transform the cough output. This is made possible by “plasticity” within the central network [110]. Plasticity may be short term (minutes: leading to the transient interruption of normal respiration to allow the production of cough), long-term (minutes to days), synaptic (affecting the cough signal across the synapse: i.e. leading to increased neurotransmitter release) or intrinsic (leading to changes in the excitability of the post synaptic neurones) [111-113]. Rather than relaying a single stimulus from the afferent neurone downstream, the central neurones integrate spatially and temporally complex information to enable plasticity of the afferent nerves, neurotransmitters, circulating mediators and intrinsic excitability to cause altered cough response[110].

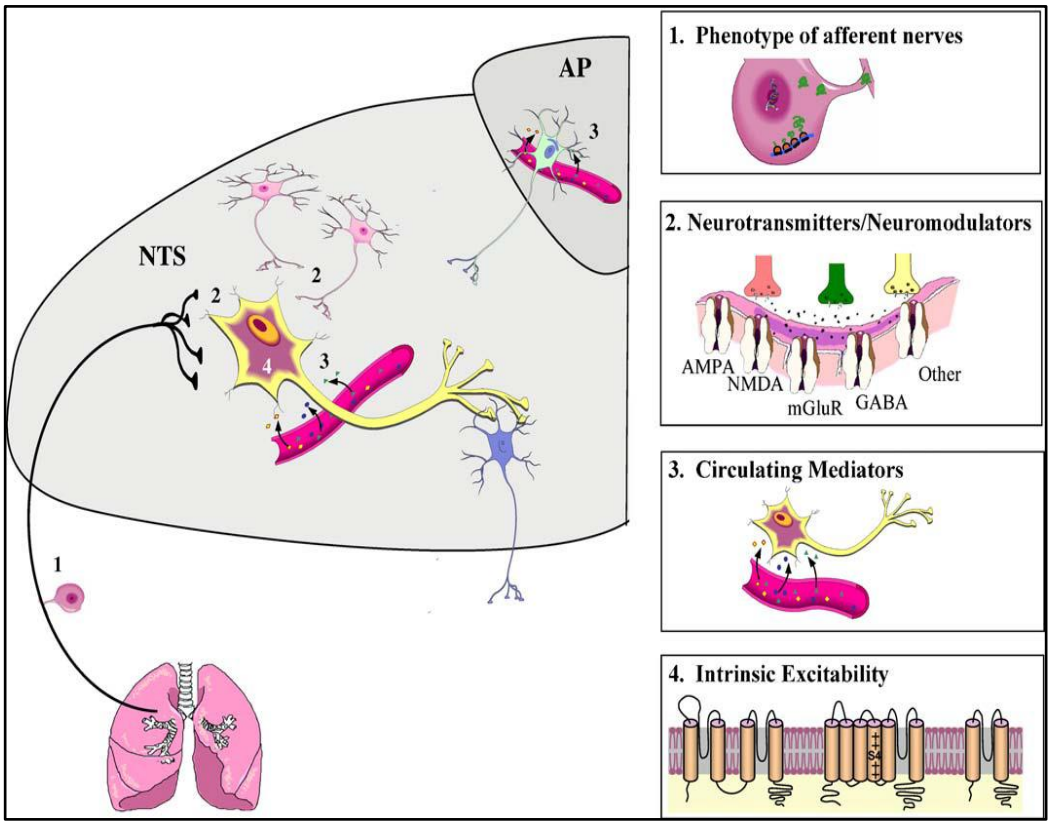


Figure 3 Central integration of the cough reflex and potential mechanisms for inducing neuroplastic change [110].

There are at least 4 potential mechanisms that can lead to neuroplastic change (1-4 in diagram above) within the NTS and AP. The hypothesis is that substance P is implicated in all 4 mechanisms of neuroplastic change. The source of substance P could be a phenotypic change in C-fibres (1) or higher circulating levels from tumour (3). Furthermore, there may be an upregulation of NK1 receptors at the 2nd order neuron (2) and this may result in a change in the intrinsic excitability of the 2nd order neuron (4).

NTS=nucleus tractus solitarius, AP= area posterema, GABA= gabaaminobutyric acid, NMDA= N-Methyl-D-Aspartate, mGluR=metabotrophic glutamate receptor, AMPA α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid**,** NK1= neurokinin 1 receptor

Sensory input to the nTS

As shown in Figure 3 above, peripheral stimuli at the level of the vagal afferent neurons can undergo plasticity as a result of exposure to cigarette smoke, inflammation and allergens[114, 115]. This is as a result of different mechanisms, including increased levels of mRNA encoding substance P in afferent nerves and increased levels of substance P in the afferent nerves, triggering the cough reflex [116, 117].This mechanism is directly relevant to patients with lung cancer since most have a strong smoking history, and many, if not all tumours will generate local and systemic inflammatory effects that may explain the high reported prevalence of cough in patients with lung cancer.

Neuromodulators and neurotransmitters

In the nTS, several neuromodulators and neurotransmitters have been implicated in plasticity of the sensory and motor cortex. Among them, substance P has been shown to depress glutamate release from sensory fibres, thereby depressing the cough reflex [118]. Whilst this may be counterintuitive since substance P is known to promote cough via the NK1 receptor, it demonstrates that substance P can have both an inhibitory *and* an excitatory action on the cough reflex as a way to regulate the output and ensure that the cough stimulus is kept in check. Animal models have shown that, compared with controls, those exposed to cigarette smoke for five weeks exhibit a heightened cough response to citric acid challenge and express high levels of substance P and NK1 receptors in the nTS[119]. Blockade of the central NK1 receptors led to a reduction in the cough response in animals exposed to smoke whilst it had no effect on the cough response in controls, exposed to filtered air[119]. As described above, most patients with lung cancer have a strong smoking history. It is therefore conceivable that the mechanisms of plasticity resulting from changes in expression of the neurotransmitter substance P may lead to augmentation of the cough response in patients with lung cancer.

Circulating mediators

It is possible that as well as changes within neural signalling controlling cough, circulating mediators may also affect cough generation. These have yet to be identified in lung cancer. However, substance P has a widespread distribution throughout the body. After binding to NK1 receptors, substance P is thought to regulate biological functions related to cancer, such as tumour cell proliferation, neoangiogenesis, the migration of tumour cells for invasion, infiltration and metastasis, and it exerts an antiapoptotic effects on tumour cells[120]. It is therefore conceivable that patients with lung cancer and a cough have developed a cough as a result of higher levels of circulating substance P that subsequently lead to local effects within the nTS. Not only this but it may be that tumour cell death in response to chemotherapy may lead to increased release of substance P in the circulation and further increase the cough response by causing plasticity within the nTS second order neurons, analogous to the processes via which substance P is thought to evoke chemotherapy induced nausea and vomiting in the area postrema. However, to date, this has not been researched.

Intrinsic plasticity of the nTS

No research to date has sought to identify the changes in the intrinsic properties of the nTS neurons in patients with lung cancer-related cough. However, in animal models (primates) of allergic asthma, it has been shown that repeated exposure to allergens led to increased excitability of the second order neurons. This may be a long term effect causing a chronic cough [121].

Another aspect of central integration of cough relates to the fact that cough is one of the few reflexes that can be consciously controlled. The sensation of something unpleasant in the throat and then the urge to cough are both conscious processes. However, an unpleasant cough stimulus does not always lead to cough generation. Rather than being

continually modulated like other vagal reflexes such as respiratory rate and blood pressure, cough is a binary reflex. It has been hypothesised that to reach the cough threshold, a specific frequency of the afferent drive needs to be achieved [103]. However, the conscious control of cough remains poorly understood.

Whilst the unconscious inhibition of cough is thought to relate to the activation of C-fibres located in the peripheral airways, descending inhibitory pathways are also thought to have a role to play in the unconscious control of cough. Medications such as opioids are thought to activate these pathways centrally.

It is clear from the above, that several different receptors, neural fibres and neural pathways are implicated in cough mechanisms. The extent to which different receptors are expressed and upregulated according to genetic factors and environmental factors such as lung pathology is not currently understood. Exposure of the lungs to environmental insults such as cigarette smoke and allergen, with consequent lung pathology may modulate the pathways of cough by either changing the expression of receptors or influencing neuroplasticity. It seems possible that different clinical presentations of cough in patients with lung cancer may be explained by these differences.

1.6.2 Cough Mechanisms

It is thought that sensitisation of the cough reflex may occur in three ways [86].

1. Peripheral sensitisation
2. Central sensitisation
3. Impaired inhibition

These potential mechanisms have implications for the treatment of cough in lung cancer.

Peripheral Sensitisation

Nociceptors are responsible for the detection of potentially harmful stimuli. Transduced/ion channel complexes located on peripheral nociceptor terminals are usually activated by high intensity stimuli. However, following exposure to inflammatory mediators and neurotrophic factors, these channels can become hypersensitive and also cause hyperalgesia [122]. It is thought that the mechanism by which patients with lung cancer develop a chronic cough may be similar to this process. In preclinical animal models exposed to cigarette smoke, higher density of substance P can be visualised within the nTS, within the airway afferent fibres “boutons” (the bulbous neuronal terminals) [123]. Tumours may release proinflammatory mediators, cause prolonged mechanical stimulation and lead to chronic infections, all of which may sensitise the vagal afferent neural pathways and hence lead to a chronic cough in some patients[124]. Peripheral sensitisation of nerve endings may also occur as a result of airway inflammation and direct nerve injury following thoracic radiotherapy.

Many patients with lung cancer anecdotally report that their cough is triggered by exposure to seemingly innocuous stimuli such as talking, laughing and exposure to cold air. This may suggest that the neuronal pathways involved in the cough reflex are hypersensitive in these patients. This may be similar to sensations of hyperalgesia and allodynia (pain in response to innocuous stimuli) in patients with chronic pain[125].

Central Sensitisation

It is thought that central neurons, involved in the integration process of cough, in response to peripheral sensory stimulation, may become

hypersensitive and have lower thresholds for activation than normal[86, 122]. Animal studies have suggested that the cough reflex can be sensitised in the brainstem [126]. Clinically, this may be applicable to certain patients with chronic cough. It is well recognised that chronic cough sometimes relates to gastro-oesophageal reflux disease. It is possible that central neurons involved in the integration of cough are stimulated by both pulmonary and oesophageal vagal afferents[86]. An alternative mechanism of sensitisation, which is also analogous to a chronic pain mechanism, is that certain receptors may become upregulated in chronic cough states leading to hypersensitivity. It is known that in animal models, AMPA glutamate receptors are upregulated in chronic pain states and are central to hyperalgesia [127]. However, this differs to acute pain where NMDA glutamate receptors are more important than AMPA glutamate receptors. It remains to be determined whether similar differential expression of activated cough receptors may explain different mechanisms that underlie acute and chronic cough states. Whether or not central sensitisation occurs in patients with lung cancer is not known. Substance P may be responsible for central sensitisation of the cough reflex [128].

Impaired Central Inhibition

In much the same way that chronic pain states lead to a reduced activation of centrally regulated inhibitory nociceptive pathways, chronic cough is thought to cause the endogenous inhibitory pathways to become less effective. However, the central inhibitory cough mechanisms have yet to be investigated in humans. It is not known how these pathways may be implicated in cough in patients with lung cancer.

The Potential Peripheral Mechanisms of Cough in Lung Cancer

In Figure 4 (adapted from Canning et al. [103]), potential peripheral mechanisms of cough in lung cancer are shown. They relate to co-morbidities, environmental, treatment and cancer-related factors. Peripheral pathways integrate into shared central pathways.

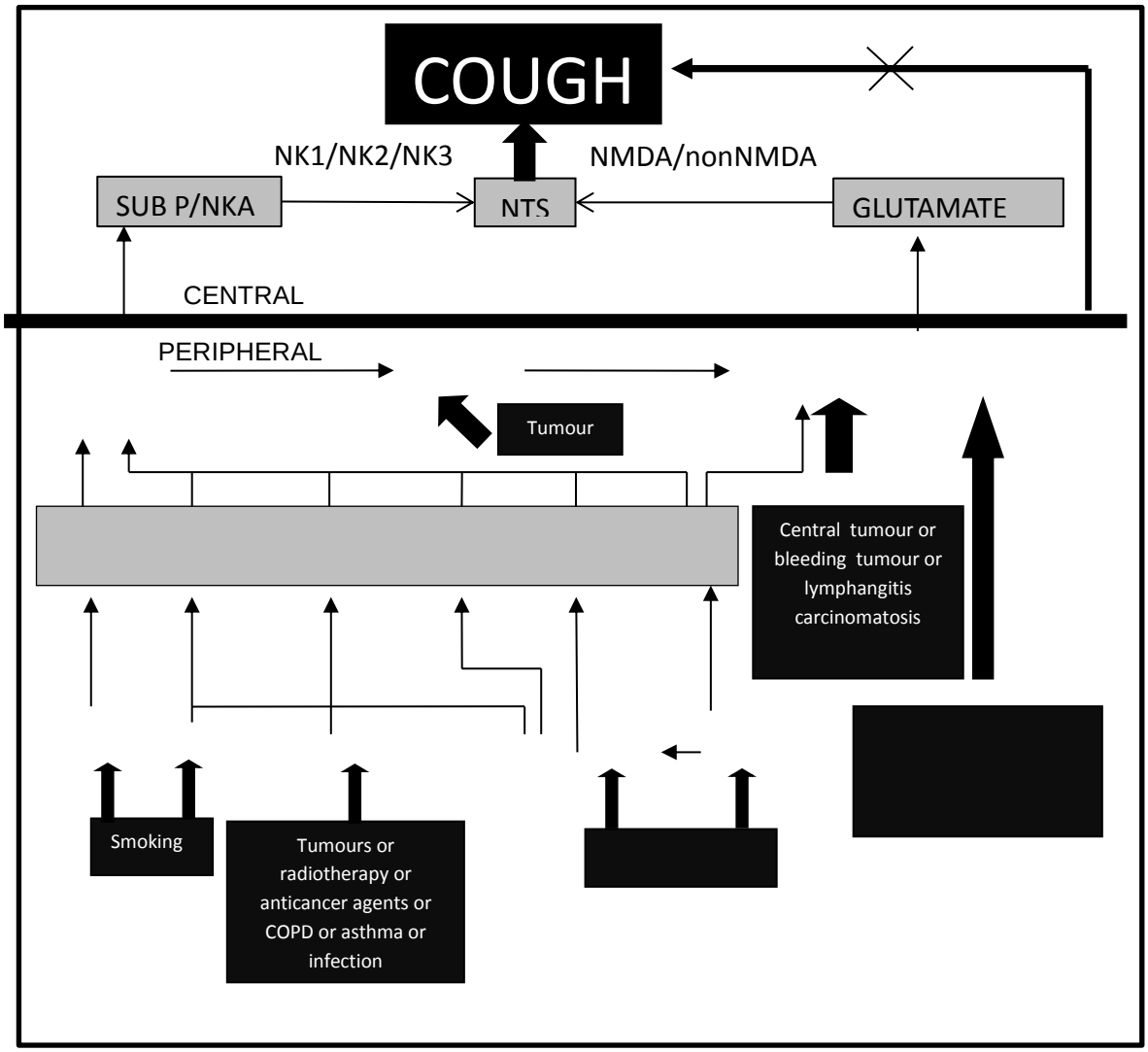


Figure 4 The potential peripheral mechanisms of cough in lung cancer

This demonstrates that cough in lung cancer has many possible causes.These are related to co-morbidities, environmental factors, treatment and cancer related factors. Peripheral pathways integrate into shared central pathways (adapted from Canning et al. [103])

COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease

1.6.3 Potential predictors of cough in lung cancer

Identifying risk factors of cough in lung cancer is paramount if patients suffering from a cough are to be identified and treatment instituted in a timely manner. Relief of symptoms improves clinical outcomes in terms of quality of life and even survival [3]. However, to date, only one study has sought to identify the predictors of cough in lung cancer [77]. This is the study previously described by Skaug et al. in which 247 patients had their case notes retrospectively reviewed for the prevalence and predictors of symptoms in the terminal stage of lung cancer [77]. The only clinical factor identified as a potential cough predictor was histology; cough occurring more commonly in patients with NSCLC compared to patients with SCLC: 36% vs 28%: p=0.04. However several possible clinical predictors of cough were not evaluated in this study. These included tumour histology sub-type (other than NSCLC vs. SCLC), concurrent medications, smoking and co-morbidities. These may well be clinical factors that are associated with cough in patients with lung cancer.

Despite the little available research in this area, potential risk factors for cough in lung cancer can be derived from the widely accepted causes of cough in patients with lung cancer and known risk factors for cough in other diseases. These are summarised below.

Cancer Related Causes

Tumour location

Both peripheral and central neural pathways are likely to be involved in cough relating to lung cancer tumours. Although no study has sought to

determine the frequency of cough according to tumour location, it is generally thought that central tumours are more likely to cause coughing than peripheral tumours since they often cause central airway obstruction. The vagal afferent pathways responsible for cough are in the larger, proximal airways and are likely to be mechanically stimulated by factors such as airway obstruction and chemically stimulated by factors such as increased sputum production and reduced sputum clearance. Many cough sensors such as the Aδ-fibres implicated in the cough reflex are located in large airways. Whether these are the main cough sensors involved in coughing by central tumours remains to be determined.

Tumour histology

Certain types of histology are related to tumour position. SCLC and squamous cell carcinoma (SCC) tend to present with central rather than peripheral tumours. However, tumour histology may relate to the prevalence of cough for other reasons. For example, bronchioalveolar carcinomas are commonly related to cough since they produce high volumes of thin sputum. They also tend to be diffuse tumours that may trigger the cough reflex via C-fibres. It may be that the inhibitory peripheral C fibres are interrupted by the diffuse malignant infiltration, thereby reducing the cough threshold. It may also be that the high volume of sputum secreted by these tumours tracts to the larger airways and activates the Aδ fibres causing a cough.

Different histologies may also release different inflammatory mediators that may be implicated in the initiation of cough. It is known that inflammation leads to TRPV1 receptor activation and C fibre stimulation, causing cough [103]. To date, the only published study by Skaug et al. found no association between histology and cough, however histological subtypes of lung cancer (other than NSCLC and SCLC) were not assessed[77].

Cancer stage

Advanced stages of lung cancer may more commonly be associated with cough than early stage lung cancer. However, there is little objective evidence upon which to base this statement. The previously quoted study by Skaug et al found no association between cough prevalence and stage of cancer towards the end of life. A more widespread malignancy may activate Aδ fibres in the larger airways and interrupt inhibitory C fibres in the peripheries, causing a cough more readily than a tumour isolated to one area of the lung.

Co-morbidities

It is likely that the cause of cough in patients with lung cancer is multi-factorial. Conditions other than the lung cancer may be implicated. These might include common co-morbid conditions such as COPD, gastro-oesophageal reflux disease (GORD), heart failure and concurrent respiratory infections. Many patients with lung cancer suffer from several conditions at any one time and hence recognition and treatment of these different diseases by treating physicians may significantly improve a patient's cough. However, the prognosis is often poor for patients with lung cancer. Hence, optimising the treatment of co-morbid conditions such as COPD may not always be possible. There is therefore a need for general anti-tussive therapies that work across a broad range of pathologies for this group of patients.

Cough is often a symptom which predates the development and diagnosis of lung cancer [73-76]. As a result, this may influence the reporting of this symptom amongst patients with lung cancer. Anecdotally, in terms of cough, three distinct patient groups exist within the lung cancer population: those who report a cough as a new symptom, who have a lung cancer diagnosis made as a result of this new symptom; those who report a

change in a pre-existing cough, who have a lung cancer diagnosis made as a result; and those who have a diagnosis of lung cancer but who do not report a cough at diagnosis. The frequency of cough (with respect to the number of coughs in a given time period) has never been described in lung cancer. It is likely that those patients with lung cancer who report a cough suffer from more frequent coughing or coughing that has a greater impact on their activities of daily living. Patients with more severe co-morbid conditions such as COPD may find a cough more limiting (i.e.: in terms of dyspnoea). However, this remains to be determined.

Chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease (COPD) related cough is well documented. The presence of cough and other respiratory symptoms forms part of the assessment and diagnosis of COPD [129]. In large population based studies, cough has been shown to affect 69% - 87% of COPD patients [130, 131]. Its causes include concurrent acute and chronic respiratory tract infections [132], associated co-morbidities such as gastro-oesophageal reflux disease (GORD)[133], and smoking [132].

It is likely that several mechanisms of cough exist in COPD. They probably relate to airway inflammation and sputum clearance [134]. It is known from COPD studies assessing bronchioalveolar lavage (BAL) fluid, induced sputum and spontaneous sputum that many proinflammatory substances such as prostaglandins and tachykinins are present. These substances are known tussive agents (e.g. prostaglandins) or involved in the cough reflex and mucous production (e.g. tachykinins [135]) but their role in the direct stimulation of cough remains unknown [134] . COPD is also associated with increased sputum production and impaired ciliary clearance. These relate to acute and chronic infections and smoking. Smoking cessation has been shown to lead to an 80% reduction in self-reported chronic cough over a five-year period [136]. However, of note,

cough sensitivity studies conducted in COPD patients who were active smokers or ex-smokers revealed no difference in their cough sensitivity [137]. It therefore seems likely that the reduction in cough following smoking cessation in COPD may relate to causes other than a reduction in cough sensitivity.

Interestingly, some studies suggest that the more advanced the COPD, the fewer patients tend to cough [131, 138]. However, this has led to much debate in the literature. It may be that in advanced COPD, there is deposition of connective tissue in the airways and therefore a reduction in the migration of inflammatory cells. This may lead to a reduction in sputum production and cough.

Many patients with lung cancer also suffer from COPD since both conditions are caused by smoking. It therefore stands to reason that patients with lung cancer who have a history of COPD are likely to cough more than patients without COPD. However, this remains to be demonstrated.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is a recognised cause of chronic cough. Its treatment is advocated in many chronic cough treatment algorithms. However, its exact role in chronic cough remains debated. Both chronic cough and GORD are common complaints and may well coexist in patients in the absence of a direct relationship. Whilst some chronic patients appear to benefit from acid suppression therapy, this is not always the case, even when GORD has been diagnosed. In order to understand this further, the possible cough mechanisms relating to GORD have been investigated.

To date, cough has been shown to relate temporally to distal oesophageal reflux in 20-50% chronic cough patients [139-141]. Patients with a chronic

cough have a heightened cough reflex sensitivity [142, 143]. Oesophageal acid infusion appears to lead to this heightened cough reflex sensitivity in patients who have both GORD and a respiratory condition such as asthma [142, 143]. However, the latter is not the case for patients who have GORD but no cough [143]. This suggests a common neurological pathway for reflux and cough, which is augmented in certain patients. There is currently no evidence to suggest that GORD leads to micro-aspiration, proximal oesophageal or pharyngeal reflux to cause increases in coughing [144]. It is thought that acid reflux may lead to activation of the bradykinin-2 receptors (BK2) and Acid Sensing Ion Channels (ASIC) stimulating both C fibres and Aδ fibres [103].

GORD is a common co-morbidity associated with patients with lung cancer. It is often exacerbated during the course of anti-cancer therapy, frequently requiring treatment. Its association with cough in patients with lung cancer has yet to be demonstrated.

Heart Failure

Heart failure is a recognised cause of cough. In a large hospital based study in the USA, 51% patients admitted for heart failure reported a cough.[145] However, its mechanisms remain poorly understood. Whilst the use of ACE inhibitors may cause cough in patients with heart failure, pulmonary oedema resulting from heart failure can also cause coughing. Interestingly, ACE inhibitor coughing appears to differ in its prevalence according to heart failure severity, being more prevalent in patients with New York Heart Association (NYHA) Class I & II heart failure compared to more advanced stages [146].

A possible mechanism of cough in heart failure, includes the triggering of Aδ fibres and C fibres by extra vascular fluid [147]. Early heart failure is characterised by the accumulation of fluid in the proximal airways. Aδ

fibres located in the proximal airways can be triggered by pulmonary congestion. This may then cause a reflex increase in respiratory rate, tracheal tone and mucus secretion from the airways. Aδ fibres may play a significant role in monitoring changes in the extravascular fluid volume of the airways and mediate the respiratory reflexes such associated with acute heart failure, including the cough reflex [127].

Since many patients with lung cancer suffer from cardiac as well as respiratory co-morbidities that relate to smoking. It may be that a significant proportion of patients with lung cancer also suffer from heart failure. Since heart failure is likely to significantly limit treatment options for lung cancer, it is therefore rarely seen by cancer physicians. However, it is possible that a significant proportion of patients with lung cancer who are in the wider community have a cough relating to co-existing heart failure rather than lung cancer. However, it is also possible that cancer related complications such as pericardial effusions compound cardiac function in a proportion of cancer patients, directly causing heart failure and its associated symptoms such as cough.

Asthma

Asthma is characterised by cough, wheeze, dyspnoea and chest tightness. It is one of the commonest causes of cough in the adult population. Its cough mechanisms are complex but increasing research in this field is shedding some light on the potential receptor and cellular/tissue level interactions that lead to it.

In broad terms, cough in asthma is thought, in part, to reflect increased airway inflammation which leads to a heightened cough reflex sensitivity. Studies assessing sputum cellular composition have shown that the requirement for steroids is greater in patients who have both neutrophils and eosinophils present in their sputum compared to patients who have neutrophils alone. It has also been shown that patients with severe asthma

have higher levels of sputum neutrophils and eosinophils than patients with moderate asthma. This inflammation, mediated by eosinophils and mast cells, may cause airway narrowing and remodelling and lead to cough [148].

In studies where asthmatic patients have been challenged with hypertonic saline, a cough occurring during nebulisation in the absence of significant airway narrowing has been demonstrated. However, bronchoconstriction of the smaller airways (within five minutes of administration of hypertonic saline) can also lead to cough and hence coughing after administration of the saline, may be secondary to this constriction [149].

Respiratory Infection

Respiratory infections are common reasons for seeking medical attention. The main symptom is often a cough. Around 44% patients with symptoms of the common cold report a cough [150]. Currently, little is known about the pathophysiology of cough in this context. However, it is believed that cough relating to a respiratory infection reflects a heightened protective physiological response to the airway insult such that it can occur spontaneously, even in the absence of an obvious physical stimulus such as mucous [151]. An increase in cough sensitivity, mediated by sensory nerves in the airway during the course of the respiratory tract infection, is thought to underlie coughing relating to respiratory infections [152, 153].

Viruses are known to primarily affect the respiratory epithelium. They are thought to potentiate the effect of tachykinins by increasing their expression and release, inhibiting their breakdown, increasing the expression of the NK1 receptors and increasing the sensitivity of airway afferents [154]. All these effects are likely to lead to increased coughing in patients infected by a respiratory virus.

Many respiratory infections, whether viral or bacterial in origin, lead to increased mucous production. Mucous activates Aδ fibres leading to increased coughing. Inflammation relating to infections may also exacerbate mucous production since inflammation leads to TRPV1 receptor activation, C fibre stimulation and consequent mucous production.

Patients with lung cancer frequently suffer from respiratory tract infections. This relates to their reduced immunity and the abnormal lung architecture surrounding tumours predisposing them to infections. It seems very likely that patients suffering from a co-existing respiratory infection following the diagnosis of lung cancer are at greater risk of developing a cough. However, to date no research has been conducted to determine the potential mechanisms of cough in the context of coexistent respiratory infection and lung cancer.

Iatrogenic

Whilst treatment with both curative and palliative intents has been shown to improve symptoms such as cough in many patients with lung cancer, there are a proportion of patients whose symptom of cough may be attributable to the cancer therapy. Treatment related cough may relate to a number of different conditions, including veno-occlusive disease and pleural effusions [155], however it is generally believed that most treatment-related cough in lung cancer is as a result of interstitial lung disease (ILD). The mechanisms that underlie cough in interstitial lung disease are not yet fully understood.

Interstitial lung disease relating to anticancer therapies

Interstitial lung disease (ILD) refers to a wide range of pulmonary fibrotic disorders that are often difficult to accurately diagnose. ILD is characterised by diffuse parenchymal lung disease that affects the lung

alveoli, the most typical form of which is idiopathic lung fibrosis. However, certain forms arise due to exposure to agents such as radiation or chemotherapy. Recent observations have demonstrated an association with tyrosine kinase inhibitors such as Gefitinib (IRESSA) and Erlotinib (Tarceva).

The symptoms of ILD include dyspnoea and dry cough, fever, weight loss, musculoskeletal aches and fatigue. Clinically, the diagnosis of ILD is difficult to make since symptoms may relate to lung cancer. Patients with lung cancer often have lymphangitis carcinomatosis, respiratory tract infections, pulmonary oedema or even pulmonary haemorrhage, all of which can present similarly. The diagnosis is therefore usually made by high-resolution computed tomography (HRCT). However, despite imaging, the diagnosis is not always easy to make.

Since ILD tends to affect the peripheral airways, it is possible that the peripheral inhibitory C-fibres are interrupted by the pathological process leading to loss of inhibition and a consequent dry cough. To date little research has sought to determine the mechanisms of cough in ILD that relates to systemic anticancer therapy. If substances such as substance P are implicated, it is possible that the NK receptor antagonists may be effective treatments for cough caused by anticancer therapy-related ILD.

ILD treatment differs according to the cause. If agents such as erlotinib, gefitinib, gemcitabine or docetaxel are the cause, discontinuation of the drug is sometimes sufficient to reverse the disease process provided it is recognised early in the course of the disease, prior to the development of significant pulmonary fibrosis. However corticosteroids are often used, sometimes at very high doses [156, 157]. This can lead to an improvement in the symptoms of cough and remains the main treatment for this troublesome symptom and underlying pathology. In patients whose respiratory function deteriorates significantly, mechanical ventilation may be indicated.

Radiotherapy and cough reflex sensitivity

Airway inflammation can sensitize cough nerve-endings in airway mucosa [114]. It is also likely that direct damage to nerve endings by radiotherapy may sensitise them. Therefore, it is intuitive that thoracic irradiation may influence cough sensitivity. However, how this relates to the development of pneumonitis is not known. Javorkova et al suggested that patients who had received lung irradiation had heightened cough reflex sensitivities [158]. Although all patients received 3D conformal radiotherapy, this study was significantly limited by the fact that widely different radiotherapy doses were used between individual patients. The mean lung doses differed significantly as did the tumour doses. The previous treatments were not described in the paper. The last cough challenge was five weeks post radiotherapy. It is likely that the cough reflex sensitivity changes significantly over a longer period since radiation induced lung changes occur over months to years. No further follow-up of patients was conducted, therefore no indication of whether this heightened cough reflex sensitivity related to the development of pneumonitis (a very relevant clinical endpoint) or an increase in frequency of cough. The authors concluded that cough reflex sensitivity testing may offer a better marker of radiation induced lung damage than pulmonary function tests, citing a paper by Li et al in which cough frequency (measured by ACM) in stable asthmatic children was shown to correlate poorly with lung function tests. Cough frequency and cough reflex sensitivity have not always been shown to correlate well across different diseases [59, 159].

Therefore much work remains to be done to determine whether cough reflex sensitivity is indeed heightened in patients who receive lung radiotherapy. Quantifying the relationship between radiotherapy (i.e. total dose of radiotherapy/proportion of lung irradiated/radiotherapy regimen) and cough sensitivity may be of interest. Relating it to the subsequent development of pneumonitis is critical if we are to consider using cough challenges rather than pulmonary function tests to determine patients at risk of subsequent pneumonitis, both prior to and post radiotherapy.

Other Medications

ACE inhibitor related coughing is present in 5-20% Caucasian patients [160]. The prevalence appears to differ between ethnic groups. Its mechanisms are thought to relate to the reduction in breakdown of circulating bradykinin (BK) [161], although this remains controversial. It has been shown that ACE-inhibitor cough is more prevalent in patients with a genetic variant of the bradykinin receptor 2 promoter [162]. This promoter is implicated in the stimulation of the C fibres by bradykinin. This activation leads to the release of prostaglandins such as PGE2 locally.

An animal study comparing two ACE inhibitors: ramipril and zofenopril at equivalent doses for heart failure, has shown that coughing was induced by citric acid in the group treated with ramipril but not with the zofenopril treatment group [160]. The effect was dose-related. Levels of BK and PGE2 were increased in the post treatment ramipril group compared to the zofenopril group. There was no change in levels pre and post zofenopril. The use of a BK inhibitor (MEN16132) inhibited the cough in the ramipril treated group by 25% and by 35% in the control group. This suggests that BK is implicated in cough mechanisms but that this may not be the primary mechanism of action of ACE inhibitor related cough. Further research is required in humans in order to confirm these potential mechanisms and treatments for ACE inhibitor related coughing.

Many patients with lung cancer suffer from both lung cancer and other smoking related co-morbidities such as heart failure. The proportion of patients with lung cancer on ACE inhibitors is not known. However, it is likely that some patients with lung cancer may have a cough that relates to the ACE inhibitor rather than lung cancer. Whether the ACE inhibitor cough differs in terms of severity or frequency in patients with lung cancer is not known.

Environmental

Smoking

Despite the fact that smoking is one of the most recognised causes of cough in the community, relatively little is known about smoking related coughing in terms of frequency, severity or pathophysiology. Many patients with a lung cancer diagnosis have a smoking history. It therefore seems likely that patients with lung cancer who have a smoking history will be more susceptible to coughing than other patients, however the pathophysiology underlying this remains to be clarified.

The relative contribution of both RARs and C-fibres to smoking related coughing is the cause of debate [163]. Animal studies have shown that smoking activates these different cough sensors [164, 165]. In addition, nicotinic acetylcholine receptors are known to be present in the neuronal membranes of airway sensory receptors (smooth muscle and cholinergic ganglion neurons) [163]. These are activated by inhaled nicotine causing acute airway irritation. Human studies have confirmed that inhalation of nicotine evokes significant coughing in healthy non-smokers [166]. This reaction to nicotine can be diminished by inhaling hexamethonium aerosol, further confirming the role of nicotinic acetylcholine receptors in the initiation of cough[166].

Despite the fact that several studies have now been conducted in both animal models and humans to determine the effects of smoking on cough reflex sensitivity, the results are conflicting and significant debate remains to explain the difference in findings [167-170]. The research is hampered by the fact that smoking exposure is not always easy to determine accurately, that smokers frequently have co-existing respiratory conditions that can influence cough reflex sensitivity in their own right and smoking can have both acute and chronic effects on airway sensitivity. To date, most studies investigating cough and smoking have

used cough reflex sensitivity testing rather than objective measurements of cough. It may be that changes in cough reflex sensitivity do not accurately reflect changes in cough frequency or intensity. In COPD, cough frequency is known to only moderately correlate with cough reflex sensitivity [63] .

Demographic

Age

Few studies have sought to determine whether the prevalence of cough in lung cancer differs according to age. A study of 187 patients with NSCLC showed that cough prevalence was highest in older patients [171]. However, no statistical significance tests were given. A further study also investigated cough at the time of lung cancer diagnosis in terms of age [172]. The incidence of cough was 50% in patients <40 years and 59% in patients >80 years. The p-value was not statistically significant at 0.233. A more recent study conducted in Norwegian patients (n=270) immediately prior to lung cancer surgery showed no statistically significant difference in the prevalence of cough in patients <65 years and those >65 years (65% vs 63% respectively) [173]. Although the patient characteristics between the two groups were well matched on the whole, it is interesting to note that the patients differed significantly in terms of their concurrent medications, with 26% of younger patients taking opioids but 0% of older patients on opioids at the time of the study. This suggests that opioids are ineffective antitussive agents for many patients. The study also suggested that whilst cough was the most prevalent reported symptom, it was not reported as a distressing or severe symptom.

In other disease groups such as chronic cough, age does appear to be associated with cough prevalence. In a study by Kelsall et al. age was associated with higher objective cough frequency at night [159]. The causes for this association are not known but it is possible that as patients age, their sleep quality deteriorates. Cough frequency rates are known to be higher in patients who are awake compared to patients who are asleep. It is also possible that as the authors

suggest, deficits in inhibitory mechanisms could also explain this phenomenon, similar to the deterioration seen in endogenous inhibitory pain control mechanisms which starts in middle age.

None of these studies adequately answers the question of whether age is a predictor of cough in patients with lung cancer. Based on our knowledge of the pathophysiological processes causing cough, it seems likely that factors such as stage or location of tumour are more important determinants of cough. However, age is an important clinical factor to investigate in future cough research.

Gender

The afore mentioned study by Kelsall et al., compared cough reflex sensitivity, age, sex and objective cough frequency [159]. Women had higher objective cough frequencies than men (16.6 coughs/hour, 95%CI 13.0 – 21.1,vs. 9.4 coughs/hour, 95%CI 6.4-13.9, p=-0.01)[159]. The objective cough frequency increased as the cough reflex sensitivity increased in both sexes. The difference in cough frequency between men and women increased as the cough sensitivity threshold increased. Cough frequency (24-hour) was independently predicted by sex (p=0.01), age ((B=0.01 (95% CI 0.004 to 0.018), p=0.002) and cough reflex sensitivity logC5 (B=20.38 (95% CI 20.52 to 20.24), p=0.001). It also showed that the cough rates fell significantly overnight, in keeping with other diseases. To date, no data have been published on cough frequency differences between genders.

1.6.4 Summary

Numerous factors are likely to cause or predict for cough in lung cancer however, few have been studied. Determining clinical factors may identify populations that are most at risk of developing cough. There is a need to develop lung cancer specific animal models in order to characterise and identify neurophysiological processes involved in cough relating to patients with lung cancer. These models are essential to elucidate potential therapeutic targets and to test novel therapies.

For too long, the development of animal models in the context of cancer symptom research has been largely neglected by cancer symptom researchers. Whilst some research centres are developing some animal models for cancer related fatigue and pain, there is no known animal model for cancer related cough.

1.7 Antitussive therapy for cough in lung cancer

In 2010, a Cochrane Systematic Review “Interventions for Cough in Cancer” was published [174]. The same year, “Clinical Expert Guidelines for the Management of Cough in Lung Cancer” were also published (see appendix 8) [175]. Whilst the review and the cough guidelines showed that the evidence base for the use of antitussive therapy in patients with lung cancer was extremely poor, a pragmatic approach to the treatment of cough in lung cancer was suggested by the cough guidelines (Figure 5).

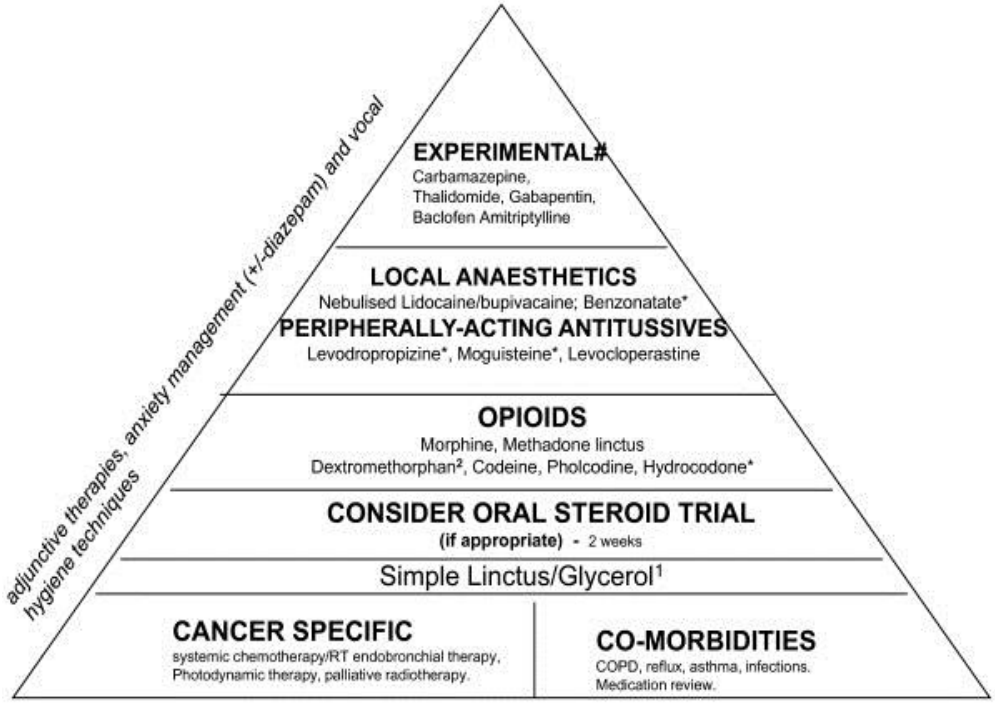


Figure 5 Cough treatment pyramid

[1](e.g. Benylin tickly coughs; Lemsip cough dry). [2](e.g. Actifed dry coughs; Meltus dry coughs; Benylin cough & congestion; Benylin dry coughs; Day & Night Nurse-also includes pholcodine-; Night Nurse; Vicks cold & flu care medinite complete syrup; Robitussin for dry coughs oral or soft pastilles). Dextromethorphan is in variable concentrations in each of these preparations, containing 6.5-11.5 mg/ml. *Not available in the UK and some other countries. #Not recommended, but to consider if everything else has failed.

From the clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough[175]

Their conclusions were supported by a further review [176]. Cough can rarely be treated by a single therapy. Its management may depend on the adequate treatment of the cancer and any associated co-morbidities. However, as emphasised in the literature, there is an urgent need for research in this field in order for specific therapeutic targets to be identified to develop more effective antitussives. Unfortunately, since publication of the review and cough guidelines, no antitussive therapy trials have been published in the context of lung cancer.

In the sections below, the treatments used for the management of cough in patients with lung cancer and their evidence base will be described.

1.7.1 Cancer specific treatments

Chemotherapy and targeted agents

Despite the fact that cough is an extremely common symptom, there are few effective treatments. However, in the context of lung cancer, systemic cancer therapies such as chemotherapy and targeted agents have a significant role to play. Whilst most systemic treatments are given with little or no chance of cure, the improvements they can bring to certain patients, in terms of quality of life improvement and symptom control, are well recognised. In most cancer therapy trials, symptom control and quality of life improvement are secondary endpoints, with overall survival or progression free survival being the usual primary endpoints. Although validated generic quality of life tools such as the EORTC QLQ C30 + LC13 tools are commonly used, no published lung cancer intervention study to date has used a validated cough assessment tool. It is therefore difficult to use these studies to determine the effect a systemic treatment has on a specific symptom such as cough. Nevertheless, symptom burden in lung cancer that often relates, in part, to cough is known to improve following systemic treatment in a

significant proportion of patients undergoing chemotherapy and targeted therapies [177-188].

Radiotherapy

Like chemotherapy, radiotherapy has long been established as an effective treatment for cough in certain patients with lung cancer. Since radiotherapy is a localised treatment, its potential benefits rest with patients whose cough relates to the local effects of a tumour, such as tumours causing obstruction and local irritation in terms of haemoptysis and sputum production. A Cochrane systematic review by Lester et al. has shown that the radiotherapy trials that sought to show the effects of thoracic radiotherapy on symptoms consistently showed an improvement. However, the assessment of symptoms was limited by the fact that few studies used validated symptom assessment tools and the radiotherapy regimens differed across different studies. The authors felt that they whilst radiotherapy improved symptoms, the evidence was not strong enough to conclude that higher doses lead to better palliation or longer duration of palliation [189]. This has also be shown in a more recent meta-analysis of high-dose vs lower-dose palliative radiotherapy for the treatment of lung cancer symptoms [190]. Again, this publication was limited by the symptom assessment tools used. These were often single-items in questionnaires that are likely to be too blunt to show differences in prevalence, severity and impact of cough specifically.

Endobronchial Brachytherapy

A systematic review for the Cochrane Database investigated the use of endobronchial brachytherapy in the context of Non Small Cell Lung Cancer (NSCLC) [191]. Its main aim was to determine whether endobronchial brachytherapy improved survival and/or symptom control in the palliative setting compared to external beam radiotherapy and other endoluminal treatments, best supportive care and chemotherapy. However, the randomised controlled trials

included were not designed to assess cough specifically but rather survival, quality of life and respiratory symptoms more broadly. Therefore validated cough assessment tools were not used [192, 193]. Its authors concluded that overall, external beam radiotherapy was a superior treatment to endobronchial brachytherapy in the first line setting in terms of symptom palliation. The rate of grade 3-4 toxicities (such as fatal haemoptysis) was similar between both treatments. In the context of locally recurrent endobronchial treatment following external beam radiotherapy, the authors suggested that brachytherapy could be considered in selected cases.

A further Cochrane systematic review assessing cough treatments in cancer by Molassiotis et al. also sought to review the data regarding brachytherapy in lung cancer [174]. This review aimed to determine whether pharmacological and non pharmacological treatments such as endobronchial brachytherapy improve cough specifically, quality of life and survival in the context of lung cancer. However, the review excluded all external beam radiotherapy trials since the authors explained that the systematic review by Lester et al. had shown that radiotherapy was beneficial in the context of lung cancer symptoms such as cough. In so doing, several endobronchial brachytherapy trials were therefore excluded since they compared endobronchial brachytherapy to external beam radiotherapy. The quality of the remaining trials assessing endobronchial brachytherapy was extremely poor. The author's conclusion from this review was that despite the extremely poor quality of the available data, brachytherapy was an effective treatment for the management of cough relating to airway obstruction. The studies included in this review all showed that in patients with central airway obstruction, endoluminal brachytherapy appears to be effective to relieve obstruction and improve symptoms such as cough [194-200]. However, these studies were not able to adequately answer questions regarding the optimal dose and schedule of brachytherapy for lung cancer patients with airway obstruction.

Brachytherapy is not without its complications. In the palliative setting, the toxicity profiles of treatments such as brachytherapy need to be carefully considered. On the whole, brachytherapy is well tolerated by the majority of patients and

complication rates are low. However, older patients with a lower performance status are often underrepresented in clinical studies, and these patients may suffer more complications than others. They represent a significant proportion of patients with lung cancer. Complications such as fatal haemoptysis, broncho-oesophageal fistulae, odynophagia, radiation pneumonitis, pneumothoraces, radiation induced endobronchial stenosis and cough have all been reported [195-198, 200].

Essentially, whilst endobronchial therapy is often used in clinical practice to treat patients with endoluminal obstruction and its related symptoms such as cough, the quality of the evidence in relation to the treatment of cough specifically is poor. It is likely that external beam radiotherapy offers better palliation of cough than endobronchial therapy alone. However, brachytherapy is likely to be an effective treatment for cough in the context of recurrent endobronchial tumour following external beam radiotherapy.

1.7.2 Treatment of co-morbidities

Since cough in patients with lung cancer is likely to be multi-factorial, it is important to identify co-morbidities that may contribute to the presence, severity and impact of cough. Where possible, these co-morbid conditions need to be treated in order to maximise the antitussive effect of therapies. However, the short prognosis of many patients also needs to be considered. It is not always a realistic goal to optimise co-morbidities. In these circumstances, antitussive therapies need to be used in order to relieve the symptom of cough and improve the quality of life of patients with lung cancer quickly.

1.7.3 Antitussives

Antitussives can be classified into three main categories:

1. Peripherally acting antitussives that inhibit peripheral cough sensitisation

2. Centrally acting antitussives that inhibit central cough sensitisation
3. Centrally acting antitussives that activate descending inhibitory pathways

Peripherally acting antitussives that inhibit peripheral cough sensitisation

Hydropropizine/Levodropropizine

Hydropropizine is a derivative of dropropizine, a non opioid peripherally acting antitussive. Similar compounds such as levodropropizine, have been shown to exert their action on peripheral inhibitory C-fibres [201]. Hydropropizine has been compared to oxadiazol in 40 patients with different respiratory conditions, of whom 12 had lung cancer [202]. It was shown to be more effective than oxadiazol to control cough. However, hydropropizine at high doses was shown to have a sedative effect, suggesting a central mode of action at these doses. This agent is not available in the UK but features in the cough treatment pyramid (Figure 5). A recent review of levodropropizine as an antitussive for cancer or non-malignant chronic respiratory diseases has shown that levodropropizine may be superior to placebo as an antitussive but appears to be equivalent to moguisteine and dihydrocodeine. However, the quality of the four randomised controlled trials included in this review was limited by heterogeneous patient populations, the use of unvalidated cough assessment tools, small patient samples and poorly described methods for blinding and randomisation [203]. Its equivalent efficacy to dihydrocodeine has also been suggested by Luporini et al. in the lung cancer setting [204]. In this randomised controlled study of 140 patients, there appeared to be significantly less somnolence in the patients treated with levodropropizine compared to those treated with dihydrocodeine.

Leukotriene receptor antagonists

Anti-inflammatory agents such as Montelukast and Zafirlukast have been shown to reduce cough in patients with cough-variant asthma [205, 206]. It is not known

how these agents exert their antitussive effects. However, it may be that by reducing inflammatory mediators, they reduce afferent neural signals and hence reduce cough. No studies of these medications have been conducted in the context of lung cancer to date.

Local anaesthetics

Benzonatate is related to ester local anaesthetics. It is thought to improve cough by decreasing the sensitivity of stretch receptors in the lower airway and lung, thereby reducing the drive to cough after taking a deep breath. In the context of advanced cancer, case reports have suggested that it can be particularly effective in opioid resistant cough [207]. It is taken orally. Benzonatate is not available in the UK.

Lidocaine and bupivacaine are alternative local anaesthetics that can be used to improve cough. They are both non-selective voltage gated sodium channel blockers. Both are administered via a nebuliser. Like benzonatate, these agents have never been assessed in the context of a clinical trial in lung cancer. However, case reports have suggested that they may be of use for patients with intractable cough in the terminal phase of their illness [208]. Again their use is supported by the cough guideline treatment pyramid above.

The use of such agents is limited since patients are unable to eat and drink for a minimum of two hours following nebulised treatment since the oropharynx is numb rendering activities such as swallowing extremely difficult, if not impossible. The risk of aspiration is great until the numbness resolves. The implications of this are therefore significant if patients are to maintain their quality of life. Such treatments tend to be reserved for patients in the final stages of life.

Centrally acting antitussives that inhibit central cough sensitisation

These agents are thought to exert their action by increasing the threshold of central neurons involved in cough generation. It is thought that patients who suffer from chronic cough may have sensitisation of these centrally integrating relay neurons, akin to central sensitisation in chronic pain [103].

Gabapentin and Pregabalin

These anticonvulsants are thought to exert their action by binding to and inhibiting the pre-synaptic α2δ subunit of calcium channels, inhibiting the release of glutamate into the central synapse [209]. Some studies have shown an improvement in chronic cough but these have all been uncontrolled studies [210, 211]. No study has sought to determine the effect of these medications in the context of lung cancer. Many patients with lung cancer may suffer from central sensitisation of the cough reflex with cough stimuli that may persist for long periods of time. These agents may therefore be extremely useful in the context of lung cancer- related chronic cough.

Baclofen and other $GABA_B$ receptor agonists

Baclofen inhibits calcium channels by binding to pre-synaptic $GABA_B$ receptors. Its antitussive effects have been shown in animal models [212]. In these trials, intracerebral administration of $GABA_B$ receptor antagonists led to the reversal of the antitussive effects of baclofen. Its role in lung cancer is not currently known. However, its use is likely to be limited by its central CNS effects (sedation and respiratory rate). A recent study in guinea pigs by Canning et al. has shown that the peripherally restricted $GABA_B$ receptor agonist lesogabaran may reduce citric acid induced coughing but have little, or no effect on the respiratory rate, thereby

suggesting that this agent may be of interest as a novel antitussive for use in humans. This agent was originally developed as a treatment for GORD by reducing the frequency of transient lower oesophageal sphincter relaxations. However its antitussive effects are thought to be independent of this action [213]. The use of agents such as baclofen remains limited since it can be associated with significant side effects that include drowsiness, dizziness, weakness, tiredness, headache, trouble sleeping, nausea, increased urination, and constipation. Any treatment to improve a troublesome symptom such as cough, in the context of often incurable lung cancer must be well tolerated if it is to improve the quality of life of patients.

Dextromethorphan and Ketamine

Dextromethorphan and ketamine are N-Methyl-D-Aspartate (NMDA) receptor antagonists. The up regulation of these receptors is critical to the initiation and maintenance of central cough sensitisation. They are activated by glutamate. Dextromethorphan has been shown to exert antitussive effects in animal models when it was injected directly in the nucleus tractus solitaries (nTS). It has also been shown to activate sigma-1 receptors. These are present in large numbers in the nTS and may explain the antitussive effects of dextromethorphan. A few studies in humans have shown that dextromethorphan may reduce objective cough frequencies in patients with COPD and acute cough [214, 215]. Dextromethorphan has been shown to be more effective than codeine in controlling cough, including in patients with lung cancer [216]. However, like many other potential antitussive agents, these treatments are not always well tolerated. Ketamine is known to cause agitation, confusion and psychosis among others. Elevated blood pressure and muscle tremors are relatively common, while low blood pressure and a decrease in breathing is less so. Spasms of the larynx may rarely occur. More recently, urinary complications such as "ketamine-induced ulcerative cystitis" or "ketamine-induced vesicopathy" have been reported. They include urge incontinence, decreased bladder compliance, decreased bladder volume, detrusor overactivity, and painful haematuria (blood in urine). This is a feature of long term use of ketamine. Therefore, prolonged use for the treatment of

cough is therefore not safe nor desirable for patients with a lung cancer-associated cough.

Centrally acting antitussives that activate descending inhibitory pathways

Opioids

Opioid antitussives such as morphine and codeine have been used for many years for the treatment of cough. However, the evidence that supports their use is also extremely limited. In the few studies that have included patients with lung cancer, the trial populations have been heterogeneous with different types of cancer included. The numbers have been small and the assessment of cough has usually been without a validated cough assessment tool. Most have been single centre case series or case studies. Not only this, but it is known that there is patient to patient genetic variability that may explain differences in opioid efficacy and metabolism [217]. This is known to be relevant in terms of analgesic effects and may therefore also relate to antitussive efficacy of these agents [86].

Morphine, methadone linctus, codeine linctus, pholcodine and hydrocodone have all been used as anti-tussives. In the section below, some of the studies assessing opioids for the treatment of cough will be briefly described.

A three arm double-blind randomised controlled trial by Dotti et al. assessed a combination antitussive containing the equivalent of 30mg codeine base + 10mg phenyltoloxamine, lactose (placebo) versus 30mg dibenzonium bromide + lactose [218]. The patient population was mixed with patients having lung cancer, chronic tuberculosis or “bronchopulmonitis”. This study showed that codeine and phenyltoloxamine was well tolerated. In the second phase of the study, this treatment was compared to a mixture containing 5mg dihydrocodeine and 1g pentamethylene tetrazole. This study suggested that the preparation containing codeine was more effective than the preparation with dihydrocodeine. However,

not all the data appeared to have been published (missing data relating to patients with lung cancer). A further study comparing dihydrocodeine to placebo in 40 patients with different respiratory conditions showed that dihydrocodeine was more effective than placebo for the treatment of cough [219]. A further non randomised study comparing a synthetic morphine derivative to codeine appeared to show that both treatments were as effective as each other but no doses were reported in the publication [220]. In a larger double blind RCT published by Luporini et al. compared dihydrocodeine and levodropropizine [204] in 140 patients (of whom 107 had primary lung cancer). It showed that both treatments were equally effective at controlling a dry cough, with similar toxicity profiles other than for somnolence (22% vs. 8%: dihydrocodeine vs. levodropropizine).

As seen above, the evidence that supports the use of opioids in the context of cough in lung cancer is limited. However, it seems likely that opioids exert their action by stimulating descending inhibitory pathways. The μ opioid receptor is known to be activated by morphine and codeine. Some studies have already shown that whilst μ opioid receptors exist in the peripheral airways [221], it is likely that in humans most of the antitussive effect of morphine and codeine is exerted via activation of the centrally expressed μ opioid receptors [103, 222, 223]. Further research with more rigorous methodology is required in better defined populations in order to improve our understanding of the role of opioids in the treatment of cough in patients with lung cancer, particularly since the development of validated lung cancer-specific cough assessment tools

Other antitussive therapies

There are no studies assessing the agents such as paroxetine, gabapentin, carbamazepine or amitriptyline in the context of lung cancer-associated cough. However, there is increasing evidence that these agents may be effective anti-tussives [210, 211, 224, 225]. In chronic cough sufferers who were known to have a viral induced vagal neuropathy causing their cough, amitriptyline was shown to significantly improve cough compared to codeine/guaifenesin [226]. These are centrally acting drugs that already have established roles in the treatment of neuropathic pain. There may be similar pathways, including supramedullary pathways, controlling cough that may be interrupted by these treatments [227].

They remain to be evaluated for the treatment of cough in patients with lung cancer.

Corticosteroids

Anecdotally, steroids are often prescribed empirically for cough in the context of lung cancer and other respiratory conditions. The rationale for their use is that coughing in some patients with lung cancer may relate to inflammation of the airways and obstruction of the airways. Steroids may reduce the inflammation, improve airway patency, reduce Aδ fibre stimulation and therefore reduce coughing in these patients. However, in the systematic review by Molassiotis et al. assessing pharmacological treatments for cough in lung cancer, no studies assessing corticosteroids in this context were described and no new studies since the review have been published. There is therefore no evidence other than anecdotal evidence upon which to base the decision to treat cough with corticosteroids. Corticosteroids do have a proven use in co-morbidities such as asthma and COPD. It may be that the some of the effect that is often described in patients with lung cancer relates to these conditions. It is also possible that corticosteroids reduce TRPV1 activation and consequent C-fibre stimulation, thereby improving cough. To date, no research has been conducted in this area. Pragmatically, the cough guidelines recommend the use of corticosteroids since they are unlikely to cause harm if used for a short course, in the context of lung cancer.

Simple linctus

Simple linctus is a demulcent containing soothing substances, such as syrup or glycerol. It may temporarily relieve a dry irritating cough. It is readily available as an over the counter (OTC) medication. It is harmless and inexpensive. In the community, it is often used first-line for acute cough. There are no published data regarding its use in lung cancer. However, two studies have assessed its role in the patients with COPD [228] [229]. Both studies showed that glycerol improved

cough in these patients. The cough guidelines treatment pyramid above recommend the use of simple linctus in the first line setting since it is unlikely to cause harm and may help some patients.

Sodium cromoglycate

Sodium cromoglycate is a mast cell stabiliser used for the treatment of asthma. However, it has also been used for the treatment of cough. In a small randomised controlled trial involving 20 patients with advanced NSCLC, sodium cromoglycate appeared to show a statistically significant reduction in cough compared to placebo [230]. A significant flaw in this study was that no information on co-morbidities (such as asthma) was collected. The treatment effect may have related to a concurrent diagnosis of asthma rather than a true effect on cancer-related cough. No validated cough assessment tool was used. The sample population was extremely small.

Butamirate citrate

Butamirate citrate has also been evaluated for the treatment of cough. A study by Charpin et al. involved 67 patients with different respiratory conditions (only 14 had cancer). This was a double-blind randomised controlled trial of butamirate citrate vs. clobutinol [231]. Both groups showed significant improvements in cough frequency and severity. However, in the small number of cancer patients, the effect seemed to be greatest for the patients treated with butamirate citrate. The numbers are too small in order to draw the conclusion that butamirate citrate is better than clobutinol in cancer patients. Further studies are required in order to answer this question more fully.

Anxiolytics (diazepam)

No anxiolytic has been assessed in a clinical trial for the treatment of cough. Despite this, there is anecdotal evidence that suggests that diazepam may be of

benefit to patients with severe cough. In a case with a severe cough relating to metastatic renal cell carcinoma, the use of diazepam was shown to lead to a significant improvement in cough [232]. The patient in question had been prescribed the diazepam for anxiety. Whilst it is known that the cough reflex can be voluntarily elicited or inhibited, the role of anxiolytics in this context has not been established. Whether the diazepam had a direct effect on the cough reflex or on higher orders of cortical cough regulatory function is not known. However, any sedative is known to exert antitussive actions. It is well recognised that cough reduces during sleep. The mechanisms that underlie the improvement in cough during sleep are not understood. Once these are elucidated, it may be possible to minimise the sedative effects whilst maximising the antitussive effects of some antitussive agents. However, diazepam is commonly associated with drowsiness and trouble with coordination.Serious side effects, although rare, include suicide and respiratory depression. Occasionally agitation may occur. Prolonged use can lead to tolerance, dependence and withdrawal symptoms upon dose reduction. Abrupt stopping after long term use can be potentially dangerous. After stopping cognitive problems may persist for six months or longer. Therefore shorter-acting benzodiazepines such as lorazepam may be safer agents to prescribe. However, to date there is no published literature reporting their use as antitussive agents.

Speech Therapy

A study by Vertigan et al. has shown that in 87 patients with chronic cough, speech therapy had a significant reduction in cough [233]. Of note, the placebo group also demonstrated an improvement in cough but not of the same magnitude. Speech therapy techniques train patients to suppress cough. This may not be appropriate for certain patients with lung cancer. These techniques need further evaluation in lung cancer patients before further recommendations can be made regarding their utility in this context.

Future Antitussives

Our limited understanding of cough and its underlying pathophysiology has hampered research into novel antitussives to date. However, recent research in

the non cancer setting has elucidated further pathways involved in coughing, adding to our knowledge of the central nervous system circuitry and leading to a more comprehensive understanding of cough neurochemistry and higher order control of coughing. As a result, new potential targets for antitussives therapy have been identified and may be relevant to patients with lung cancer.

Interrupting these pathways through centrally acting pharmacological agents is the focus of current cough research. A range of novel therapies targeting neuronal receptors are being developed in animal models. To date, these have been non-cancer animal models. Several agents are in early phase development and proof of concept trials. These include TRPV1, P2X3, TRPA1, voltage gated sodium channel receptor blockers, NMDA and NK antagonists. Of these, we report the use of aprepitant (a centrally acting neurokinin 1 antagonist for the treatment of cough in lung cancer.

Neurokinin receptor antagonists

Neurokinin (NK) receptor antagonists have been shown in animal models to significantly reduce cough across five different species [107]. NK receptors are present in peripheral airways as well as centrally [103, 108, 109]. To date, the results of human trials have been disappointing [108, 109]. It is thought that the reason for this may be that the peripheral NK receptors do not have a large role to play in the cough reflex (unlike in animals) and that it is the centrally acting NK receptors which are most relevant. So far, the NK antagonists trialled in humans (such as DNK333 and Talnetant), do not readily cross the blood brain barrier. This may explain their lack of efficacy. The substance P/NK-1 pathway is of particular relevance to patients with lung cancer since many patients receive NK-1 antagonists to cope with their chemotherapy-induced nausea. We therefore know that centrally acting NK-1 antagonists such as aprepitant are well tolerated by patients with lung cancer. In addition, conditions such as chronic cough are also known to be associated with gastro-intestinal comorbidities. This may relate to the shared vagal innervation between the gastro-intestinal tract and the airways,

specifically the common pathways at the level of the second order neurons within the nTS and with the area postrema. Therefore, the substance P/NK-1 pathway may be a relevant therapeutic target for patients with lung cancer and cough.

Aprepitant

Aprepitant (Emend) is a centrally acting NK1 receptor antagonist commonly used for the prevention and treatment of chemotherapy-induced nausea. NK1 is a G protein-coupled receptor located in the central and peripheral nervous system. This receptor has a dominant ligand known as Substance P. Substance P is a neuropeptide, found in high concentrations in the vomiting center of the brain. When activated, it results in the vomiting reflex [234].

Aprepitant has been shown to inhibit both the acute and delayed emesis induced by cytotoxic chemotherapeutic drugs by blocking substance P binding to central NK1 receptors. It has also been shown to increase the activity of the 5-HT3 receptor antagonists ondansetron and the corticosteroid dexamethasone, which are also used to prevent nausea and vomiting caused by chemotherapy[234].

Aprepitant is taken orally. Its average bioavailability is around 60-65%. Aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Aprepitant can increase plasma concentrations of co-administered medicinal products that are metabolized through CYP3A4. Following IV administration of a ^{14}C-labeled prodrug of aprepitant (L-758298), which is converted rapidly and completely to aprepitant, approximately 57% of the total radioactivity is excreted in the urine and 45% in faeces.

One of the main advantage aprepitant has over other chemotherapy-induced side-effect treatments, is its ability to selectively antagonize NK_1 receptors, while having very low affinity to other receptors such as serotonin, dopamine, and corticosteroid. It is estimated that aprepitant is at least 3,000 times more selective to NK_1 receptors compared to other enzyme transporter, ion channels. Aprepitant is given as a 125 mg capsule one hour before chemotherapy, followed by 80 mg the following 2 days.

Although its reported side effects include alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea, it is generally very well tolerated [235].

1.7.4 Summary

Effective symptom management for patients with lung cancer is crucial if health care professionals are to meet their needs. Previous studies have shown that the majority of patients with advanced NSCLC would choose to receive treatments that lead to symptom benefit but no improvement in overall survival rather than treatments that are associated with a marginal survival advantage but no improvement in symptoms [236]. Therefore, there needs to be a much greater focus and emphasis on the development of novel antitussives. Traditional research models “from bench to bedside” using laboratory based research to inform the robust design of clinical intervention trials need to be used if significant advances are to be made in this field of research.

1.8 Summary, objectives and aims

Current research literature suggests that cough is a common and severe symptom of lung cancer, with a significant impact on the quality of life of many patients. Yet, there are few effective therapies for its treatment and little understanding of its predictors and underlying mechanisms. There is therefore a huge unmet clinical need for thousands of patients with lung cancer who suffer from a cough.

Too often, trials have been limited by heterogeneous and ill-defined patient populations, making it difficult to interpret results beyond the context of the published trials. Few studies report the use of validated symptom tools and none report the use of validated, lung cancer *and* cough-specific subjective assessment tools. In addition, no study has reported the use of objective cough measures in patients with lung cancer, further limiting a comprehensive characterisation of cough in these patients. In addition, the systematic Cochrane review "Interventions for Cough in Lung Cancer" demonstrated that there was "absence of credible evidence …. the majority of antitussive intervention trials were of low methodological quality …" thereby making it impossible for its authors to recommend specific interventions for the effective treatment of cough.

Whilst significant funds are being allocated to determining future lung cancer therapies, little research is currently carried out in the field of lung cancer related symptoms. Despite recent advances in the treatment of lung cancer, few patients are cured. It is therefore imperative to also focus research attention on the management of symptoms such as cough to improve the quality of life of patients, many of whom have an extremely short prognosis. Even those who may be cured of their lung cancer may suffer from a cough that has a significant negative impact on their quality of life. Unlike other symptoms such as pain, cough mechanisms remain poorly understood and its treatments extremely limited.

Objectives

- To comprehensively characterise cough in the context of lung cancer using validated subjective and objective lung cancer specific cough assessment tools for the first time.

Primary Aims

- To determine cough prevalence using a cross-sectional design study, its severity and impact and their change over time using a longitudinal observational cohort study, and to determine clinical factors and confounders that were associated with cough severity and cough impact scores.
- To explore the role of the neurokinin-1 pathway as a driver for cough in patients with lung cancer by assessing aprepitant as a treatment for cough.

Secondary Aims

- To compare the different subjective and objective cough assessment tools and their performance in the context of lung cancer.
- To evaluate the newly developed Manchester Cough in Lung Cancer Scale to provide further data on its use and applicability in the wider clinical setting.

2. Methodology

2.1 Regulatory approvals

The clinical research presented complies with Good Clinical Practice (GCP), local regulatory requirements and legal requirements. Every trial participant provided written informed consent prior to trial entry. Each research trial was prospectively approved by a local Research Ethics Committee (REC). The REC approval numbers are as follows: longitudinal study: 11/NW/0374, cross-sectional study: 13/NE/0066 and aprepitant intervention trial: 13/NW/0084.

2.2 Strategy of Investigation

The aims were met by conducting 3 clinical studies. These included:

- Cross-sectional study to assess the prevalence of cough in lung cancer
- Longitudinal single-arm cohort study to assess cough in lung cancer
- Single arm randomised, double-blind, placebo-controlled feasibility trial assessing aprepitant for the treatment of cough in lung cancer

2.3 Cross-sectional cough prevalence study

Aims

The aims of this study were to determine the prevalence of cough in a cohort of lung cancer patients and to characterise the cough in terms of its severity and impact and potential predictors. We hypothesized that a significant proportion of lung cancer patients would suffer from a severe cough that significantly impacted on their quality of life and that cancer characteristics would predict cough severity and cough impact.

Endpoints

The primary endpoint was the percentage prevalence of cough. The secondary endpoints were the cough severity VAS scores, the cough impact MCLCS scores and the clinical factors associated with the presence of cough.

Study design

Consecutive patients attending lung cancer oncology outpatient clinic appointments at The Christie NHS Foundation Trust were approached by their healthcare team during a predefined five week period. All patients were asked whether they had a cough. Demographic, cancer and cancer treatment data were collected on all patients. If patients consented to the cross-sectional study, they were asked additional questions about the presence of reflux symptoms. If they had reported a cough, they were asked further about their cough and completed the Manchester cough in lung cancer scale and the cough severity visual analogue scale on the same day. No other trial procedures were carried out.

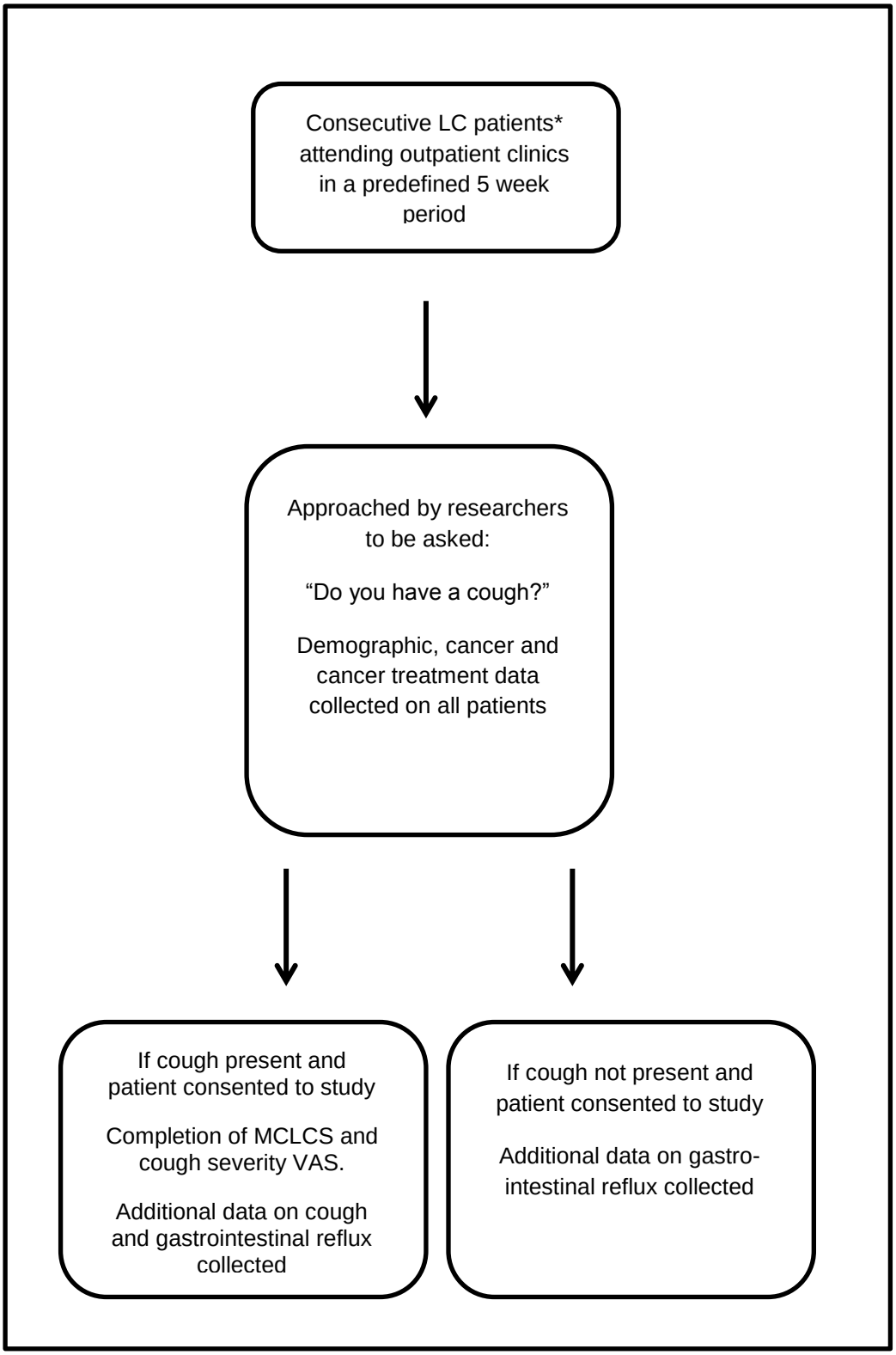


Figure 6 The cross-sectional cough prevalence study design

LC= Lung Cancer, MCLCS=Manchester Cough in Lung Cancer Scale, VAS= Visual Analogue Scale

*Non Small Cell Lung Cancer and Small Cell Lung Cancer

Patients

Consecutive patients who presented to the outpatient thoracic oncology clinic in a pre-defined five week period were invited by their oncologists to enrol in the study. No additional screening or recruitment measures were used. Patients were eligible to participate if they had a diagnosis of lung cancer (NSCLC or SCLC), were fit enough and able to read and respond to questions in English.

Assessments

Cough severity was measured using the cough severity visual analogue scale (Appendix 2). The impact of cough was measured using the Manchester cough in lung cancer scale (Appendix 1).

Data Collection

Participants completed baseline questionnaires on the day of trial entry in the outpatient setting. All questionnaires were completed on paper. Data were entered manually into an Xcel spreadsheet.

Statistical analysis

Since this study was primarily a prevalence study, there was no pre-defined ceiling to the number of patients enrolled. The clinical factors identified as being potentially associated with the presence of cough were: time from diagnosis, age, gender, smoking (never vs current/ex), stage (early vs late), histology (SCLC vs NSCLC), self-reported co morbidities and performance status.

A never smoker was defined as a patient who has smoked <100 cigarettes in a lifetime (US Centres for Disease Control definition).

An ex-smoker was defined as a patient who has stopped smoking more than three months before study entry.

A current smoker was defined as a patient who has smoked within the last three months prior to study entry.

Statistical analyses were performed with the use of SPSS software, version 19.0 (SPSS). Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the study variables.

2.4 Longitudinal single-arm cohort study to assess cough over time

Aims

The aim of this study was to assess clinical factors associated with cough severity and impact at baseline, their change over time and to compare and evaluate subjective and objective cough assessment tools.

We hypothesized that patients with lung cancer would suffer from a severe cough that significantly impacted on their QoL, that cancer characteristics would predict cough severity and cough impact and that cough-specific cough assessment tools would measure cough more comprehensively and robustly than oncology-specific symptom and QoL tools.

Endpoints

The primary endpoint was to determine the cough severity, frequency and impact scores and to identify their potential predictors. The secondary endpoint was to compare and evaluate subjective and objective cough assessment tools.

Study Design

Patients attending lung oncology outpatient appointments at The Christie Hospital and the University Hospital of South Manchester were enrolled in a 60-day longitudinal single-arm cohort study to assess cough. Patients were assigned to Group A if they consented to the study but declined 24-hour ambulatory cough monitoring (ACM), or to Group B if they consented both to the study and to ACM.

All patients were assessed at three time points: baseline, day 30 and day 60. Data on patient demographics, cancer characteristics, anticancer treatment, co-morbidities and concurrent medications were collected on all patients at the three study assessment points. They all underwent subjective cough assessment tools and a subjective gastro-oesophageal reflux disease questionnaire: the Brief Reflux Inventory (BRI).

Baseline	Day 30	Day 60
Cough severity VAS	Cough severity VAS	Cough severity VAS
MCLCS	MCLCS	MCLCS
CTCAE v4 Cough Scale	CTCAE v4 Cough Scale	CTCAE v4 Cough Scale
CSD		CSD
EORTC QLQ C30+LC13		EORTC QLQ C30+LC13
BRI		BRI
24-hour ACM (Group B only)		24-hour ACM (Group B only)

Table 4 The assessment schedule for the longitudinal single-arm cohort study to assess cough over time

VAS = visual analogue scale, MCLCS = Manchester Cough in Lung Cancer Scale, CTCAE v4 = Common Terminology Criteria for Adverse Events version 4, CSD= Cough Severity Diary, EORTC QLQ C30+LC13 = European Organization of Treatment and Research of Cancer Quality of Life Questionnaire Core30 and Lung Cancer 13 module, BRI = Brief Reflux Inventory, ACM = Ambulatory Cough Monitoring.
See appendices 1-6 for the MCLCS, VAS, EORTC QLQC30+LC13, CTCAE v4, BRI and the CSD respectively.

Patients

Patients who presented to the outpatient thoracic oncology clinic were invited by their oncologists to enrol in the study if they reported a cough. No additional screening or recruitment measures were used. Patients were eligible to participate if they had a diagnosis of lung cancer, were fit enough to comply with the trial schedule and were able to read and respond to questions in English.

Assessments

Cough severity was measured using cough-specific cough assessment tools that included the cough severity visual analogue scale (appendix 2) and the cough severity diary (appendix 6). Cough severity was also measured using oncology specific assessment tools such as the EORTC QLQ C30+LC13 that has Item 31 on cough severity specifically “Over the past week, how often have you coughed?” and the physician reported cough CTCAEv4 score. The impact of cough was measured using the Manchester cough in lung cancer scale. Health-related quality of life was measured using the full EORTC QLQ C30+LC13 questionnaire. Gastro-oesophageal reflux disease was determined using the brief reflux inventory. Patients in Group B also underwent 24-hour ambulatory cough monitoring. All assessment tools are described in detail in Chapter 1.

Data Collection

Participants completed baseline questionnaires on the day of trial entry in the outpatient setting. Follow-up assessments were completed 30 days later (+/- 7 days) and 60 days later (+/- 7 days). Participants who had no scheduled clinic visit at 30 days received the questionnaires by mail. However, at day 60, patients with no scheduled outpatient appointment were asked to attend the hospital for the study assessments. All questionnaires were completed on paper. Data were entered manually into DBS Database. Quality control checks were completed once the first 10% patients were enrolled onto the study by an independent researcher who had no other involvement in the clinical study to ensure correct data entry.

Statistical Analysis

We estimated that 178 patients would be recruited for a sample size for analysis of 160. This is based on Peduzzi [237] for ten participants per correlate per outcome in binary logistic regression, assuming an attrition rate of 10%, the estimated percentage presenting with a severe cough to be 50%, and the number of cough predictors to be eight. The clinical factors investigated were: time from diagnosis, age, gender, smoking (never vs current/ex), stage (early vs late), histology (SCLC vs NSCLC), tumour location (peripheral vs central), presence of co morbidities and conmedications.

A central tumour was defined as a primary tumour located in the main airways or within 2cm of the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi. All other primary tumours were considered to be peripheral tumours.

Airflow obstruction suggestive of COPD was defined as a reduced FEV1/FVC ratio (where FEV1 was forced expiratory volume in one second and FVC was forced vital capacity), such that FEV1/FVC was less than 0.7. (NICE 2010 guidelines)

A never smoker was defined as a patient who has smoked <100 cigarettes in a lifetime (US Centres for Disease Control definition).

An ex-smoker was defined as a patient who has stopped smoking more than three months before study entry.

A current smoker was defined as a patient who has smoked within the last three months prior to study entry.

Forty patients were recruited for ambulatory cough monitoring in order to detect medium-to-high (0.40) and high (0.50) correlations between quality of life and subjective measures and ambulatory cough monitoring. The numbers needed to reject the null hypothesis (correlation=0.00) at 5% significance and 80% power with a one-sided test were 37 and 23 respectively for Pearson's and Spearman's correlation.

Statistical analyses were performed with the use of SPSS software, version 19.0 (SPSS). Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the study variables. Multivariate linear regression analyses, adjusted for baseline scores, were used to determine predictors of cough severity, frequency and impact and their change over time.

Comparison and evaluation of cough assessment tools was conducted by calculating correlations between the subjective cough assessment and objective cough assessment tools. Very weak correlation was defined as 0 – 0.29, weak correlation was defined as 0.3 – 0.49, moderate correlation was defined as 0.50-0.69, strong correlation was defined as 0.70 – 0.89, very strong correlation was defined as 0.9-1.0.

Intra-class correlation coefficients were calculated between day 0 and day 60 scores to assess the repeatability of cough measures over time.

2.5 Single arm randomised, double-blind, placebo-controlled proof of concept trial assessing aprepitant for the treatment of cough in patients with lung cancer

Aims

The aim of this intervention trial was to determine whether the neurokinin-1 pathway was a relevant target for the treatment of cough in patients with lung cancer to warrant further research.

We hypothesised that aprepitant may be an effective antitussive since neurotransmitters such as neurokinins are known to be important mediators of cough in the central nervous system in animal models across five different species. Therefore, centrally-acting neurokinin receptor antagonists, such as aprepitant, may prove to be effective treatments for cough in humans. Aprepitant is a highly selective NK1 receptor antagonist which readily crosses the blood-brain barrier. The NK1 pathway is also implicated in nausea, and aprepitant is licensed for the treatment of chemotherapy-induced nausea and vomiting. Gastro-intestinal co-morbidities have been shown to relate to cough in other conditions such as chronic cough. This is thought to relate to the shared vagal innervation between the gastro-intestinal tract and airways. There is therefore good scientific rationale for exploring the antagonism of NK1 receptors with a centrally acting neurokinin receptor such as aprepitant. To date, no human studies have been conducted to explore the role of centrally acting neurokinin receptor antagonists for cough.

Study Design

Eligible patients attending lung cancer oncology outpatient clinic appointments at The Christie NHS Foundation Trust (Manchester, UK) were enrolled in a 14-day exploratory single-arm randomised double-blind cross over trial assessing

aprepitant for the treatment of cough in patients with lung cancer. The cross-over design enabled a smaller sample size since cough varies significantly between individuals. Individuals therefore acted as their own controls. It was a double-blind trial. This was achieved through the use of identical active and placebo treatments.

Patients received both treatments but the treatment order was randomised (to minimise potential bias) between aprepitant and placebo. Participants receiving treatment took a fixed dose-titration schedule of aprepitant, starting with 125mg on day 1 and then reducing the dose to 80mg on day 2 and day 3. Those participants receiving placebo received matched capsules on days 1, 2 and 3. On days 4-6 inclusive, both groups of participants stopped their treatment (wash-out period). Participants then crossed over to the alternative treatment (placebo or aprepitant) and received this treatment for 3 consecutive days (days 7-9 inclusive).On day 13 or 14, investigators contacted patients by telephone to ensure that there was no AE or SAE that required intervention and reporting (Figure 7). The doses of aprepitant in the CALC Trial were identical to the doses used to prevent nausea. It is known that these doses are safe in humans and block the NK1 receptors very effectively. It was believed by the trial investigators that these doses would therefore be sufficient to block the NK1 receptors involved in the cough pathway.

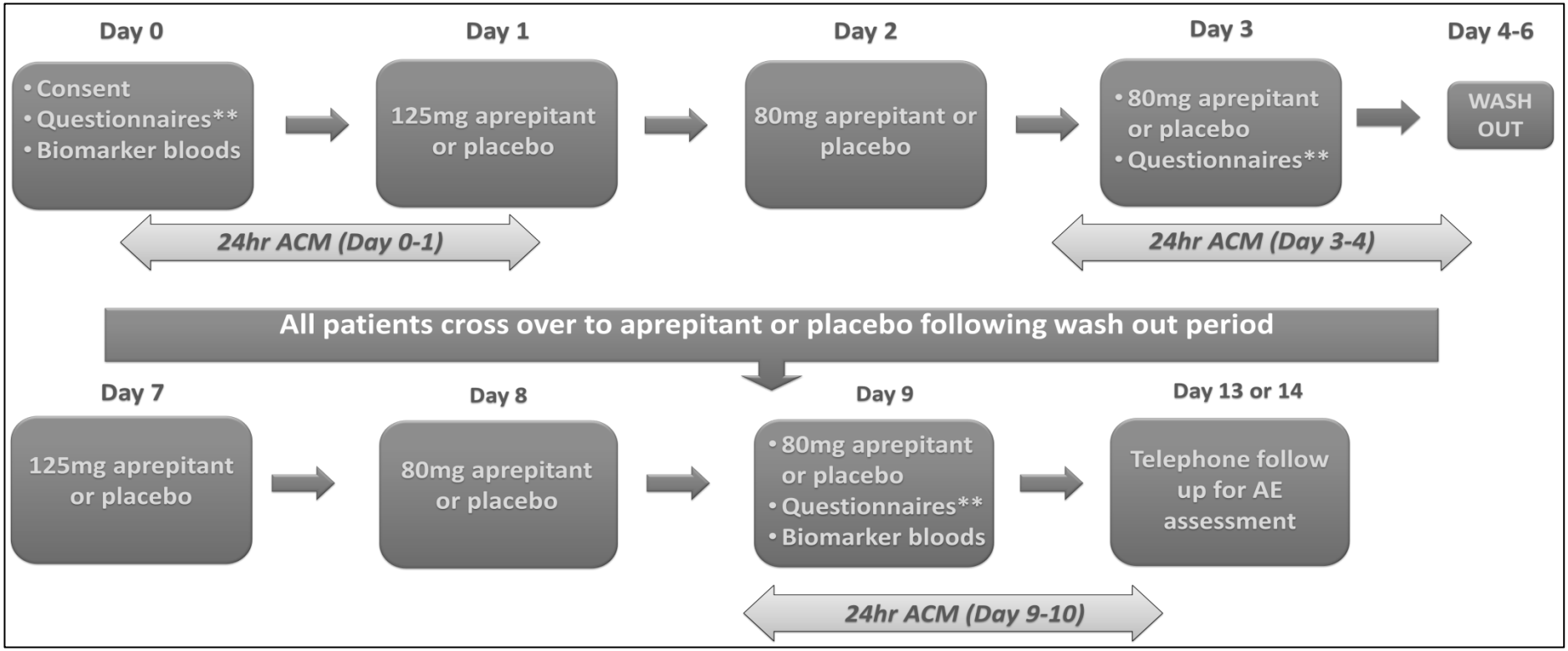


Figure 7 Study design for the single arm randomised, double-blind, placebo-controlled trial assessing aprepitant for the treatment of cough in patients with lung cancer

**Manchester Cough in Lung Cancer Scale, Cough severity visual analogue scale, EORTC QLQ C30 + LC13.
24hr ACM = 24 hour ambulatory cough monitoring , AE = adverse event.

Participants completed a VAS and the Manchester Cough in Lung Cancer Scale (MCLCS) and underwent 24 hour ambulatory cough monitoring on days 0, 3 and 9. The Global Rating of Change Scale (GRCS) was completed on days 3 and 9 only. Participants also completed the Brief Reflux Inventory (BRI) and the EORTC QLQ C30+LC13.

All patients were assessed at three time points: baseline, day 3 and day 9. Data on patient demographics, cancer characteristics, anticancer treatment, co-morbidities and concurrent medications were collected at baseline. They all underwent subjective cough assessment tools (see Table 5 below). All patients also completed a subjective gastro-oesophageal reflux disease questionnaire: the Brief Reflux Inventory (BRI).

Baseline	Day 3	Day 9
Cough severity VAS	Cough severity VAS	Cough severity VAS
MCLCS	MCLCS	MCLCS
CTCAE v4 Cough Scale	CTCAE v4 Cough Scale	CTCAE v4 Cough Scale
EORTC QLQ C30+LC13	EORTC QLQ C30+LC13	EORTC QLQ C30+LC13
BRI	BRI	BRI
24-hour ACM	24-hour ACM	24-hour ACM
	GRCS	GRCS

Table 5 The assessment schedule for the single arm randomised, double-blind, placebo-controlled trial assessing aprepitant for the treatment of cough in patients with lung cancer

VAS = visual analogue scale, MCLCS = Manchester Cough in Lung Cancer Scale,
CTCAE v4 = Common Terminology Criteria for Adverse Events version 4, CSD= Cough Severity Diary, EORTC QLQ C30+LC13 = European Organization of Treatment and Research of Cancer Quality of Life Questionnaire Core30 and Lung Cancer 13 module, BRI = Brief Reflux Inventory, ACM = Ambulatory Cough Monitoring, GRCS = Global Rating of Change Scale

See appendices 1-6 and 9 for the MCLCS, VAS, EORTC QLQC30+LC13, CTCAE v4,
BRI, CSD and the GRCS respectively**.**

Patients

Adults with lung cancer (NSCLC and SCLC) and a cough (≥ four weeks' duration) attending a thoracic oncology outpatient clinic appointment were recruited. We included all patients with a WHO performance status score of 0-2, who were able and willing to participate in and comply with the trial schedule**.** Patients were excluded if they were within six weeks of commencement of chemotherapy, were receiving or within twelve weeks of completion of thoracic radiotherapy, had started on a TKI within eight weeks of the trial, were due to commence anticancer therapy during the period of the trial, were already receiving aprepitant therapy, had had a respiratory tract infection within four weeks of the trial enrolment, had had a previous adverse event to aprepitant, has AST level >2.5 times the upper limit of normal, had constipation grade 2 or above (CTCAE v4), were scheduled to undergo elective surgery or other procedures requiring sedation or general anaesthesia during the trial period, were potentially fertile women of child-bearing age, were participants receiving concurrent medications including warfarin, OCP, midazolam, ketoconazole, rifampicin, pimozide, terfenadine, astemizole , cisapride, or diltiazem (for rarer drugs see Appendix 1.5), were currently participating in another research trial involving an investigational product or had any other significant disease or disorder which, in the opinion of the investigator, may have put the participant at risk because of participation in the trial or affected the participant's ability to participate in the trial.

Randomisation and blinding

Patients were randomly assigned (1:1) to a sequence of either aprepitant once a day for three days, followed by placebo once a day for three days or placebo once a day for three days followed by aprepitant once a day for three days. The Medical Statistics Department at the Manchester Academic Health Science Centre Clinical Trials Unit computer generated the randomisation sequence (block size 20) and study treatment was dispensed by the The Christie Clinical Trials Unit pharmacy. Patients, health-care providers, investigators and the sponsor were all masked to the treatment sequence assignment.

Procedures

Patient screening included medical history and a blood sample to determine the AST level if a sample had not been taken within two weeks of trial entry. Patients were randomly assigned to a sequence of two treatment periods, of three days' duration each, separated by a three day washout period; a final follow-up telephone evaluation was done on days 13 or 14. Safety was assessed through monitoring adverse events and medical history. All other trial procedures are outlined in Table 6 above.

Endpoints

The primary endpoint was a comparison of the change from baseline in daytime cough count for aprepitant versus placebo. The secondary endpoints were a comparison of the change from baseline in the VAS and MCLCS scores, an exploratory analysis of correlation between the presence of GORD and nausea and cough severity and treatment response, an exploratory analysis of the correlation between global quality of life and cough severity and an exploratory analysis of global rating of change scale responses to estimate the minimum important difference (MID) for the Manchester Cough in Lung Cancer Scale

Statistical Design

Sample size calculation

The recruitment target was 20 patients for a sample size for analysis of 18 participants. No objective cough count data existed in participants with lung cancer at the time of trial design. However, in a previous trial of participants with chronic cough, the change in 24hr objective cough frequency was normally distributed with a standard deviation of 36.5%. Based on a paired t-test, 18 participants were needed to detect a difference in cough frequency of 30% between aprepitant and placebo, at 5% significance and 90% power.

Data in participants with isolated chronic cough would suggest a 50% reduction is likely to be clinically meaningful; a 33% decrease in cough frequency has been shown to be appreciated by participants[64].

The drop-out rate was not felt likely to exceed 10%. This was based on data from the longitudinal cough study. The trial period was very short and the proposed trial treatment well tolerated. These factors were thought to limit drop-out rates significantly. Allowing for 10% attrition, the required sample size was 20 participants.

Statistical analysis

Data were summarised and means with standard deviations and medians interquartile ranges depending in whether the data were normally distributed or not. Daytime and 24hr cough frequency data were normalised by logarithmic transformation (base 10) and therefore geometric means and 95% confidence intervals are presented. Night cough data cannot easily be log transformed due to a number of zero values in patients who did not cough at all at night, therefore medians and interquartile ranges were used to summarise the raw data.

The effect of treatment (aprepitant versus placebo) on cough frequency was assessed using General Estimating Equations (GEE) modelling of the log transformed data. For night cough frequency a value of 0.01 was added to all values prior to transformation to remove the zero values. In addition to the effect of treatment, models included parameters describing treatment sequence (aprepitant/placebo versus placebo/aprepitant) and treatment period (first or second period) and log base 10 of the baseline cough frequency. Similar models were used to assess the effect of treatment on cough severity VAS, CTCAE score and EORTC question 31 responses.

2.6 Subjective measurement of cough

The methods used to assess cough subjectively were the MCLCS, cough severity VAS, EORTC QLQC30+LC 13 item 31 and the CTCAE version 4.

Manchester cough in lung cancer scale

The Manchester Cough in Lung Cancer Scale (MCLCS) is a 10-item cough-related Quality of Life (QoL) questionnaire which includes items on cough frequency, distress, impact and severity [40]. It is presented in Appendix 1. Scores range from 1-50, with higher scores indicating a worse cough-related QoL. Items 1 to 9 have five response categories: “never”, “some of the time”, “often”, “most of the time” and “all of the time”. Item 10, relating to cough severity, has five response categories: “very mild”, “mild”, “moderate”, “severe” and “very severe”. Patients are asked to circle the response categories that best describe their experience over the week prior to the questionnaire completion.

The total questionnaire score is the sum of the individual items. Therefore a patient with no cough would score 1/50, whereas the minimum possible score for patients who have a cough is 11/50. The higher the total score, the worse the impact of the cough on quality of life. To date, there is no baseline reference value for this questionnaire in lung cancer patients since this is a newly developed tool.

Cough severity visual analogue scale

The cough severity Visual Analogue Scale (VAS) is a 100mm line marked “no cough” at 0mm and “worse cough” at 100mm [55, 57]. It is presented in Appendix 2. Patients are asked to mark the line to indicate the severity of their cough. A score is derived by measuring in millimetres from the start of the line to the patient mark; the worse their cough, the higher the score. It is presented in Appendix 2.

A clinically significant change has not been defined in the lung cancer population. However, in the acute cough patient population, it is known to be 13mm [238].

Cough severity diary

The Cough Severity Diary (CSD) is a seven-item cough severity assessment tool developed by Vernon et al [61]. It is presented in Appendix 6. This is a tool that has seven 11-point scales ranging from scores of 0 to 10 that assess severity in terms of disruptiveness (two items), frequency (three items) and intensity (two items). Each scale has descriptive words at the start and ends of the scales such as “never” and “always”; the higher the score, the worse the cough. All items refer to the cough the day before completion of the questionnaire.

The CSD has a total score derived as the average score of the seven items. The CSD total score can be reported as a daily score or averaged over specified intervals (i.e. weekly score). Domain scores are calculated as the average score (or item score) of the domains. A daily score is calculated only if six or more items are complete for each day.

This tool was recently developed for patients with chronic cough or sub acute cough (cough duration <eight weeks). A clinically significant change has yet to be defined for any clinical population, including the lung cancer population.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer Module-13

The European Organisation for Research and Treatment of Cancer QoL Questionnaire C30 (EORTC QLQ C30) is a validated 30 item questionnaire to assess QoL in cancer patients [239]. It comprises of symptom, QoL and functional scales. It is used, in the context of lung cancer patients, with a 13-item lung cancer specific module, the LC-13[240].

Of the 43 items in the combined questionnaires, there is only one item on cough severity (Item 31): “In the past week, how often have you coughed?

All items refer to the patient experience over the week prior to questionnaire completion. Other than Items 29 &30, they have four Likert response categories:

“not at all”, “a little”, “quite a bit” and “very much”. Items 29 & 30, relating to overall health and QoL, each have seven response categories ranging from 1 to 7. The

response category 1 is marked “very poor” and the response category 7 is marked “excellent”.

Scores are derived according to the EORTC QLQ C30 and modules scoring manual.

For all scales, the Raw *Score (RS)* is the mean of the component items:

$$RawScore = RS = (I1 + I2 + \cdots In)/n$$

For **functional scales:**

$$Score = \left\{1 - \frac{RS-1}{range}\right\} \times 100$$

For **symptom scales/items** and **global health status/QoL:**

$$Score = \left\{\frac{RS-1}{range}\right\} \times 100$$

The range is three for all functional subscales and symptom subscales. It is six for the global health status and QoL subscale.

The scoring of the LC13 module is identical to that of the QLQ C30 questionnaire. The range for each of the symptom subscales in the LC-13 module is three.

All scores range from 0-100, where a high score on the QoL and functional scales represents a high QoL and high level of functioning, whereas a high score on a symptom scale represents a high level of symptomatology. Both questionnaires are presented in Appendix 3.

Full reference scores (for all stages of LC patients) are presented in Appendix 7. However, for Item 31 on cough severity the mean score (SD) is 37.4 (27) and median score [IQR] is 33.3 [33.3-66.7].

Common Terminology criteria for adverse events, version 4.0

The Common Terminology Criteria for Adverse Events (CTCAE), Version 4 is a standardised *physician-reported* scale that enables adverse events to be reported in a systematic way. A grading (severity) scale is provided for each symptom. Most scales range from 1 to 5, where “1” is a mild symptom and “5” results in death. The CTCAE cough scale ranges from “1” to “3”; where “1” represents a mild symptom: no prescription intervention is indicated, “2” represents a moderate symptom: a prescription intervention is indicated and limits instrumental activities of daily living. The category “3” represents a severe symptom which limits self-care activities of daily living. It is presented in Appendix 4.

The National Cancer Institute does not provide reference values for the Common Terminology Criteria for Adverse Events version 4.0 scales. However, the scales have been used extensively in the published literature. Despite this, the patient cohorts in whom the CTCAE version 4.0 cough scale have been used do not represent “real-life” clinic populations since patients are receiving cancer therapies and therefore tend to represent patients of good performance status, who are well enough to receive cancer therapy.

2.7 Objective measurement of cough

To assess cough frequency, 24-hour ambulatory cough monitoring was used in a subset of patients.

Twenty-four hour ambulatory cough monitoring

An Ambulatory Cough Monitor (ACM is an objective cough assessment tool to determine the frequency of cough events [62, 241]. A motion sensor and microphone is applied below the sternal notch and connected to the VitaloJAK Cough Monitor® (Vitalograph Ltd, UK) and a 24 hour digital sound recording is made. The monitor is carried in a waist bag. Participants are encouraged to continue their usual daily routine whilst wearing the monitor, the only restriction being not being able to get the monitor wet, i.e. no bath or shower. Patients remove the cough monitor after 24hrs and return it to the hospital at their next hospital visit or at a scheduled time with the researchers.

The device writes a 24 hour long file (8 kHz, 16 bit wave format) to a four gigabyte (GB) compact flash card, which is downloaded onto a password-protected computer and backed-up to a digital versatile disc (DVD). Confidentiality is assured: names are removed from recordings and secure storage is guaranteed (in a fire-proof safe in a coded room with limited access). Validated custom-written software algorithms are then used to compress the recording from 24 hours to a shorter file by detecting all potential cough sounds and cutting out non-cough sounds such as silence, background noise and speech. Trained staff listens to the reduced file and manually tag the number of explosive cough sounds within the recording using an audio editing software package called Adobe® Audition® 3.0. The tagged positions are extracted from the recordings using custom-written reporting software which then produces an hour by hour cough count report including day, night and total cough rates. Overall, 10% of cough recordings are quality control checked by a second trained counter.

2.8 Subjective measurement of gastro-oesophageal reflux disease

To assess GORD, the Brief Reflux Inventory was used.

Brief reflux inventory

The Brief Reflux Inventory (BRI) is a validated five-item questionnaire that assesses gastro-oesophageal reflux disease[242]. It is presented in Appendix 5. Its items relate to symptoms of regurgitation, chest pain and nocturnal symptoms. Each item has five response categories; “never”, “rarely”, “once a month to once a week”, “at least twice a week” and “daily”. The scale is scored 0-5, where 0 = “never“ and 5 = “daily”.

Each item was weighted as described below[242]:

Item 1=actual score x 5.61

Item 2=actual score x 4.15

Item 3=actual score x 1.94

Item 4=actual score x 4.05

Item 5=actual score x 5.23

A total weighted score for the scale was calculated as described below:

Total weighted score = sum of the weighted scores for the 5 individual items of the inventory.

The total BRI score was then expressed as a percentage of the maximal possible score on the weighted scale:

$$Total\ BRI\ score = \left(\frac{Total\ Weighted\ Score}{83.92}\right) \times 100$$

Patients who had a total BRI score above 31.6 were defined as those with reflux disease[242].

2.9 Measurement of change

To assess change and to determine a minimal important difference for the Manchester Cough in Lung Cancer Scale, the Global Rating of Change Scale (GRCS) was used.

Global Rating of Change Scale

The GRCS is a 15 point scale (seven ratings for improvement, seven ratings for worsening and one rating for no change) to assess changes in cough severity and cough frequency at the end of each treatment period (appendix 9). This validated instrument asks participants to quantify the improvement or deterioration in the cough frequency. Patients completed it on day 3 and day 9 of the trial.

2.10 Data analysis and statistics summary

Cross-sectional study

As described above, there was no ceiling to the number of patients recruited to this study. The analysis was descriptive and inferential. Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the study variables.

Longitudinal study

The recruitment target was 178 patients for a sample size for analysis of 160. There were 10 participants per correlate per outcome in binary logistic regression, assuming an attrition rate of 10%, the estimated percentage presenting with a severe cough to be 50%, and the number of cough predictors to be eight. The statistical analysis was descriptive and inferential.

The target recruitment number for ambulatory cough monitoring was 40, in order to detect medium-to-high (0.40) and high (0.50) correlations between quality of life and subjective measures and ambulatory cough monitoring. The numbers needed to reject the null hypothesis (correlation=0.00) at 5% significance and 80% power with a one-sided test were 37 and 23 respectively for Pearson's and Spearman's correlation.

Multivariate linear regression analyses, adjusted for baseline scores, were used to determine predictors of cough severity, frequency and impact and their change over time. Correlations between the assessment tools and between day 0 and day 60 were determined for their evaluation.

Aprepitant for the treatment of cough in lung cancer trial

The recruitment target was 20 patients for a sample size for analysis of 18 participants. No objective cough count data existed in participants with lung cancer at the time of trial design. However, in a previous trial of chronic cough patients, the change in 24hr objective cough frequency was normally distributed with a standard deviation of 36.5%. Based on a paired t-test, 18 participants were needed to detect a difference in cough frequency of 30% between aprepitant and placebo, at 5% significance and 90% power[64].

Data in participants with isolated chronic cough would suggest a 50% reduction is likely to be clinically meaningful; a 33% decrease in cough frequency has been shown to be appreciated by participants[64].

The drop-out rate was not felt likely to exceed 10%. This was based on data from the longitudinal study. The trial period was very short and the proposed treatment well tolerated. These factors were thought to limit drop-out rates significantly.

Data were summarised and means with standard deviations and medians interquartile ranges depending in whether the data were normally distributed or not. Daytime and 24hr cough frequency data were normalised by logarithmic transformation (base 10) and therefore geometric means and 95% confidence intervals are presented. Night cough data cannot easily be log transformed due to a number of zero values in patients who did not cough at all at night, therefore medians and interquartile ranges were used to summarise the raw data.

The effect of treatment (aprepitant versus placebo) on cough frequency was assessed using General Estimating Equations (GEE) modelling of the log transformed data. For night cough frequency a value of 0.01 was added to all values prior to transformation to remove the zero values. Models also included parameters describing treatment sequence (aprepitant/placebo versus placebo/aprepitant) and treatment period (1^{st} or 2^{nd} period) and log base 10 of the baseline cough frequency. Similar models were used to assess the effect of treatment on cough severity VAS, CTCAE score and EORTC question 31 responses.

3. Results

3.1 Cross-sectional cough prevalence study

Brief study design

A cross sectional study was conducted in consecutive patients attending thoracic outpatient clinics over a pre-defined five week period. Patients completed the MCLCS and cough severity VAS at a single time point. The primary endpoint was the percentage prevalence of cough. The secondary endpoints were the cough severity VAS and cough impact MCLCS scores.

Recruitment

All consecutive patients attending the thoracic oncology outpatient clinics at The Christie NHS Foundation Trust UK were recruited over a 33 day period from the 13th May 2013 to the 14th June 2013. A total of 223 patients were screened, forming the “screened population”. Of these, 90.6% consented to participate in the cross-sectional cough prevalence study, forming the “research population” (Figure 8).

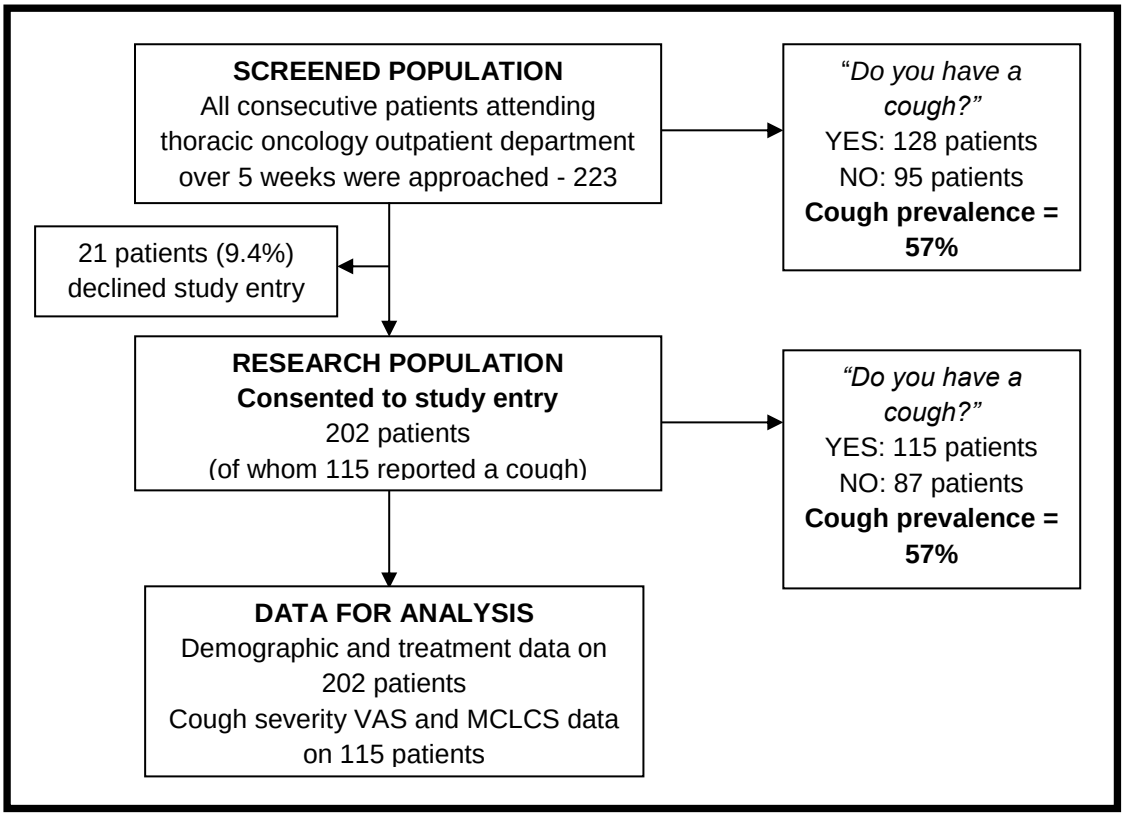


Figure 8 Recruitment to the cross-sectional cough prevalence study

This shows that of the screened population, 9.4% patients declined to consent to the study. The cough prevalence was the same in the screened population as the research population.

Cough severity VAS = cough severity visual analogue scale
MCLCS = Manchester Cough in Lung Cancer Scale questionnaire

Patient compliance rates and missing data

There was very high compliance with the study schedule and consequently little missing data. No variable had more than 1% missing data, with absolute numbers ranging from 199 to 202 for each demographic, cancer, treatment or cough variable assessed. The questionnaire completion rates were also very high. All patients who reported a cough (100%) completed the cough severity VAS and 113 out of 115 patients who reported a cough (98%) completed the total MCLCS questionnaire. The analyses below were performed on the maximum dataset available for each variable.

3.1.1 Clinical characteristics of the study population

Demographics

The research population's mean age was 66 years (SD 8.93). Just over half the population, 106 (53%) patients, was male. The majority had a history of smoking; with 135 (67%) patients being ex-smokers, 47 (23%) patients being current smokers and 19 (10%) patients having never smoked. Their median number of pack years was 36.8 (25^{th}-75^{th} IQR 17.5-49.7). With respect to co-morbidities, 75 (37%) patients reported symptoms of nausea and 106 (53%) patients reported symptoms of gastro-oesophageal reflux disease.

Cancer and treatment characteristics

Less than half the patients were of good performance status, with 27 patients (13%), 72 patients (36%), 71 patients (35%) and 32 patients (16%) of performance status 0, 1, 2 and 3 respectively. The majority, 135 patients (67%), had NSCLC; 63 patients (31%) had SCLC and three patients (2%) were of mixed lung cancer histology. Of those with NSCLC histology, the predominant histological subtype was adenocarcinoma. There were 84 patients (60%) with adenocarcinoma, 41

patients (29%) with squamous carcinoma, and 13 patients (9%) with a NSCLC histological subtype that was not otherwise specified, two patients (1%) with mixed histological subtypes and one patient (1%) with large cell NSCLC. The majority of patients had advanced lung cancer with 110 patients (55%) having stage IIIB or above NSCLC, 46 patients (23%) having extensive stage SCLC, 26 patients (13%) having early stage (≤IIIA) NSCLC and 17 patients (9%) having early stage SCLC. Less than half the study population was on anticancer therapy, with 91 patients (46%) on cancer treatment. Of these patients, the vast majority were on palliative intent treatment - 81 patients (89%). Most patients on treatment were on systemic therapies, with 58 patients (64%) on chemotherapy, 26 patients (29%) on tyrosine kinase inhibitors, four patients (4%) on concurrent chemoradiotherapy and three patients (3%) on radiotherapy. Of the patients who were not receiving anticancer therapy, the majority (42 patients, 38%) were on follow-up following palliative treatment. Overall, 31 patients (28%) were newly diagnosed and pre-treatment, 29 patients (26%) were post curative treatment on follow-up and only nine patients (8%) were in the final phase of their lung cancer, with no further treatment possible.

A comparison of clinical characteristics between patients with and without a cough

Any patient who reported the presence of a cough at trial entry was assumed to have a cough, irrespective of its cause, severity or impact. All other patients were defined as having no cough. Overall, 115/202 patients reported a cough; therefore the cough prevalence rate was 57%. The analysis presented below compares the patients who reported a cough to those that did not report a cough.

Patient baseline demographic and cancer characteristics such as age, sex, smoking history, performance status, stage of cancer, histology, NSCLC histological subtype, cancer treatment intention, cancer treatment type and reasons for not receiving cancer treatment did not differ significantly between the two groups. The only variable that differed significantly between the two groups was the proportion of patients receiving anticancer therapy (Table 6).

Characteristic	Subgroup	Cough N (%)	No Cough N (%)	p-value
Mean age in years (SD)		67years (+9.02)	66years (+8.85)	0.56
Male sex		57 (50)	49 (56)	0.34
Smoking status	Never	12 (10)	7 (8)	0.44
	Former	73 (64)	62 (72)	
	Current	30 (26)	17 (20)	
Median no. pack years (25^{th}-75^{th} IQR)		38 (17.5-46)	33 (17.5-50)	1.00
Performance status	0	15 (13)	12 (14)	0.09
	1	33 (29)	39 (45)	
	2	46 (40)	25 (29)	
	3	21 (18)	11 (12)	
Stage*	Early NSCLC (inc IIIA)	14 (12)	12 (14)	0.61
	Advanced NSCLC	63 (56)	47 (55)	
	LS SCLC	12 (11)	5 (6)	
	ES SCLC	24 (21)	22 (25)	
Histology	NSCLC	76 (67)	59 (68)	1.00
	SCLC	36 (31)	27 (31)	
	Mix	2 (2)	1 (1)	

NSCLC histological subtype	Adenocarcinoma	44 (55)	40 (65)	0.29
	Squamous	25 (31)	16 (26)	
	Not otherwise specified	10 (13)	3 (5)	
	Mixed	1 (1)	1(2)	
	Large cell	0 (0)	1(2)	
On anticancer therapy	***Yes***	***45 (40)***	***47 (54)***	***0.04***
What type of anticancer therapy	Chemotherapy	28 (62)	30 (65)	0.44
	Radiotherapy	3 (7)	0 (0)	
	Concurrent	2 (4)	2 (4)	
	TKI	12 (27)	14 (31)	
If not on anticancer therapy, why not	Pre-treatment	16 (23)	13 (31)	0.33
	Post palliative treatment	24 (34)	18 (43)	
	Post curative treatment	6 (9)	3 (7)	
	No further treatment	24 (34)	8 (19)	

Table 6 The comparison of clinical characteristics between patients with and without a cough.

The only statistically significant difference between the two groups was the proportion of patients receiving anticancer therapy.
SD=standard deviation, IQR=interquartile range, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer, LS=limited stage, ES=extensive stage, TKI=tyrosine kinase inhibitor. Bold type italic = p value < 0.05

*cancer staged according to 7th Edition of TNM in Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2009

In terms of co-morbidities, there were no significant differences between the two groups. Overall, 42 patients (36%) reported the symptoms of nausea compared to 33 patients (38%) in patients with a cough and those without a cough respectively (p-value 0.79). A total of 62 patients (54%) reported symptoms of GORD compared to 44 patients (51%) in patients who reported a cough and those who did not report a cough respectively (p-value 0.70).

Characteristics of cough in the study population

More than twice as many patients felt that their cough warranted treatment, than reported their cough to be painful. The median VAS score showed that most patients graded their cough at the milder end of the spectrum (32mm, 25^{th}-75^{th} IQR 20-51) whilst the median MCLCS score showed a moderate cough impact score of 22 (25^{th}-75^{th} IQR 16-27) (Table 7).

Characteristic	Cough Yes vs No	Comment
Is cough painful? N (%)	26 (23) vs 89 (77)	
Does cough warrant treatment? N (%)	60 (52) vs 55 (48)	
Median cough severity VAS score* (25^{th}-75^{th} IQR)	32mm (20-51)	Higher score = worse cough severity
Median MCLCS score (25^{th}-75^{th} IQR)	22 (16-27)	Higher score = worse cough impact

Table 7 The cough characteristics in the study population

Over half the study population (52%) reported that their cough was severe enough to warrant treatment, yet under quarter (23%) of patients reported their cough as painful.

VAS=Visual Analogue Scale: total score range 0-100mm

IQR=interquartile range

MCLCS=Manchester Cough in Lung Cancer Scale: total score range 0-50, lowest possible MCLCS score if patient has a cough = 11

3.2 Clinical factors associated with cough severity and impact over time and the measurement of cough in lung cancer

Brief study design

The aim of this longitudinal study was to assess clinical factors associated with cough severity and impact at baseline, their change over time and to compare and evaluate subjective and objective cough assessment tools at baseline.

The study was designed and conducted as described in “Methods” (section 2.2.1) to assess cough longitudinally in patients with lung cancer. In brief, patients completed the cough severity VAS and CSD scales, the cough impact MCLCS questionnaire, the EORTC QLQ C30+LC13 quality of life questionnaire, the BRI gastro-oesophageal reflux disease questionnaire and hand-held spirometry. Researchers completed the CTCAE v4 cough severity scale. Assessments were conducted at baseline (day 0), on day 30 and on day 60. A subset of patients underwent 24-hour ACM on day 0 and on day 60. The use of both patient-reported and physician reported subjective cough assessment tools and the use of objective cough assessment tools enabled the evaluation and comparison of these cough assessment tools.

Recruitment

The diagram (Figure 9) showing recruitment and attrition rates, is shown below.

Overall, 178 patients were recruited to the study between October 2010 and November 2012. The overall attrition rate was 12%. In the figure below, the recruitment and attrition are shown in more detail.

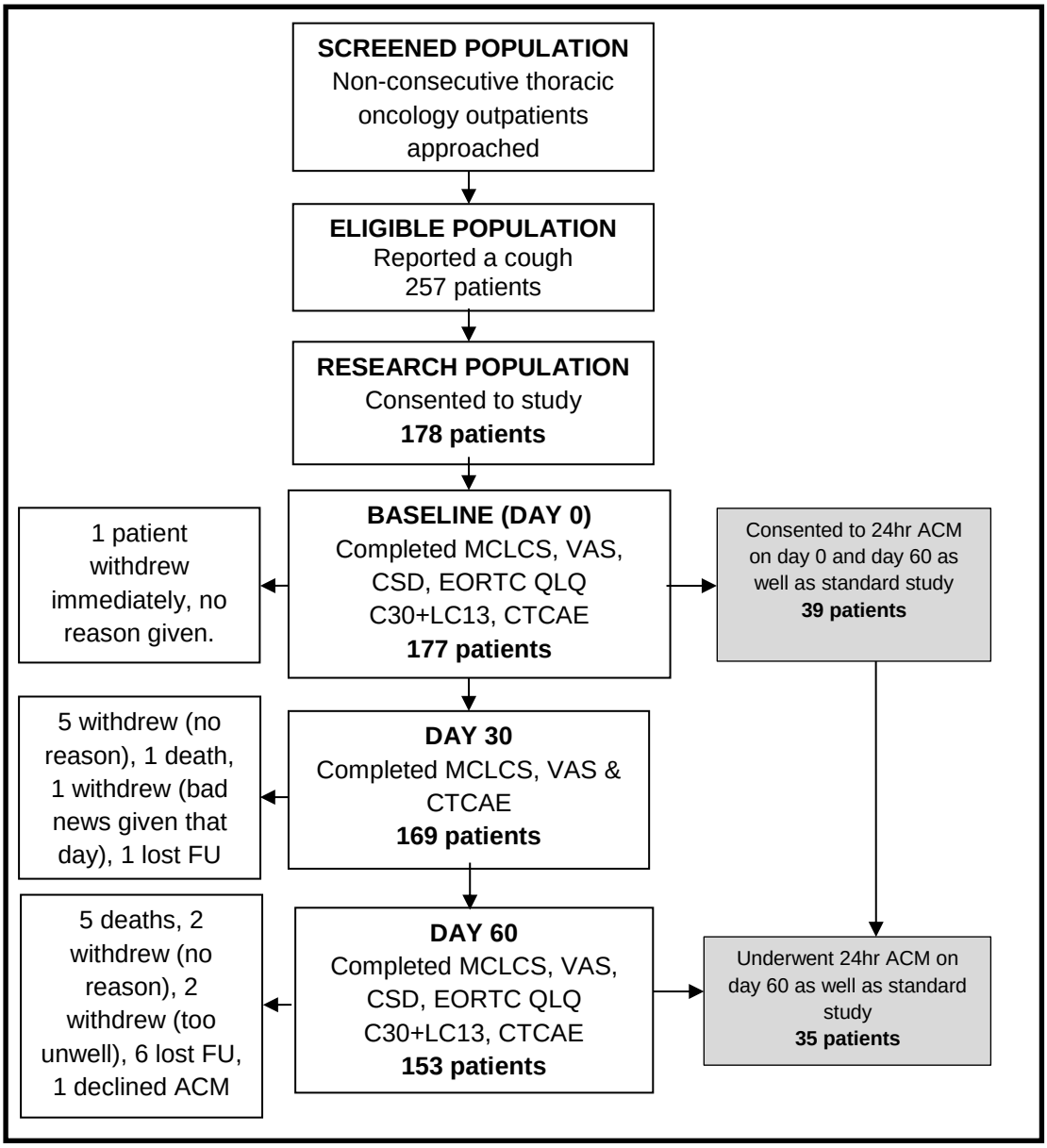


Figure 9 Recruitment to the longitudinal study

This shows the assessment schedule and attrition throughout the study period. The attrition rate (proportion of patients who withdrew from the study, whatever the cause) was 25/178 patients (14%).

MCLCS = Manchester Cough in Lung Cancer Scale questionnaire (*patient reported)*
VAS = cough severity visual analogue scale (*patient reported)*
CSD = cough severity diary (*patient reported)*
EORTC QLQ C30+LC 13= European Organization for the Research and Treatment of Cancer Quality of Life Core30 questionnaire and Lung Cancer LC13 module (*patient reported),* CTCAE = Common Terminology for Adverse Events cough severity grading scale *(physician reported),*FU = follow-up, ACM = ambulatory cough monitoring

Questionnaire completion rate

As shown in Figure 10 all patients were required to complete a number of questionnaires at serial time points during the study (day 0, day 30 and day 60). The baseline questionnaire completion rate was high for all questionnaires and remained high for most of the subsequent assessments (Table 8). The lowest questionnaire completion rate was at day 30, for the cough severity VAS (62%).

Assessment Time	Day 0 No. (% completed)	Day 30 No. (% completed)	Day 60 No. (% completed)
No. evaluable patients	177	169	153
Discontinuation of protocol	0	7	16
Questionnaires*			
MCLCS	165 (93)	163 (96)	136 (89)
Cough Severity VAS	171 (97)	105 (62)	147 (96)
EORTC QLQ C30+LC13	173 (98)	NA	150 (98)
Cough Severity Diary	85 (96)[&]	NA	75 (86)[^]
Brief Reflux Inventory	170 (96)	NA	146 (95)

Table 8 Questionnaire completion rate in the longitudinal study showing the percentage of questionnaires completed at each study assessment point.

The compliance rates were between 86-98% for all questionnaires except the cough severity VAS at day 30. The compliance rate for the cough severity VAS at day 30 was lower (62%).
MCLCS = Manchester Cough in Lung Cancer Scale questionnaire (*patient reported),*VAS = cough severity visual analogue scale (*patient reported)*
CSD = cough severity diary (*patient reported),*EORTC QLQ C30+LC 13= European Organization for the Research and Treatment of Cancer Quality of Life Core30 questionnaire and Lung Cancer LC13 module *(patient reported)*
[*] Data shown relate to questionnaires completed with no items missing
[&] 89 evaluable patients only since CSD was a late addition to trial schedule
[^] 87 evaluable patients only since CSD was a late addition to trial schedule

3.2.1 Patient characteristics at baseline

Patient demographics at baseline

The study population comprised 177 patients. Unless stated otherwise, all variables at baseline had complete data. At day 0, the study population had a mean age of 65 years (SD 9.07). Overall, 94 patients (53%) were male. The majority had a smoking history with 115 patients (65%) being ex-smokers and 50 patients (28%) being current smokers. The study population had a significant smoking history with a median number of pack years of 38 (25^{th}-75^{th} IQR 26-58). Not all study patients were physically able to complete spirometry on day 0. The majority of patients had abnormal lung function as demonstrated by a median FEV1 of 1.52l (25-75^{th} IQR 1.20-2.03, n=158); a median percentage predicted FEV1 of 61% (25^{th}-75^{th} IQR 50.00-76.75, n=156); a median FEV6 of 2.21l (25-75^{th} IQR 1.74-2.98, n=158) and a median percentage predicted FEV6 of 74% (25^{th}-75^{th} IQR 58.25-87.00, n=156). Overall, the median FEV1/FEV6 ratio was 0.70 (25^{th}-75^{th} IQR 0.62-0.79, n=158) showing that half the population had an obstructive respiratory defect.

Patient co-morbidities and concurrent medications at baseline

Study patients reported the presence of a number of co-morbidities at baseline (day 0). About a third of patients reported COPD (61 patients, 35%), a quarter of patients reported a chest infection at the time of study entry (43 patients, 24%), just under a quarter of patients reported asthma (39 patients, 22%) and very few patients reported having heart failure (two patients, 1%). Just under half of patients reported symptoms of GORD (87 patients, 49%). This was a higher proportion of patients than those who reached the criteria for GORD according to the BRI questionnaire score (61 patients, 36%). Seven patients failed to complete the BRI at baseline.

Patients also reported their concurrent medications at baseline. Nearly half of patients took oral or inhaled steroids (76 patients, 43%). A similar proportion of

patients took regular proton pump inhibitors (75 patients, 42%). Just over a third of patients were on regular opioids (66 patients, 37%). Although 2% patients had reported heart failure as a co-morbidity, 27 patients (15%) were on regular ACE inhibitors (15%). Fewer patients were on antibiotics than reported a chest infection. There were 24 patients (14%) on antibiotics. A minority of patients (26 patients, 15%) were on over-the-counter antitussives. About a fifth of patients (37 patients, 21%) were taking other medications (such as anticholinergics and gabapentin) that may affect cough.

Patient cancer characteristics and treatment at baseline

Many patients in this study had a poor performance status score. Few patients had a performance status score of 0 (11 patients, 6%). Just under half of patients had a performance status score of 1 (85 patients, 48%). Over a third of patients had a performance status score of 2 (59 patients, 34%) and 21 patients (12%) had a performance status score of 3. Performance status score was not available in one patient.

Most patients had NSCLC histology (141 patients, 81%), the remainder (34 patients, 19%) having SCLC histology. Histology was not known in two patients. The predominant histological subtype was adenocarcinoma (65 patients, 46%), followed by squamous cell carcinoma (51 patients, 36%). Rarer subtypes included large cell (three patients, 2%), mixed (one patient, 1%) and other (21 patients, 15%). The histological subtype was not known in two patients.

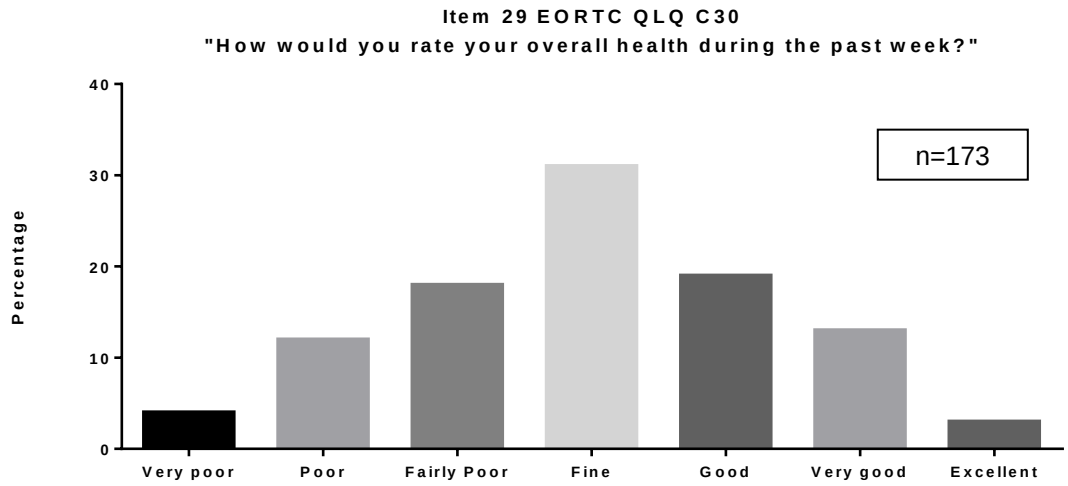
Patients in this study had advanced stage lung cancer more commonly than early stage disease. Overall, there were 37 patients (21%) with stage IIIB NSCLC, 52 patients (29%) with stage IV NSCLC and 17 patients (10%) with extensive stage SCLC. There was one patient (1%) with stage IA NSCLC, six patients (3%) with stage IB NSCLC, five patients (3%) with stage IIA NSCLC, five patients (3%) with stage IIB NSCLC, 33 patients (19%) with stage IIIA NSCLC and 20 patients (11%) with limited stage SCLC. Stage was unknown in one patient.

Of 171 patients for whom tumour location data were available, the majority (96 patients, 56%) had a central tumour.

The patients varied significantly in terms of the number of days since their lung cancer diagnosis at baseline (day 0). The median for the population was 164 days with a 25^{th}-75^{th} IQR of 56-568 days. There were six patients for whom this data were unavailable. The study population was recruited at any stage of treatment or follow-up. At baseline (day 0), just over a third of patients (62 patients, 35%) were on anticancer therapy. Of these, 40 patients (64%) were on chemotherapy, 14 patients (23%) were on tyrosine kinase inhibitors, five patients (8%) were receiving concurrent chemoradiotherapy, and three patients (5%) were receiving thoracic radiotherapy. Over half the study population was on follow-up at baseline (day 0). There were 49 patients (28%) post curative intent treatment, 40 patients (22%) post palliative treatment, four patients (2%) for whom further treatment was not possible and 19 patients (11%) were pre-treatment, newly diagnosed with lung cancer. All study patients had treatment data.

Patient symptom and quality of life scores at baseline

In order to further define the patient population, global and quality of life scores (according to the EORTC QLQ C30 questionnaire) were obtained at baseline for all patients. The mean baseline (day 0) global health score (Item 29 of the questionnaire) was 50.29 (SD 23.74) (Figure 10). The mean baseline overall quality of life score (Item 30 of the questionnaire) for the study population was 53.90 (SD 25.65) (Figure 11). The score range for both Item 29 and Item 30 is 0-100, where high scores represent better health and quality of life. The median BRI score at baseline was 20.83 (25^{th}-75^{th} IQR 7.14-38.30) (Figure 11).



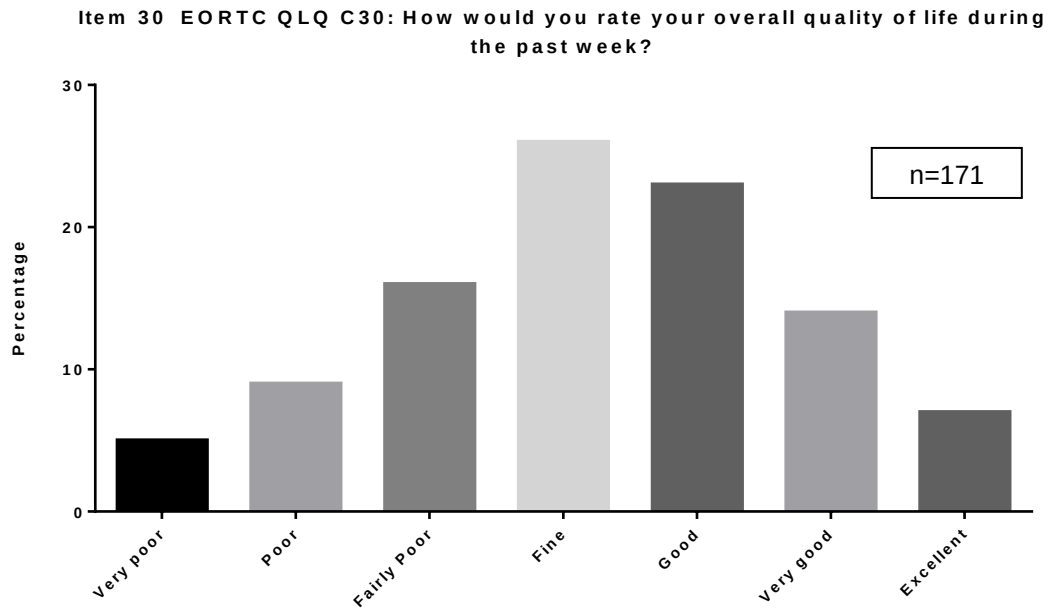
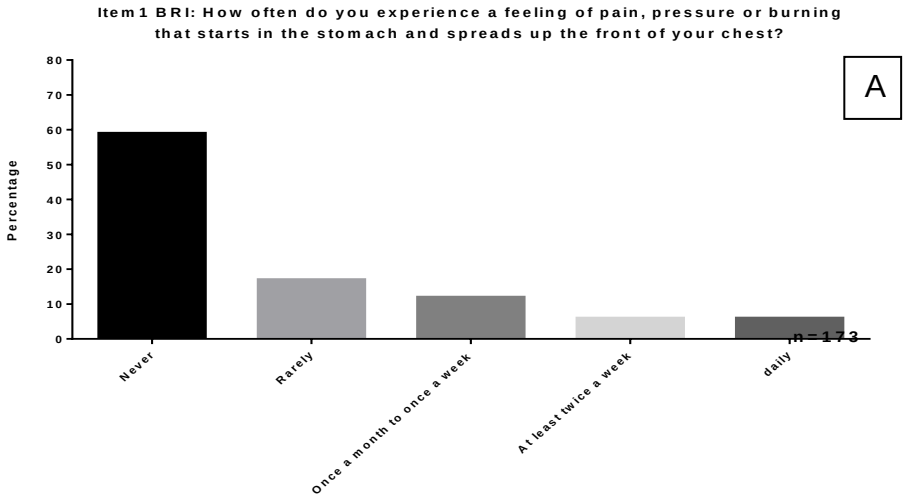
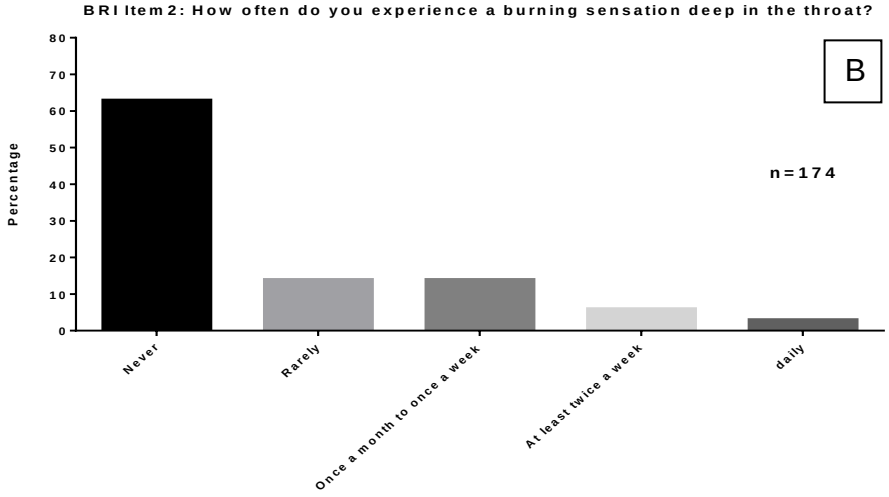


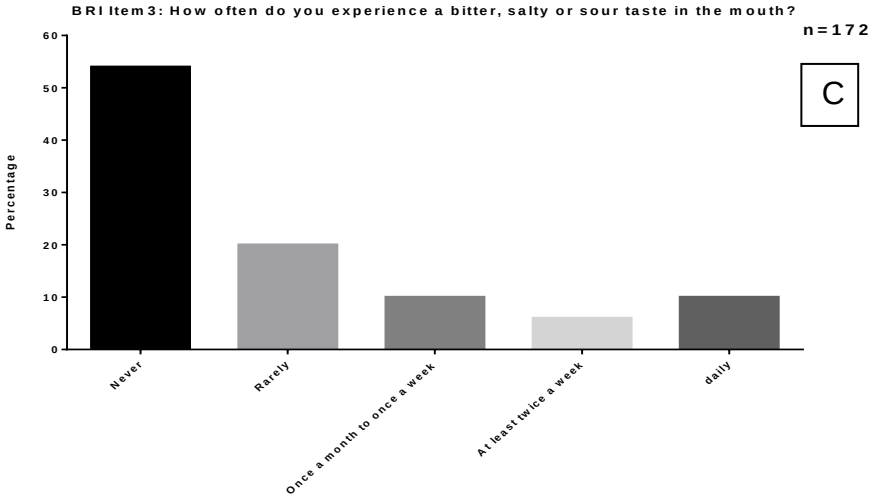
Figure 10 The spread of responses for the individual EORTC QLQ C30 items on overall health (Item 29) and global quality of life (Item 30)

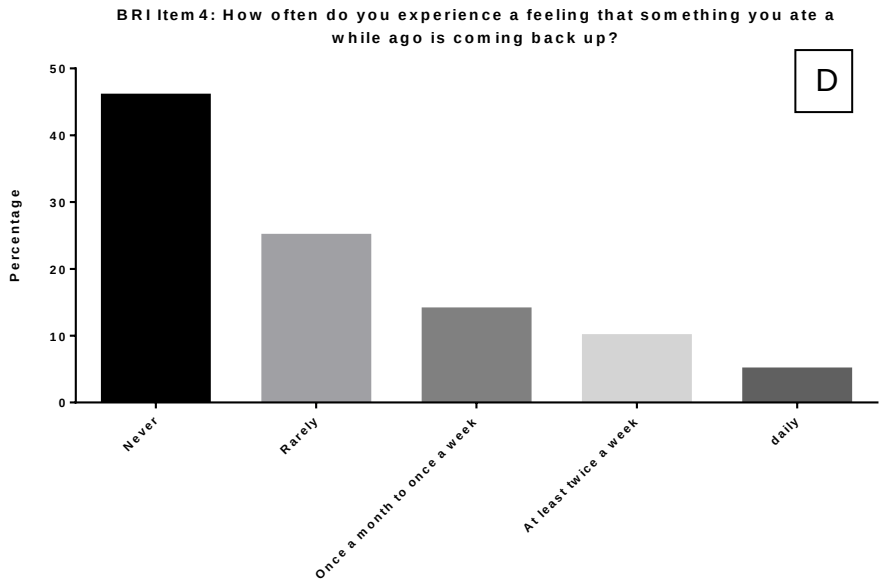
This shows that about half the population felt that they experienced poor overall health and quality of life.

EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire.


Item1 BRI: How often do you experience a feeling of pain, pressure or burning that starts in the stomach and spreads up the front of your chest?
A
Percentage
80
70
60
50
40
30
20
10
0
n=173
Never
Rarely
Once a month to once a week
At least twice a week
daily


BRI Item2: How often do you experience a burning sensation deep in the throat?
B
Percentage
80
70
60
50
40
30
20
10
0
n=174
Never
Rarely
Once a month to once a week
At least twice a week
daily


BRI Item3: How often do you experience a bitter, salty or sour taste in the mouth?
n=172
C
Percentage
60
50
40
30
20
10
0
Never
Rarely
Once a month to once a week
At least twice a week
daily



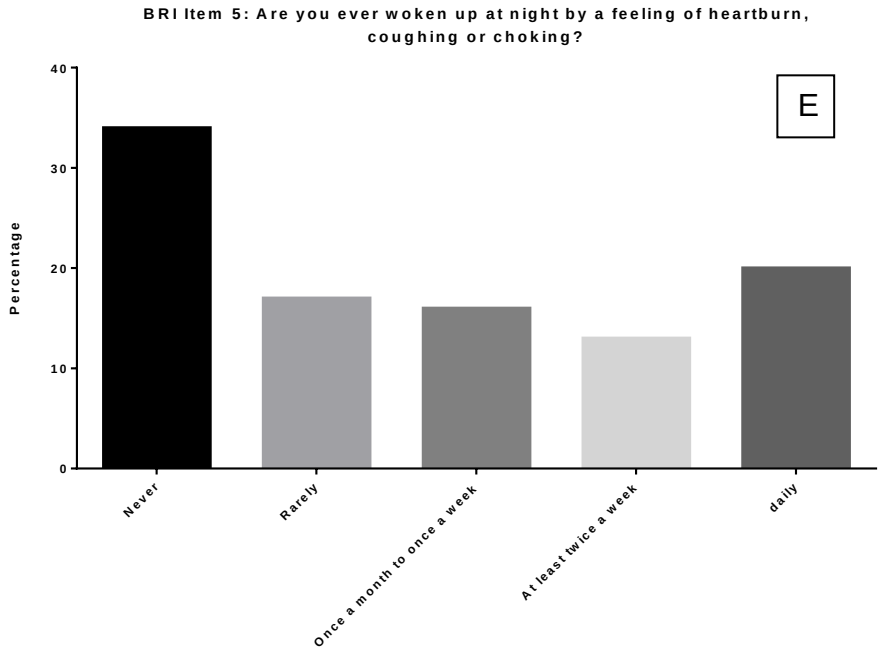


Figure 11 The spread of responses for each brief reflux inventory questionnaire item (A-E)

More patients experienced the symptoms described in item 5 than any other item, showing that their sleep was significantly affected by symptoms of coughing, choking or heartburn. Most patients did not report symptoms of heartburn, burning in the throat or a bitter/salty taste in the mouth (Items 1-3).

BRI = Brief Reflux Inventory questionnaire

Patient cough characteristics and cough scores at baseline

At baseline (day 0), most patients had had a cough for a prolonged period of time, with a median of 52 weeks with a wide range (25^{th}-75^{th} IQR 8.5-260). The majority of coughs were productive with 113 patients (64%) reporting a productive cough. Data were missing on two patients. Nearly two-thirds of patients (106 patients, 64%) felt that their cough was severe enough to warrant treatment No data were available on 10 patients.

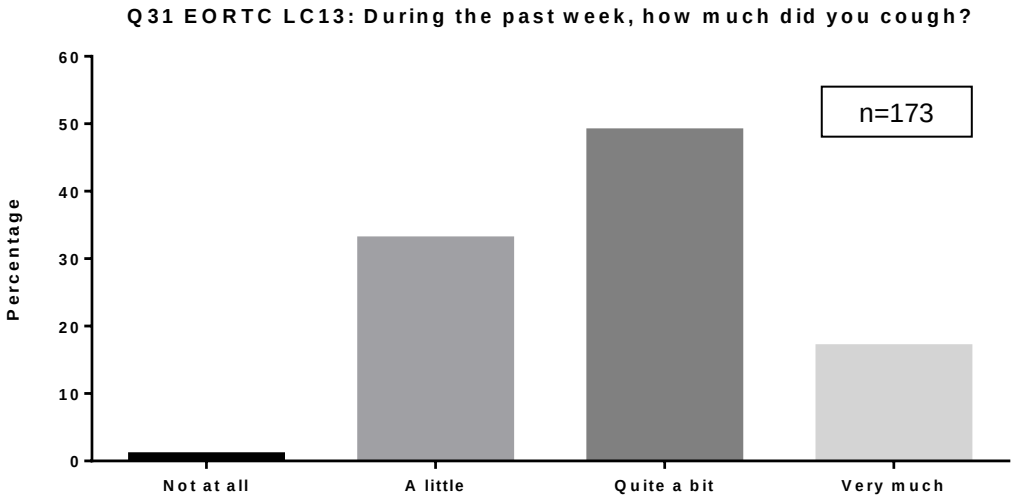
Patients subjectively assessed the severity of their cough using the cough severity visual analogue scale (VAS – appendix 2) and the cough severity diary (CSD – appendix 6).

The median cough severity VAS score was just under half the total possible score at 40mm (25^{th}-75^{th} IQR 20-69, score range 0-100 where higher scores represent worse cough severity, n=171).

The median CSD score was at the lower end of the score range at 2.93 (25^{th}-75^{th} IQR 1.5-5.0, range 0-10 were higher scores represent worse cough severity). CSD data were available in 84 patients at baseline since this was a late addition to the study schedule.

The median Manchester Cough in Lung Cancer Scale (MCLCS) score was about half the total score range at 24 (25^{th}-75^{th} IQR 18-32, range 1-50 where higher scores represent worse cough impact, n=165).

Overall, the mean EORTC Lung Cancer 13 Item 31 score was 60.7 (SD 29, 173 patients) where higher scores indicate worse cough severity on a scale of 0-100. Two thirds of the patients (114 patients, 66%) reported that they coughed “quite a bit” or “very much” over the week prior to study entry. Most patients (152 patients, 87%) did not report any haemoptysis in the week before study entry (Figure 12).



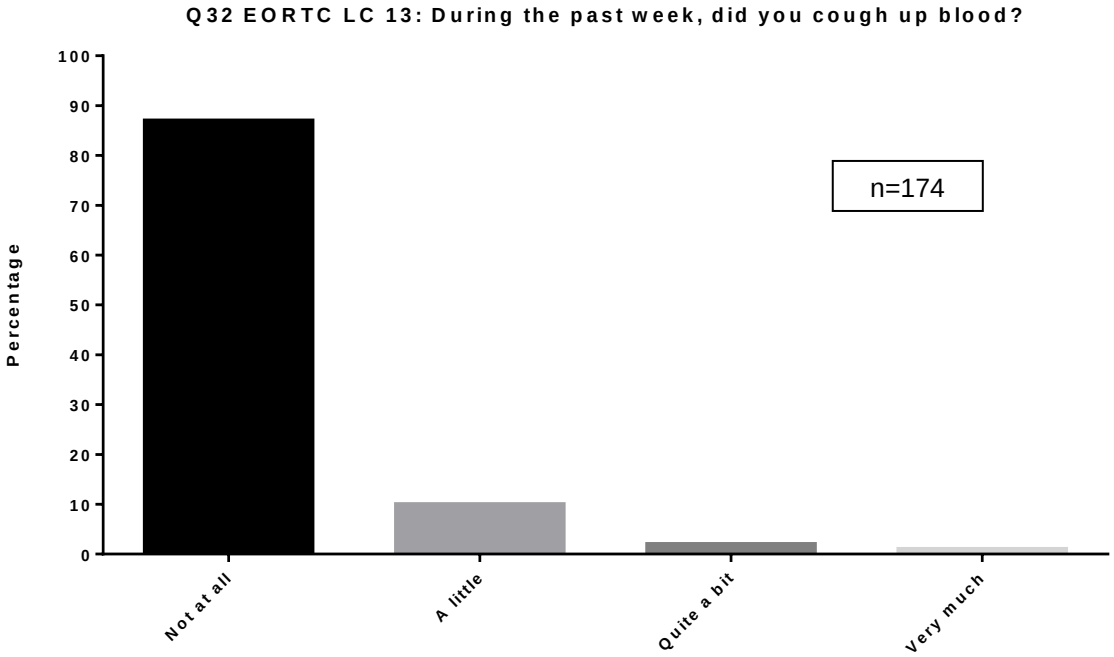


Figure 12. The spread of responses for the EORTC Lung Cancer Module 13 Items 31 and 32 for the study population at baseline

This shows that most patients reported having coughed “quite a bit” or “very much” in the week prior to study entry and that almost no patients reported haemoptysis at baseline.

EORTC LC13 = European Organization for the Research and Treatment of Lung Cancer lung cancer questionnaire module LC 13.

Researchers scored each study patient's cough according the Common Terminology Criteria for Adverse Events (CTCAE) version 4 at baseline (day 0) (Figure 14). This was the only *physician-rated* subjective cough assessment tool used during the study. Only two patients (1%) were thought to have severe symptom that interfered with self-care activities of daily living (Grade 3).

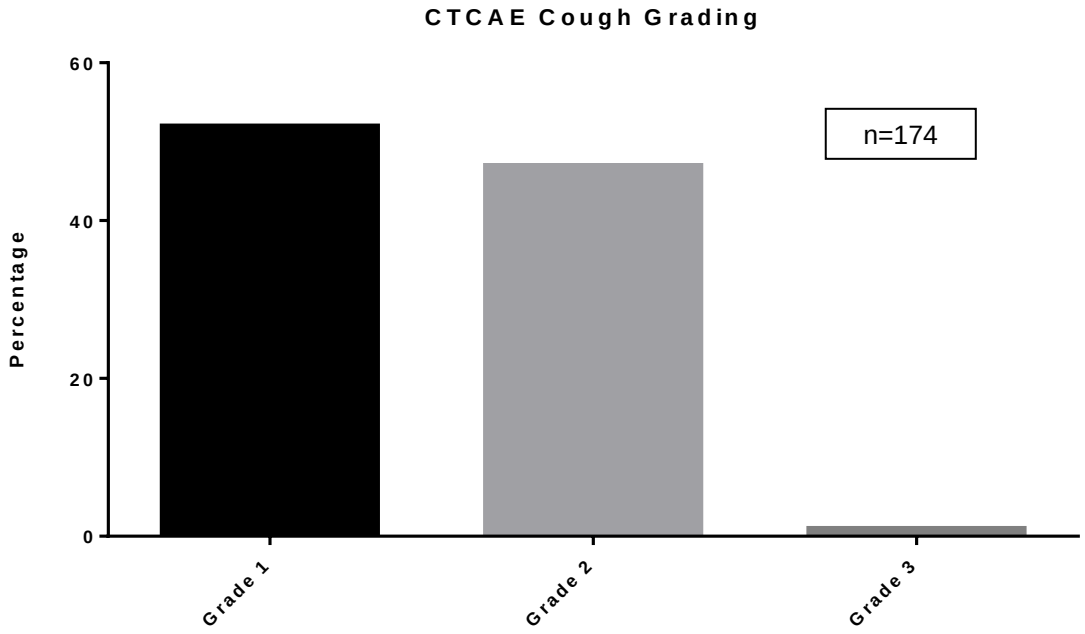


Figure 13 The spread of physician-rated responses for the Common Terminology criteria for adverse events cough grading scale at baseline (day 0).

This shows that almost no patients had a cough score “Grade 3”.

CTCAE = Common terminology criteria for adverse events version 4.

Grade 1 = mild symptom, non prescription intervention indicated.

Grade 2 = moderate symptom, medical intervention indicated.Interferes with instrumental ADLs

Grade 3 = severe symptom, interferes with self-care ADLs

Objective cough monitoring was conducted in a subset of 39 patients at baseline (day 0). Of these, daytime recordings failed in two patients. One recording failed overnight. The baseline cough frequency over 24 hours was 14.1coughs/hour with a 25^{th}-75^{th} IQR of 6.3-31.9. The daytime (defined as hours patient awake) cough frequency was 18.4 coughs/hour with a 25^{th}-75^{th} IQR of 8.6-40.0. The night-time (defined as hours patient asleep) cough frequency was 5.9 coughs/hour with a 25^{th}-75^{th} IQR of 1.2-12.1. The cough frequency correlation between day and night was moderate with a Spearman correlation coefficient of 0.59. In all but four patients (11%), the cough frequency per hour was lower in the night than the day. Of these four patients, one patient had a daytime cough frequency of 23.2coughs/hour and a night-time cough frequency of 110.5coughs/hour. The range of 24-hour cough frequency was wide with some patients coughing 0.8 coughs/hr compared to others who had a cough frequency of 156.3coughs/hour (Figure 14).

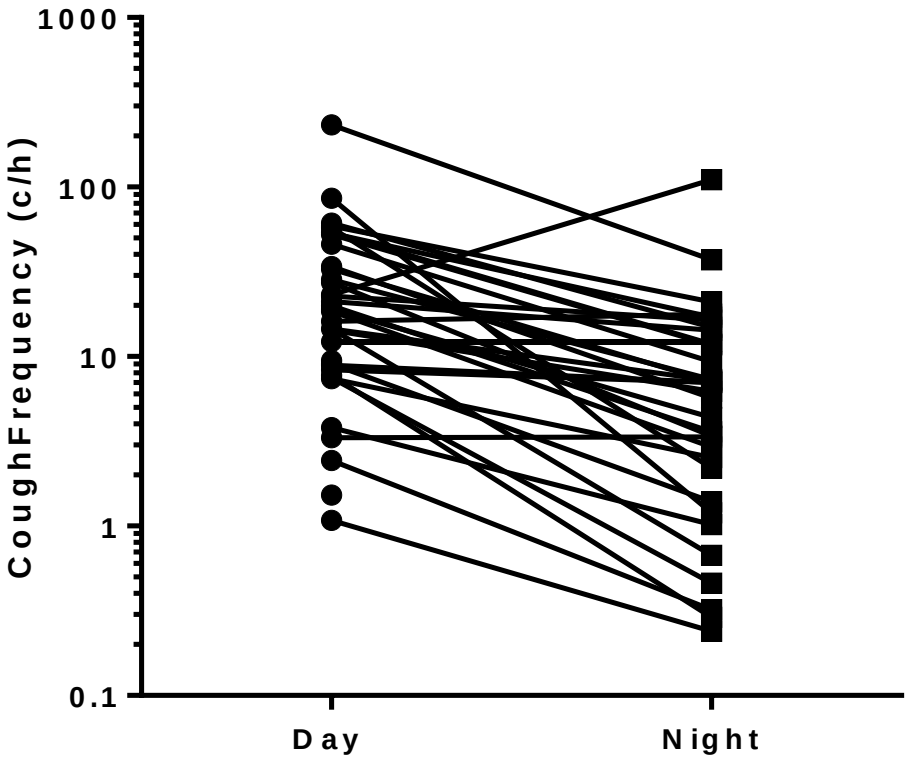


Figure 14 Daytime and night-time objective cough frequency for individual patients who underwent 24-hour ambulatory cough monitoring

The logarithmic scale was necessary in view of the large range in cough frequency. Night-time cough frequency was lower in all but 4 patients than daytime cough frequency.

c/h = coughs/hour

3.2.2 Changes in patient clinical characteristics over the course of the study period

Changes in spirometry, concurrent medications and cancer treatment at serial assessment points (day 30 and day 60) after initial assessment at baseline

The patient clinical characteristics were assessed at three time points during the course of the study: day 0, day 30 and day 60 (Table 9). Overall, the study population was stable in terms of the proportion of patients taking different concurrent medications.

The only variables that changed significantly over the course of the study were the FEV1 and FEV6 values, the proportion of patients receiving anticancer therapy, and the proportion of patients who were pre cancer therapy. Although the median FEV1 and FEV6 values improved slightly between day 0 and day 60, this was not matched by statistically significant improvements in percentage predicted FEV1 and FEV6 values, nor FEV1/FEV6 ratio. At day 0, the median FEV1 was 1.52l (25^{th}-75^{th} IQR 1.20-2.03), whilst at day 60, it was 1.62l (25^{th}-75^{th} IQR 1.24-1.63), p-value 0.05. Similarly, at day 0, the median FEV6 was 2.21l (25^{th}-75^{th} IQR 1.74-2.98), whilst at day 60, the median FEV6 was 2.31l (25^{th}-75^{th} IQR 1.84-2.95), p-value 0.03. The proportion of patients receiving anticancer therapy was highest at day 30 with 81/167 patients (49%) on treatment, compared to 62/176 patients (35%) at day 0 and 61/149 patients (40%) on day 60, p-value 0.04. At day 0, 23/176 patients (13%) were pre-treatment, whereas at the subsequent assessment points, no patients were in this category, p-value <0.001.

	Day 0	Day 30	Day 60	p-value
SPIROMETRY	n=156-158	NA	n=108-111	
FEV1, median in litres (25^{th}-75^{th} IQR)[$]	1.52 (1.20-2.03)	NA	1.63 (1.24-1.63)	***0.05***
Percentage predicted FEV1, median (25^{th}-75^{th} IQR)	61 (50.00-76.75)	NA	63 (49.75-78.00)	0.21
FEV6 , median in litres (25^{th}-75^{th} IQR)	2.21 (1.74-2.98)	NA	2.31 (1.84-2.95)	***0.03***
Percentage predicted FEV6, median (25^{th}-75^{th} IQR)	74 (58.25-87.00)	NA	74 (59.25-86.00)	0.22
FEV1/FEV6 ratio , median (25^{th}-75^{th} IQR)	0.70 (0.62-0.79)	NA	0.73 (0.62-0.78)	0.83
CONCURRENT MEDICATIONS	n=177	n=165	n=149-150	
On ACE inhibitors, n (%)	27 (15)	23 (14)	21 (14)	0.93
On opioids, n (%)	66 (37)	65 (39)	52 (35)	0.69
On proton pump inhibitors, n (%)	75 (42)	74 (45)	63 (42)	0.85
On antitussives, n (%)	26 (15)	18 (11)	15 (10)	0.37
On steroids, n (%)	76 (43)	69 (42)	59 (40)	0.80
On antibiotics, n (%)	24 (14)	18 (11)	15 (10)	0.57
Other medication that may affect cough (i.e.: gabapentin), n (%)	37 (21)	37 (22)	29 (19)	0.80

	Day 0	Day 30	Day 60	p-value
CANCER TREATMENT	n= 176	n=167	n=153	
On cancer treatment (any type), n (%)	62 (35)	81 (49)	61 (40)	***0.04***
Chemotherapy, n (%)*	40 (64)	52 (64)	38 (62)	0.19
TKI, n (%)*	14 (23)	18 (22)	17 (28)	0.56
Radiotherapy, n (%)*	3 (5)	6 (8)	4 (7)	0.55
Concurrent chemoradiotherapy, n (%)*	5 (8)	5 (6)	2 (3)	0.56
Where is the patient, on the disease trajectory?				
Pretreatment	23 (13)	0 (0)	0 (0)	***<0.001***
Post curative treatment on follow-up	43 (24)	41 (25)	41 (27)	0.86
Post palliative treatment on follow-up	47 (27)	44 (26)	49 (32)	0.45
On curative treatment	7 (4)	12 (7)	6 (4)	0.30
On palliative treatment	53 (30)	68 (41)	55 (36)	0.12
No further treatment possible	3 (2)	2 (1)	2 (1)	0.92

Table 9 Changes in clinical characteristics in the study population

This shows the change in proportions for each variable on day 0, day 30 and day 60 of the study. Few variables changed over the course of the study. However, there was a statistically significant improvement in FEV1 and FEV6 values. This was not matched by significant changes in percentage predicted FEV1 and FEV6 values, nor FEV1/FEV6 ratio. In terms of cancer treatment, more patients were on anti-cancer treatment mid-study. At day 30 and day 60, no patients were pre-treatment, in contrast to day 0.

FEV1=forced expiratory volume in the first second of expiration, FEV6=forced expiratory volume in the first 6 seconds of expiration, ACE=angiotensin converting enzyme, TKI=tyrosine kinase inhibitor

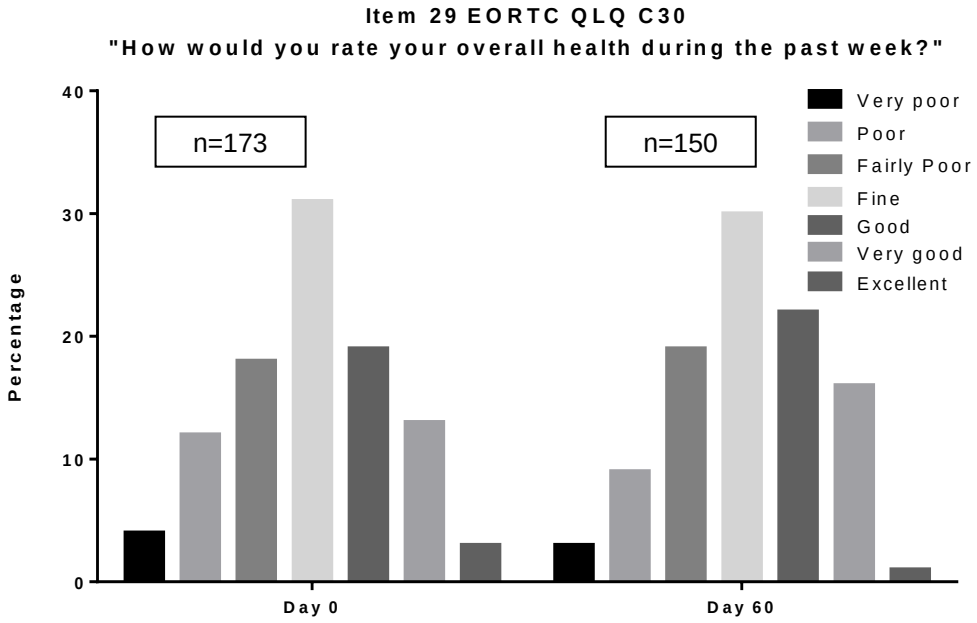
*Percentage of patients taken from total number of patients on cancer treatment rather than from total study population

p-values in bold and italic denote clinical characteristics that have changed significantly over the course of the study period.

Subjective symptom scores and quality of life scores at serial time points (day 30 and day 60) after initial assessment at baseline

Overall, cough reflux scores were stable in the study population over the course of the study period. There was no statistically significant difference between the median BRI scores or the proportion of patients who met the criteria for GORD according to the total BRI score between day 0 and day 60. The median BRI score at baseline was 20.83 (25^{th}-75^{th} IQR 7.14-38.30, n=170) compared to 20.04 (25^{th}-75^{th} IQR 4.62-38.48, n=146, p-value 0.08). At baseline, 61 patients (26%) reached the criteria for GORD according the BRI score, compared to 44 patients (30%) at day 60 (p-value=0.28).

During the course of the study, the baseline global health values and quality of life values were stable. The mean baseline global health score was 50.29 (SD 23.74) on day 0 and 50.11 (SD 22.21) on day 60. These were not statistically significantly different, p-value 0.38. The mean baseline global quality of life score was 53.90 (SD25.65) and 55.22 (SD 24.66) on day 60. These values were not statistically significantly different, p-value 0.54. The spread of responses to both these items was similar (Figure 15).



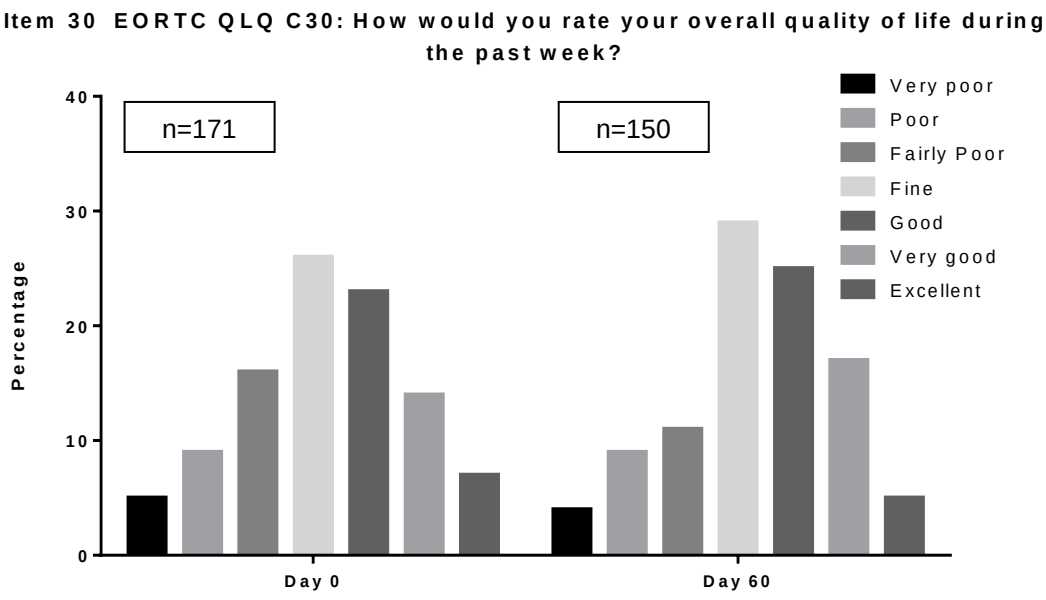


Figure 15 The spread of responses between day 0 and day 60 for item 29 and item 30 of the EORTC QLQ C30 quality of life questionnaire.

The patient population is stable in terms of its patient-rated overall health and quality of life.

EORTC QLQ C30: European Organization for the Research and Treatment of Cancer Quality of Life Core 30 Questionnaire

Characteristics of cough in patients with lung cancer at serial time points (day 30 and day 60) after initial assessment at baseline

Both objective and subjective cough scores improved over the course of the study (Figure 17). Most of the improvement was seen at day 30 rather than day 60 for the cough severity VAS and MCLCS scores.

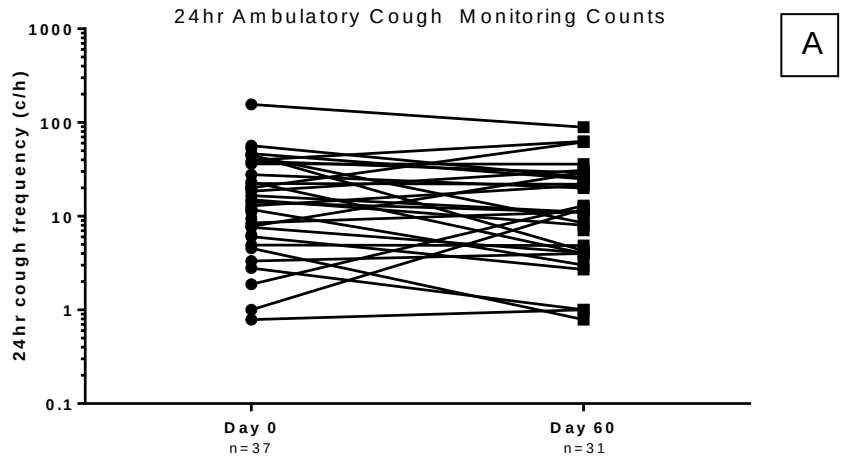
At days 0, 30 and 60, the median cough severity VAS scores with 25^{th}-75^{th} IQR were 40mm (20-69), 32mm (15-52) and 33mm (11-52) respectively, p-value 0.05. The median CSD scores (25^{th}-75^{th} IQR) at day 0 and day 60 were 2.93 (1.46-5.00) and 1.86 (0.57-4.00) respectively, p value 0.01) (Figure 16).

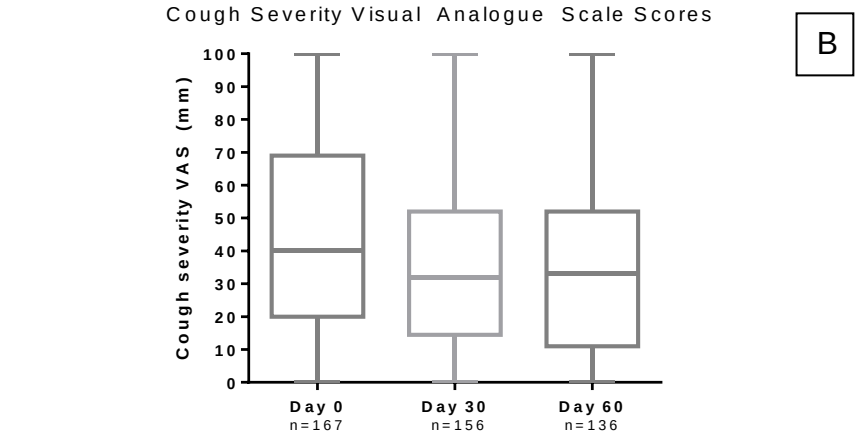
At day 0, 30 and 60, the median cough impact MCLCS scores with 25^{th}-75^{th} IQR were 24 (18-32), 20 (15-27) and 21 (16-28) respectively, p-value <0.001 (Figure 16).

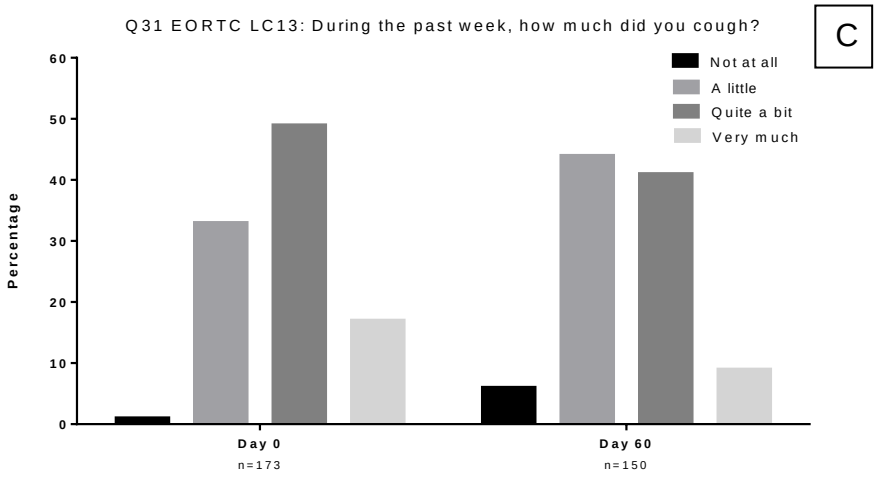
The median 24 hour cough frequency was 14.1 (25^{th}-75^{th} IQR 6.4 – 32.0) at baseline and 11.1 (25^{th}-75^{th} IQR 4.1-26.0) at day 60, p-value 0.23 (Figure 16). The median daytime cough frequency was 18.5 (25^{th}-75^{th} IQR 8.6 – 40.0) at baseline and 13.0 (25^{th}-75^{th} IQR 5.0-37.0) at day 60, p-value 0.13. The median night-time cough frequency was 6.0 (25^{th}-75^{th} IQR 1.3 – 12.2.0) at baseline and 4.4 (25^{th}-75^{th} IQR 1.0-11.0) at day 60, p-value 0.61.

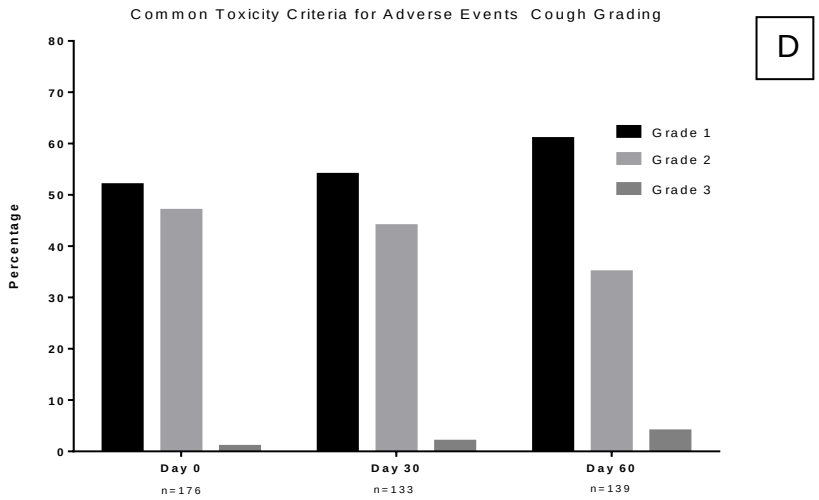
Other characteristics such as the proportion of patients who reported a productive cough were stable (113 patients (64%) on day 0, 99 patients (74%) on day 30 and 86 patients (68%) on day 60, p-value 0.22.

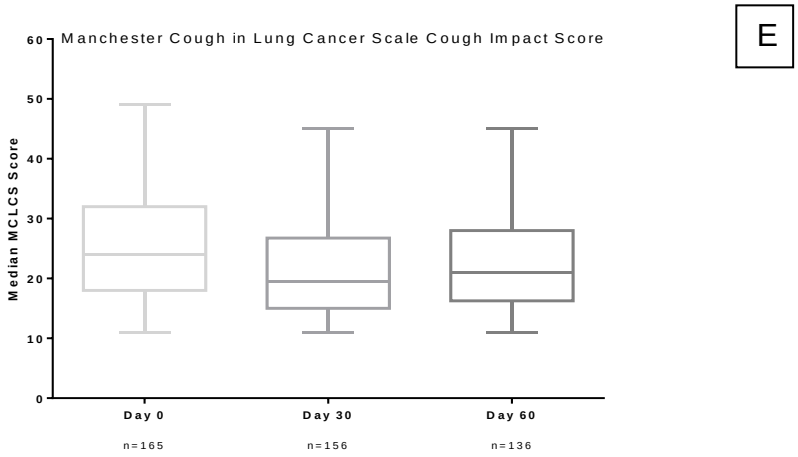
Nearly two-thirds of patients felt that their cough was severe enough to warrant treatment at baseline. However, over the course of the study, this proportion reduced. At day 0, 106/167 patients (64%) felt that their cough was severe enough to warrant treatment; at day 30, 67/131 patients (51%) felt that their cough was severe enough to warrant treatment and at day 60, 57/137 patients (42%) felt that their cough was severe enough to warrant treatment, p-value 0.01.


24hr Ambulatory Cough Monitoring Counts
A
24hr cough frequency (c/h)
1000
100
10
1
0.1
Day 0
n=37
Day 60
n=31


Cough Severity Visual Analogue Scale Scores
B
Cough severity VAS (mm)
100
90
80
70
60
50
40
30
20
10
0
Day 0
n=167
Day 30
n=156
Day 60
n=136


Q31 EORTC LC13: During the past week, how much did you cough?
C
Not at all
A little
Quite a bit
Very much
Percentage
60
50
40
30
20
10
0
Day 0
n=173
Day 60
n=150





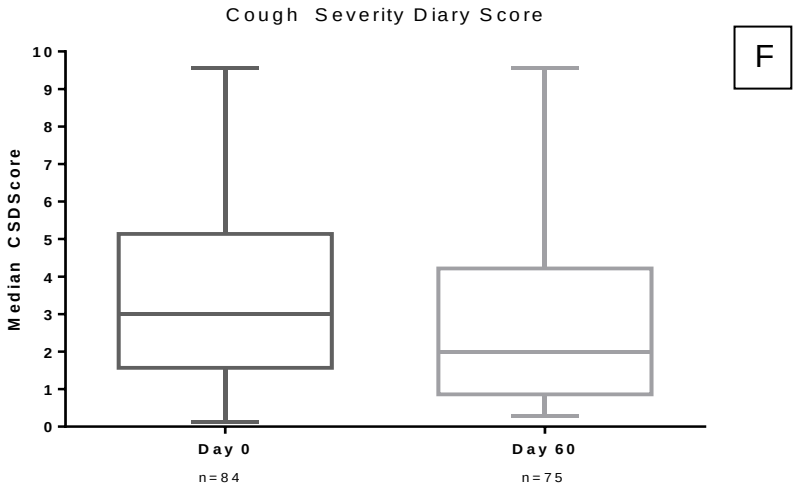


Figure 16 Change in subjective and objective cough scores (A-F) at serial time points during the study (day 0, day 30 and day 60) for the study population as a whole

Only the cough severity VAS, common terminology criteria for adverse events (CTCAE) cough grading and Manchester cough in lung cancer scale (MCLCS) were assessed at day 30. The cough scores improved over the course of the study. Most of the improvement was seen at day 30 for the cough severity VAS and MCLCS scores. There was significant overlap of scores between all time points for all cough tools.

Most patients had a cough severity score that did not change significantly between “baseline-day 30” and between “day 30-day 60” (Figures 17-25). However, a greater proportion of patients improved between “day 0-day 30” (40%) than improved between “day 30 and day 60” (20%). In the graphs below, the change in cough severity VAS, cough impact MCLCS, cough severity CTCAEv4, cough severity CSD and cough frequency (24-hour ACM) scores are shown for the time periods Day0-30 and Day0-60.

The variation in cough scores during the day0-day30 time and day0-day60 time periods was much greater using the cough severity VAS, cough impact MCLCS and cough severity CSD scales than the 3-point CTCAE v4 scale and the four-point Item 31 of the EORTC QLQ C30+LC13 scale.

The change in cough scores during the Day0-Day 60 period showed a similar pattern using subjective and objective cough assessment tools.

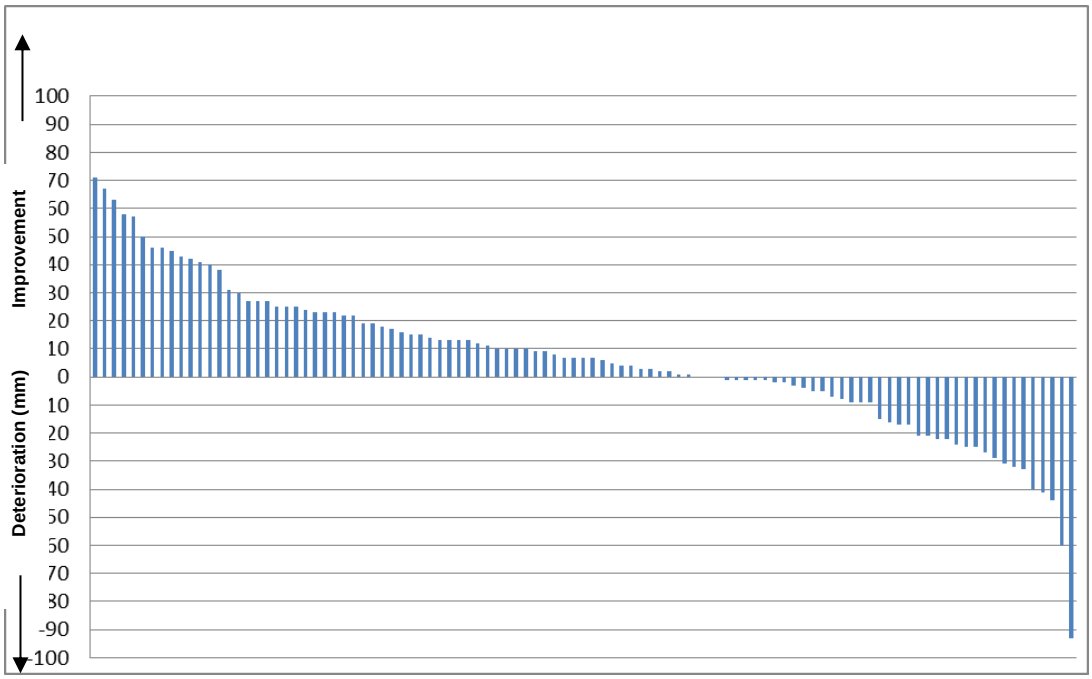


Figure 17 The change in cough severity visual analogue scale (VAS) score between day 0 and day 30 for individual patients.

This shows that most patients improved or had stable cough severity scores during this period.

VAS = Visual Analogue Scale

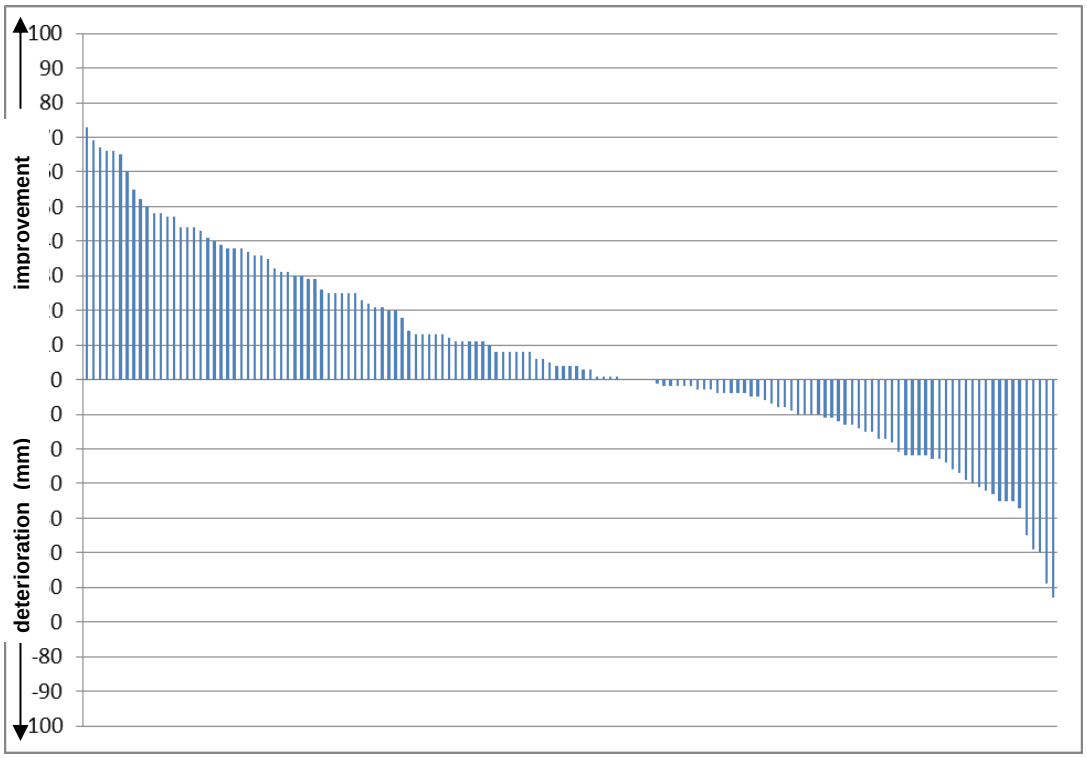


Figure 18 The change in cough severity visual analogue scale (VAS) Score between day 0 and day 60 for individual patients.

This shows that most patients improved or had stable cough severity scores during this period.

VAS = Visual Analogue Scale

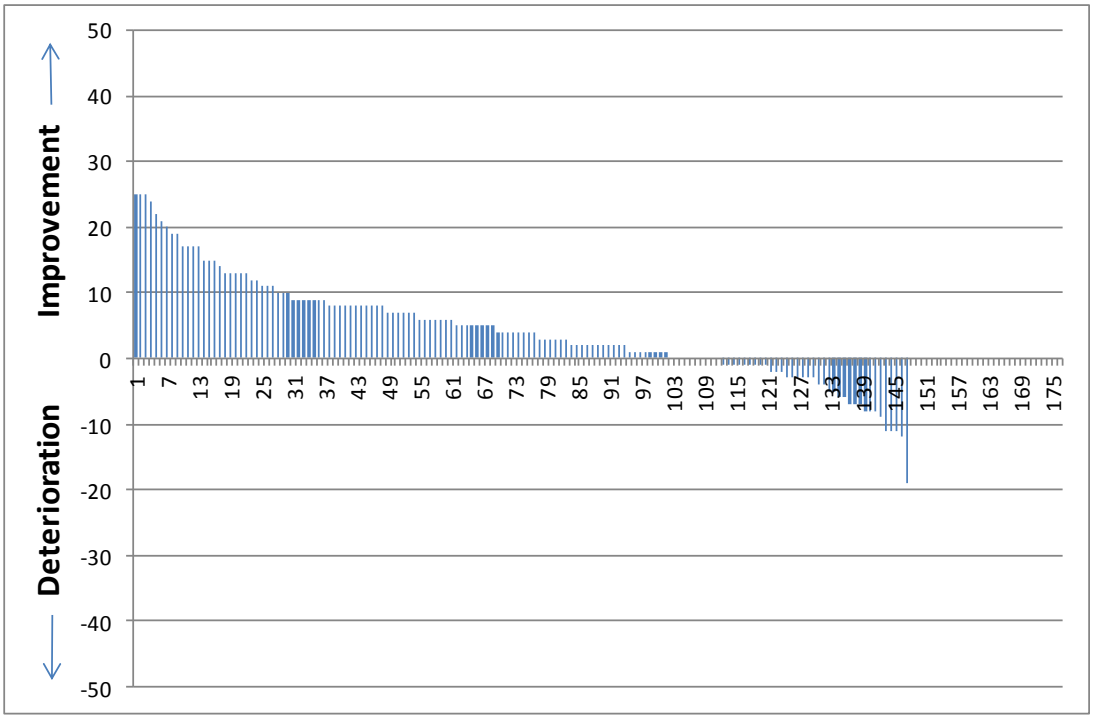


Figure 19 The change in cough impact Manchester Cough in Lung Cancer Scale (MCLCS) score between day 0 and day 30 for individual patients.

This shows that most patients improved or had stable cough severity scores during this period.

MCLCS = Manchester Cough in Lung Cancer Scale

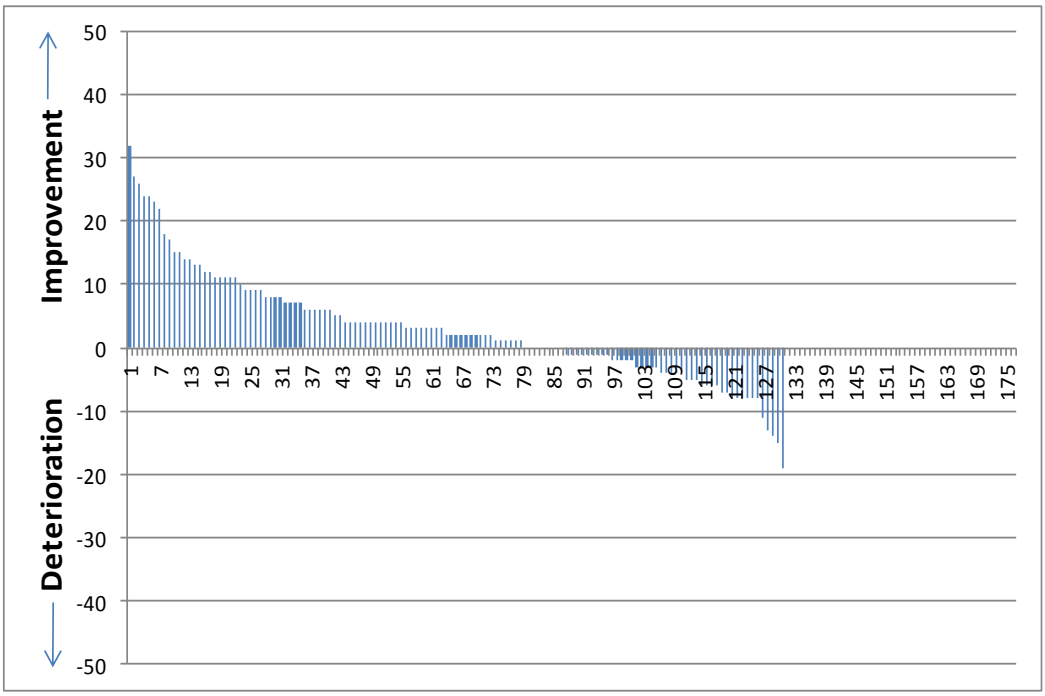


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Figure 20 The change in cough impact Manchester Cough in Lung Cancer Scale (MCLCS) score between day 0 and day 60 for individual patients

This shows that most patients improved or had stable cough severity scores during this period.

MCLCS = Manchester Cough in Lung Cancer Scale

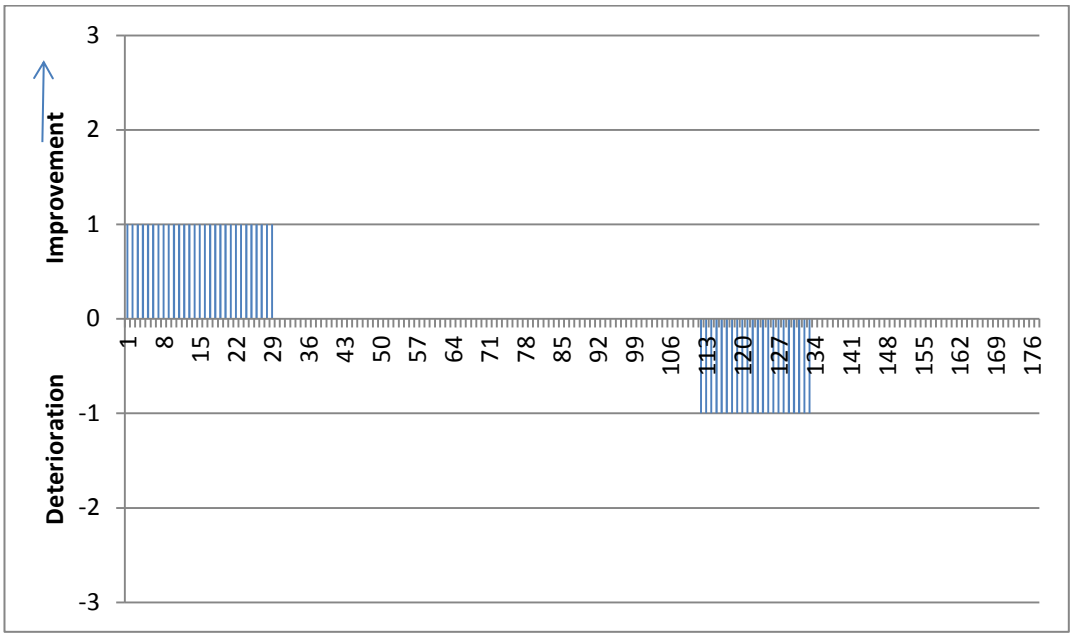

Figure 21 The change in cough severity Common Terminology Criteria version 4.0 (CTCAEv4) score between day 0 and day 30 for individual patients

The cough severity score did not change for most patients during the study**.**

CTCAEv4 = Common Terminology Criteria

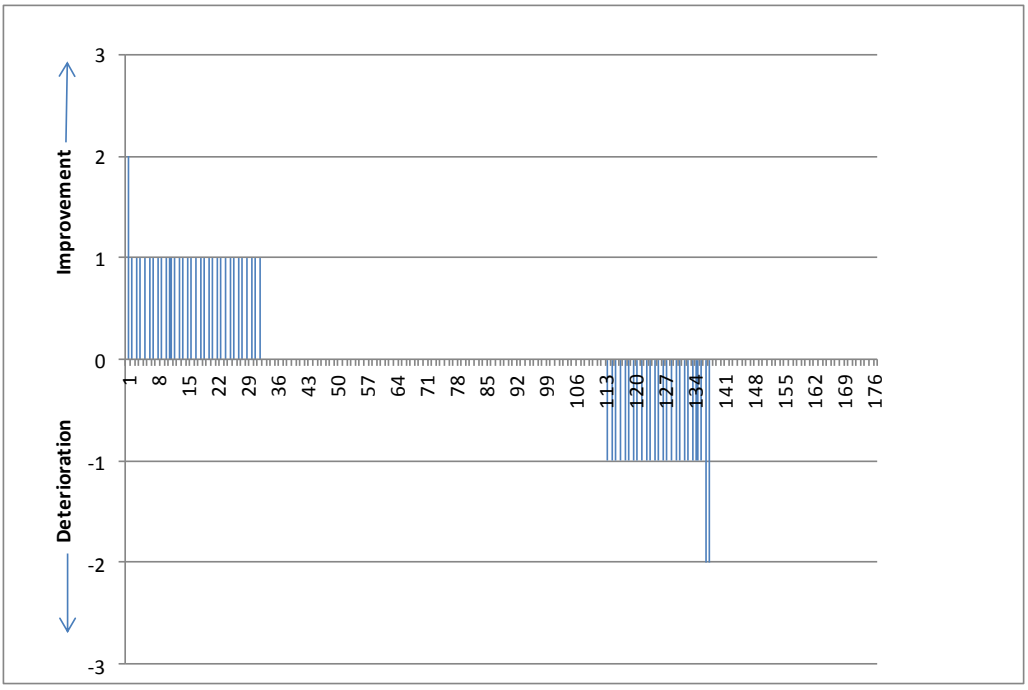

Figure 22 The change in cough severity Common Terminology Criteria version 4.0 (CTCAEv4) score between day 0 and day 60 for individual patients

The cough severity score did not change for most patients during the study.

CTCAEv4 = Common Terminology Criteria

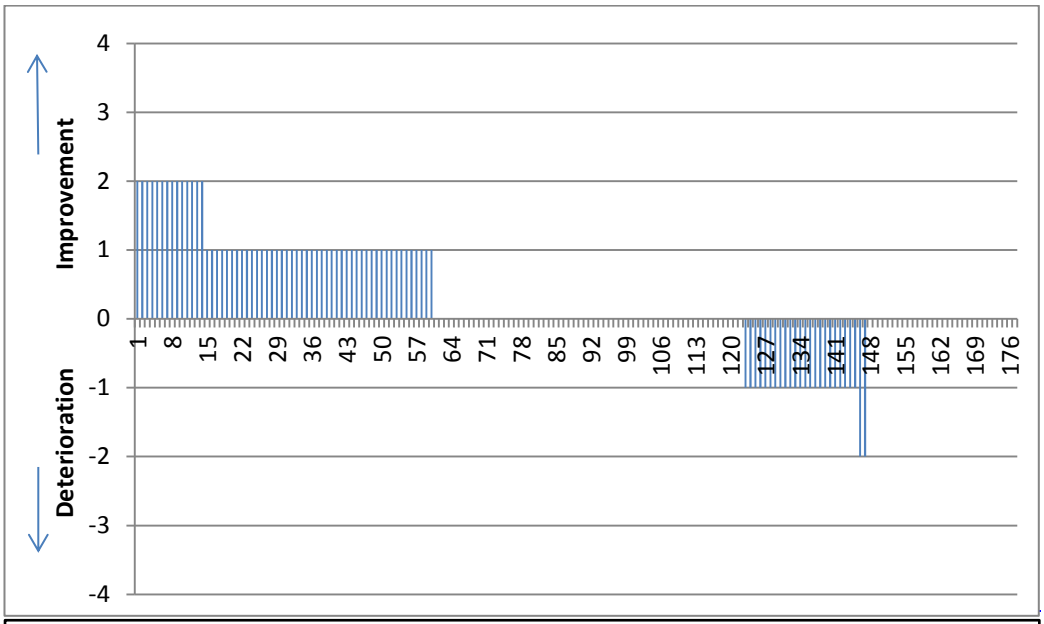

Figure 23 The change in cough severity EORTC QLQ C30+LC13 Cough severity "Item 31" scores between day 0 and day 60 for individual patients.

This shows that most patients improved or had stable cough severity scores during this period.

EORTC QLQ C30+LC13 = European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 + Lung Cancer 13 questionnaire module

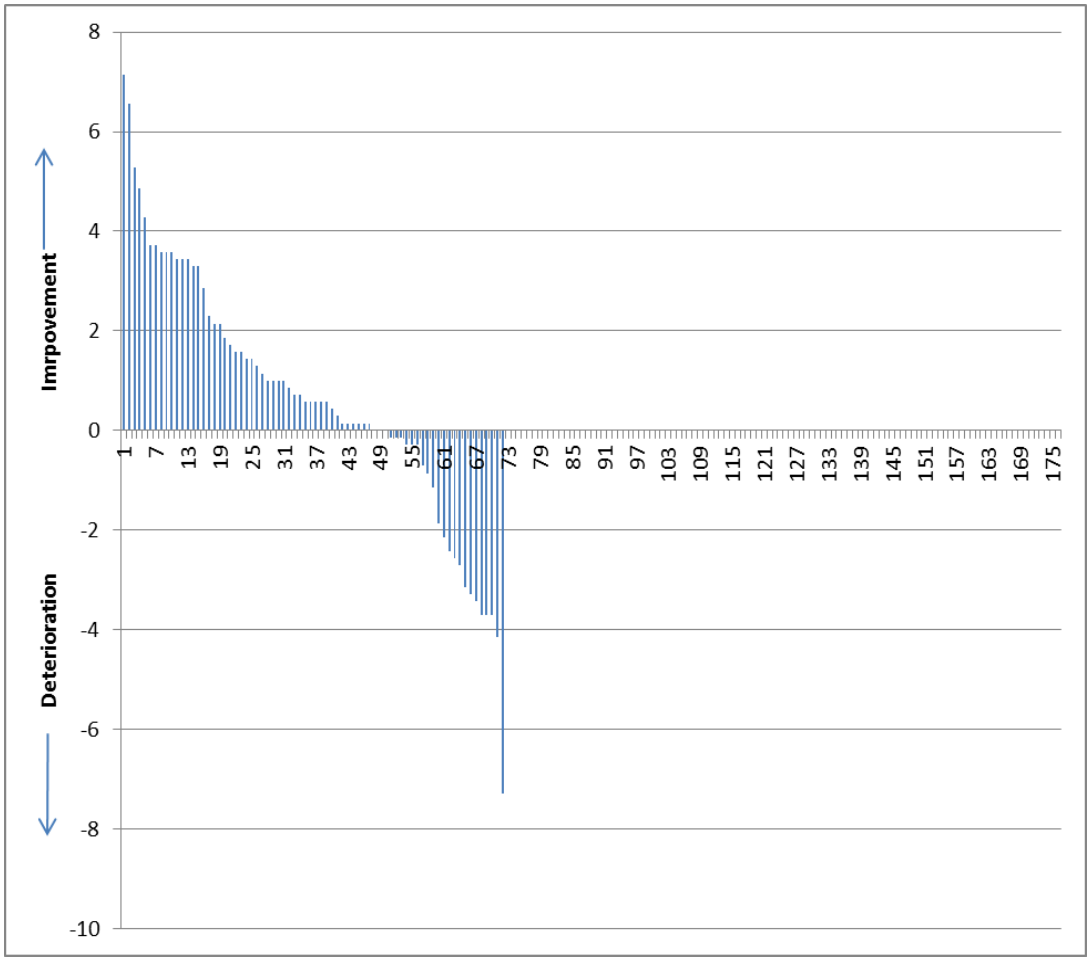

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Figure 24 The change in cough severity diary (CSD) score between day 0 and day 60 for individual patients

This shows that most patients had improved cough severity scores during this period. Seventy-two patients completed the CSD at day 0 and day 60 since the CSD was a late addition to the protocol.

CSD = Cough Severity Diary

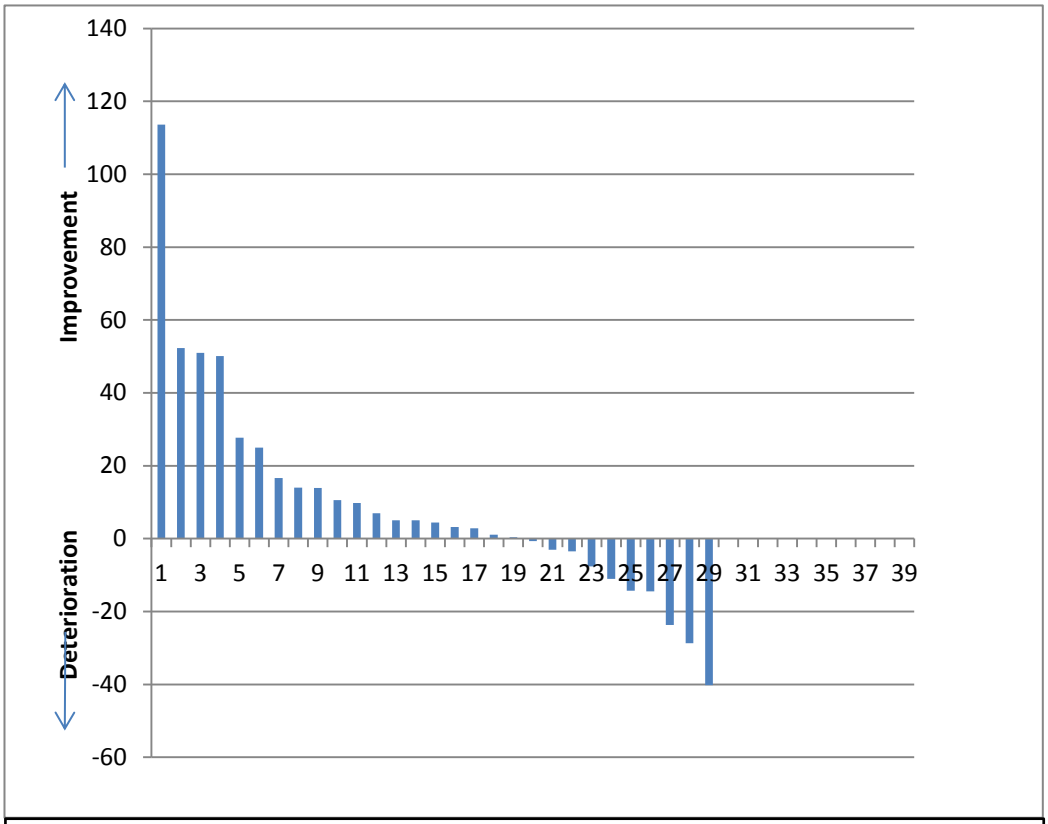


Figure 25 The change in cough frequency score (cough/hour awake) between day 0 and day 60 for individual patients.
This shows that most patients had improved cough severity scores during this period. Twenty-nine patients completed ambulatory cough monitoring at day 0 and day 60.

ACM = Ambulatory Cough Monitoring

3.2.3 Clinical characteristics associated with cough at baseline in patients with lung cancer

The association between clinical characteristics and cough severity VAS scores at baseline

To determine the association between clinical characteristics and cough severity, the baseline cough severity VAS scores were used. The following clinical characteristics were analysed: age, sex, performance status, smoking status (ex, current and never), self-reported chest infection, self-reported asthma, self-reported COPD, self-reported GORD, the diagnosis of GORD according to the BRI score, self-reported nausea according to Item 14 of the EORTC QLQ C30 questionnaire, stage of disease (early vs advanced), histology (NSCLC vs SCLC), tumour location (central vs peripheral), anticancer treatment (on or off treatment), being on opioids, steroids, over the counter antitussives, proton pump inhibitors and ACE inhibitors.

Univariate analysis

Statistically significant associations between worse cough severity score and clinical factors were observed for female sex (p-value 0.048), poor performance status (p-value <0.001), presence of self-reported chest infection (p-value 0.02), GORD according to the BRI questionnaire (p-value <0.001) and self-reported nausea according to the EORTC QLQ C30 item 14 (p-value 0.011), being off anticancer therapy (p-value 0.048) and being on over the counter antitussives (p-value 0.01) (Table 10).

Clinical Characteristic (n=169-171)	**p-value**	**Description**
UNIVARIATE ANALYSIS		
Age	0.08^	
Sex	***0.048****	Women had a more severe cough
Performance Status	***<0.001***$	Worse cough severity with poorer PS
Smoking (Ex vs Current vs Never)	0.19$	
Self-reported Chest Infection	***0.02****	Patients with a chest infection had a worse cough severity
Self-reported Asthma	***0.02****	Patients with asthma had worse cough severity
Self-reported COPD	0.58*	
Self-reported GORD	0.96*	
GORD according to BRI score	***<0.001****	Patients with GORD had worse cough severity
Nausea (item14 EORTC QLQ C30)	***0.011***$	Patients with nausea had worse cough severity
Stage (early vs advanced)	0.09*	
Histology (NSCLC vs SCLC)	0.35*	
Tumour Location (Central vs Peripheral)	0.49*	
Anticancer Treatment (on treatment vs off treatment)	***0.048****	Patients off treatment had a worse cough severity
Opioids	0.50*	
Steroids	0.43*	
Over the counter antitussives	***0.01****	Patients on antitussives had a worse cough severity
Proton Pump Inhibitors	0.19*	
ACE inhibitors	0.49*	

Table 10 Significant clinical factors associated with cough severity.

These included, female sex, performance status, self-reported chest infection, self-reported asthma, GORD according to the BRI score, nausea according to the EORTC QLQ C30 Item 14 score, anticancer therapy and the use of over the counter antitussives.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer, SCLC = Small Cell Lung Cancer, ACE = angiotensin converting enzyme.

^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test,

Multivariate analysis

Significant influences on cough severity VAS scores were further explored in a multivariate model, including significant or near significant variables in the univariate analyses. A quarter of the variability in subjective cough severity VAS scores ($R^2$25%, p-value<0.001) could be explained by a combination of female gender (p-value 0.048), performance status (p-value 0.001), asthma (p-value 0.04) and Item 4 of the BRI on symptoms of regurgitation: “How often do you experience the feeling that something you ate a while ago is coming back up?” (p=0.005) (Table 11). Item 5 of the BRI was excluded from the model since it contained a question about being woken up at night by coughing. Therefore, patients who were female, had a poor performance status, had asthma, and who had symptoms of regurgitation were those who were most likely to have a worst cough severity VAS score.

Clinical Characteristic (n=168)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =25%**
Sex	**0.048**	Women had a more severe cough
Performance Status	***0.001***	Worse cough severity with poorer PS
Self-reported Asthma	***0.04***	Worse cough severity with presence of asthma
Self-reported COPD	0.15	
Self-reported Chest Infection	0.90	
GORD according to BRI score		
(1)A feeling of pain, pressure or burning that starts in the stomach and spreads up the front of your chest.	0.91	
(2) A burning sensation deep in the throat.	0.12	
(3) A bitter, salty or sour taste in the mouth.	0.84	
(4) A feeling that something you ate a while ago is coming back up.	***0.005***	Patients with regurgitation had worse cough severity
(5) Are you ever woken up at night by a feeling of heartburn, coughing or choking?	excluded	Item 5 excluded from model since contained cough in the question

Table 11 Significant clinical factors associated with cough severity on multivariate analysis.

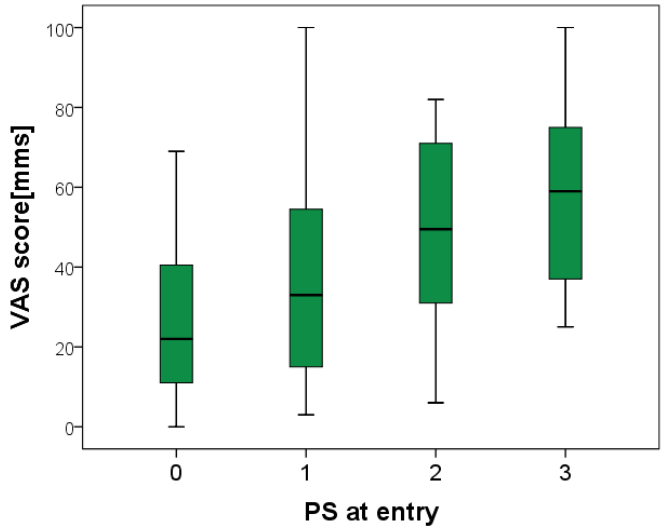
These included female sex, poor performance status, the presence of self-reported asthma and the presence of symptoms of regurgitation according to the BRI Item 4 score. These factors together explained 25% of the total variability in the cough severity VAS scores.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory.

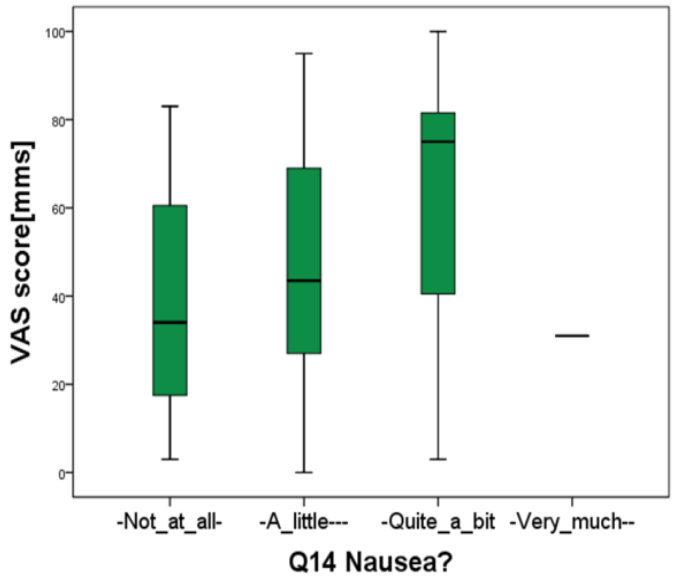
The factors that were found to be significantly associated with cough severity scores are shown graphically in Figure 26 (A-E). This figure shows that there is significant overlap of scores between groups for each variable, with a wide range of scores in all subgroups.

Patients with a positive smoking history did not have a more severe cough. Cancer-related factors such as stage, histology and tumour location did not significantly influence cough severity. Being on treatments such as opioids and steroids were not found to relate to cough severity.

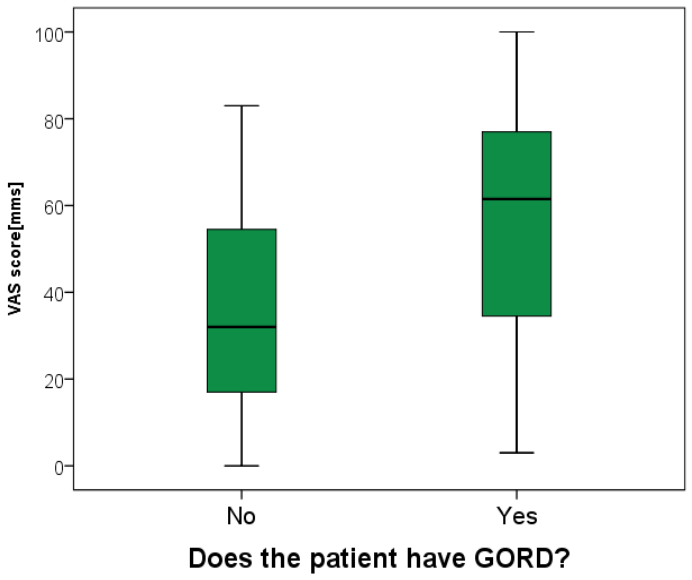
A

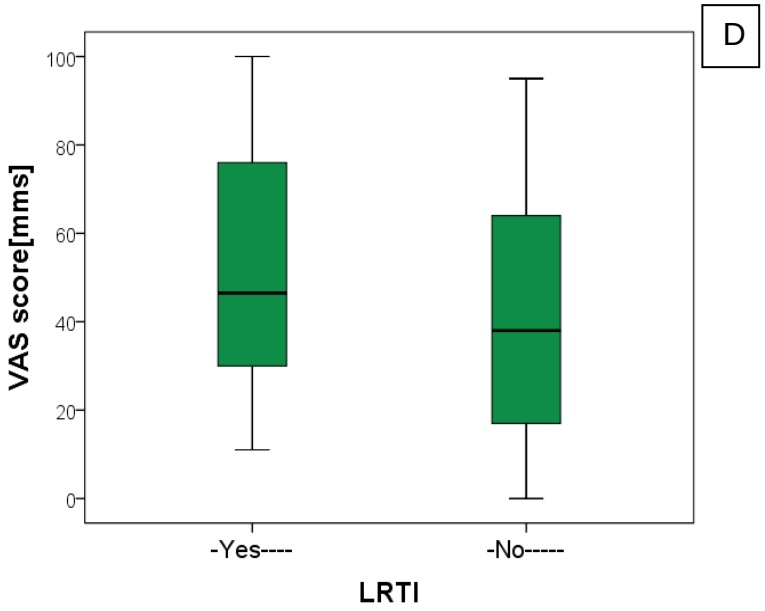

VAS score[mms]
100
80
60
40
20
0
0
1
2
3
PS at entry

B


VAS score[mms]
100
80
60
40
20
0
-Not_at_all-
-A_little---
-Quite_a_bit
-Very_much--
Q14 Nausea?

C


VAS score[mms]
100
80
60
40
20
0
No
Yes
Does the patient have GORD?



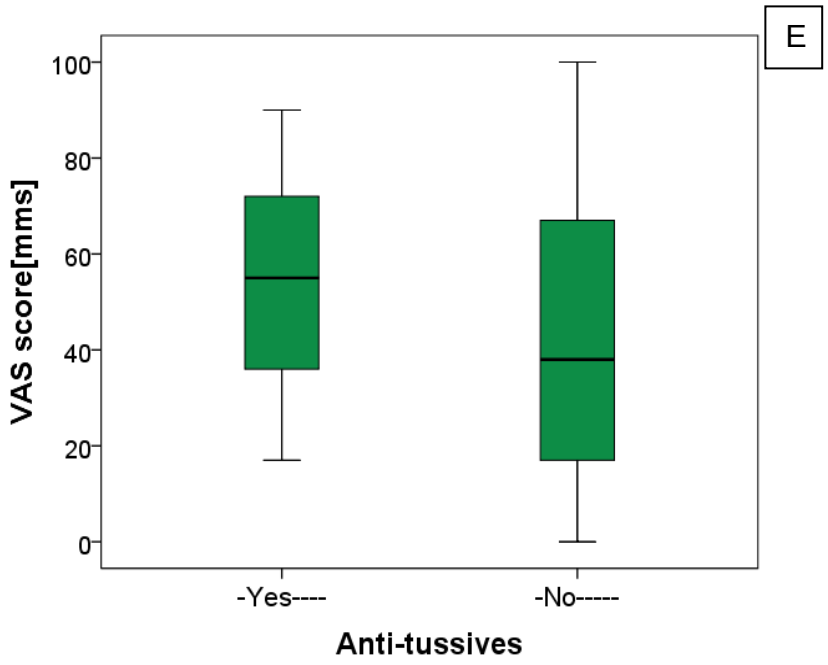


Figure 26 The clinical factors that were significantly associated on univariate analysis with cough severity (A-E)

This shows that patients with a poorer performance status, a respiratory tract infection, nausea, on antitussives and gastro-oesophageal reflux disease had a worse cough severity.

PS =performance status, LRTI = lower respiratory tract infection, Q14 Nausea = Item 14 of the EORTC QLQ C30 questionnaire, GORD = gastro-oesophageal reflux disease.

The association between clinical characteristics and cough impact MCLCS scores at baseline

To determine the association between clinical characteristics and cough impact, the baseline cough impact MCLCS scores were used. The same clinical characteristics that were analysed for their association with cough severity were analysed for this analysis: age, sex, performance status, smoking status (ex, current and never), self-reported chest infection, self-reported asthma, self-reported COPD, self-reported GORD, the diagnosis of GORD according to the BRI score, self-reported nausea according to Item 14 of the EORTC QLQ C30 questionnaire, stage of disease (early vs advanced), histology (NSCLC vs SCLC), tumour location (central vs peripheral), anticancer treatment (on or off treatment), being on opioids, steroids, over the counter antitussives, proton pump inhibitors and ACE inhibitors.

Univariate analysis

Statistically significant associations between worse cough impact scores and clinical factors were observed for poor performance status (p-value <0.001), the presence of a chest infection (p-value =0.04), the presence of nausea according to Item 14 of the EORTC QLQ C30 questionnaire (p-value <0.001), the presence of GORD according to the BRI questionnaire (p-value <0.001), having a central tumour (p-value= 0.04), being on opioids (p-value=0.02), being on steroids (p-value 0.02) and being on proton pump inhibitors (p-value=0.02) (Table 12). Being on treatments such as opioids and steroids were found to relate to worse cough impact scores.

Patients with a positive smoking history did not have a greater cough impact score, nor did patients with self-reported COPD or asthma. Cancer-related factors such as stage and histology did not significantly influence cough impact scores.

The clinical factors that were found to predict baseline cough impact MCLCS scores on univariate analysis are presented graphically in Figure 27 (A-H) below.

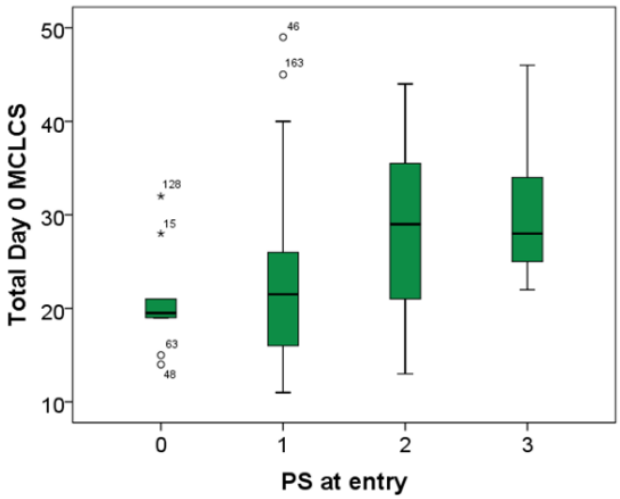
Clinical Characteristic (n=160-165)	**p value**	**Description**
UNIVARIATE ANALYSIS		
Age	0.70^	
Sex	0.17*	
Performance Status	***<0.001$***	Worse cough impact if poorer performance status
Smoking (Ex vs Current vs Never)	0.36$	
Self-reported Chest Infection	***0.04****	Worse cough impact if had a chest infection
Self-reported Asthma	***0.05****	Worse cough impact if had asthma
Self-reported COPD	0.13*	
Self-reported GORD	0.56*	
GORD according to BRI score	***<0.001****	Worse cough impact if had GORD
Nausea (item14 EORTC QLQ C30)	***<0.001$***	Worse cough impact if had nausea
Stage (early vs advanced)	0.17*	
Histology (NSCLC vs SCLC)	0.27*	
Tumour Location (Central vs Peripheral)	***0.04****	Worse cough impact if had a central tumour
Anticancer Treatment (on treatment vs off treatment)	0.07*	
Opioids	***0.02****	Worse cough impact if on opioids
Steroids	***0.02****	Worse cough impact if on steroids
Over the counter antitussives	0.07*	
Proton Pump Inhibitors	***0.02****	Worse cough impact if on PPI
ACE inhibitors	0.43*	

Table12 Significant clinical factors associated with cough impact MCLCS scores.

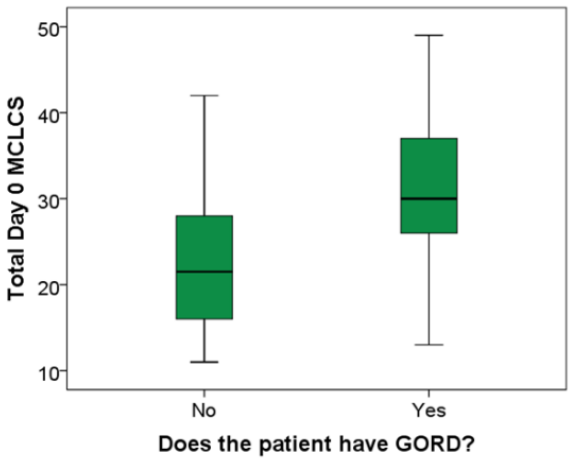
These included, performance status, self-reported chest infection, self-reported asthma, GORD according to the BRI score, nausea according to the EORTC QLQ C30 Item 14 score, tumour location and being on opioids, steroids or proton pump inhibitors.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer, SCLC = Small Cell Lung Cancer, ACE = angiotensin converting enzyme, PPI = proton pump inhibitor, ^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test.

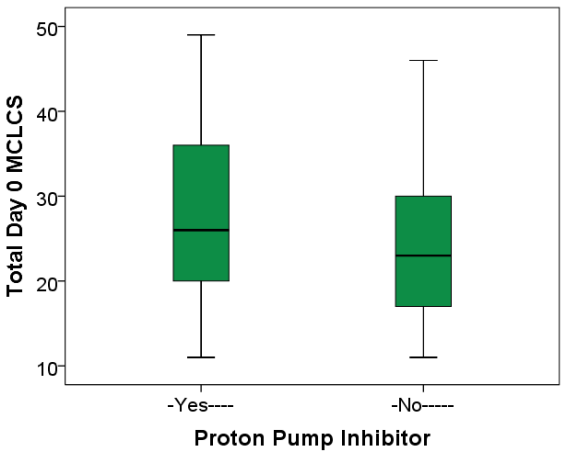
A


Total Day 0 MCLCS
50
40
30
20
10
46
163
128
15
63
48
0
1
2
3
PS at entry

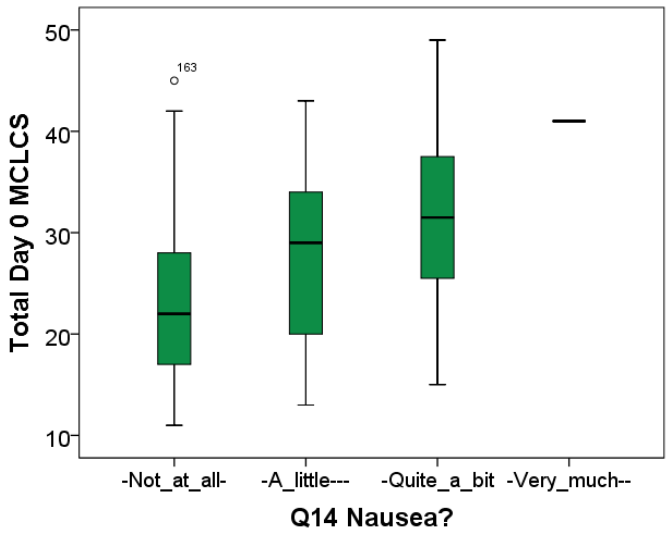
B


Total Day 0 MCLCS
50
40
30
20
10
No
Yes
Does the patient have GORD?

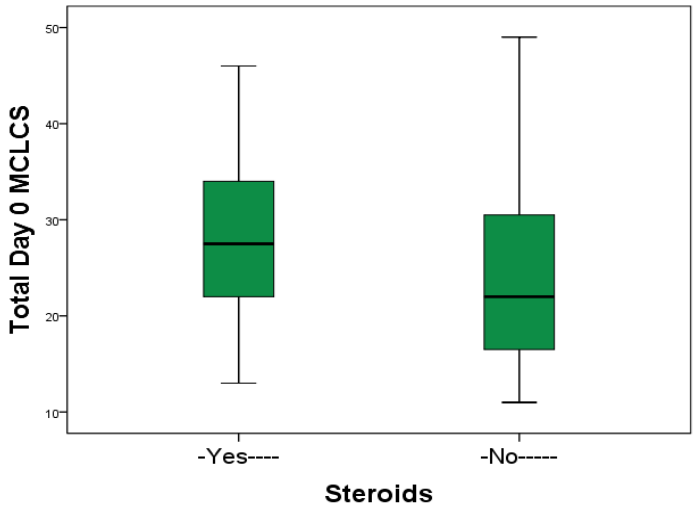
C


Total Day 0 MCLCS
50
40
30
20
10
-Yes----
-No-----
Proton Pump Inhibitor

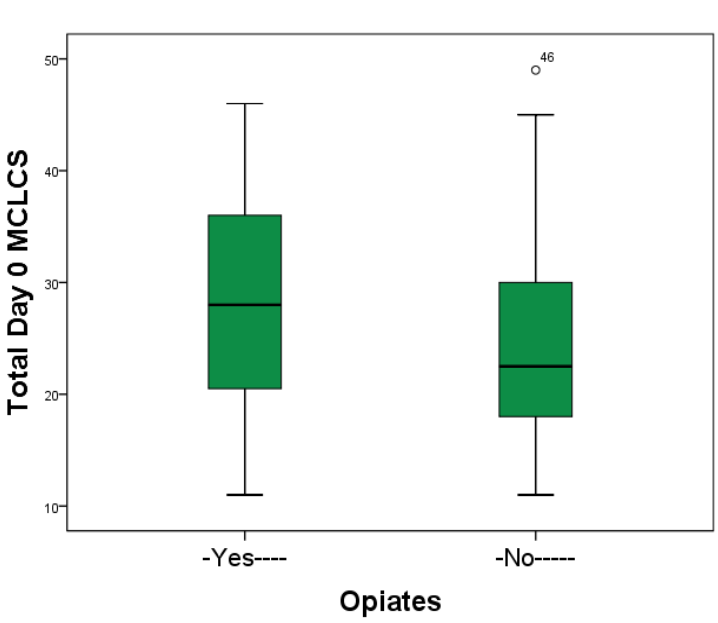
D


Total Day 0 MCLCS
50
40
30
20
10
163
-Not_at_all-
-A_little---
-Quite_a_bit
-Very_much--
Q14 Nausea?

E


Total Day 0 MCLCS
50
40
30
20
10
-Yes----
-No-----
Steroids

F


Total Day 0 MCLCS
50
40
30
20
10
46
-Yes----
-No-----
Opiates

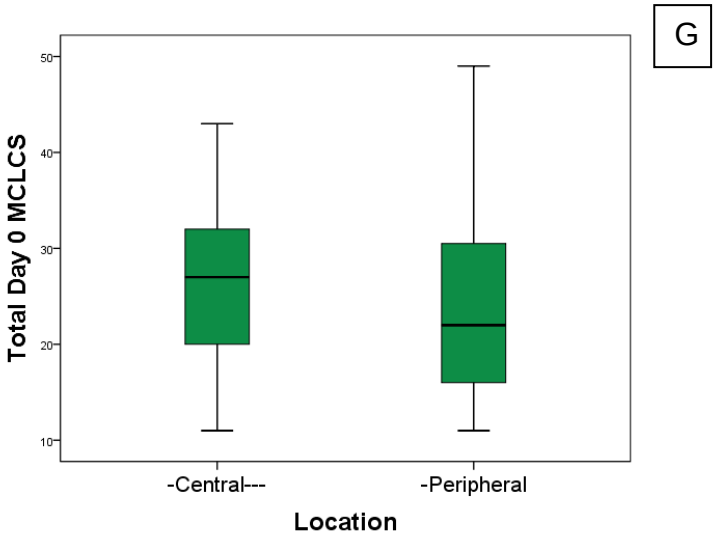


Figure 27 The clinical factors that were significantly associated on univariate analysis with the cough impact Manchester Cough in Lung Cancer Scale score (A-H)

This shows that patients with a poorer performance status, a central tumour, gastro-oesophageal reflux disease, those who were on opioids, on steroids, on proton pump inhibitors, those with a respiratory tract infection, and those with nausea had a worse cough impact score.

PS =performance status, Location = location of tumour, Q14 Nausea = Item 14 of the EORTC QLQ C30 questionnaire, GORD = gastro-oesophageal reflux disease.

Multivariate analysis

Significant influences on cough impact MCLCS scores were further explored in a multivariate model, including variables significant or near significant in the univariate analyses. Just under a third of the variability ($R^{2=}$29%) in subjective cough impact MCLCS scores (p-value<0.001) could be explained by a combination of performance status (p-value 0.001) and nausea reported using Item 14 of the EORTC QLQ C30 questionnaire (p-value = 0.02) (Table 13). Patients with a worse performance status at baseline and patients who reported nausea at baseline had a worse cough impact MCLCS score.

Clinical Characteristic (n=168)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =29**
Performance Status	***0.001***	Worse cough impact with poorer PS
Self-reported Asthma	0.24	
Self-reported COPD	0.98	
Self-reported Chest Infection	0.13	
GORD according to BRI score (1)A feeling of pain, pressure or burning that starts in the stomach and spreads up the front of your chest. (2) A burning sensation deep in the throat. (3) A bitter, salty or sour taste in the mouth. (4) A feeling that something you ate a while ago is coming back up. (5) Are you ever woken up at night by a feeling of heartburn, coughing or choking?	 0.79 0.57 0.63 0.12 excluded	 Patients with regurgitation had worse cough impact Item 5 excluded from model since contained cough in the question
Nausea (Item 14 EORTC QLQ C30)	***0.02***	
Location	0.08	

Table 13 Significant clinical factors associated with cough impact MCLCS scores at baseline on multivariate analysis.

Patients who had a worse performance status and patients who had symptoms of nausea according to item 14 of the EORTC QLQ C30 questionnaire had a worse cough impact MCLCS score. These factors, together, explained 29% of the total variability on the MCLCS scores.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. PS = performance status, EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Quality of Life Core 30 questionnaire.

The association between clinical characteristics and changes in cough severity VAS scores between time periods "day 0 to day 30" and "day 0 to day 60"

To determine the association between clinical characteristics and cough severity, the change in cough severity VAS scores between the assessment points were calculated for two periods: "day 0 to day 30" and "day 0 to day 60". The same baseline clinical characteristics that were analysed for their association with cough severity at baseline were analysed for this analysis: age, sex, performance status, smoking status (ex, current and never), self-reported chest infection, self-reported asthma, self-reported COPD, self-reported GORD, the diagnosis of GORD according to the BRI score, self-reported nausea according to Item 14 of the EORTC QLQ C30 questionnaire, stage of disease (early vs advanced), histology (NSCLC vs SCLC), tumour location (central vs peripheral), anticancer treatment (on or off treatment), being on opiioids, steroids, over the counter antitussives, proton pump inhibitors and ACE inhibitors.

Univariate analysis for change in cough severity VAS scores for the time period "day 0 to day 30"

The mean change in VAS scores between "day 0 to day 30" was +6.5mm (n=103), indicating that the study population's cough severity improved slightly during the first month of the study. In univariate analysis, the factors associated with a change in cough severity score for the period "day 0 to day 30" were performance status (patients with a performance status of 1 at baseline, had a greater probability of change in cough severity, p-value <0.04), the presence of GORD according to the BRI questionnaire (the worse the BRI score at baseline, the greater the improvement in cough severity, p-value <0.04), being on opioids (those on opioids at baseline had a greater probability of change in their cough severity scores, p-value=0.01), being on over the counter antitussives (those on antitussives at baseline had a greater probability of change in their cough severity scores, p-value 0.02) and the baseline cough severity score (those with a worse

cough severity VAS score at baseline had a greater probability of change in the cough severity score, p-value <0.01) (Table 14).

Smoking history was not associated with a change in cough severity scores over time, nor was the presence or absence of co-morbidities. Cancer related factors such as stage, histology or being on anticancer treatment did not influence changes in cough severity scores either.

Clinical Characteristic n=103	p value	Description
UNIVARIATE ANALYSIS		
Age	0.81^	
Sex	0.25*	
Performance Status	***0.04$***	***Patients of PS 1 at baseline had a greater probability of change***
Smoking (Ex vs Current vs Never)	0.79$	
Self-reported Chest Infection	0.89*	
Self-reported Asthma	0.60*	
Self-reported COPD	0.84*	
GORD according to BRI score	***0.04****	***Patients with worse reflux score at baseline had a greater probability of change***
Nausea (item14 EORTC QLQ C30)	0.19$	
Stage (early vs advanced)	0.83*	
Histology (NSCLC vs SCLC)	0.48*	
Tumour Location (Central vs Peripheral)	0.46*	
Anticancer Treatment (on vs off treatment)	0.54	
Opioids	***0.01****	***Patients on opioids at baseline had greater probability of change***
Steroids	0.66*	
Over the counter antitussives	***0.02****	***Patients on OTC anti-tussives at baseline had a greater probability of change***
Proton Pump Inhibitors	0.21*	
Baseline VAS score	***<0.001^***	***Those with higher baseline VAS scores had a greater probability of change***

Table 14 Significant clinical factors associated with changes in cough severity VAS scores between day 0 and day 30 of the study.

These included, performance status, GORD according to the BRI score, nausea according to the EORTC QLQ C30 Item 14 score, tumour location and being on opioids, steroids or proton pump inhibitors.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer, SCLC = Small Cell Lung Cancer, ACE = angiotensin converting enzyme, PPI = proton pump inhibitor, ^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test

Multivariate analysis for change in cough severity VAS scores for the time period "day 0 to day 30"

Significant influences on changes in cough severity VAS scores were further explored in a multivariate model, including variables significant or near significant in the univariate analyses. Just over a third of the variability (R^2 36.7%) in the change in cough severity VAS scores (p-value<0.001) between "day 0 to day 30" could be explained by a combination of being on opioids (p-value 0.01) and the baseline cough severity VAS score (p-value<0.001) (Table 15). Patients who were on opioids at study entry and patients with a high baseline cough severity score had the greatest improvement in cough severity VAS score in the first 30 days of the study.

Baseline performance status was not found to be independently associated with a change in cough severity scores between day 0 and day 30, nor was gastro-oesophageal reflux disease.

Clinical Characteristic (n=168)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =29%**
Opioids at baseline	***0.01***	Greater change in cough severity if on opioids at baseline
Over the counter antitussives at baseline	0.12	
Baseline cough severity VAS score	***<0.001***	Greater change in cough severity if worse cough severity at baseline

Table 15 Significant clinical factors associated with a change in cough severity scores for the period "day 0 to day 30" on multivariate analysis.

Patients who were on opioids at baseline and patients who had high baseline cough severity VAS scores had the greatest improvement in cough severity scores between "day 0 to day 30". Together, they explained 29% of the variability in the change in cough severity VAS scores. VAS = visual analogue scale

Univariate analysis for change in cough severity VAS scores for the time period "day 0 to day 60"

The mean change in VAS scores between "day 0 to day 60" was +7.2mm (n=145), indicating that the study population's cough severity continued to improve during the course of the study. In univariate analysis statistically significant associations between a change in cough severity score for the period "day 0 to day 60" and clinical factors were being on opioids (those on opioids at baseline had a greater probability of change in their cough severity scores, p-value=0.04), being on over the counter antitussives (those on antitussives at baseline had a greater probability of change in their cough severity scores, p-value 0.001) and the baseline cough severity score (those with a worse cough severity VAS score at baseline had a greater probability of change in the cough severity score, p-value 0.008) (Table 16). These three clinical factors were also found on univariate analysis to predict for cough severity VAS change between day 0 and day 30.

However, unlike for the period "day 0 to day 30", neither performance status, nor gastro-oesophageal reflux disease were found to be associated with a change in cough severity VAS scores for the period "day 0 to day 60". Smoking history was not associated with a change in cough severity scores over time, nor was the presence or absence of any co-morbidity. Cancer related factors such as stage, histology or being on anticancer treatment did not influence changes in cough severity scores either.

Clinical Characteristic (n=145)	**p value**	**Description**
UNIVARIATE ANALYSIS		
Age	0.26^	
Sex	0.46*	
Performance Status	0.24$	
Smoking (Ex vs Current vs Never)	0.12$	
Self-reported Chest Infection	0.06*	
Self-reported Asthma	0.78*	
Self-reported COPD	0.63*	
GORD according to BRI score	0.61*	
Nausea (item14 EORTC QLQ C30)	0.68$	
Stage (early vs advanced)	0.43*	
Histology (NSCLC vs SCLC)	0.99*	
Tumour Location (Central vs Peripheral)	0.11*	
Anticancer Treatment (on vs off treatment)	0.92*	
Opioids at baseline	***0.04****	***Those on opioids had greater probability of change in cough VAS***
Steroids at baseline	0.54*	
Over the counter antitussives at baseline	***0.001****	***Those on OTC anti-tussives had greater probability of change in cough VAS***
Proton Pump Inhibitors at baseline	0.21*	
Baseline VAS score	***0.08^***	***Those with higher baseline VAS scores had greater probability of change in cough VAS***

Table 16 Significant clinical factors associated with changes in cough severity VAS scores between day 0 and day 60 of the study.

These included being on opioids at baseline, being on OTC antitussives and having a high baseline cough severity VAS score. PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer, SCLC = Small Cell Lung Cancer, PPI = proton pump inhibitor, ^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test

Multivariate analysis for change in cough severity VAS scores for the time period “day 0 to day 60”

Significant influences on changes in cough severity VAS scores were further explored in a multivariate model, including variables significant or near significant in the univariate analyses. Just over a third of the variability (R^2 32.9%) in the change in cough severity VAS scores (p-value<0.001) between “day 0 to day 60” could be explained by a combination of being on antitussives at baseline (p-value 0.04) and the baseline cough severity VAS score (p-value<0.001) (Table 17). Patients who were on antitussives at study entry and patients with a high baseline cough severity score had the greatest improvement in cough severity VAS score during the course of the study. Being on opioids showed a trend towards statistical significance with a p-value of 0.07.

Clinical Characteristic (n=148)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =32.9%**
Opioids at baseline	0.07	
Over the counter antitussives at baseline	***0.04***	Greater change in cough severity if on antitussives at baseline
Baseline cough severity VAS score	***<0.001***	Greater change in cough severity if worse cough severity at baseline

Table 17 Significant clinical factors associated with a change in cough severity scores for the period "day 0 to day 60" on multivariate analysis.

Patients who were on over the counter antitussives at baseline and patients who had high baseline cough severity VAS scores had the greatest improvement in cough severity scores between "day 0 to day 60". Together, they explained 32.9% of the variability in the change in cough severity VAS scores between day 0 and day 60.

VAS = visual analogue scale

The association between clinical characteristics and changes in cough impact MCLCS scores between time periods "day 0 to day 30" and "day 0 to day 60"

To determine the association between clinical characteristics and cough impact, the change in cough impact MCLCS scores between the assessment points were calculated for two periods: "day 0 to day 30" and "day 0 to day 60". The same baseline clinical characteristics that were analysed for their association with cough severity change over time were analysed for this analysis: age, sex, performance status, smoking status (ex, current and never), self-reported chest infection, self-reported asthma, self-reported COPD, self-reported GORD, the diagnosis of GORD according to the BRI score, self-reported nausea according to Item 14 of the EORTC QLQ C30 questionnaire, stage of disease (early vs advanced), histology (NSCLC vs SCLC), tumour location (central vs peripheral), anticancer treatment (on or off treatment), being on opioids, steroids, over the counter antitussives, proton pump inhibitors and ACE inhibitors.

Univariate analysis for change in cough impact MCLCS scores for the time period "day 0 to day 30"

The mean change in MCLCS scores between "day 0 to day 30" was +4.4 (n=148), indicating that the study population's cough-related QoL improved slightly during the first month of the study. In univariate analysis, statistically significant associations between a change in cough impact MCLCS score for the period "day 0 to day 30" and clinical factors were observed for performance status (patients with a performance status of one at baseline, had a greater probability of change in cough impact scores, p-value 0.007); the presence of GORD according to the BRI questionnaire (the worse the total BRI score at baseline, the greater the improvement in cough severity, p-value <0.04); having symptoms of regurgitation according to Item 4 of the BRI (having symptoms of regurgitation at baseline was

associated with a greater probability of change in MCLCS score, p-value 0.04); Item 5 of the BRI (being woken at night by a feeling of heartburn, coughing or choking at baseline was associated with a greater probability of change in MCLCS score during the first month of the study, p-value <0.001); having nausea according to item 14 of the EORTC QLQ C30 questionnaire (patients with nausea at baseline had a greater probability of change in their cough impact MCLCS score over time; being on opioids (those on opioids at baseline had a greater probability of change in their cough impact scores over time, p-value<0.001); being on over the counter antitussives (those on antitussives at baseline had a greater probability of change in their cough impact scores, p-value 0.001) and the baseline cough impact MCLCS score (those with a worse cough impact MCLCS score at baseline had a greater probability of change in the cough impact MCLCS score, p-value 0.001) (Table 18).

Smoking history was not associated with a change in cough impact scores over time, nor was the presence or absence of co-morbidities. Cancer related factors such as stage, histology or being on anticancer treatment did not influence changes in cough impact scores either.

Clinical Characteristic n=148	p value	Description
UNIVARIATE ANALYSIS		
Age	0.86^	
Sex	0.75*	
Performance Status	0.007$	Patients with PS 1 at baseline had greater probability of change in MCLCS
Smoking (Ex vs Current vs Never)	0.13$	
Self-reported Chest Infection	0.94*	
Self-reported Asthma	0.83*	
Self-reported COPD	0.47*	
GORD according to BRI score	0.04*	Patients with worse reflux at baseline had greater probability of change in MCLCS
GORD according to BRI score (1)A feeling of pain, pressure or burning (2) A burning sensation deep in the throat. (3) A bitter, salty or sour taste in the mouth. (4) A feeling that something you ate a while ago is coming back up. (5) Woken up at night by a feeling of heartburn, coughing or choking?	 0.45 0.94 0.95 ***0.04*** ***<0.001***	Patients with worse Item 4&5 scores had greater probability of change in MCLCS
Nausea (item14 EORTC QLQ C30)	0.04$	Patients with worse nausea at baseline had greater probability of change in MCLCS
Stage (Early vs Advanced)	0.40*	
Histology (NSCLC vs SCLC)	0.50*	
Tumour Location (Central vs Peripheral)	0.23*	
Anticancer Treatment (on vs off treatment)	0.66*	
Opioids	***<0.001****	Those on opioids at baseline had greater probability of change in MCLCS
Steroids	0.51*	
Over the counter antitussives	***0.001****	Those on OTC anti-tussives at baseline had greater probability of change in MCLCS
Baseline MCLCS score	***<0.001***^	Those with higher baseline MCLCS scores improved more

Table 18 Significant factors associated with changes in cough impact MCLCS scores between day 0 and day 30

These included performance status, GORD according to the BRI score, items 4 and 5 of the BRI questionnaire, being on opioids, being on over the counter antitussives and the baseline MCLCS score.

MCLCS = Manchester Cough in Lung Cancer Scale, PS =performance status, COPD = chronic obstructive pulmonary disease, SCLC = Small Cell Lung Cancer, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer,

^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test

Multivariate analysis for change in cough impact MCLCS scores for the time period “day 0 to day 30”

Significant influences on changes in cough impact MCLCS scores were further explored in a multivariate model, including variables significant or near significant in the univariate analyses. Over a third of the variability (R^2 37.5%) in the change in cough impact MCLCS scores (p-value<0.001) between “day 0 to day 30” could be explained by a combination of being on Opioids (p-value 0.03) and the baseline cough severity MCLCS score (p-value<0.001) (Table 19). Patients who were on Opioids at study entry and patients with a high baseline cough impact score had the greatest improvement in cough impact MCLCS score in the first 30 days of the study.

Baseline performance status was not found to be independently associated with a change in cough impact scores between day 0 and day 30, nor was gastro-oesophageal reflux disease.

Clinical Characteristic (n=146)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =37.5%**
BRI Item 4	0.36	
Nausea	1.00	
Opioids	***0.03***	
Baseline MCLCS	***<0.001***	

Table 19 Significant clinical factors associated with a change in cough impact MCLCS scores for the period "day 0 to day 30" on multivariate analysis.

Patients who were on Opioids at baseline and patients who had high baseline cough impact MCLCS scores had the greatest improvement in cough severity scores between "day 0 to day 30". Together, they explained 37.5% of the variability in the change in cough impact MCLCS scores.

BRI = Brief Reflux Inventory, MCLCS = Manchester cough in lung cancer scale

Univariate analysis for change in cough impact MCLCS scores for the time period “day 0 to day 60”

The mean change in MCLCS scores between “day 0 to day 60” was +3.1 (n=131), indicating that the study population’s cough impact scores continued to improve slightly beyond the first month of the study. In univariate analysis, the factors associated with a change in cough impact score for the period “day 0 to day 60” were performance status (patients who had a performance status of one at baseline had a greater probability of change in the MCLCS score during the course of the study, p-value 0.003), oOpioids (patients on oOpioids at baseline had a greater probability of change in cough impact MCLCS scores, p-value <0.001) and the baseline MCLCS score (having a worse cough impact MCLCS score at baseline was associated with a greater probability of change in cough impact MCLCS scores over the course of the study, p value <0.001) (Table 20).

Clinical Characteristic (n=145)	p value	Description
UNIVARIATE ANALYSIS		
Age	0.94^	
Sex	0.59*	
Performance Status	***0.003$***	Patients with PS 1 at baseline had a greater probability of change in cough-related QoL compared to other patients
Smoking (Ex vs Current vs Never)	0.43$	
Self-reported Chest Infection	0.39*	
Self-reported Asthma	0.80*	
Self-reported COPD	0.36*	
GORD according to BRI score	0.59*	
Nausea (item14 EORTC QLQ C30)	0.07$	
Stage (early vs advanced)	0.98*	
Histology (NSCLC vs SCLC)	0.93*	
Tumour Location (Central vs Peripheral)	0.08*	
Anticancer Treatment (on vs off treatment)	0.83*	
Opioids at baseline	***<0.001****	Those on opioids at baseline had greater probability of change in their MCLCS score
Steroids at baseline	0.14*	
Over the counter antitussives at baseline	0.13*	
Baseline MCLCS score	***<0.001^***	Those with higher baseline MCLCS scores improved more

Table 20 Significant clinical factors associated with changes in cough impact MCLCS scores between day 0 and day 60

These included performance status, being on opioids at baseline and having a high baseline cough impact MCLCS score.

PS =performance status, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, BRI = Brief Reflux Inventory. EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Core 30 Quality of Life Questionnaire, NSCLC = Non Small Cell Lung Cancer, SCLC = Small Cell Lung Cancer, PPI = proton pump inhibitor, ^ Spearman's correlation coefficient, *Mann-Whitney-U Test, $Kruskall-Wallis Test

Multivariate analysis for change in cough impact MCLCS scores for the time period “day 0 to day 60”

Significant influences on changes in cough impact MCLCS scores were further explored in a multivariate model, including variables significant or near significant in the univariate analyses. About a third of the variability (R^2 32.9%) in the change in cough impact MCLCS scores (p-value<0.001) between “day 0 to day 60” could be explained by a combination of being on opioids at baseline (p value <0.001) and the baseline cough impact MCLCS score (p-value<0.001) (Table 21). Patients who were on opioids at study entry and patients with a high baseline cough impact score had the greatest improvement in cough impact MCLCS score during the course of the study.

Clinical Characteristic (n=148)	p-value	Description
MULTIVARIATE ANALYSIS	**<0.001**	**R^2 =35.7%**
Opioids at baseline	***0.03***	Greater change in cough impact score if on Opioids at baseline
Baseline cough impact MCLCS score	***<0.001***	Greater change in cough impact score if worse cough impact score at baseline

Table 21 Significant clinical factors associated with a change in cough impact MCLCS scores for the period "day 0 to day 60" on multivariate analysis.

Patients who were on opioids at baseline and patients who had high baseline cough impact MCLCS scores had the greatest improvement in cough impact MCLCS scores between "day 0 to day 60". Together, they explained 35.7% of the variability in the change in cough impact MCLCS scores between day 0 and day 60.
MCLCS = Manchester cough in lung cancer scale

Summary of results for clinical characteristics associated with cough severity and cough impact at baseline and over time

Similar clinical characteristics were associated with cough severity and cough impact at baseline and over time. On multivariate analyses, performance status was associated with cough severity and cough impact scores at baseline. Gastro-intestinal symptoms such as nausea and regurgitation were independently associated with baseline cough severity and cough impact scores respectively. Being on opioids at baseline independently predicted an improvement in both cough severity and cough impact scores over time. Being on over the counter antitussives independently predicted an improvement in cough severity scores over the duration of the study period. Both baseline cough severity VAS scores and baseline MCLCS scores were independently associated respectively with changes in cough severity and cough impact scores over time. Other than tumour location which was associated with the cough impact MCLCS score at baseline on univariate analysis alone, no other cancer related factor was associated with either cough severity or cough impact scores in any of the analyses conducted. Clinical characteristics such as smoking history or having COPD were not found to be associated with cough severity or cough impact scores (Table 22).

Cough Severity Scores at baseline (VAS)		Cough Impact Scores at baseline(MCLCS)	
Univariate	**Multivariate**	**Univariate**	**Multivariate**
Female sex Performance status Asthma Chest infection Total GORD score (BRI) *Item 1 Heartburn* *Item 2 Burning in throat* *Item 3 Bitter/salty taste* *Item 4 Regurgitation* *Item 5 Woken by cough/choking* Nausea OTC antitussives	Female sex Performance status Asthma BRI Item 4 *Regurgitation*	Performance Status Asthma Total GORD score (BRI) Nausea Tumour location Opioids OTC antitussives Proton pump inhibitors	Performance status Nausea
Cough Severity Scores "Day 0 - Day 30" (VAS)		**Cough Impact Scores "Day 0 – Day 30" (MCLCS)**	
Univariate	**Multivariate**	**Univariate**	**Multivariate**
Performance status Total GORD score (BRI) Opioids OTC antitussives Baseline VAS score	Opioids Baseline VAS score	Performance status BRI Item 4 *Regurgitation* BRI Item 5 *Woken by cough/choking* Opioids OTC antitussives Baseline MCLCS score	Opioids Baseline MCLCS score
Cough Severity Scores "Day 0 - Day 60" (VAS)		**Cough Impact Scores "Day 0 – Day 60" (MCLCS)**	
Univariate	**Multivariate**	**Univariate**	**Multivariate**
Opioids OTC antitussives Baseline VAS score	OTC antitussives Baseline VAS score	Performance status Opioids Baseline MCLCS score	Opioids Baseline MCLCS score

Table 22 Significant clinical factors associated with cough severity VAS and cough impact MCLCS scores at baseline and over time for the univariate and multivariate analyses.

Similar clinical characteristics were associated with cough impact and cough severity scores. Performance status was associated with both baseline cough severity and cough impact scores. Gastro-intestinal co-morbidities such as reflux and nausea were independent predictors of cough severity and cough impact scores at baseline. Concurrent medications such as opiates and OTC antitussives were independently associated with changes in cough severity and cough impact scores over time. Cancer related factors such as stage, histology, cancer therapy and factors such as COPD and smoking history were not found to be associated with cough severity or cough impact scores.

VAS = visual analogue scale, MCLCS = Manchester cough in lung cancer scale, GORD = gastro-oesophageal reflux disease, BRI = brief reflux inventory, OTC = over the counter, COPD = chronic obstructive pulmonary disease

3.2.4 Comparison and evaluation of subjective and objective cough assessment tools in patients with lung cancer

Correlations between subjective cough assessment tools

The five cough assessment scales VAS, MCLCS, CSD, item 31 of the EORTC QLQ C30+LC 13 questionnaire, and the Common Terminology Classification (version 4.0) for cough were correlated for each patient (Table 23). There was a highly statistically significant correlation between all the assessment tools. Strong correlations were observed between the MCLCS and CSD (0.77, $p<0.001$) and between the MCLCS and Item 31 (0.72, $p<0.001$). The weakest correlation was observed between item 31 and the *physician-reported* CTC grading score (0.48, $p <0.001$). CTC grading correlated less strongly with the other cough assessment tools compared to the other 3 assessment tools.

	EORTC QLQC30 Q31 (patient reported) Correlation coefficient (No.)	Cough impact MCLCS (patient reported_ Correlation coefficient (No.)	Cough Severity Diary (patient reported) Correlation coefficient (No.)	CTCAE (physician reported) Correlation coefficient (No.)
Cough Severity VAS (patient reported)	0.67**(170)	0.68** (163)	0.69**(83)	0.50**(170)
EORTC QLQC30 Q31 (patient reported)		0.72** (164)	0.74** (83)	0.48** (172)
Cough Impact MCLCS (patient reported)			0.77** (81)	0.56** (164)
Cough Severity Diary (patient reported)				0.59** (84)

Table 23 Correlation coefficients between different subjective cough assessment tools (both patient-reported and physician-reported).

The MCLCS scores strongly correlated with the CSD and Q31 of the EORTC QLQ C30 questionnaires. The weakest correlations were between the *physician-reported* CTCAE cough grade and the *patient-reported* subjective cough assessment tools such as the MCLCS, CSD and cough severity VAS.
VAS = visual analogue scale, EORTC QLQ C30 Q31 = question 31 from the European Organization for the Research and Treatment of Cancer Core 30 questionnaire, MCLCS = Manchester cough in lung cancer scale, CSD = cough severity diary, CTCAE = Common Terminology Criteria for Adverse Events.

= high correlation
= moderate correlation
** = p-value <0.001, Spearman's correlation coefficient

See Appendices 1-6 for examples of the VAS, EORTC QLQ C30 Q31, MCLCS, CSD and CTCAE.

Correlations between subjective and objective cough assessment tools

The subjective cough severity VAS and the cough impact MCLCS scores were correlated against the objective 24-hour ACM scores. These correlations are shown in Table 24. This table shows that there was a highly statistically significant correlation between all the assessment tools, except the MCLCS and log cough/hr asleep scores. There were moderate correlations between the objective and subjective cough assessment tools. There were strong correlations between the subjective cough severity VAS and the subjective cough impact MCLCS (correlation coefficient 0.73, p-value <0.001), between the objective 24hour frequency and objective asleep cough frequency scores (correlation coefficient 0.70, p-value <0.001) and near perfect correlation between the objective 24 hour frequency and objective awake cough frequency scores (correlation coefficient 0.99, p-value <0.001).

	Cough Impact MCLCS Correlation coefficient (No.)	Log Cough/hr Asleep Correlation coefficient (No.)	Log Cough/hr Awake Correlation coefficient (No.)	Log Cough/hr 24-hour Correlation coefficient (No.)
Cough severity VAS	0.73**(37)	0.45*(34)	0.60**(37)	0.59**(37)
Cough impact MCLCS		0.34 (32)	0.52*(35)	0.48*(35)
Log Cough/hr Asleep			0.62**(34)	0.70**(34)
Log Cough/hr Awake				0.99**(37)

Table 24 Correlation between objective (24-hour ambulatory cough monitoring) and subjective cough assessment tools (the MCLCS and cough severity VAS)

There were moderate correlations between subjective and objective cough monitoring. VAS = visual analogue scale, MCLCS = Manchester cough in lung cancer scale, Log Cough/hr Asleep: $\log_{10}$ number of coughs/hour during sleep, Log Cough/hr Awake: $\log_{10}$ number of coughs/hour during awake period, Log Cough/hr 24-hour: $\log_{10}$ number of coughs/hour during 24-hour period.

= high correlation
= moderate correlation
= low correlation

** = p-value <0.001, Spearman's correlation coefficient

3.3 Further evaluation of the MCLCS

In order to measure the complex cough experience of the lung cancer population, a promising tool, the Manchester cough in lung cancer scale (MCLCS) was developed by Molassiotis et al. [40]. Since this tool has subsequently been used both in the cross-sectional cough prevalence study and the longitudinal cough study, this has provided data on a combined population of nearly 300 LC patients. To date, no studies have reported the use of the MCLCS other than the original MCLCS development study [40]. No independent evaluation of the MCLCS has been published. The data presented therefore enabled an analysis, beyond the original development study analysis, to re-examine its performance.

The aspects of performance analysed were to determine:

1) The MCLCS completion rates to obtain a measure of clinical feasibility.
2) The questionnaire's "item floor to ceiling effects" to determine whether the questionnaire items could each distinguish between subjects among the top end of the scale (ceiling effects) and discriminate between patients among the lower end of the items scales (floor effects).
3) The reliability of the scale by deriving the internal consistency (Cronbach alpha) score. This score described the extent to which all the items in the MCLCS measured the same concept or construct (i.e.: the impact of cough). It therefore measured the "inter-relatedness" of the items. Reliability was also assessed by determining the item-to-total correlations.
4) The criterion validity of the MCLCS to measure the effectiveness with which the MCLCS score predicted the score in alternative cough

questionnaires such as the cough severity VAS. This was possible since data were available in the same patients using the cough severity VAS.

3.3.1 Study population characteristics

There were 277 patients eligible for this analysis. They comprised of 115 patients who consented to the cross-sectional cough prevalence study who reported a cough and completed the MCLCS and 174 patients who consented to the longitudinal single-arm cohort study to assess cough in lung cancer who completed a baseline MCLCS. Patients who were in both studies (n=12) were removed from the longitudinal study database so that each patient had only completed one MCLCS in this analysis (Figure 28). Unless stated, all variables had complete data.

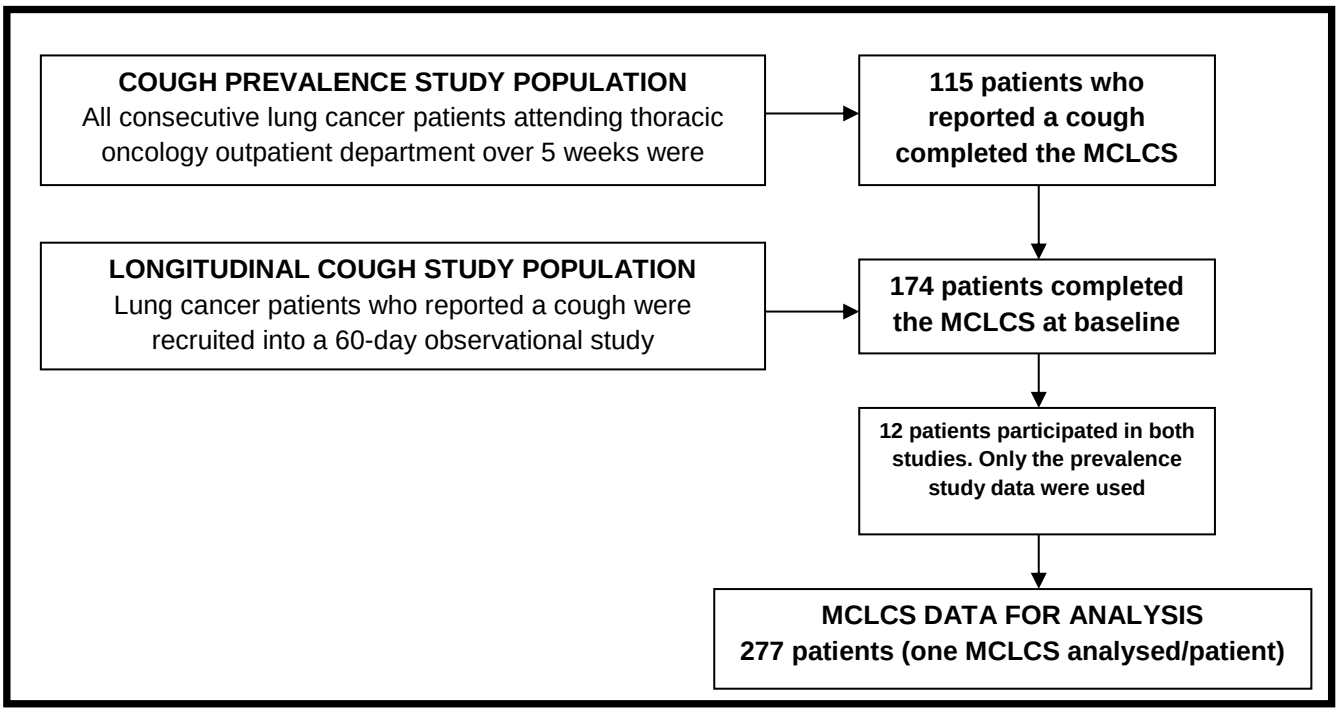


Figure 28 The data analysis population for the further evaluation of the Manchester cough in lung cancer scale questionnaire.

Since 12 patients had completed the MCLCS in both the cough prevalence study and the longitudinal cough study, their data from the longitudinal study were censored such that only one MCLCS was analysed/patient in the analysis. Overall, data on 277 individual patients were analysed.

MCLCS = Manchester Cough in Lung Cancer Scale questionnaire (*patient reported)*

The mean age was 66 years (SD 9.17). Just over half the population, 145 patients (52%) were male. The study population had a significant smoking history; with 175 patients (63%) being ex-smokers, 79 patients (29%) being current smokers and only 23 patients (8%) having never smoked. Their median number of pack years was 40.0 (25^{th}-75^{th} IQ range 22.5-57.0, n=276). The majority of patients, 202 patients (74%) had NSCLC, a quarter, 70 patients (25%) had SCLC and only two patients (1%) were of mixed lung cancer histology (n=274). Most patients had advanced stage disease (183 patients, 67%, n=275). Overall, patients had had a diagnosis of lung cancer for a median of five months prior to trial entry (25^{th}-75^{th} IQR 2.0 – 15.0, n=271). Just over a third of the patients, 101 patients (36%), were on anticancer therapy. Of the patients on treatment, two-thirds (65%, 66 patients) were on chemotherapy, nearly a quarter (23%, 23 patients) were on tyrosine kinase inhibitors, six patients (2%) were on radiotherapy and six patients (2%) were on concurrent chemoradiotherapy. Half the patients were of poorer performance status. Few patients had a performance status score of 0 (25 patients, 9%). Under half of patients had a performance status score of 1 (114 patients, 41%). Just over a third of patients had a performance status score of 2 (98 patients, 35%) and 40 patients (15%) had a performance status score of 3. The majority of patients, 156 patients (56%), felt that their cough was severe enough to warrant treatment. The median cough severity VAS score was 36mm (25^{th}-75^{th} IQR 20-57, n=274, range 0-100mm). The median cough impact MCLCS score was 23 (25^{th}-75^{th} IQR 17-29, n=267, range 1-50). Higher scores represent worse cough severity (VAS) and worse cough impact (MCLCS). Ten patients failed to complete all the items in the MCLCS.

The comparison between the original MCLCS development study population and the combined population for the further evaluation of the MCLCS is shown below (Table 25).

Characteristic	Subgroup	Original MCLCS study population N (%) N=139	Combined MCLCS evaluation population N (%) N=277
Mean age in years (SD)		69 years (+9)	66years (+9)
Male sex		89 (64)	145 (52)
Stage*	Stage I NSCLC	(9)[$]	Early NSCLC[^] 62 (23)
	Stage II NSCLC	(13)[$]	Advanced NSCLC[^] 142
	Stage III NSCLC	(25)[$]	(52)
	Stage IV NSCLC	(35)[$]	
	LS SCLC	(4)[$]	29 (11)
	ES SCLC	(3)[$]	41 (15)
	No information	15 (11)	0 (0)
Histology	NSCLC	110 (86)	70 (74)
	SCLC	(9)[$]	202 (25)
	Mesothelioma	(5)[$]	0 (0)
	Mixed	0 (0)	2 (1)
On anticancer therapy	Yes	"broadly half"[$]	101 (36)
Mean total MCLCS score (SD)		18.3 (8.0)	23.8 (8.4)

Table 23 showing the comparison of clinical characteristics between patients in the original MCLCS development study and the combined population of the cough prevalence study and longitudinal cough study

SD=standard deviation, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer, LS=limited stage, ES=extensive stage

Bold type italic = p value < 0.05

*cancer staged according to 7th Edition of TNM in Lung *Cancer* of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2009

[$] No absolute numbers published

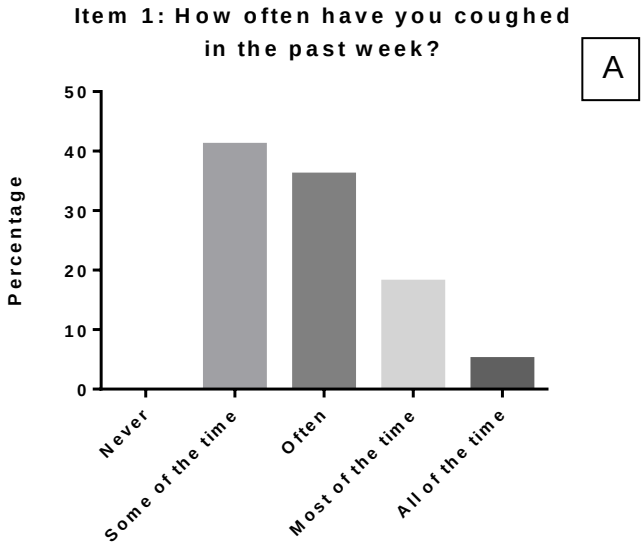
[^] Absolute numbers and percentages not available for each stage of NSCLC. Early stage included stage IIIA. Advanced included stages IIIB and IV.

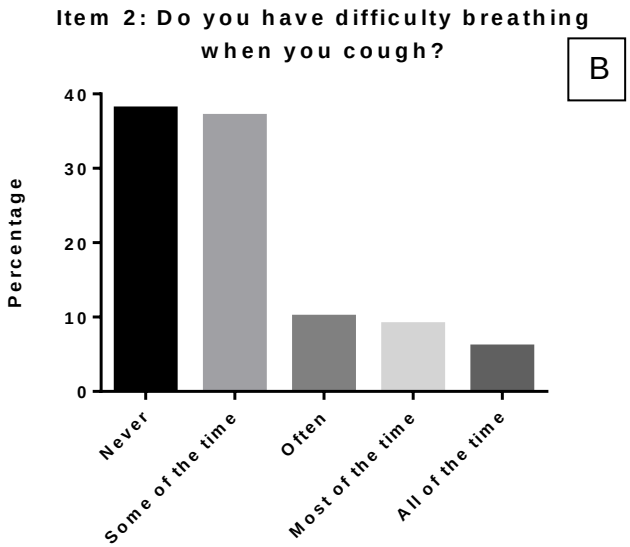
Question completion rates

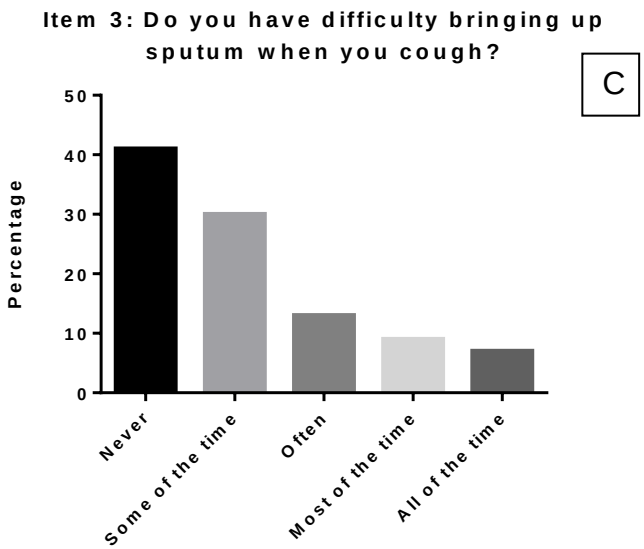
There was minimal failure to complete questionnaire items. Most items had 100% completion. Item 10, relating to cough severity, had the greatest proportion of missing values (1.4%). Items 1, 2 4 and 6 all had missing values that were under 1% (n=277). In the original MCLCS development study no item had missing data greater than 4%.

Floor and ceiling effects

No item demonstrated any floor or ceiling effects. Similarly, in the original MCLCS development study, the ten final MCLCS items showed no floor or ceiling effects. Therefore no item had greater than 50% positive responses to “Never” or greater than 50% responses to “All the time”. See Figure 29 (A-E) below.

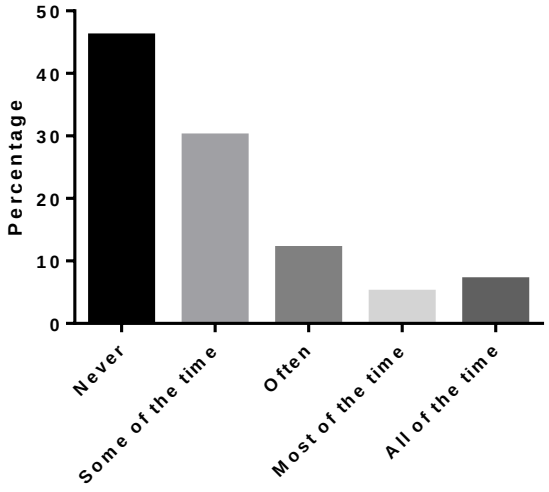

Item 1: How often have you coughed in the past week?
A
Percentage
50
40
30
20
10
0
Never
Some of the time
Often
Most of the time
All of the time


Item 2: Do you have difficulty breathing when you cough?
B
Percentage
40
30
20
10
0
Never
Some of the time
Often
Most of the time
All of the time


Item 3: Do you have difficulty bringing up sputum when you cough?
C
Percentage
50
40
30
20
10
0
Never
Some of the time
Often
Most of the time
All of the time

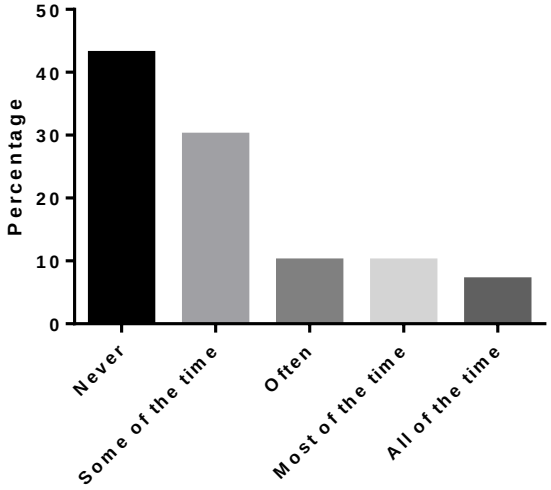
Item 4: Does your cough disturb your sleep?

D



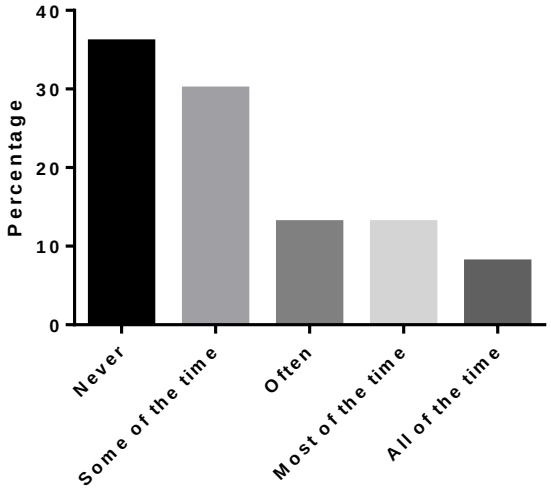
Item 5: Does your cough distress you?

E



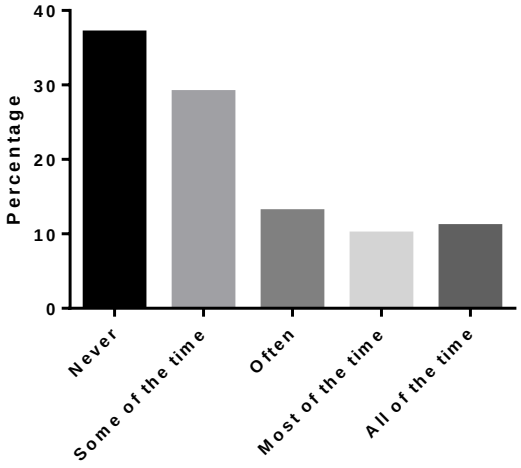
Item 6: Does coughing make you frustrated

F



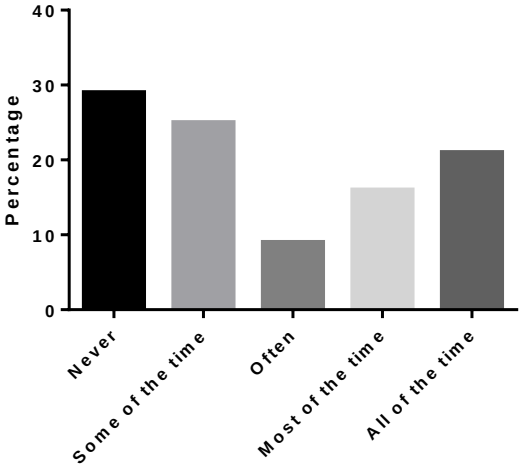
Item 7: Do you worry that your cough means that your cancer is getting worse?

G



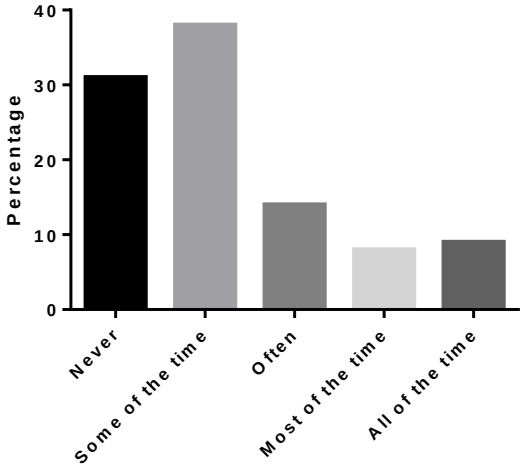
Item 8: Do you feel in control of your cough?

H



Item 9: Does coughing interrupt your conversations or telephone calls?

I



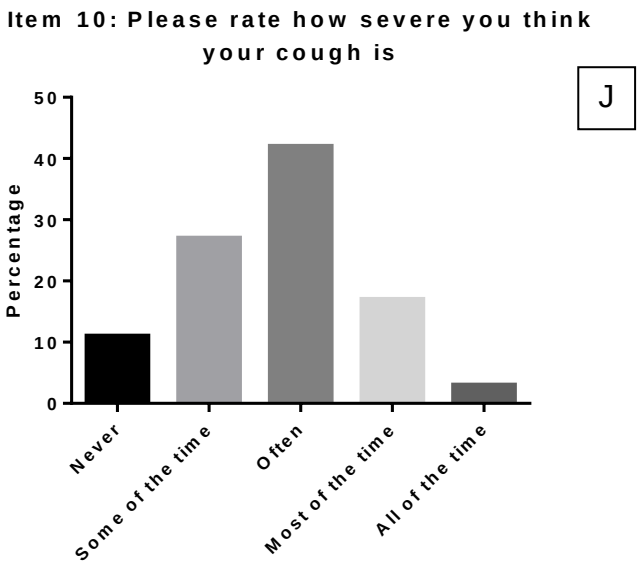


Figure 29 (A-J) showing the spread of responses from patients enrolled in the original MCLCS development study and the patients in the the cough prevalence study and longitudinal cough study.

No item demonstrated floor or ceiling effect.

Internal reliability

The Cronbach alpha reliability for the sample for the 10-item scale also was 0.87. In the MCLCS development study, the Cronbach alpha reliability for the 10-item scale was 0.86, nearly identical to our analysis.

Item to total score correlations

The 10 items had high item to total correlations, ranging from 0.49 to 0.81 ($p<0.001$). These were slightly higher than the item to total correlations from the original MCLCS study where correlations of 0.40-0.76, $p<0.0001$ were reported.

Criterion validity

Overall, 274 patients had completed a cough severity VAS and 265 had completed the full MCLCS questionnaire. The Spearman's correlation coefficient between the cough severity VAS scale scores and the total MCLCS scores was 0.67 demonstrating a high correlation between these two scales (Figure 30). No comparative data are available from the original MCLCS development study.

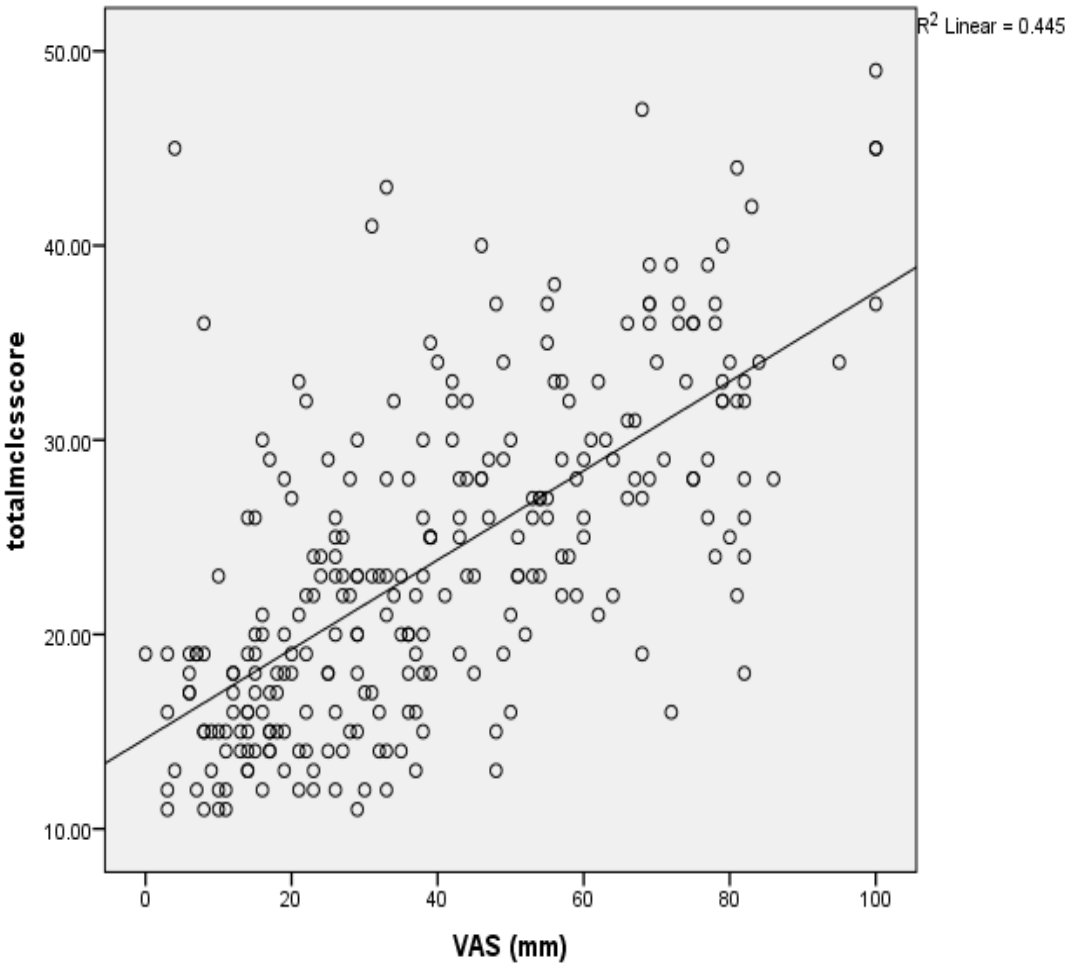


Figure 30 showing the correlation between the cough severity VAS score and the total cough impact Manchester Cough in Lung Cancer Scale score

VAS = cough severity visual analogue scale score,

totalmclcsscore = total cough impact Manchester Cough in Lung Cancer Scale score

3.4 Single arm, randomised, double-blind, placebo-controlled proof of concept trial assessing aprepitant for the treatment of cough in lung cancer

Brief study design

A single arm randomised, double-blind, placebo-controlled proof of concept trial assessing aprepitant for the treatment of cough in patients with lung cancer was conducted in patients attending thoracic oncology outpatient clinics. Patients underwent 24-hour ambulatory cough monitoring and completed the MCLCS, cough severity VAS, BRI, EORTC QLQ C30+LC-13 and physicians completed the CTCAEv4.0 at baseline. These assessments were subsequently repeated on days 3 and 9. In addition, patients completed a global rating of change scale (GRCS) on days 3 and 9. A follow-up telephone assessment was conducted on day 13 or 14 of the trial.

The primary endpoint was a comparison of the change from baseline in cough count for aprepitant versus placebo. The secondary endpoints were a comparison of the change from baseline in the VAS and MCLCS scores, an exploratory analysis of correlation between the presence of GORD and nausea and cough severity and treatment response, an exploratory analysis of the correlation between global quality of life and cough severity and an exploratory analysis of global rating of change scale responses to estimate the minimum important difference (MID) for the Manchester Cough in Lung Cancer Scale

Recruitment

Twenty patients attending the thoracic oncology outpatient clinics at The Christie NHS Foundation Trust (Manchester, UK) were recruited from the 7th October 2013 to the 3rd November 2014 (Figure 31). Of 72 patients who were deemed eligible for the trial, 52 patients were not recruited. The reasons were that three patients felt that their cough was not bothersome, 10 patients had had

antibiotics within four weeks of trial entry, four patients had had a respiratory infection within four weeks, one patient was unable to swallow tablets, one patient had had a previous adverse event to aprepitant (hiccups), one was on warfarin, two women were potentially fertile and of child-bearing age and thirty patients were unwilling to travel to the hospital for assessments

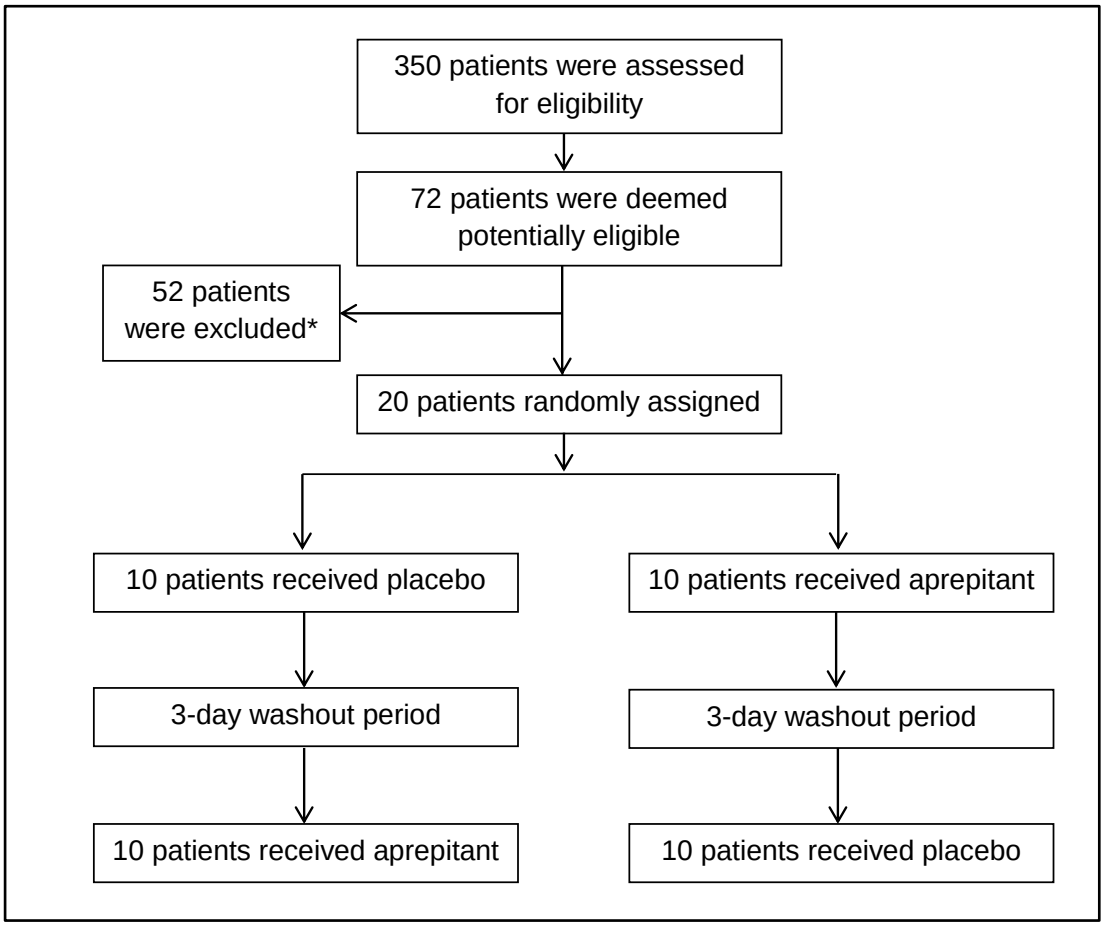


Figure 31 Recruitment to the single arm, double-blind, randomised, placebo-controlled cross-over trial assessing aprepitant for the treatment of cough showing the recruitment and treatment schedule and attrition throughout the trial period.

There was no attrition during the trial**.**

*****Reasons are 3) not bothersome cough, 10) antibiotics within 4 weeks, 4) respiratory infection within 4 weeks,1)unable to swallow tablets, 1)previous adverse event to aprepitant (hiccups), 1)on warfarin, 2)potentially fertile, of child-bearing age 30)unwilling to travel to the hospital for assessments

Patient compliance rates and missing data

There was very high compliance with the study schedule and consequently little missing data. Only one patient was unable to complete the trial protocol since they developed a chest infection on day 9 of the protocol. This patient's day 9 data were therefore missing. A further patient commenced their trial medication at baseline instead of day 1. These data were censored.

3.4.1 Clinical characteristics of the study population

Demographics

The research population's mean age was 66years (SD 7.69). Nearly two thirds of the population, 12 (60%) patients, was female. The majority had a history of smoking; with 14(70%) patients being ex-smokers, five (25%) patients being current smokers and one (5%) patients having never smoked. Their median number of pack years was 37 (25^{th}-75^{th} IQ range 15-60).

Patient co-morbidities and concurrent medications at baseline

Study patients reported the presence of a number of co-morbidities at baseline (day 0). About a third of patients reported COPD (six patients, 30%), no patients reported asthma. Just under half of patients reported a diagnosis of gastro-oesophageal reflux disease (nine patients, 45%). This was a higher proportion of patients than those who reached the criteria for GORD according to the BRI questionnaire score (seven patients, 35%). Overall, (11 patients, 55%) patients reported symptoms of nausea.

Patients also reported their concurrent medications at baseline. Half of patients took regular proton pump inhibitors (10 patients, 50%). Just under half of patients were on regular oOpioids (ninepatients, 45%). Fewer patients took oral or inhaled steroids (three patients, 15%). Only one patient (5%) was on regular ACE inhibitors. No patients were on over-the-counter antitussives. About a fifth

of patients (four patients, 20%) were taking other medications (such as anticholinergics and salbutamol) that may affect cough.

Cancer and treatment characteristics

Most of the patients were of good performance status, with four patients (20%), eleven patients (55%), five patients (25%) of performance status 0, 1 and 2 respectively. The majority, 16 patients (80%), had NSCLC; four patients (20%) had SCLC. Of those 16 patients with NSCLC histology, the predominant histological subtype was squamous histology. There were seven patients (45%) with squamous histology, five patients (31%) with adenocarcinoma, one patient (6%) with a NSCLC histological subtype that was not otherwise specified, one patient (6%) with mixed histology, one patient (6%) with a bronchioalveolar subtype and one patient (6%) with large cell NSCLC. Half the patients had advanced lung cancer with 10 patients (50%) having stage IIIB or above NSCLC. No patients had extensive stage SCLC but six patients (30%) had early stage (≤IIIA) NSCLC and four patients (20%) had early stage SCLC. Less than a quarter of the study population was on anticancer therapy, with four patients (20%) on cancer treatment. Of these four patients, all were on palliative intent treatment. All patients on treatment were on chemotherapy, four patients (20%). No patients were on tyrosine kinase inhibitors. Of the patients who were not receiving anticancer therapy, the majority (nine patients, 45%) were on follow-up following palliative treatment. Overall, one patient (5%) was newly diagnosed and pre-treatment, six patients (30%) were post curative treatment on follow-up (Table 26).

Patient symptom and quality of life scores at baseline

In order to further define the patient population, global and quality of life scores (according to the EORTC QLQ C30 questionnaire) were obtained at baseline for all patients. The mean baseline (day 0) global health score (Items 29 and 30 of the questionnaire) was 53.7 (SD 17.2). The score range is 0-100, where high scores represent better health and quality of life. The median BRI score at baseline was 19.5 (25^{th}-75^{th} IQR 6.2 – 37.0).

Characteristic	Participants (N=20) N (%)
Gender	
Women	12 (60)
Men	8 (40)
Age (years)	66 (SD 6.74)
Performance Status (WHO)	
0	4 (20)
1	11 (55)
2	5 (25)
Co-morbidities (self-reported)	
GORD	9 (45)
Asthma	0 (0)
COPD	6 (30)
Other	13 (65)
Reflux according to BRI score	
No	13 (65)
Yes	7 (35)
Smoking History	
Never	1 (5)
Ex	14 (70)
Current	5 (25)
Median No Pack Years (25^{th}-75^{th} IQR)	37 (20-47)
Histology	
NSCLC	16 (80)
SCLC	4 (20)
Histological Sub-type (if NSCLC)	
Squamous	7 (44)
Adenocarcinoma	5 (32)
Large	1 (6)
Mixed	1(6)
Not otherwise specified	1(6)
Bronchioalveolar	1 (6)
Stage*	
ES SCLC	0 (0)
LS SCLC	4 (20)
IIIA NSCLC	6 (30)
IIIB NSCLC	4 (20)
IV NSCLC	6 (30)
Tumour Location	
Central	13 (65)
Peripheral	7 (35)
Anticancer Therapy	
On treatment	4 (20)
Off treatment	16 (80)
Prior Anticancer Therapy**	
Chemotherapy	12 (60)
TKI	3 (15)
Radiotherapy (thoracic)	12 60)
Radiotherapy (brain)	3 (15)
Radiotherapy (bones)	1 (5)
Thoracic Surgery	0 (0)
Median Duration of Cough weeks (SD)	76 (346)
Type of Cough	
Dry	9 (45)
Productive	11 (55)

Table 24 Baseline clinical characteristics of the trial population

SD=standard deviation, IQR=interquartile range, GORD=Gastro-oesophageal reflux disease, COPD=Chronic Obstructive Pulmonary Disease, BRI=Brief Reflux Inventory, NSCLC=non small cell lung cancer, SCLC=small cell lung cancer, LS=limited stage, ES=extensive stage, TKI=tyrosine kinase inhibitor, CTCAEv4.0=Common Terminology Criterira for Adverse Events version 4.0.
*cancer staged according to 7th Edition of TNM in Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2009

Patient cough characteristics and cough scores at baseline

There were no missing data for cough characteristics and cough scores at baseline (day 0). Most patients had had a cough for a prolonged period of time, with a median of 76 weeks with a wide range (25^{th}-75^{th} IQR 35-140). The majority of coughs were productive with 11 patients (55%) reporting a productive cough.

Patients subjectively assessed the severity of their cough using the cough severity visual analogue scale (VAS – appendix 2).

The median cough severity VAS score was over half the total possible score at 59mm (25^{th}-75^{th} IQR 37-66, score range 0-100 where higher scores represent worse cough severity.

The median Manchester Cough in Lung Cancer Scale (MCLCS) score was about half the total score range at 25.5 (25^{th}-75^{th} IQR 20-31, range 1-50 where higher scores represent worse cough impact.

Overall, the mean EORTC Lung Cancer 13 Item 31 score was 61.6 (SD 19.6) where higher scores indicate worse cough severity on a scale of 0-100. Three-quarters of the patients (15 patients, 75%) reported that they coughed “quite a bit” or “very much” over the week prior to study entry. Most patients (19 patients, 95%) did not report any haemoptysis in the week before study entry.

Researchers scored each study patient’s cough according the Common Terminology Criteria for Adverse Events (CTCAE) version 4 at baseline (day 0). This was the only *physician-rated* subjective cough assessment tool used during the study. A quarter of patients (five patients, 25%) had a cough that was felt to be mild, and/or for which only non-prescription interventions were indicated (Grade 1). Nearly two thirds of patients (12 patients, 60%) had a cough that was felt to be moderate, and/or for which medical intervention was indicated and/or which limited instrumental activities of daily living (grade 2). Only three patients (15%) were thought to have severe symptom that interfered with self-care activities of daily living (Grade 3).

Objective cough monitoring was conducted in 20 patients at baseline (day 0) but one patient was excluded since they commenced treatment at baseline in error rather than on day 1. Of these, no recordings failed. The baseline geometric mean cough frequency over 24 hours was 13.3 coughs/hour with a 95%CI of 8.2-21.6 (n=19). The daytime (defined as hours patient awake) cough frequency was 15.9 coughs/hour with a 95% CI of 10.1-28.3 (n=19). The night-time (defined as hours patient asleep) the median cough frequency was 5.6 coughs/hour with a 25^{th}-75^{th} IQR of 1.9-10.7 with a total range of 0-17.45 (n=19). The cough frequency correlation between day and night had a Spearman correlation coefficient of 0.44 with a p-value of 0.06. Eighteen of nineteen patients coughed more during the day than at night.

3.4.2 The effect of aprepitant and placebo on cough frequency, cough severity and cough impact scores

During aprepitant treatment, the objective cough frequency significantly improved compared to placebo treatment. The day-time, night-time and 24-hour cough frequency all reduced on aprepitant compared to placebo. However, only the night-time cough frequency did not reach statistical significance (Table 27).

Subjective cough severity and cough impact scores also significantly improved on aprepitant compared to placebo (Table 27).

There was a significant effect of treatment order for day cough frequency (p=0.043) but not for 24hr cough frequency (p=0.219) or any of the other endpoint. However, aprepitant remained effective in both sequences, aprepitant-placebo and placebo-aprepitant, as evidenced by the lack of interaction between treatment order and treatment effect (p=0.505). The cough frequency values are lower for those on aprepitant irrespective of treatment order (Figure 32). The change in cough counts for the two periods was not statistically significant. However, patients who received aprepitant-placebo had a higher cough count than those who received placebo-aprepitant than would have been expected by chance alone.

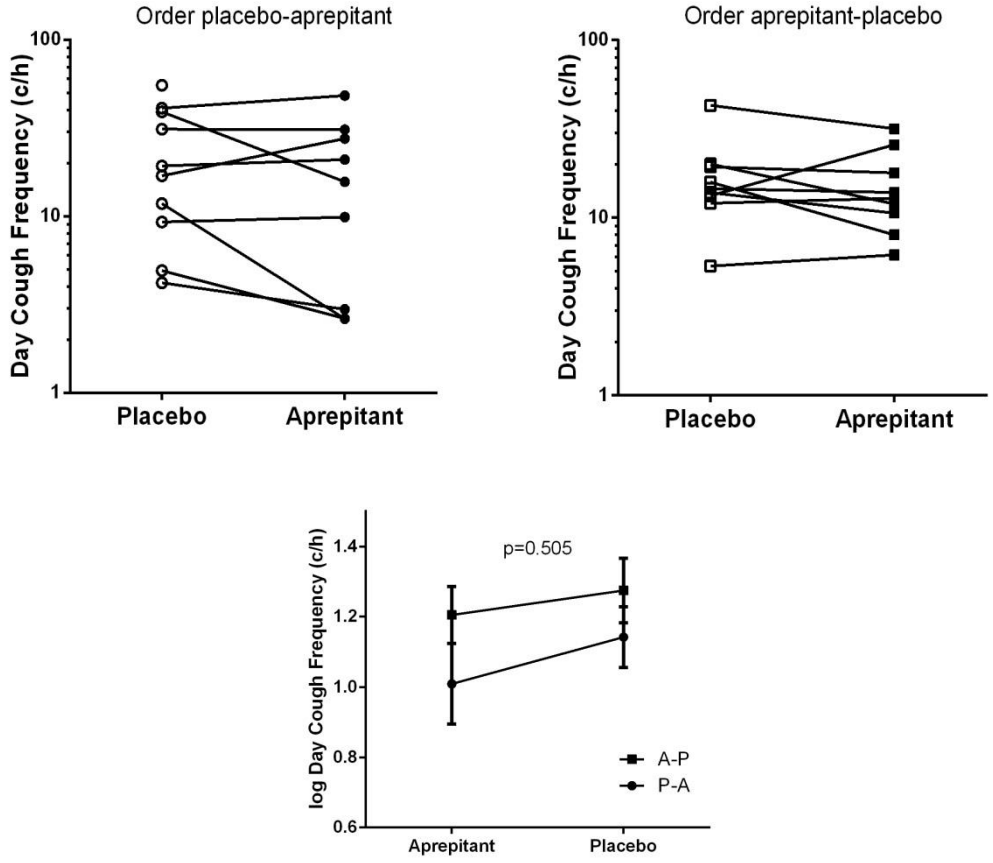


Figure 32 The effect of treatment for the treatment order: placebo-aprepitant versus aprepitant-placebo. The lower graph shows the average cough frequency for aprepitant and placebo divided by treatment order.

A=aprepitant, P=placebo

The treatment type was significant. This was shown for both the objective cough frequency and the subjective cough scores such as the cough severity VAS, Item 31 of the EORTC QLQ C30+LC 13 questionnaire, the MCLCS cough impact questionnaire and even the CTCAE v4.0 scale ($p=0.006$, $p=0.016$, $p<0.001$ and $p=0.019$ respectively) (see Table 27).

Cough Assessment Tool	Baseline	Aprepitant	Placebo	Model Difference	p-value
Daytime Cough Frequency* Patients in analysis Coughs per hour (95%CI)	19 15.9 (10.1-28.3)	18 12.8 (8.7-18.8)	19 16.2 (11.3-23.0)	1.3 (1.0-1.6)	**0.03**
Night-time Cough Frequency* Patients in analysis Coughs per hour (95%CI)	19 3.4 (1.6-8.7)	18 1.8 (0.1-4.2)	19 4.0 (2.2-7.3)	2.3 (0.8-7.6)	0.13
24-hour Cough Frequency* Patients in analysis Coughs per hour (95%CI)	19 13.3 (8.2-21.6)	18 9.8 (6.6-14.6)	19 13.4 (9.0-19.8)	1.4 (1.1-1.7)	**0.01**
Cough Severity VAS Patients in analysis Mean Score mm (95%CI)	19 57.0 (47.4-67.2)	18 40.8 (34.3-47.3)	19 49.8 (44.2-55.4)	9.0 (2.6-15.4)	**0.006**
Cough Impact MCLCS Patients in analysis Mean Score (95%CI)	19 25.2 (23.0-28.0)	18 19.5 (17.8-21.2)	19 21.7 (20.3-23.1)	2.2 (1.1-3.4)	**<0.001**
CTCAE v4.0 Patients in analysis Mean Score (95%CI)	19 2.0 (1.7-2.3)	18 1.7 (1.4-1.9)	19 1.9 (1.7-2.1)	0.2 (0.0-0.4)	**0.019**
Item 31 EORTC QLQ-C30+LC13 Patients in analysis Mean Score (95%CI)	19 2.8 (2.6-3.1)	18 2.4 (2.1-2.6)	19 2.6 (2.3-2.8)	0.2 (0.0-0.4)	**0.016**

Table 25 showing the difference between cough measures and scores for the total trial population on aprepitant and on placebo

Aprepitant led to a statistically significant improvement in cough frequency, cough severity (VAS and Item 31 EORTC QLQ C30-LC13), cough impact (MCLCS) and the physician reported CTCAE v4.0 cough severity scale**.**

Model derived geometric means and 95% confidence intervals, For night-time cough 0.01 was added to cough frequency in order to enable logarithmic base 10 transformation. AS = visual analogue scale (scale 0-100, 100mm=worse cough severity), MCLCS = Manchester cough in lung cancer scale (scale 0-50, 50=worse cough impact), CTCAEv4.0=Common Terminology Criteria for Adverse Events version 4.0 (Scale 1-3, Grade 3 = worse cough severity), EORTC QLQ C30+LC 13= European Organization for the Research and Treatment of Cancer Quality of Life Core30 questionnaire and Lung Cancer LC13 module (Score 0-100, Score 100 = worse cough severity). Model difference = Model difference between aprepitant and placebo

This small proof of concept trial was not powered nor designed to assess the predictors of response to aprepitant treatment. However, given the positive result of this study, we explored the effect of smoking on aprepitant efficacy. In this small sample, we compared ex-smokers (n=14) to current smokers (n=5) but this did not significantly predict cough responses (p=0.44).

3.4.3 Comparison of cough measures on aprepitant and on placebo for individual patients

Within the trial population, a subset of patients responded to treatment with aprepitant and showed marked improvement in both their subjective and objective cough scores (Figures 33-34). However, other patients showed no improvement in their cough counts or subjective measures. The baseline day-time cough frequency did not predict or influence the response to treatment ($p=0.17$). Since the CTCAE v4.0 and EORTC QLQ LC13 scales are three and four-point scales respectively, there was little change in the overall score for individual patients during treatment with placebo and aprepitant (Figure 33). Most patients had stable cough severity CTCAE scores throughout the trial. Of the 19 patients, physicians reported an improvement from baseline of one point in four (20%) patients receiving aprepitant compared to two (10%) patients receiving placebo. There was no worsening of cough severity on treatment (aprepitant or placebo) compared to baseline using this scale during the trial. Similarly, the EORTC QLQ LC13 cough item only varied by one point for individual patients. Overall, eight (40%) patients reported an improvement from baseline of one point in cough severity on aprepitant compared to five (25%) patients reporting an improvement on placebo from baseline.

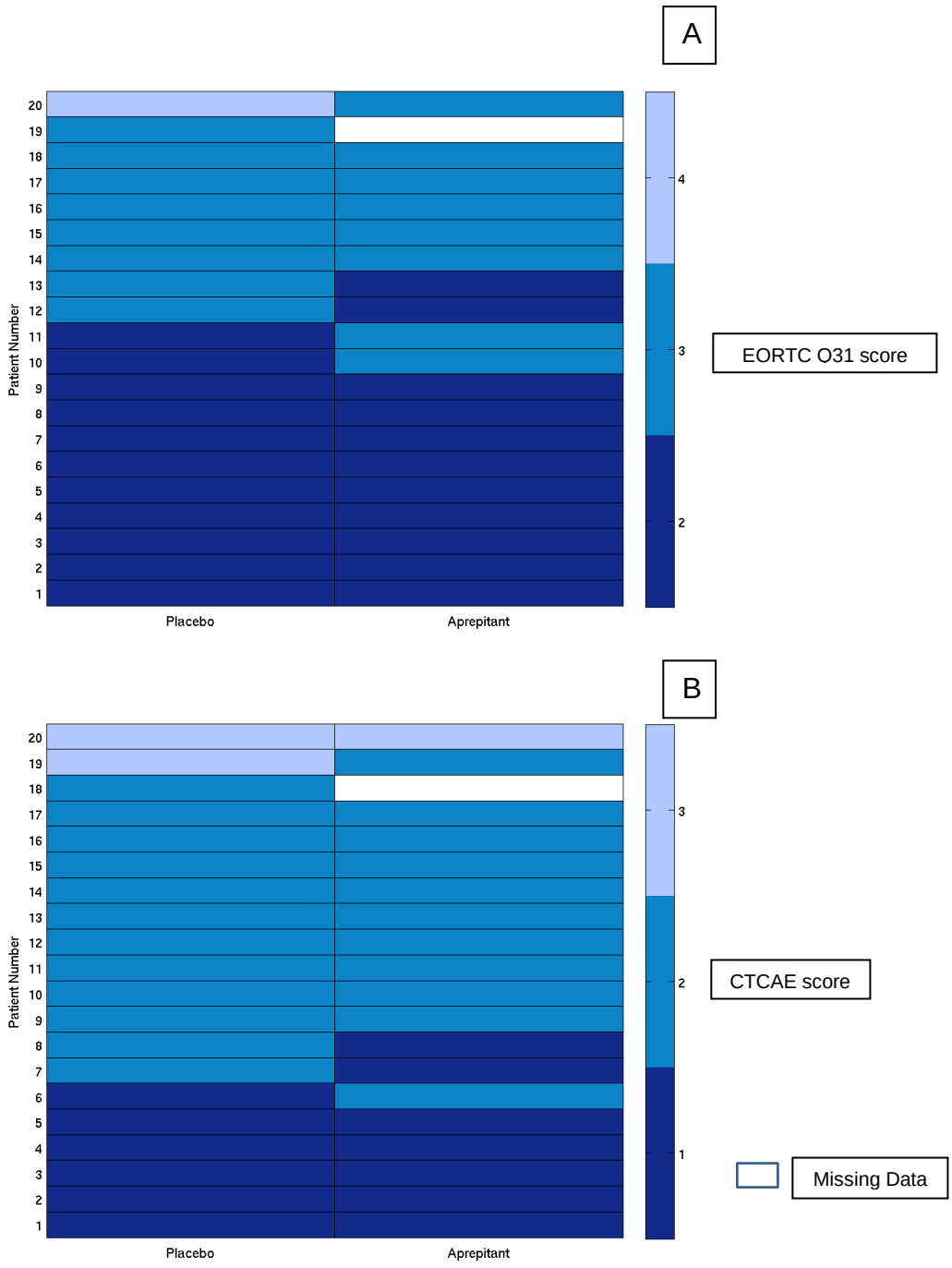
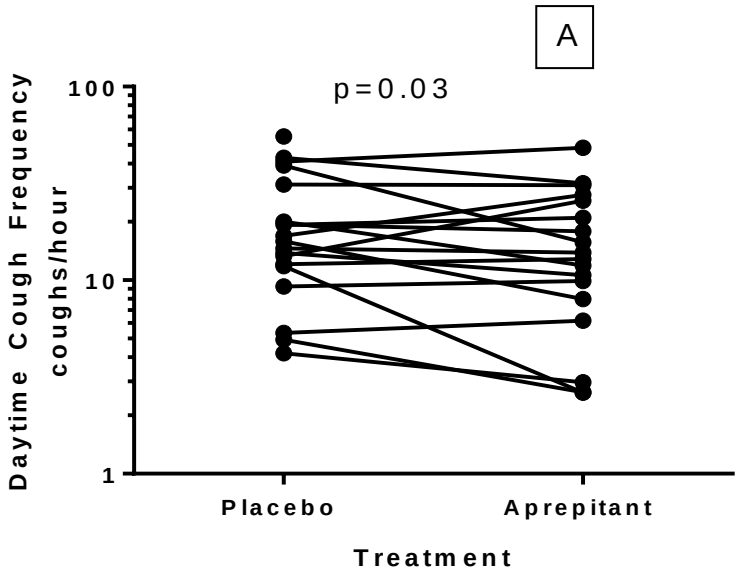
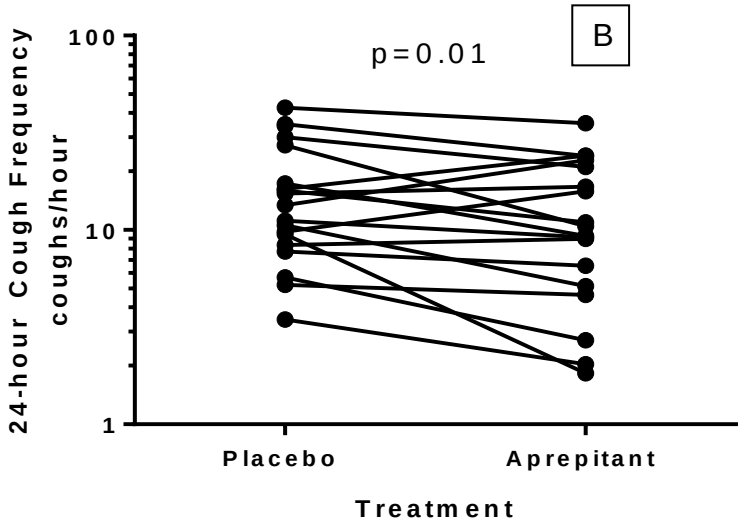


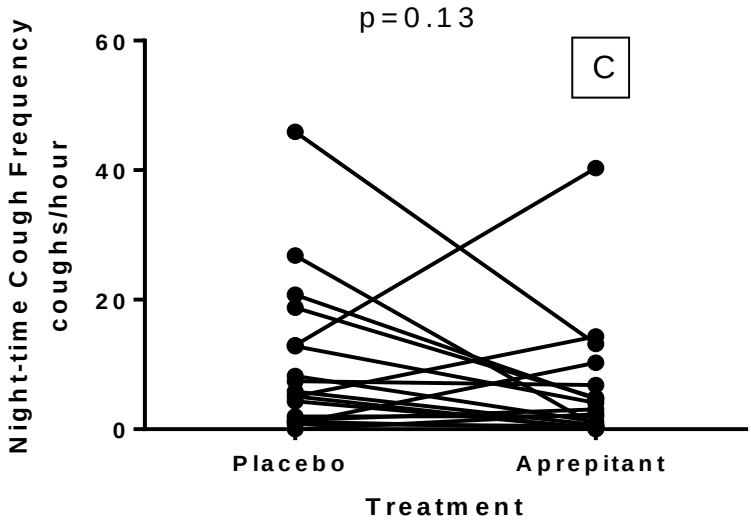
Figure 33 showing the EORTC scores (A) and the CTCAE scores (B) for individual patients on placebo and on aprepitant

These scores show that few patients had a change in cough scores using these scales.

CTCAEv4.0=Common Terminology Criteria for Adverse Events version 4.0 (grade 3=worse cough severity). EORTC QLQ C30+LC 13= European Organization for the Research and Treatment of Cancer Quality of Life Core30 questionnaire and Lung Cancer LC13 module (score 4=worse cough severity)


A
p=0.03
Daytime Cough Frequency
coughs/hour
100
10
1
Placebo
Aprepitant
Treatment


B
p=0.01
24-hour Cough Frequency
coughs/hour
100
10
1
Placebo
Aprepitant
Treatment


C
p=0.13
Night-time Cough Frequency
coughs/hour
60
40
20
0
Placebo
Aprepitant
Treatment

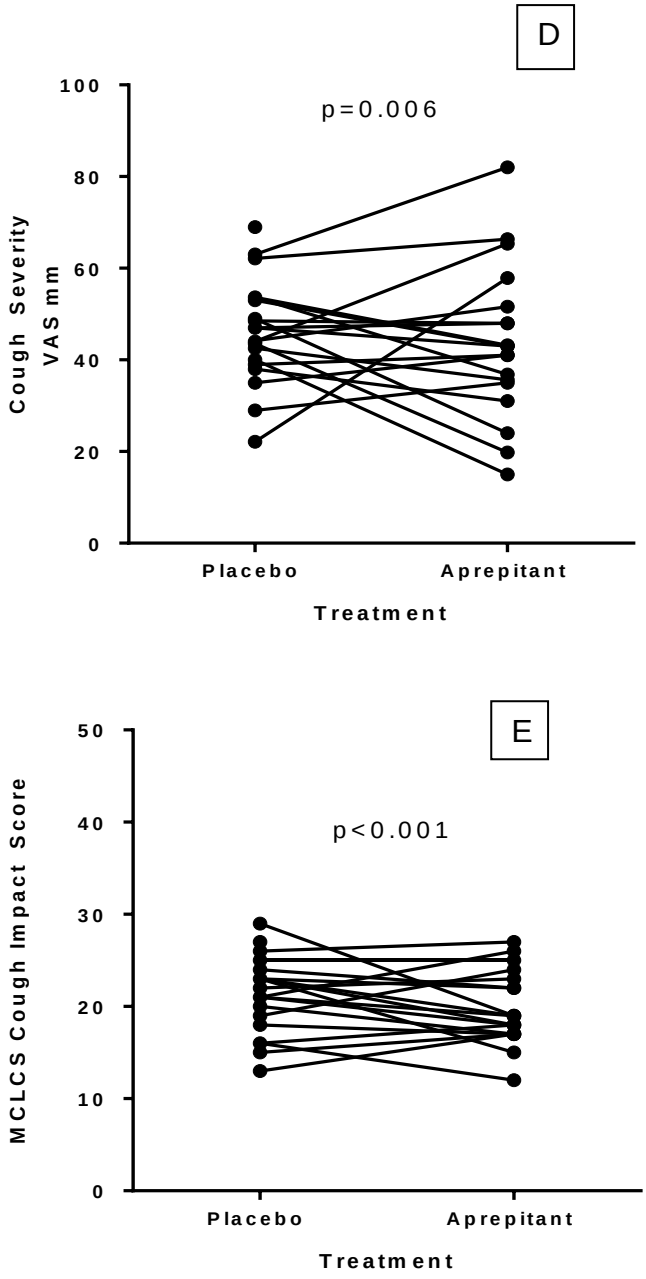


Figure 34 comparing the cough scores and cough frequency (A-E) for each individual patients on aprepitant and on placebo.

These scores show that there are some patients who are responders to aprepitant whilst others do not respond to aprepitant therapy.

VAS = visual analogue scale (100mm=worse cough severity), MCLCS = Manchester cough in lung cancer scale (50=worse cough impact), CTCAEv4.0=Common Terminology Criteria for Adverse Events version 4.0 (grade 3=worse cough severity), EORTC QLQ C30+LC 13= European Organization for the Research and Treatment of Cancer Quality of Life Core30 questionnaire and Lung Cancer LC13 module (score 4=worse cough severity)

*for purposes of analysis, log10 cough counts used

3.4.4 Correlations between cough counts and subjective measures

The correlation between objective cough frequency rates, the cough severity VAS scale and the global rating of change scale (GRCS) for cough severity and cough frequency were explored. In contrast to Table 27, in which a statistically significant improvement was shown for patients receiving aprepitant using the subjective cough assessment measures, the global rating of change scale for cough severity and cough frequency failed to show a similar improvement in cough for patients on aprepitant.

3.4.5 Adverse events

There were no serious adverse events during the trial. Aprepitant was well tolerated with few reported adverse events. All reported events were graded 1 or 2 according to the CTCAE v4.0. None led to the early discontinuation of the trial treatment. Only two adverse events were thought to possibly relate to aprepitant therapy. One was constipation and the other was fatigue. Both adverse events were graded 1 (Table 28).

Adverse Event*	Placebo n=19	Aprepitant n=19
Constipation	0 (0%)	1 (5.5%) Started 2 days after aprepitant stopped
Vomiting	1 (5.2%)	0 (0%)
Fatigue	0 (0%)	2 (11%)
Vertigo	1 (5.2%)	2 (11.0%) (started 1 day after aprepitant 2 patients)
Headaches	1 (5.2%)	0 (0%)
Dyspnoea	0 (0%)	1 (5.5%) Started day after aprepitant stopped
Gastro-Oesophageal Reflux Disease	1 (5.2%)	0 (0%)
Chest Infection	0 (0%)	1 (5.5%)
Pruritus Vagina	0 (0%)	1 (5.5%)
Conjunctivitis	1 (5.2%)	0 (0%)
Diarrhoea	0 (0%)	1 (5.5%)
Malaise	0 (0%)	1 (5.5%) started day after stopped aprepitant

Table 26 showing the few adverse events reported by trial participants on placebo and on aprepitant treatment.

The aprepitant treatment was well tolerated.

*Adverse events were reported according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4).

Each participant may have reported more than one adverse event.

4 Discussion

4.1 Introduction

By demonstrating robust cough assessment methods using subjective and objective cough-specific assessment tools, the data have shown the feasibility and acceptability of novel tools such as 24-hour ambulatory cough monitoring and the Manchester Cough in Lung Cancer Scale questionnaire in a lung cancer population. The use of these complimentary tools has provided novel data on their performance in a “standard of care” lung cancer outpatient population. The assessments have enabled the comprehensive characterisation of cough and the identification of potential clinical predictors and confounders of cough in lung cancer. This has generated hypotheses about potential mechanisms driving cough in patients with lung cancer and informed the design of the intervention trial assessing aprepitant for the treatment of cough. It is hoped that these data will lead to the identification of relevant clinical trial populations, inform future trial design and facilitate the interpretation of trial results in the context of potential confounding factors. Such intervention trials will also provide insights into potential mechanisms of cough in patients with lung cancer whether the trials demonstrate an antitussive effect or not.

4.2 Cough-specific objective and subjective assessment tools rather than standard subjective oncology assessment tools are necessary for the robust assessment of cough

In line with the European Respiratory Society (ERS) guidelines and the American College of Chest Physicians (ACCP) guidelines, the robust assessment of cough is crucial for research advances to be made in this field and for effective treatments to be developed [52, 54]. Key recommendations from these guidelines include the use of validated subjective and objective cough assessment tools, the use of cough severity visual analogue scales (VAS) and cough-specific quality of life questionnaires. Objective cough monitors should be ambulatory, capable of being digitally processed and permit prolonged (24-hr) recording [52, 54]. A comparison of objective and subjective cough assessment tools is presented in Table 29.

	Type of Tool	Rater	Validated for the assessment of cough	Validated in cancer patients	Tool Outcome Measure	Number of Items relating to cough
24-hour ACM **Cough specific tool**	Objective	N/A	Yes	No	Cough Frequency (No. coughs/hour)	N/A
Cough severity VAS **Cough specific tool**	Subjective	Patient-rated	No	No	Cough severity (100mm VAS scale (higher scores = worse cough severity)	N/A
MCLCS **Cough specific tool**	Subjective	Patient-rated	Yes	Yes	Impact on QoL (score out of 50 higher scores = worse cough impact on QoL)	10
CSD **Cough specific tool**	Subjective	Patient-rated	Yes	No	Cough severity (score out of 100 higher scores = worse cough severity)	10
EORTC QLQ C30 Q31 Oncology specific tool	Subjective	Patient-rated	No	Yes	Cough severity (4-point Likert scale higher scores = worse cough severity	1

	Type of Tool	Rater	Validated for the assessment of cough	Validated in cancer patients	Tool Outcome Measure	Number of Items relating to cough
CTCAEv4.0 **Oncology specific tool**	Subjective	Physician-rated	No	Yes	Cough severity (score out of 3 higher score = worse cough severity)	1
FACT-L (cough item) **Oncology specific tool**	Subjective	Patient-rated	No	Yes	Cough severity (5-point Likert scale higher score = worse cough severity)	1
LCSS (2 scales: each with cough items) **Oncology specific tool**	Subjective	Patient-rated scale and an observer-rated scale	No	Yes	Cough severity (100mm VAS scale, higher score = worse severity, observer score on a 5-point categorical scale (100 = none; 75 = mild; 50 = moderate; 25 = marked; 0 = severe)	1 in each scale
TSSD-LC **Oncology specific tool**	Subjective	Patient-rated	No	Yes	Cough distress (-3 to +3 higher scores indicated worse cough distress) The more patients select one symptom over another, the higher its score)	N/A – pairwise comparison between 9 symptoms (one of which is cough).

Table 27 Cough assessment tools.

The oncology specific cough assessment tools are not validated for the assessment of cough specifically.The cough severity VAS has not been formally validated. The MCLCS is the only cough assessment tool that has been formally validated for the assessment of cough in the context of lung cancer. VAS = visual analogue scale, EORTC QLQ C30 Q31 = question 31 from the European Organization for the Research and Treatment of Cancer Core 30 questionnaire, MCLCS = Manchester cough in lung cancer scale, CSD = cough severity diary, CTCAE = Common Terminology Criteria for Adverse Events, FACT-L = Functional Asssessment of Cancer Therapy– Lung, LCSS = Lung Cancer Symptom Scale. TSSD-LC: Thurston Scale of Symptom Distress – Lung Cancer

All the cough-specific assessment tools presented above, including the newly validated lung cancer specific and cough specific quality of life questionnaire, the Manchester Cough in Lung Cancer Scale and the objective 24-hour ambulatory cough monitoring have been applied. This enables the first comprehensive assessment of cough in lung cancer in terms of its prevalence, severity, frequency and impact on quality of life.

Whilst a newly validated subjective cough assessment tool has recently been developed for use in patients with lung cancer, no publications beyond the original validation paper have yet reported its use[40]. The data presented demonstrate that the MCLCS correlates most strongly with the Cough Severity Diary (CSD), the cough severity visual analogue scale (VAS) and Item 31 of the EORTC QLQ C30+31 questionnaires (Table 25). This newly developed cough assessment tool is measuring similar cough constructs such as cough severity, disruptiveness and frequency. However, the correlation is not perfect since the MCLCS measures other aspects of cough too such as its impact on physical, social and psychological domains. It adds to the CSD, Item 31 of the EORTC QLQ C30+LC13 and to the cough severity VAS by identifying specific issues relevant to patients with cough and lung cancer. It therefore provides richer data on the impact of cough than either the CSD or Item 31 of the EORTC QLQ C30+LC13 can. The MCLCS is a robust comprehensive subjective cough assessment tool with a high compliance rate. It effectively assesses cough in lung cancer patients.

Traditionally, oncology trials have characterised cough using single-item oncology-specific tools, such as the Common Terminology Criteria for Adverse Events v4.0 (CTCAEv4.0) cough item. In contrast to cough-specific assessment tools, single item tools are relatively blunt and underestimate the likely prevalence, severity and impact of cough in patients with lung cancer.

The CTCAEv4.0 cough item assesses in item: severity, impact on activities of daily living and the necessity for treatment. Each of the scale increments is not equal in size. The lack of concordance between patient and clinician reporting is

not new [5-7]. Despite the fact that patient-reported outcomes are widely accepted as a gold-standard in quality of life research, the field of oncology relies heavily on the physician-rated scales such as the CTCAE v4.0 for the assessment of symptoms in patients with cancer. This leads to the frequent and systematic underestimation of symptoms such as cough in lung cancer, thereby impairing the ability of clinicians to recognise and meet the holistic needs of patients with lung cancer.

In line with this, our data have shown that the Common Terminology Criteria for adverse events item on cough severity correlates poorly with more robust, cough assessment tools such as the cough severity VAS. Clinicians only scored 1% patients in the longitudinal study “Grade 3” (the most severe value) for their cough severity whilst nearly 66% of patients using the EORTC QLQ C30 Item 31 “How often did you cough in the past week?” rated their cough “quite a bit” and “very much”. It emphasises the fact that an observer-rated, 3 point scale is too blunt an instrument to be useful in the clinical setting or research setting, despite its widespread use in oncology toxicity assessment trials.

Therefore, this single item does not perform well compared to more comprehensive cough assessment tools. The data generated demonstrate that these tools are not necessarily equivalent (Table 24). Whilst some oncology-specific cough assessment tools perform well against more established cough assessment tools such as cough severity VAS scale and CSD, others do not.

Our data do demonstrate that Item 31 of the EORTC QLQ C30+LC 13 questionnaire performs well against the cough severity VAS, CSD and MCLCS with high correlations between this item and the cough-specific assessment tools. In view of the correlations between the EORTC QLQ C30+LC 13 Item 31 and the cough severity VAS, it may be that if the quality of life cancer questionnaire is to be used during a study, the additional use of the cough severity VAS may not always be necessary. Although the VAS scale is a single item, its advantage is that since it is a 100mm scale, it is more sensitive to

change than a four-point Likert scale and may demonstrate small differences in cough severity scores.

Our findings have also demonstrated moderate correlations between the subjective MCLCS and objective cough frequency monitoring (Table 25). Since the MCLCS has an item on cough frequency and an item on cough severity, it is not surprising that there should be correlation between the tools. However, since the MCLCS also measures different constructs such as the impact of cough on physical, psychological and social aspects of living, the correlations are moderate rather than high. The MCLCS is complimentary to objective cough monitoring. Both subjective and objective cough assessment tools are necessary to fully characterise cough.

Patients with lung cancer are commonly affected by cough which is both severe and has a significant impact on their lives. Our data are in keeping with the little published literature on this subject. Our findings highlight the huge unmet clinical need faced by healthcare professionals and the imperative to use validated cough assessment tools in order to robustly assess and characterise cough in patients with lung cancer. The future development of effective antitussive therapies for patients with lung cancer depends on valid, reliable cough assessment tools to enable researchers to identify the novel interventions that lead to clinically meaningful differences in cough scores.

4.3 Ambulatory cough monitoring is feasible in patients with lung cancer and provides an objective endpoint for cough intervention trials

The data presented demonstrate the first use of 24-hour ambulatory cough monitoring in patients with lung cancer. Twenty-four hour cough monitoring has been shown for the first time to be feasible and valid in this patient population. Our study's cough frequency measured using 24-hour cough monitoring are in keeping with their cough severity VAS scores. Our results show that objective cough frequency and subjective cough severity scores correlate moderately (Table 25). This is not surprising since a severe cough is not necessarily a frequent cough. If a patient is so dyspnoeic that any coughing episode is associated with significant worsening of dyspnoea and prevents activities such as dressing, a patient may describe an infrequent cough as a severe cough.

Objective and subjective cough assessment tools assess different aspects of cough and are therefore complimentary. Subjective tools are vulnerable to patient factors such as motivation, mood and fatigue which may affect the way in which the patients complete the scales. However, objective cough monitoring provides cough frequency over a prolonged period that is not affected by such issues.

The data presented highlight that the frequency of cough in patients with lung cancer is extremely significant and like cough severity, often more problematic than for patients with other respiratory conditions [60, 159, 243] (Figure 35). This is in keeping with the relationships between cough severity VAS scores for lung cancer and COPD [243], asthma [60] and chronic cough [159], thereby internally validating our findings.

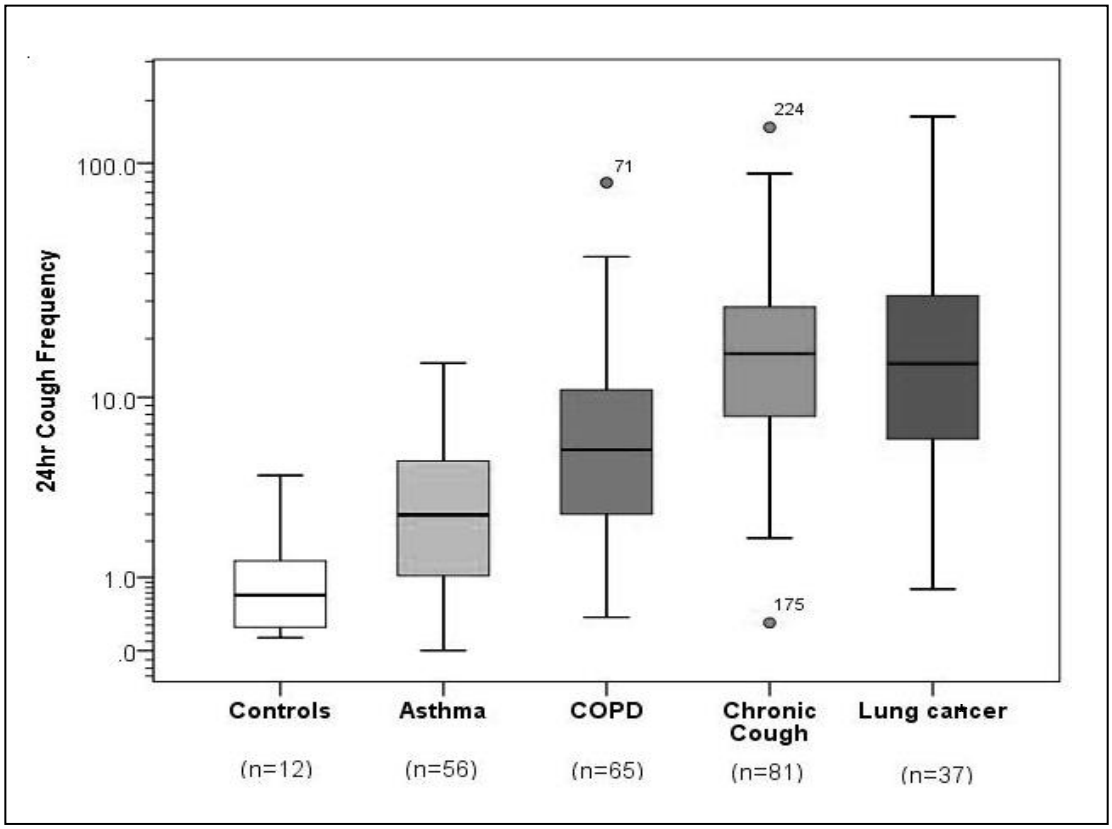


Figure 35 Comparison of cough frequency between different respiratory diseases

This demonstrates that lung cancer patients have a cough frequency that is higher than patients with asthma [241] and COPD [60] and in keeping with patients with chronic intractable cough [159] presenting to specialist cough clinics.

COPD = chronic obstructive pulmonary disease
* Data from the longitudinal cough study

As previously shown in Figure 13, the daytime scores are higher compared to night-time scores. This is a well-recognised phenomenon in cough research although it is poorly understood. It is believed to relate to the fact that there is reduced exposure to tussive stimuli at night and decreased cough reflex sensitivity [244]. Studies of anaesthetised humans have shown that the cough reflex is suppressed; however, the expiratory reflex (where an explosive exhalation is produced without a preceding inspiration) is less affected [245]. Although an expiratory reflex sounds to the human ear like a cough, a true cough reflex is preceded by an inspiratory phase. It is thought that the expiratory reflex protects the airway from aspiration [246]. Whether these mechanisms explain the reduction in cough frequency in patients with lung cancer, or other mechanisms are relevant is not known. Understanding this physiology might contribute to the future development of effective therapies for patients with lung cancer.

It is logical that the subjective cough severity VAS scores should correlate more strongly with day-time cough frequency since the subjective cough assessment tools were completed during the day and, as explained above, most coughing occurs during the day. Therefore day-time cough frequency rather than 24-hour cough frequency tends to be used as the objective endpoint of antitussive trials.

Ultimately, the value of an objective cough frequency score in the context of research is that it provides researchers with a robust endpoint for antitussive intervention trials. If we are to develop effective antitussive therapies for patients with lung cancer, researchers need to familiarise themselves with and incorporate objective cough assessments into their trial designs. Previous studies have reported the use of ambulatory cough monitoring for shorter periods such as four hours but these studies fail to provide the objective assessment of cough for a period that is long enough to cope with the episodic nature of cough [247]. In the study by Ryan et al. monitors were placed on patients who were kept in hospital for the duration of a relatively short recording. The advantage of a 24-hour recording is that patients are encouraged to return to the usual environment and activities, giving a more “real-life” assessment of a

patients cough. Patients often report that they temporarily forget that they are carrying a 24-hour cough monitor, thereby reducing the likelihood of conscious control of cough in an experimental context. It is also known that physical activity can affect cough. For this reason, a patient sat in a hospital bed for the duration of the cough recording does not provide the optimal measure of cough.

Whilst the presumption is often that cough severity in lung cancer relates to cancer specific clinical factors such as advanced stage of disease, or location of the tumour, there is little evidence from our study or the published literature to support this. Lung cancer is an aggressive cancer which leads to rapid decline in health. It can change significantly over a 60-day period. Despite this, cough frequency in our study population, remained quite constant.

No studies could be found describing the use of 24-hour ambulatory cough monitoring in a lung cancer population. It is therefore difficult to ascertain whether our results are a true reflection of changes in cough frequency over time. Although cough monitoring was conducted in a subset of patients, it is a powerful tool that is not vulnerable to issues such as poor compliance, recall or mood disturbances. Therefore smaller sample sizes are required to provide a robust assessment of cough frequency compared to those required for subjective cough severity questionnaires. Our sample is therefore likely to be representative of our main study population. However, future longitudinal studies will also need to include objective cough monitoring in order to confirm or refute our findings.

4.4 Smoking, chronic obstructive pulmonary disease and cancer-related characteristics fail to predict cough prevalence, severity or its impact

Smoking

Although smoking and cancer related factors such as stage of disease and location of tumour are thought by many to relate to cough, our studies did not demonstrate that these factors were associated with cough prevalence, severity or impact. The smoking status or pack year history were not significantly different between “coughers” and “non-coughers” in the cross sectional study population. Smoking status was not associated with either cough severity or cough impact scores in the longitudinal cough study. This is counter-intuitive. In a study by Chen et al., patients with SCLC were followed up for five years after their diagnosis. It showed that smokers tended to have higher symptom burden and worse quality of life compared to patients who were ex-smokers. This included worse cough severity scores (measured using LCSS). There were no “never smokers” included in the analysis. [248]. In a smaller study by Sarna et al. in which 147 long term survivors of NSCLC underwent quality of life assessments, smoking was not shown to have an effect on quality of life, however, symptoms of lung cancer such as cough were more likely to be present in patients who had been exposed to second-hand smoking [249, 250].

It is not clear why our data did not demonstrate an association between cough and smoking. It may be that when patients have active cancer such as those included in our longitudinal study, other clinical factors are more important drivers of cough than factors such as smoking. It may also be that patients with lung cancer who smoke are more likely to be those patients who do not develop significant smoking-related symptoms such as cough. Patients with lung cancer who smoke may also adapt to their symptoms and consider cough to be normal and therefore fail to report it on subjective cough assessment tools. There is

evidence that long term lung cancer survivors adapt to their symptom burden [82]. Equally, patients with lung cancer who describe themselves as having a “smoker’s cough” may in fact be reporting a longstanding cough that relates to underlying lung pathology rather than a “true” smoker’s cough.

Chronic Obstructive Pulmonary Disease

In terms of co-morbidities, the overall spirometry FEV1/FEV6 ratio for the study population shows that most patients did not have an obstructive respiratory defect despite many having a significant smoking history. This shows that although smokers frequently develop lung cancer, a significant proportion never develop conditions such as COPD. Cough is known to be a common symptom associated with COPD, affecting 69% - 87% of COPD patients [130, 131]. COPD is also a known independent risk factor for lung cancer [251]. It is therefore surprising that it was not found to be associated with cough severity scores. Our findings demonstrate that other factors may be more important predictors of cough than the presence of COPD. It may also be that patients with severe COPD are unlikely to attend medical oncology outpatient clinics since their significant co-morbidity and its consequent performance status often precludes them from receiving anticancer therapies. Such patients may therefore not have been represented in our study population.

Ultimately, only 25-33% of the variance in VAS scores is explained by the multivariate models (Tables 12, 16 & 18) showing that there are other factors that are associated with cough severity. This is also highlighted by the significant overlap between groups in the boxplots in Figure 26. Cough severity is complex and relates to multiple factors beyond those measured in this analysis and beyond the cancer specific characteristics that are often thought by treating physicians to explain this difficult symptom. As a first study trying to characterise cough in lung cancer, it was important to have a heterogeneous sample of lung cancer patients to generate hypotheses. However with small numbers in subgroups of patients, it is harder to identify single factors associated with changes in cough severity. For future studies, it may be

necessary to identify subgroups of patients and repeat these analyses in order to elucidate some of these interactions further.

Cancer related factors such as stage, histology, cancer treatment intent or type of treatment were not associated with the presence of cough in the cross-sectional prevalence study. Whilst many clinicians often consider these factors to be important determinants of cough, this is not borne out in our data, showing that improving lung-cancer related cough requires more than better cancer therapies. In the study by Walling et al. (Table 2), in which over 2400 patients with newly diagnosed lung cancer were assessed, stage of cancer was not found to be associated with cough prevalence rates (82% vs 84%, early vs late stage) further corroborating our findings. Anecdotally, patients with lung cancer sometimes report worsening of their cough, yet their radiology scans fail to demonstrate disease progression. It may be that these patients have a cough that persists and worsens due to a “cough hypersensitivity syndrome” rather than due to cancer progression.

Cancer-related characteristics

Published literature suggests that anticancer therapies such as chemotherapy, targeted agents and radiotherapy may be useful treatments for lung cancer-related cough [174, 175, 177, 186, 189]. This implies that some patients with lung cancer have a cough that is driven by cancer-specific pathological processes. When these are reversed by treatment, the cough improves. However, in our observational studies, cough prevalence, severity and impact were not found to be associated with cancer related characteristics such as stage, histology or anticancer therapy on multivariate analysis. On univariate analysis, the only cancer-related factors associated with cough were “being on anticancer therapy” and centrally located tumours; patients on treatment being less likely to have a cough and patients with centrally located tumours reporting a worse cough impact MCLCS score. This demonstrates that cough is driven by different pathophysiological mechanisms in different patients with lung cancer. Indeed, several studies in lung cancer survivors demonstrate that cough persists in patients even several years after curative treatment indicating that

cough in these patients may relate to the long-term effects of treatment rather than lung cancer directly [81, 82, 248, 250].

There is therefore a need for researchers to refocus their attention on other mechanisms of cough if effective antitussive therapies are to be developed. It may be that, like in patients with chronic cough, some patients with lung cancer have a cough that relates to chronic hypersensitivity states rather than to a physical stimulus such as a tumour causing airway obstruction. Our study populations included few patients who were receiving or had received thoracic radiotherapy. Future observational studies in patients with lung cancer should include these patients. It may be that radiotherapy is associated with cough. These studies ought to be longitudinal since the acute and late effects of radiotherapy need to be taken into account when assessing cough.

4.5 Gastro-intestinal comorbidities such as nausea and reflux disease are associated with cough severity and the impact of cough

In contrast to cough prevalence, key independent factors associated with worse cough severity VAS scores included a poor performance status, the female gender, gastro-intestinal co-morbidities such as regurgitation (Item 4 of the Brief Reflux Inventory, BRI) and respiratory conditions such as asthma.

Gastro-intestinal symptoms (nausea, and the items of the BRI and its total score) were all found to relate to cough severity scores on univariate analysis. However, Item 5 of the BRI was subsequently removed from the multivariate analysis since this item referred to being “woken at night by symptoms of *coughing* or choking”. It was therefore important to ensure that the significant association between the BRI total score and the cough severity VAS score was not reflective of this confounder rather than a true association with GORD symptoms.

Our rationale for including the BRI questionnaire in the study protocol related to the fact that many published papers demonstrate an association between chronic cough and acid and non-acid reflux events and describe potential mechanisms to explain this association [133, 139-141, 143, 252-254]

The association with regurgitation is intriguing since it is known that the airways and oesophagus have common embryonic origins and therefore share vagal innervation. These common neural pathways are centrally integrated in the midbrain, specifically the nucleus Tractus Solitarius (nTS). It may be that in some patients, this central integration is abnormal such that patients with gastro-intestinal pathology like regurgitation develop a chronic cough, otherwise known as an “oesophago-bronchial reflex”.

To date, a small number of studies in chronic cough patients have sought to explore possible gastro-intestinal mechanisms associated with cough. Three mechanisms may link reflux and the airway: oesophageal reflux, laryngopharyngeal reflux and micro aspiration.

Oesophageal reflux

Chronic cough researchers have shown that infusing acid into the oesophagus was temporally associated with episodes of cough and led to a heightened cough reflex [141, 143]. In the study by Smith et al. assessing the relationship between reflux events (acid and non acid) and cough events in patients with chronic cough, there was a temporal association between reflux and cough in about 72% of patients, with 48% exhibiting a positive association for cough preceded by reflux and 56% for reflux preceded by cough and 33% for both, suggesting a self-perpetuating cycle of cough-induced reflux and reflux-induced cough [141].However, this was not shown in healthy volunteers. This may imply that there is a central mechanism for the sensitisation of the cough reflex. In addition to this, non-acid reflux events (i.e.: above pH 4) have also shown to be temporally associated with coughing episodes [252]. This may explain why in the chronic cough population, the use of proton pump inhibitor therapy may not always be of clinical benefit, even if reflux is present. Further studies are required to investigate the effects of reflux treatments on cough in order to establish a true causal relationship between reflux and cough.

Laryngopharyngeal reflux

Some reflux events may reach the proximal oesophagus and laryngo-pharynx. Although some studies have shown that such events occasionally occur in chronic cough patients, these episodes happen rarely (2-3 times in a 24-hour period) [252]. They therefore fail to explain the frequency of cough episodes. However, it should also be noted that the measurement of such episodes is complex and to date, we have no established methods to detect high reflux events reliably.

Micro-aspiration

This is often discussed in the cough research literature as a potential cause for cough, whether by reaching the vocal cords or indeed stimulating the airways beyond the vocal cords. However, chronic cough may lead to heightened airway protection. In a study by Decalmer et al. sputum pepsin concentration was shown to be inversely proportional to cough frequency suggesting that coughing may prevent pepsin entry into the airways or improve its clearance [255]. The correlation between pepsin concentrations and proximal reflux was found to be highly significant when adjusting for cough frequency. Airway pepsin concentrations in bronchio-alveolar lavages have been shown to be the same in healthy volunteers as in chronic cough patients [254]. However, this may be a relevant mechanism in lung transplant patients who have an impaired cough reflex [256, 257].

Taken together, the facts that airway pepsin levels have not been shown to be significantly different in patients with chronic cough and healthy volunteers and that the degree of acidity of reflux events does not appear to be related to cough frequency but is linked to cough reflex sensitivity, suggest that there is a shared neural sensitisation in patients with chronic cough that may lead to a self-perpetuating cycle of reflux inducing cough inducing reflux [141, 255].

Our data is the first published to show an association between cough and reflux in the context of lung cancer. To date, no mechanistic studies such as those described above have been conducted in patients with lung cancer, however these are now warranted. Objective measures of reflux disease such as the use of pH and impedance monitoring may be necessary. This is likely to present significant challenges in a lung cancer population, whose performance status, co-morbidities and prognosis may limit such invasive tests.

Similar clinical characteristics to those that independently predicted cough severity scores also independently predicted cough impact scores. These included performance status, gastro-intestinal symptoms such as nausea, the use of opioids and baseline MCLCS scores (Table 23).

In light of the association between cough severity VAS scores and regurgitation, it was revealing to identify nausea as a potential predictor of cough impact MCLCS scores. Although nausea was not associated with cough severity, our findings suggest that there may be a shared mechanism between gastrointestinal pathology and cough both in terms of its severity and its impact. Nausea may not cause necessarily cough but may be a consequence of severe cough. It may be exacerbated by reflux events as has previously been described in chronic cough patients [141, 143].There appears to be a linear association on univariate analysis between Item 14 EORTC QLQ C30+LC13 scores (item on nausea severity) and cough severity VAS scores (Figure 26ble). Cleeland et al. have shown in a symptom cluster analysis relating to the development of the MD Anderson Inventory that several gastro-intestinal symptoms including nausea tend to be co-reported by patients with cough and breathlessness [258] (Figure 36).

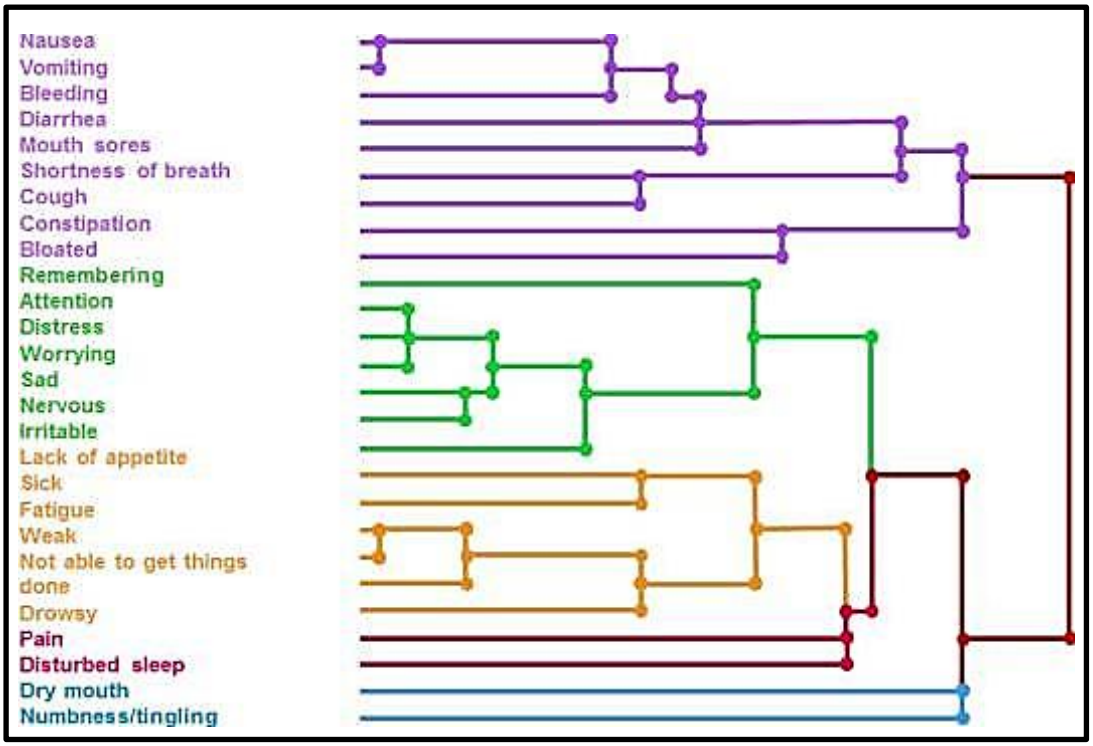


Figure 36 A symptom cluster analysis adapted from Cleeland et al showing clusters of symptoms reported by cancer patients (all types of cancer) in the development of the MD Anderson Symptom Inventory Scale[258].

This shows that cough was co-reported by patients together with several gastro-intestinal symptoms including nausea. Co-reported symptoms (colour-coded) may have shared underlying physiological mechanisms.

As Cleeland suggests, the clusters of co-reported symptoms may be explained by shared physiological mechanisms and this particular cluster of symptoms is in keeping with a symptoms mediated by the vagus nerve. This remains to be demonstrated in research exploring the underlying mechanisms of cough neurophysiology. Clearly, had nausea also been shown to be associated with cough severity VAS scores, this would have strengthened the case for a shared mechanism.

The association between nausea and MCLCS cough impact scores may also be explained by the well described relationship between nausea and quality of life (QoL). It may be that the association shown in our data reflect this rather than a cough-related worsening of quality of life specifically, it is also possible that patients who have a poorer QoL score higher on the MCLCS and may, as a consequence of general malaise, suffer from more nausea.

Anecdotally, patients with lung cancer often report that coughing causes vomiting [1]. Whilst we have not shown such an association, it may be that the vomiting assessment tools used in our studies were not robust enough to show this association. Patients report that coughing may lead to vomiting, even in the context of a dry cough. The vomiting may therefore not necessarily relate to the gag reflex being elicited by sputum in the hypopharynx.

Vomiting is a further reflex (like cough) that can be consciously controlled sometimes. It may be that the higher centres implicated in cough are also shared in vomiting.

Since the data demonstrate an association between gastro-intestinal co-morbidities and cough, this supports the choice of aprepitant as a novel antitussive warranting testing in the context of lung cancer related cough. Initially, aprepitant was chosen since it was known to be safe and well-tolerated in the lung cancer population. There was also significant research demonstrating that centrally acting neurokinin antagonists had antitussive

activity across five different species of animals. However, since data from our observational studies show that both nausea and reflux are associated with cough, this further enhances the hypothesis that the neurokinin-1 pathway is implicated in lung cancer-related cough.

4.6 Over half of patients with lung cancer suffer from a cough; with over two-thirds of these feeling that their cough warrants treatment and a quarter reporting a painful cough.

Cough prevalence

The data presented provide a “snapshot” of cough prevalence in a large “real-life” UK outpatient oncology clinic population has been established. Just over half (57%) of patients with lung cancer attending oncology outpatient appointments are affected by cough.

Since consecutive patients were approached, the potential for selection bias was minimised. This is supported by the finding that the prevalence was identical between the screened and research populations.

The current literature varies significantly in terms of the cough prevalence figures quoted for patients with lung cancer. However, two recently published studies by Iyer et al. quote a percentage prevalence of cough in “real-world” NSCLC populations [11, 12]. In the US study, with over 400 patients, the Lung Cancer Symptom Scale (LCSS) data suggest that about 80% of patients reported a cough, but the authors add that 64.8% of the study population reported a persistent cough. The second study, based in France and Germany, in over 800 patients published a cough prevalence rate of 93% [12]. Both studies only included patients with NSCLC histology, advanced stage disease (Stage IIIB/IV) and patients receiving chemotherapy (1st, 2nd or 3rd line). Both studies used the Lung Cancer Symptom Scale (LCSS) and the Functional Assessment of Cancer Therapy – Lung (FACT-L) validated oncology lung cancer assessment tools.

A third study by Tishelman et al. describes the longitudinal variation in symptom prevalence, intensity and distress in a cohort of 400 LC patients, using the

EORTC QLQ C30+LC13 and the Thurstone Scale of Symptom Distress-Lung Cancer (TSSD-LC) at six time-points during the 1st year after diagnosis [5]. This study reported a cough prevalence of 70% at the time of lung cancer diagnosis and a prevalence of 81% in the month prior to death. This difference was not statistically significant [9].

	Iyer et al. USA Study	Iyer et al. European Study	Tishelman et al.	Cough Prevalence Study
Number of patients	450	837	400	202
Diagnosis	NSCLC	NSCLC	NSCLC and SCLC	NSCLC and SCLC
Point on disease trajectory	Cross sectional study – any point on disease trajectory -	Cross sectional study – any point on disease trajectory -	Longitudinal study from diagnosis to death (6 time points)	Cross sectional study – any point on disease trajectory -
Stage	IIIB/IV	IIIB/IV	All stages	All stages
PS score **0** **1** **2** **3** **4**	Not detailed in paper	(ECOG) 24% 53% 19% 3% 1%	Not detailed in paper	(WHO) 13% 36% 35% 16% 0%
Treatment	All on chemotherapy (1^{st}, 2^{nd} or 3^{rd} line)	All on chemotherapy (1^{st}, 2^{nd} or 3^{rd} line)	Patients could be on or off treatment (any)	Patients could be on or off treatment (any)
Cough Prevalence	80%	93%	70-81%	57%

Table 28 Comparison of study population characteristics between two recently published cross sectional lung cancer studies, a longitudinal study of symptom distress by Tishelman et al and the cough prevalence study

NSCLC = Non-small cell lung cancer, SCLC, Small cell lung cancer, PS = performance status score, ECOG = Eastern Cooperative Oncology Group

Since our study did not select its patients according to stage, histology or cancer therapy, its cough prevalence figure is likely to be more representative of a general lung cancer outpatient population compared to the studies by Iyer et al. Furthermore, over 50% of our patients had a performance status of 2-3, whilst only 23% of patients in the European Iyer study had a performance status >1. In our study, there was a trend ("cough" PS 0-1 42% vs PS 2-3 58% and "no cough" PS 0-1 59% vs PS 2-3 41%: p=0.09: see Table 6) suggesting that patients with a poor performance status were more likely to have a cough than patients with a performance status score of 0-1. Performance status was found to predict both cough severity and cough impact, the "trend" for its association with cough prevalence is therefore noteworthy. Since patients with a poor performance status are often excluded from trial entry, it is likely that their symptom burden remains largely underestimated in the medical literature. Yet, such patients are commonly seen in the outpatient setting. Cough is a significant problem for these patients. Performance status has previously been shown to be a predictor of symptom burden and quality of life in lung cancer [11, 12]. The prognosis is often shorter in patients with a poor performance status compared to patients with a better performance status score [3, 4]. Optimising their quality of life during their remaining life-time is of critical importance if we are to maximise their well-being and potentially their overall survival [3, 4]. Given the high proportion of patients of good performance status in Iyer's study, it is surprising that the cough prevalence figure is as high.

The mean values of the EORTC QLQ C30 global health status and quality of life scale for our study population are in keeping with the published EORTC reference values showing that our population is representative of other lung cancer populations of similar age, stage and histology [259].

Our cough prevalence study found that the only clinical factor related to cough prevalence was "being on anticancer therapy". Those patients who were on treatment were less likely to have a cough than patients who were not receiving treatment (40% vs 54%, p<0.04). Interestingly, the cough prevalence rates in both Iyer's studies were high despite the fact that all patients were receiving

chemotherapy. It is likely that factors other than being on anticancer treatment also predict the prevalence of cough in lung cancer and may explain the differences in cough prevalence rates between studies. Indeed, this adds weight to the argument that effective antitussives are required for the lung cancer population despite the advent of more effective lung cancer therapies. Treating lung cancer is not sufficient to alleviate this troublesome symptom.

The mean cough severity scores according to the LCSS were lower in Iyer's European study than the US study. The higher cough prevalence rate may therefore reflect a significant number of patients with a very mild cough. The European study does not report an attempt to discern between a normal physiological cough and a pathological cough. The methods in our cross sectional study were such that patients were only asked to rate their cough severity if they identified themselves as "having a cough" on the day of study entry. Had consecutive patients been approached to complete the MCLCS and cough severity VAS irrespective of the reporting of the presence of a cough, the cough prevalence may have been higher and therefore less representative of a "clinically meaningful" cough in this patient population.

The tools used in Iyer's studies included the LCSS and FACT-L questionnaires. These are validated for use in patients with lung cancer but are not cough-specific tools. They each only have one item relating to cough. The FACT-L item is: "I have been coughing: Not at all, A little bit, Somewhat, Quite a bit, Very much". The LCSS patient rated item is a 100-mm visual analogue scale for "cough" extending from 'as good as it could be' to 'as bad as it could be'. The patient is asked to place a mark along the line to best describe their cough severity. The LCSS also has an observer rated scale with a single item on cough which is marked "100 = none; 75 = mild; 50 = moderate; 25 = marked; 0 = severe". It is not clear how data on "persistent cough" were collected, particularly since these studies had a cross-sectional design.

In the US study by Iyer, the observer-rated cough prevalence rate differed from patient-reported cough prevalence rate (~70% observer-rated vs ~80% patient-

rated). Such discrepancies between observer-reported and patient-reported outcome measures have been described in the symptom and quality of life assessment literature [39, 260]. It is likely that health care professionals frequently underestimate the prevalence of cough in their patient populations and emphasises the importance of using patient reported outcome measures[260].

Iyer's European study showed that cough was more prevalent in patients on 2nd line chemotherapy compared to patients on 1st line chemotherapy, suggesting that there may be a difference in cough prevalence according to the time-point on the disease trajectory, with worse cough severity closer to death. This seems intuitive and may therefore demonstrate internal validity of their study findings. It may also explain their higher cough prevalence rate compared to our study since our study had 29 patients (14%) who had not yet started anticancer therapy and 51 patients (25%) who were between treatments with the prospect of further treatment if necessary. Few patients included in our study (16%) were in the final phase of their illness, with no further cancer therapy possible. These patients tend to be referred to community care rather than remain under the care of thoracic oncologists in the outpatient setting. It may be that this population is burdened by a high level of respiratory symptoms, including cough.

In the study by Tishelman et al, the prevalence of cough was 81% in the month prior to death. It was not found to be statistically significantly higher than patients who were at earlier time points in their disease trajectory. However, since we now have more comprehensive lung cancer specific validated cough assessment tools to assess prevalence, severity and impact than the single item (item 31) in the EORTC QLQ C30+LC13 scale, Tishelman's findings warrant further research in order to confirm or refute these findings. Cough, dyspnoea and fatigue form a well-recognised symptom cluster in lung cancer [13] Symptom burden is known to increase as performance status declines. Since Tishelman et al have shown that fatigue and dyspnoea significantly increase as lung cancer progresses, it is intuitive that cough prevalence and

severity may also increase throughout the lung cancer disease trajectory and that a bothersome cough affects the majority of patients with lung cancer at some point during their illness.

Cough severity

Lung cancer patients have a severe cough with over half reporting that their cough is severe enough to warrant treatment and over a quarter of patients describing their cough as painful, yet only 15% report the use of over the counter antitussives.

Our data demonstrate that the lung cancer patient population has a median cough severity VAS score of 32mm in an unselected lung cancer outpatient population (cross sectional cough prevalence study) and 40mm in the longitudinal cough study which selected patients on the basis of the presence of cough. These scores are higher than reported series of patients with asthma and COPD [60, 243] and in keeping with patients with chronic cough presenting to specialist cough clinics (Figure 37) [159].

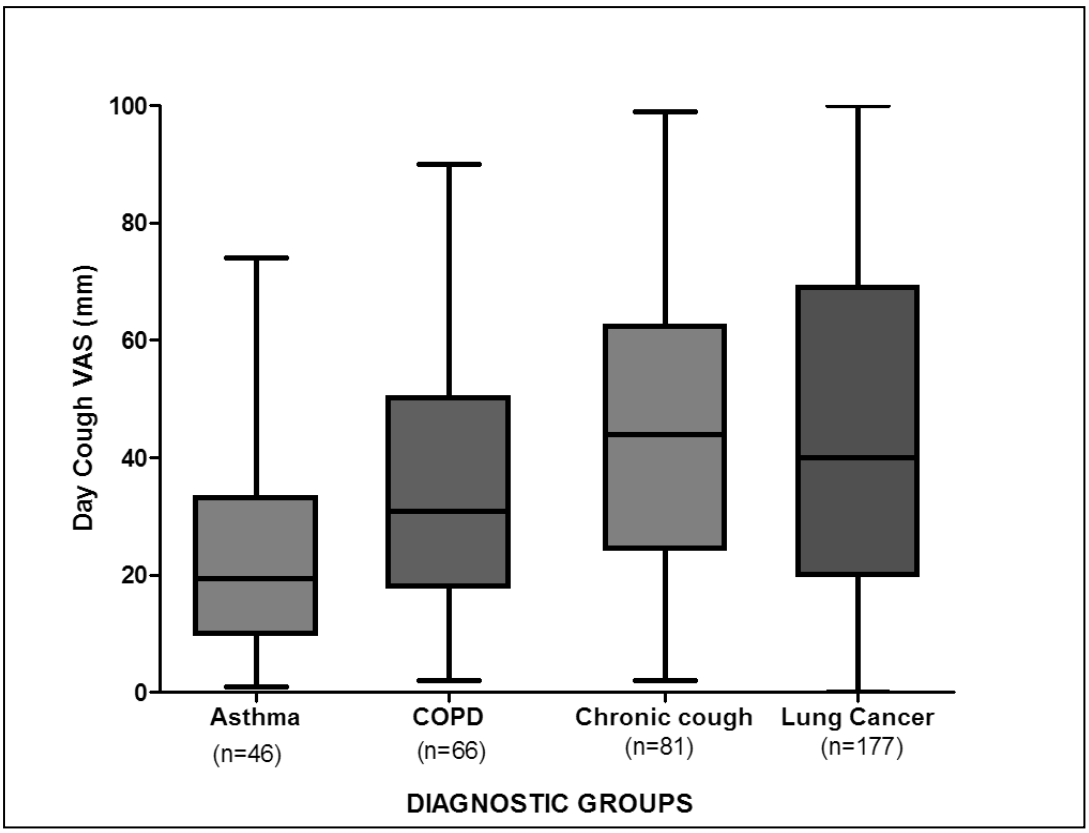


Figure 37 Comparison of cough severity VAS scores between different respiratory diseases

This demonstrates that lung cancer patients have a cough severity VAS score that is higher than patients with asthma [60] and COPD [241] and in keeping with patients with chronic intractable cough [159] presenting to specialist cough clinics.

VAS = Visual analogue scale, COPD = chronic obstructive pulmonary disease
$ - chronic cough patients present to specialist cough clinics with cough as their main medical complaint. They have chronic intractable cough with no identifiable cause.
*data from longitudinal cough study population

Cough impact

Our data demonstrate that cough has a significant impact on physical, psychological and social aspects of daily life.

The only other published figure for a mean total MCLCS score in cancer patients is 18.3 (range 1-39) in the original MCLCS development study[40]. This included 139 patients with different histologies of lung cancer including mesothelioma. It is not clear whether any patients were on active treatment at the time of the study. Despite these differences, our longitudinal study's results are similar to those of the MCLCS development study scores, if a little higher, with a median MCLCS score of 24 (IQR 18-32) and mean score of 22 (range 16-27).

The longitudinal cough study population has similar cough impact scores to the cross-sectional cough prevalence study population (median MCLCS scores 24 vs 22 respectively) showing that our studies' results are likely to be representative of cough impact scores for lung cancer outpatients. Of these patients, nearly two-thirds of patients felt that their cough was severe enough to warrant treatment, highlighting the unmet clinical need for this group of patients.

Although the Manchester Cough in Lung Cancer Scale (MCLCS) has not yet been used in published studies other than its original validation study, it is clear from our data that patients with lung cancer suffer many consequences of their cough (Figure 30)[40].

Cough in lung cancer is rarely an isolated symptom. Our data demonstrate that significant numbers suffer from fatigue, pain, anxiety, distress and frustration (Figure 30). Coughing also has a significant impact on social aspects of living such as interruption of telephone calls or conversations in many patients. Telephone use is very important to patients who are often isolated in their own homes during ill-health and treatment. If conversation is limited, social networks and social support are negatively affected.

Patients with lung cancer often have a short prognosis and a number of lung cancer-related symptoms, often with the well described symptom cluster of

cough, breathlessness and fatigue [13, 34, 261]. It is likely that these symptoms compound each other as demonstrated by Molassiotis et al [1, 262]. It is well recognised that cough has a negative impact on quality of life in a general population [21]. However, there is now increasing evidence to support this finding in the context of lung cancer. The recently published cross-sectional study by Iyer et al. showed that cough independently predicted a worse QoL in a cohort of 450 patients with NSCLC patients with advanced stage disease [11].

Whilst no formal symptom cluster analysis has been undertaken, it is clear that our data show that lung cancer patients frequently live with multiple symptoms. This has implications for the effective treatment of cough. It may be that if other symptoms such as dyspnoea or fatigue are treated, this will significantly reduce the impact of cough and improve lung cancer patients' quality of life.

Since the longitudinal study schedule was more burdensome than the cross-sectional cough prevalence study schedule, it is possible that patients with a worse cough impact score were more motivated to participate in the longitudinal study than patients with milder cough. This may explain the higher MCLCS cough impact scores in the longitudinal study compared to the cross-sectional study.

No lung cancer related publication could be found citing the proportion of lung cancer patients who described their cough as painful or severe enough to warrant treatment. However, several publications describe the consequences of cough that include physical symptoms including pain, psychological symptoms such as anxiety and social implications such as no longer going out to restaurants [1, 33, 263]. Therefore, with lung cancer-related cough severity scores as high as they are, it is not surprising that so many patients with lung cancer should feel that their cough warrants treatment. A significant proportion of patients, with lung cancer pathology that often causes chest pain and rib pain, report a painful cough since the sudden and sometimes forceful nature of a cough is likely to exacerbate this pain. Since cough is an intermittent symptom, it is difficult to predict use of analgesia to provide adequate pain relief in patients who suffer from a painful cough. The approach to such patients may

be to improve their cough rather than to treat the pain relating to the cough specifically.

To date, no study has reported cough severity scores in the lung cancer population using subjective cough-specific assessment tools such as the cough severity VAS, nor indeed the CSD. However, some studies have reported cough severity scores in the lung cancer population, using validated subjective oncology-specific tools. These are described below.

In the previously cited Iyer cross-sectional US and European studies, mean cough severity scores were 48.4 (SD 29.9, n =421) using the LCSS in the US study and 41.4 (SD 30.9, n=837) in the European study – where higher scores indicate a higher burden of symptom. Whilst the LCSS is not the same tool as the cough severity VAS, the LCSS cough item is a 100mm visual analogue scale assessing cough severity. Cross-tool comparisons are inherently flawed, however in the absence of cough severity VAS data, Iyer's cough severity scores appear to be broadly in line with our data. It should be noted however, that since the longitudinal cough study population was selected according to the presence of a cough, one might have expected higher severity scores in the present study. Of note, the FACT-L scores for the cough item were not specifically reported in either publication to enable further comparisons to be made.

The aforementioned study by Tishelman et al. quotes mean subjective cough severity scores of between 31 to 44 using Item 31 of the EORTC QLQ C30+LC13 questionnaire in a population of 400 lung cancer patients assessed at six time points prior to death [9]. These scores are lower than those for our study population which had a mean score of 60.7. Again, this is not surprising since our longitudinal cough study population comprised of patients who reported a cough prior to study entry, unlike the Tishelman study. Despite this difference between the populations, the cough severity scores published by Tishelman et al. demonstrate that a significant proportion of lung cancer patients (25-32%) rate their cough frequency as "quite a bit" or "very much".

In a phase II study by Temel et al. assessing the feasibility of integrating early palliative care in newly diagnosed lung cancer patients, FACT-L scores were published for individual symptoms including cough in 49 patients [48]. This showed that 34% were asymptomatic (scored 4), 54% reported a moderate cough (scored 2-3) and 10% patients had a severe cough (scored 0-1). This spread of responses shows, like the previously described studies, that many patients are affected by a significant cough, even early on in their disease trajectory.

The LCSS cough scores from Iyer's US study were reported for the observer-rated and the patient-rated scales. The observer-rated cough severity scores were less than the patient-rated scores. About 5% patients had their cough rated "marked" and none rated "severe" by observers compared to 45% patients rating their cough as "marked" or "severe". This demonstrates that subjective observer assessments on symptom severity in patients are likely to underestimate the true severity of the symptom, emphasising the importance of patient-reported outcomes rather than physician-reported outcomes.

As shown above, many different subjective cough severity tools have been used in published studies. In the lung cancer setting, these have been oncology-specific rather than cough-specific.

Understanding what constitutes a severe cough is complex and key to this is the appropriate selection of tools to generate robust data. A study in chronic cough patients elegantly demonstrated that cough severity had 3 domains: intensity, disruptiveness and frequency [53]. Therefore no single subjective or objective value is sufficient to fully characterise cough severity. However, the data generated from use of subjective cough severity tools demonstrate that many patients with lung cancer report a severe cough that warrants further treatment and often causes symptoms such as pain. The fact that only 15% patients with a lung cancer-related cough report using over-the-counter

antitussives further highlights the fact that current antitussive therapies are inadequate and often fail to treat this difficult symptom.

4.7 Cough severity and its impact is relatively stable over time despite other clinical interventions and changes in cancer characteristics, demonstrating the need for cough specific antitussive therapies

Although subjective cough severity scores (cough severity VAS, CSD) and the cough impact MCLCS scores showed a small but statistically significant change over time, most patients improved early on in the course of the study (between day 0-30) and then had stable cough severity and impact scores. This is in contrast to cough frequency scores which remained stable over the 60-day period (Figure 17).

Other longitudinal studies assessing cough have shown relatively stable cough severity scores using the FACT-L and Item 31 of the EORTC QLQ C30+LC13 [9, 48]. Although the data are not shown for individual symptom scores, the article by Temel et al. states that there were no significant differences in cough severity scores over time. This is in keeping with the longitudinal study by Tishelman et al. in which the mean Item 31 (EORTC QLQ C30+LC13 questionnaire) scores did not change significantly over time. In both studies, the time interval was far longer than our study schedule (from lung cancer diagnosis to <one month before death: Tishelman and 6 months: Temel).

Since no minimally important difference has yet been established for the cough severity VAS, CSD or MCLCS in the context of lung cancer, it is not possible to know whether the small improvement in cough severity and impact scores shown by our data is *clinically* significant. The discrepancy between the change in subjective cough severity scores and lack of change in the objective cough frequency scores serve to highlight how patient reported outcomes may differ from objective outcome measures and the value of having both types of measure to comprehensively cough.

The improvement in subjective cough severity and impact scores is not likely to be an artefact since it was shown using all subjective cough assessment tools except the blunt CTCAEv4.0 cough scale.

The determinants of change in cough severity and impact remain to be fully elucidated. The population characteristics were fairly stable throughout the study (Table 10) other than the proportion of patients receiving anticancer therapy. However, some clinical factors were associated with a change in cough severity. These included “being on opioids at baseline”, having a “high baseline VAS scores” and “being on over-the-counter antitussives” (Table 23).

For both time periods days 0-30 and days 0-60, the baseline cough severity VAS score was an independent predictor of change in cough severity. This may indicate that patients who were most troubled by their cough sought more help from the treating teams, leading to an improvement in their scores. Being on opioids at baseline (for the time period “baseline to day 30”) at and being on over-the-counter antitussives (for the time period “baseline to day 60”) were both independent predictors of change in cough severity VAS scores. It might be that opioids and over-the-counter antitussives were commenced by the treating team if a cough was reported at trial entry. This may have led to an improvement in cough severity and impact scores.

Although having a high baseline cough severity VAS score and being on opioids and on over-the-counter antitussives is associated with subjective improvements in cough severity VAS scores, objective cough frequency scores in a subset of patients did not appear to change significantly over time. Owing to the small number of patients who underwent 24-hour ambulatory cough monitoring, a multivariate analysis of potential cough frequency predictors was not undertaken. However, whilst these two treatments may have improved the cough severity scores in some patients, it is clear from our results that despite these treatments, the proportion of patients who felt that their cough was severe enough to warrant treatment at baseline and day 60 was similar (64% vs 58% respectively). Despite the fact that VAS scores improved, the cough remained clinically significant.

Therefore, the cough severity scores may reflect other changes. As suggested by Vernon et al., since cough severity relates to frequency, intensity and disruptiveness, these antitussive treatments may have reduced cough intensity or disruptiveness but not impacted on cough frequency [61]. Patients may also have “felt” better on antitussive therapy. This may have led to improved questionnaire scores rather than a true reflection of change in cough severity. Clearly, more effective antitussive therapies are required if a clinically meaningful change in cough severity is to be obtained.

Interestingly, factors that have been shown to be associated with baseline cough severity scores such as gender and asthma failed to be identified as independent predictors of change in cough severity VAS scores. The association between patient gender and cough prevalence is already described in conditions such as chronic cough. It has long been recognised that chronic cough affects women more commonly than men [159]. The reasons for this are not yet known. However, our study suggests that women have a more *severe* cough. This is the first study in lung cancer to show this gender association with cough severity. A study be Kelsall et al. showed that women had an increase in cough sensitivity and a higher cough frequency score compared to men[159]. The reasons for higher cough frequency scores and heightened cough reflex sensitivity are not yet known. These differences do not exist in prepubertal children [264]. Moreover, healthy post-menopausal women have a further enhancement of cough reflex sensitivities compared to pre-menopausal women [265]. It is possible that the hormonal changes act on airway cells or via airway neural pathways. Further research is necessary in lung cancer patients if we are to better understand this association with gender. Asthma is likely to be stable since patients are likely to have been diagnosed and commenced on maintenance treatment for this condition prior to trial entry. Therefore, the association between gender and asthma and cough severity is independent of time.

As previously described, patients with poor PS scores are known to have a higher burden of symptoms and hence it follows that these patients have a

worse cough severity [266, 267]. Our study findings are in keeping with those previously reported. However, performance status score at baseline was not found to be an independent predictor of change in cough severity VAS scores over time.

Performance status was not assessed longitudinally during the study. It may be that our study population changed significantly in terms of this characteristic during the course of our study and that had performance status been measured longitudinally, an association between a change in performance status and a change in cough severity VAS scores would have been identified. It may be that cough severity scores are so “sensitive” to performance status scores and performance status so changeable in this patient group that its baseline value could not predict a change in cough severity.

The relatively high proportion of patients who were post curative treatment (28%) suggests that despite potentially curative anticancer treatments, many patients continue to suffer from a cough. This is in keeping with studies published by Sarna and Cheville et al.[250, 268] demonstrating the persistence of symptoms such as cough up to five years after curative treatment. Treating the cancer is therefore not sufficient to treat the cough in many patients. Cough in this context may therefore relate to co-morbid conditions or other clinical factors. Of note, the median duration of cough prior to study entry in our population was a year, demonstrating that many lung cancer patients live with this troublesome, persistent symptom for prolonged periods of time.

4.8 The NK-1 pathway is a relevant therapeutic target for the treatment of cough in lung cancer which warrants further research

The trial assessing aprepitant is the first to assess the efficacy of a novel antitussive agent using validated subjective and objective cough measures in the lung cancer population. It is the first to investigate the effect of a centrally-acting neurokinin-1 antagonist in humans. In the non-cancer setting, gabapentin has been reported to improve cough-specific quality of life [269]. Slow release morphine and thalidomide have also been shown to exert a modest antitussive effect in patients with chronic cough [270, 271]. However, none of these studies demonstrated an effect on objective 24-hour cough monitoring. Very recently, a P2X3 inhibitor has been shown to lead to marked improvement in cough frequency and cough subjective measures in patients with chronic cough[272]. This was a ground-breaking study since it was the first to have shown an improvement in both types of cough measures since the advent of objective cough monitoring. Therefore our study is of interest even to the wider cough research community since it is the second study ever to show an antitussive effect relating to a novel antitussive, using both objective and subjective validated cough measures and the first to do so in the cancer population. These findings are the first published to support our hypothesis that the neurokinin-1 pathway is implicated in the mechanism of cough in patients with lung cancer.

Data from our longitudinal observational study have demonstrated that gastro-intestinal comorbidities such as nausea and reflux disease are associated with cough severity and the impact of cough. The results of the aprepitant trial are in keeping with these data and in keeping with previously published animal data that showed that interruption of the neurokinin pathways led to antitussive effects in five different animal species [102, 104-107]. The assessment of aprepitant for the treatment of cough in lung cancer has enabled researchers to

further explore the interaction between gastro-intestinal and airway pathophysiology for the treatment of cough in lung cancer and supports the design and development of larger clinical trials to assess neurokinin antagonists for the treatment of cough in a wider population of patients with lung cancer-associated cough.

Aprepitant was developed to treat chemotherapy-induced nausea. It had been known for many years that substance P was concentrated in the emetic centres of the brain[273]. However, it was only in the 1990s that NK1 receptors were identified and substance P antagonists were derived as antiemetics [274]. However, it was also shown that in order for them to exert their antiemetic effect, substance P antagonists needed to cross the blood brain barrier to act upon the NK1 receptors in the brainstem[275]. Hence, centrally penetrant aprepitant became the first NK1 receptor antagonist for use in chemotherapy-induced nausea. During its development, researchers used a novel PET tracer to demonstrate NK1 receptor occupancy at different aprepitant doses [234]. Their target was to achieve >90% NK1 receptor occupancy at the lowest possible dose to maximise therapeutic effect yet minimise potential toxicity and to confirm “on target” engagement (see Figure 38).

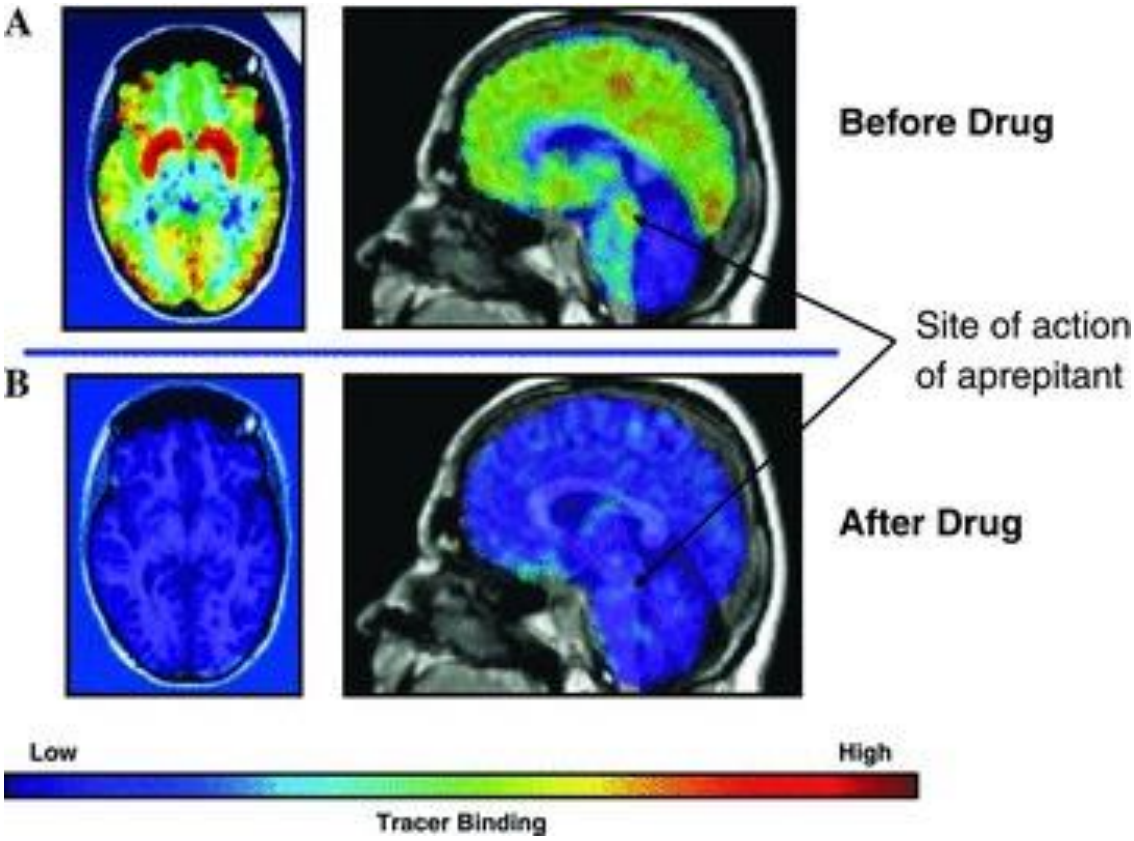


Figure 38 PET-CT scan images of a healthy volunteer showing PET tracer binding to the NK1/substance P complex before and after aprepitant dose [234]

NK1/substance P binding is inhibited centrally by aprepitant, notably in the nTS.

NK1 = neurokinin 1.

In many ways, the nausea and emesis pathophysiological pathways mirror the cough pathways. Like cough, both peripheral and central neural pathways can stimulate the second order neurons in the brainstem, to trigger vomiting. In nausea and vomiting, afferent vagal nerve signals from the gastrointestinal tract synapse in the chemoreceptor trigger zone (CRTZ) [234]. This is situated along the floor of the 4th ventricle in the area postrema outside the blood-brain barrier. These stimuli subsequently reach the nTS and integrate with other emetogenic stimuli from higher brain centres. Therefore, the nTS plays a crucial role in the processing and integration of vomiting, as it does for the cough reflex. Substance P acting at the central NK1 receptors is one of the final common mechanisms in the activation and coordination of the vomiting *and* the cough reflex. For the first time, the aprepitant trial provides researchers with clinical data to support the central role of the NK1-substance P axis in cough. In Figure 39, the potential mechanisms implicated in the NK1-substance P axis within the context of cough and nausea and vomiting in lung cancer are shown.

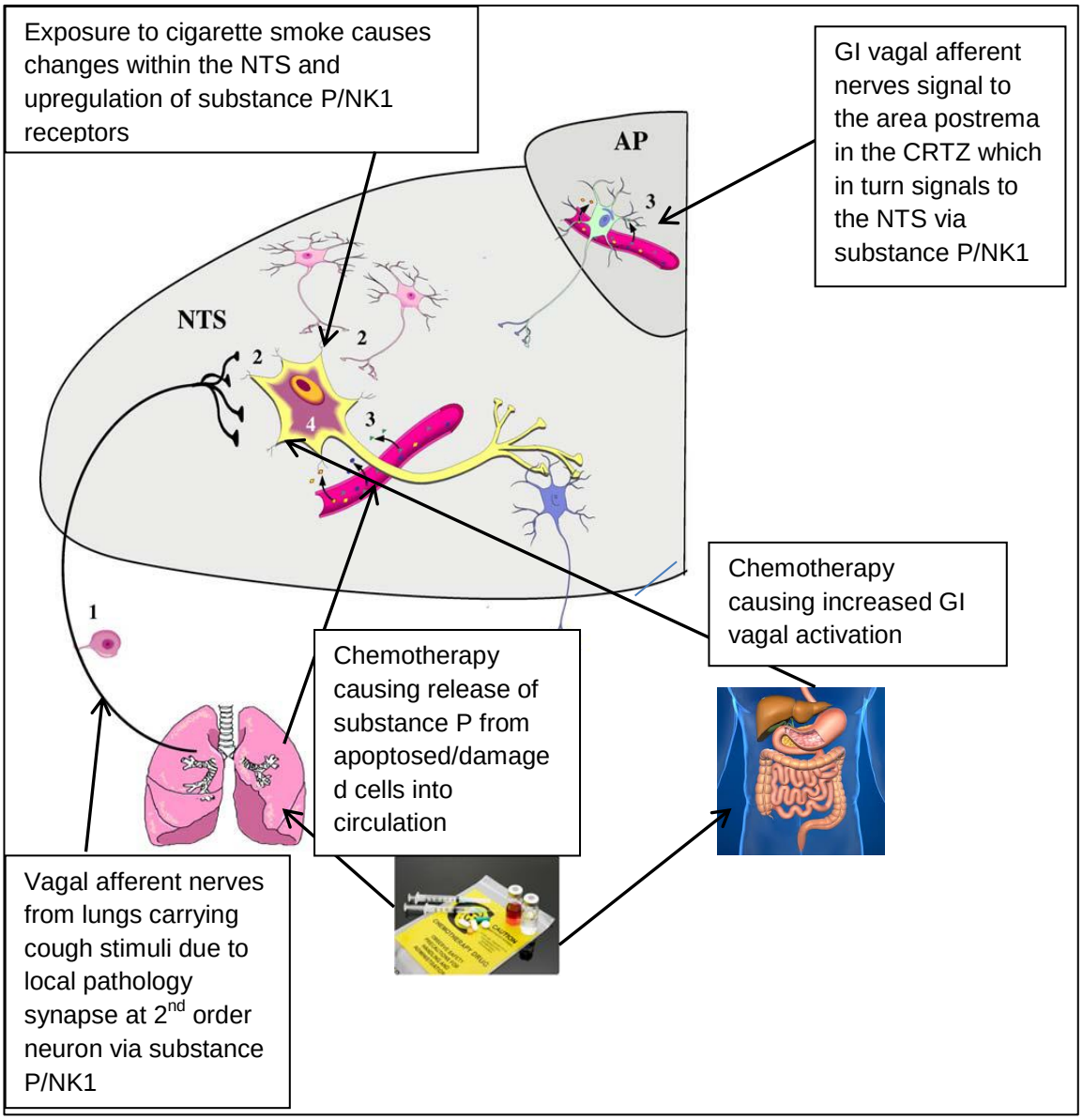


Figure 39 Proposed mechanisms for the central integration of cough in the context of lung cancer showing both gastro-intestinal and respiratory stimuli leading to heightened cough response.

GI= gastrointestinal, NTS=nucleus tractus solitarius, AP=area postrema, NK1=neurokinin-1, CRTZ=chemoreceptor trigger zone.

These results are extremely exciting. Cough is a common symptom that causes significant distress and has a negative impact on the quality of life of patients with lung cancer. The need for an effective antitussive therapy for this population of patients cannot be overstated. Despite the fact that a significant proportion of the patients eligible for our longitudinal study were on oral steroids, opioids and/or over-the-counter (OTC) anti-tussives, their cough persisted. Guidelines such as the American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines for Symptom Management in Patients with Lung Cancer (May 2013) summary of recommendations for the treatment of cough without a treatable cause recommends the use of opioids and summary of recommendations for patients with a troublesome cough attributable to chemotherapy and radiotherapy induced pneumonitis recommends the use of corticosteroids[276]. Medications such as these are commonly prescribed by physicians to treat cough, yet they fail to be effective in many patients.

It is noteworthy that only 15% of patients were on OTC antitussives, treatments specific to cough. Anecdotally, patients explained that they did not use OTC antitussives since they found them to be ineffective. Since OTC antitussives represent a range of different therapies, it is not possible to determine whether the reported lack of clinical benefit relates to the specific agents tried by individual patients or to the entire class of OTC antitussives. Millions of pounds are spent on antitussive medications annually in the UK [277]. It may be that OTC antitussives are bought by patients who suffer from conditions such as respiratory tract infections rather than lung cancer. Since an acute cough relating to a respiratory tract infection is usually self-limiting, it may be that the perceived benefit from antitussive therapy actually reflects the resolution of the infection. When cough persists beyond four to six weeks, it may be that the lack of efficacy becomes apparent to patients. However, it may be that OTC antitussives work better in patients with acute cough than patients with a cough relating to lung cancer.

Interestingly, our trial of aprepitant therapy demonstrated a positive placebo effect. This placebo effect is well described in the published literature on antitussive therapy in the non-cancer setting [278, 279]. It further validates our results and emphasises the importance of demonstrating that any trial treatment is more effective than placebo, even in the context of lung cancer.

The single arm randomised placebo controlled crossover trial enables researchers to limit bias from clinical confounders, to use patients as their own controls and is an appropriate trial design given that cough is stable over time. It is often said that palliative care trials are limited by patient populations that are often highly symptomatic with a short prognosis. The single-arm crossover design enables researchers to accommodate the well-recognised wide interpersonal variation in cough rates, using each patient as their own control. We have demonstrated that our trial design is acceptable to patients with lung cancer. There was very high compliance to the trial schedule and little drop-out.

Our single-centre proof of concept trial did not identify any safety issues with aprepitant. Aprepitant was extremely well tolerated with few adverse events attributable to its use. The doses of 125mg, 80mg and 80mg on days 1-3 were chosen since these doses are licensed for use in chemotherapy-induced nausea. Therefore it was known that at these doses, there was good CNS penetration. The use of aprepitant beyond three days was not felt to be appropriate in the context of this first proof of concept trial. However, now that an effect on cough frequency has been demonstrated, the ideal dose and schedule needs to be further explored. The development of neurokinin antagonists that can be taken over prolonged periods is an important area for future research and is likely to require the involvement and collaboration of the pharmaceutical industry.

The use of both subjective and objective validated cough assessment tools is critical for clinically meaningful robust endpoints to be used. It may be seen from our results that 24-hour ambulatory cough monitoring is acceptable to patients with lung cancer. A longer period of assessment is necessary in order to overcome the fact that cough may vary significantly over time and may also

be influenced by conscious control. By ensuring that patients return to their own environment and activities ensures that the recordings obtained are more likely to reflect the actual cough frequency.

The trial of aprepitant provides data that support further research into the use of neurokinin antagonists as antitussive therapies for use in patients with lung cancer. Since our trial demonstrated that there were “responders” and “non responders”, larger future trials would need to investigate those populations that may benefit most from a neurokinin-1 antagonist. Since our trial population was small, an analysis exploring clinical factors associated with response to aprepitant was not possible. This is likely to need to be a multi-centre study in order to maximise patient recruitment. Clinical factors that may be implicated in the response to neurokinin-1 antagonists might include concurrent gastro-intestinal symptoms and the performance status of patients. It is difficult to predict whether our findings can be applied to a larger lung cancer population and this needs to be determined in a larger trial.

Although the magnitude of the effect of aprepitant was smaller than that reported for P2X3 inhibitors [272], this may reflect the fact that in our proof of concept trial, we only treated patients with aprepitant for three days, unlike the P2X3 inhibitor trial that treated patients for two weeks. It may also reflect the fact that patients with lung cancer are a more heterogeneous group of patients compared to those with chronic cough. Their cough may be explained by multiple mechanisms, of which one is the NK1/substance P pathway. Despite the relatively small effect (~20%) on cough counts, this improvement was reported across all subjective tools by those on trial, demonstrating that this is clinically meaningful in this patient group. It might be that the improvement in subjective measures may be explained by an effect on other symptoms such as nausea, mood and sleep quality [234, 280, 281]. However, in order to confirm this, larger trials exploring these endpoints, alongside cough endpoints would need to be run. The implications of a treatment that may improve these symptoms concomitantly for patients with lung cancer are significant.

The small sample size limits the conclusions about the general applicability of aprepitant for the treatment of cough in patients with lung cancer. This also limits the analysis of predictors of response to therapy. The short duration of treatment with aprepitant may have impacted on the response to treatment. With a longer duration of treatment, we may have shown a greater effect of therapy. We may also have shown that the treatment effect is not sustained, or plateaus with time. It is imperative to develop novel antitussives that are safe and effective over time if we are to improve patient outcomes. The optimal dose of aprepitant has yet to be determined. It may be that for the purposes of its antitussive effects, a different dose may be required to achieve maximal effect. The three-day wash-out period may not have provided the best estimate of treatment effects in patients who received aprepitant first. Although not statistically significant, there was a suggestion that the effect of aprepitant may have been attenuated by the fact that it remained in the circulation by an inadequate wash-out time. We cannot explain with the current data, the higher cough frequency in patients treated with aprepitant first compared to those who received placebo first. This is most likely a chance occurrence.

Currently, the provision in the UK of both pharmacological and non-pharmacological approaches to manage respiratory symptoms in lung cancer remains adhoc and unevenly provided [282, 283]. Treating health care professionals need to be guided by a sound evidence-base in order for their treatment decisions to be consistent and effective for patients. To date, there are no evidence-based, effective antitussive therapies for the treatment of cough in lung cancer patients. This is in part, due to the lack of well-designed clinical trials incorporating validated cough assessment tools and placebo controls [174]. In addition, there is almost no research on the underlying mechanisms of cough in lung cancer, perhaps with the assumption that it is ‘simply due to the cancer’ and little understanding of the likely multifactorial aetiology of cough in patients with lung cancer. Despite more effective anticancer therapies, cough often persists [186] and studies in non-cancer related cough and preclinical models identify various neurophysiological

pathways that may be activated and contributory in patients with lung cancer [102, 105, 284].

In conclusion, we have shown that neurokinin-1 antagonism was associated with an improvement in both objective and subjective measures of cough in our single centre proof-of-concept trial. This suggests that neurokinin-1 receptors may have a key role to play in the mediation of cough in patients with lung cancer. Therefore, neurokinin-1 antagonists are a promising class of drugs that may be used as future antitussives. Further research in this area is urgently required in order to enable health care professionals to maximise the quality of life of patients with lung cancer. We believe that our trial of aprepitant therapy demonstrates to researchers that it is possible to run a robust clinical trial using validated cough assessment tools with clinically meaningful endpoints in a population with lung cancer. It has advanced our knowledge of the potential mechanisms and future treatments for cough in lung cancer.

5. Conclusions

Until the publication of these data, the prevalence, characteristics, potential predictors and treatments of cough in lung cancer were largely unknown. The data presented have provided comprehensive information on cough in lung cancer in order to enable researchers and treating healthcare professionals alike to understand its characteristics and impact on patients and to facilitate robust cough intervention trials to be developed for the benefit of future patients diagnosed with lung cancer.

We have shown that cough is a common symptom in patients suffering from lung cancer. It affects nearly two-thirds of a UK-based outpatient lung cancer population attending lung cancer oncology clinics. It represents a huge unmet clinical need since over two-thirds of patients reporting a cough felt that their cough was severe enough to warrant treatment and over a quarter of patients with a cough described their cough as painful.

In comparison to other patient populations reporting cough severity and frequency, we have shown that the cough severity and frequency in our patients with lung cancer was as severe as those who present to a specialist chronic cough clinic with cough as their primary symptom. This demonstrates that patients with lung cancer suffer from a very severe and frequent cough compared to other patient populations, even compared to patients with COPD.

The impact of cough on patients with lung cancer is considerable. We have shown that patients report a significant negative impact on physical, psychological and social aspects of their lives. It is important that health care professionals recognise this in order to ensure that patients who report a cough are identified as patients who require specialist input in order to manage this difficult symptom. Patients with a diagnosis of lung cancer and their families are under considerable stress. By relieving a patient's cough, vital activities such as using the telephone and socialising with friends and relatives become possible, ensuring that the support network is maintained for patients. Successful antitussive therapy might improve a patient's sleep and as a consequence, their carer's further enhancing their ability to cope under pressure and maximise their quality of life. It is not uncommon for patients to co-report symptoms such as

cough, fatigue and breathlessness. Improving the cough may have a significant impact on the other symptoms too.

Our data support and further validate the use of the newly developed lung cancer specific Manchester Cough in Lung Cancer Scale (MCLCS). Our research shows that this 10-item questionnaire performs well in the lung cancer population compared to other established validated cough questionnaires. It is simple to use and offers researchers with a comprehensive assessment of the physical, social and psychological impact of cough on quality of life. It is the only fully validated lung cancer specific cough assessment tool. Traditional subjective oncology-specific symptom assessment tools such as the Common Terminology Criteria for Adverse Events version4.0 (CTCAE v4.0) perform poorly in comparison to the Manchester Cough in Lung Cancer Scale. The CTCAE v4.0 cough scale is too blunt to assess cough robustly. Therefore as a subjective endpoint for clinical trials assessing cough in clinical trials, the MCLCS should be used.

Our studies have demonstrated that objective cough assessment tools such as 24-hour ambulatory cough monitoring are feasible and acceptable to patients with lung cancer. This is critical since it provides researchers with an objective endpoint for use in clinical trials. It also provides researchers with an opportunity to assess cough over prolonged periods and overcome the difficulties associated with measuring an episodic symptom that can vary significantly over short periods of time.

Since we have demonstrated that there are moderate correlations between both objective and subjective cough assessment tools, we have shown that subjective and objective cough assessment tools are complimentary. Any clinical trial should, where possible, incorporate both types of cough assessment tools in order to provide researchers with a more accurate assessment of the effects of antitussive therapy. This is in keeping with the European Respiratory Society cough assessment guidelines.

Our longitudinal observational study is the first to report that cough severity and impact is predicted by co-morbidities that include nausea and reflux disease rather than cancer related factors such as the stage of the cancer and its histology. Commonly held assumptions about the aetiology of cough in patients with lung cancer have not been borne out by our research. Neither smoking, nor the presence of COPD has been shown to be associated with neither worse cough severity nor cough-related quality of life. This is notable, particularly in light of the demonstrated efficacy of aprepitant for the treatment of cough in lung cancer.

Our proof of concept cough intervention trial is the first to demonstrate that aprepitant is associated with lower subjective cough severity and impact scores and lower cough frequency using validated cough assessment tools. No study has ever shown a positive antitussive effect using both types of cough assessment tools in the lung cancer population. To date, in the non cancer setting, only P2X3 antagonism has been shown to have an antitussive effect using both objective and subjective cough measures. Therefore our results are extremely exciting. They support the hypothesis that there is a shared vagal mechanism between gastro-intestinal symptoms and cough in patients with lung cancer. It provides evidence that the substance P/neurokinin-1 pathway, known to be central to the mediation of nausea and vomiting is also implicated in the mediation of cough in lung cancer. It therefore warrants further research.

Our data provide hope for patients who suffer from cough and health care professionals who try to treat cough relating to lung cancer on a daily basis. It also offers hope for patients suffering from chronic cough in non-malignant disease. The data presented demonstrate that there are clinical factors, neurophysiological pathways and licensed medications that have a significant role to play in our understanding and management of cough in lung cancer and potentially other pathologies. It is hoped that the knowledge of cough researchers has been advanced to enable them to develop novel antitussives for use in patients with lung cancer. The data may be also be of value to patients who suffer from a cough in the non-cancer setting. It is time that

researchers and health care professionals and industry collaborate in order for effective, evidence-based antitussive treatments to be developed for the benefit of our patients.

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7. Appendices

Appendix 1: Manchester Cough in Lung Cancer Scale

This questionnaire asks you to describe your experience of cough in the past week.

Please answer question one and then read the instructions before completing the rest of the questionnaire.

	Never	**Some of the time**	**Often**	**Most of the time**	**All of the time**
1. In the past week how often have you coughed?	1	2	3	4	5

If you answered 'Never' to question 1 please stop completing the questionnaire and return it to us.

If you indicated that you have experienced cough in the past week then please complete the rest of the questionnaire.

For each question please circle one option that best describes your experience **over the past week**.

	Never	Some of the time	Often	Most of the time	All of the time
2. Do you have difficulty breathing when you cough?	1	2	3	4	5
3. Do you have difficulty bringing up sputum (phlegm) when you cough?	1	2	3	4	5
4. Does your cough disturb your sleep?	1	2	3	4	5
5. Does your cough distress you?	1	2	3	4	5
6. Does coughing make you frustrated?	1	2	3	4	5
7. Do you worry that your cough means that your condition is getting worse?	1	2	3	4	5
8. Do you feel in control of your cough?	1	2	3	4	5
9. Does coughing interrupt your conversations or telephone calls?	1	2	3	4	5

In question 10 you should indicate how severe your cough has been in the past week.

	Very mild	Mild	Moderate	Severe	Very severe
10. Please rate how severe you think your cough is	1	2	3	4	5

Appendix 2: Cough Severity Visual Analogue Scale

To be completed by the researcher:

Protocol Identifier:	Patient's initials:	Study day:

Instructions

Please indicate with a vertical line on the scale below your perception of the severity of your cough:

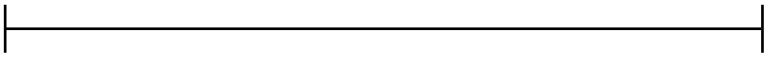
Day time score *(to be completed by the participant)*

Date of completion: / /

Day Month Year

Time of completion: :

(in 24hr format) Hour Minute



No cough **Worst cough**

Appendix 3: EORTC QLQ-C30+LC13 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 4: Common Terminology Criteria for Adverse Events Version 4.0

Cough

Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.

Grade 1	Grade 2	Grade 3	Grade 4
Mild symptoms; non-prescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-

Appendix 5: Brief Reflux Inventory

How often do you experience the following? Please circle the answer.

(1) A feeling of pain, pressure or burning that starts in the stomach and spreads up the front of your chest.

0 = never; 1 = rarely; 2 = once a month to once a week; 3 = at least twice a week; 4 = daily.

(2) A burning sensation deep in the throat.

0 = never; 1 = rarely; 2 = once a month to once a week; 3 = at least twice a week; 4 = daily.

3) A bitter, salty or sour taste in the mouth.

0 = never; 1 = rarely; 2 = once a month to once a week; 3 = at least twice a week; 4 = daily.

(4) A feeling that something you ate a while ago is coming back up.

0 = never; 1 = rarely; 2 = once a month to once a week; 3 = at least twice a week; 4 = daily.

(5) Are you ever woken up at night by a feeling of heartburn, coughing or choking?
Response scales:

0 = never; 1 = rarely; 2 = once a month to once a week; 3 = at least twice a week; 4 = daily.

Appendix 6: Common Severity Diary

Cough Diary

Please answer these questions **every night just before going to sleep**.

Circle the number that best describes your experiences with your cough **today**.

When answering these questions, note the ***descriptive words*** above each end of the "0 to 10" scale.

1. How **often** did you cough today?

Never — *Constantly*

0 1 2 3 4 5 6 7 8 9 10

2. How often did your cough turn into a coughing **fit or episode** today?

Never — *Always*

0 1 2 3 4 5 6 7 8 9 10

3. How often did you have the **urge to cough** today?

Never — *Constantly*

0 1 2 3 4 5 6 7 8 9 10

4. How **harsh** was your cough today?

Not at all — *Extremely*

0 1 2 3 4 5 6 7 8 9 10

5. How much **physical discomfort** did you have because of your cough today?

None — *Extreme*

0 1 2 3 4 5 6 7 8 9 10

Please CONTINUE to the next page.

6. How much did your cough **disrupt your activities** today?

Not at all — *Could not perform activities*

0 1 2 3 4 5 6 7 8 9 10

Now consider your sleep **last night**:

7. How much did your cough **disrupt your sleep** last night?

Not at all — *Could not sleep at all*

0 1 2 3 4 5 6 7 8 9 10

Please STOP HERE for today.

Appendix 7: EORTC Quality of Life Lung Cancer Population Scores

Lung cancer: all stages

Characteristics of the sample

Version of the QLQ-C30

	N	(%)
v 1.0	1,125	*34*
v +3	38	*1*
v 2.0	836	*25*
v 3.0	1,333	*40*
Total	3,332	

Primary disease site

	N	(%)
Lung: small cell	658	*20*
Lung: non-small cell	1,262	*38*
Mesothelioma	236	*7*
Lung: not known	1,176	*35*
Total	3,332	

Age

	N	(%)
<40	85	*3*
40-49	416	*13*
50-59	971	*29*
60-69	1,108	*33*
70-79	596	*18*
80+	60	*2*
Not known	96	*3*
Total	3,332	

Gender

	N	(%)
Male	1,925	*58*
Female	830	*25*
Not known	577	*17*
Total	3,332	

Stage

	N	(%)
Stage I-II	538	*16*
Stage III-IV	1,313	*39*
Recurrent/metastatic	307	*9*
Not known	1,174	*35*
Total	3,332	

Constructed scales

		Mean	*(SD)*	Median	*[IQR]*
Global health status/QoL	QL	56.6	*(24.3)*	58.3	*[41.7-75]*
Physical functioning	PF	71.9	*(22.9)*	80	*[60-86.7]*
Role Functioning	RF	61.5	*(33.9)*	66.7	*[33.3-100]*
Emotional functioning	EF	68.9	*(24.4)*	75	*[50-91.7]*
Cognitive functioning	CF	82.3	*(22)*	83.3	*[66.7-100]*
Social functioning	SF	71.3	*(29.4)*	83.3	*[50-100]*
Fatigue	FA	41.1	*(27.2)*	33.3	*[22.2-55.6]*
Nausea and vomiting	NV	10.8	*(19.7)*	0	*[0-16.7]*
Pain	PA	29.7	*(30.7)*	16.7	*[0-50]*
Dyspnoea	DY	37.9	*(32.2)*	33.3	*[0-66.7]*
Insomnia	SL	31.6	*(32.6)*	33.3	*[0-66.7]*
Appetite loss	AP	28.1	*(33.5)*	0	*[0-66.7]*
Constipation	CO	19.2	*(29.7)*	0	*[0-33.3]*
Diarrhoea	DI	7.4	*(17.9)*	0	*[0-0]*
Financial difficulties	FI	17.4	*(28.9)*	0	*[0-33.3]*

Lung cancer: all stages
Constructed scales

QL	N	(%)
0	80	*4*
8.3	31	*1*
16.7	95	*4*
25	59	*3*
33.3	221	*10*
41.7	121	*6*
50	412	*19*
58.3	185	*9*
66.7	371	*17*
75	147	*7*
83.3	264	*12*
91.7	79	*4*
100	110	*5*
Total	2,175	

PF	N	(%)
0	5	*0*
6.7	12	*1*
13.3	12	*1*
20	26	*2*
26.7	44	*3*
33.3	27	*2*
40	40	*3*
46.7	47	*4*
53.3	83	*6*
60	99	*8*
66.7	125	*10*
73.3	128	*10*
80	150	*12*
86.7	197	*15*
93.3	157	*12*
100	156	*12*
Total	1,308	

RF	N	(%)
0	249	*12*
16.7	111	*5*
33.3	302	*14*
50	207	*10*
66.7	417	*19*
83.3	255	*12*
100	609	*28*
Total	2,150	

EF	N	(%)
0	35	*1*
8.3	38	*1*
16.7	72	*2*
25	93	*3*
33.3	158	*5*
41.7	173	*5*
50	272	*8*

CF	N	(%)
0	32	*1*
16.7	50	*2*
33.3	136	*4*
50	229	*7*
66.7	496	*15*
83.3	822	*25*
100	1,517	*46*
Total	3,282	

SF	N	(%)
0	154	*5*
16.7	117	*4*
33.3	312	*10*
50	354	*11*
66.7	650	*20*
83.3	475	*15*
100	1,188	*37*
Total	3,250	

FA	N	(%)
0	358	*11*
11.1	270	*8*
22.2	437	*13*
33.3	692	*21*
44.4	390	*12*
55.6	344	*11*
66.7	314	*10*
77.8	157	*5*
88.9	141	*4*
100	161	*5*
Total	3,264	

NV	N	(%)
0	2,227	*68*
16.7	491	*15*
33.3	315	*10*
50	118	*4*
66.7	76	*2*
83.3	23	*1*
100	38	*1*
Total	3,288	

PA	N	(%)
0	1,171	*36*

Lung cancer: all stages
Single Items

		Not at all		A little		Quite a bit		Very much		Total
		N	(%)	N	(%)	N	(%)	N	(%)	N
1) Strenuous activities	**PF**	257	*20*	498	*38*	346	*26*	219	*17*	1,320
2) Long walk	**PF**	341	*26*	435	*33*	342	*26*	208	*16*	1,326
3) Short walk	**PF**	818	*62*	340	*26*	124	*9*	46	*4*	1,328
4) Bed or chair	**PF**	654	*49*	395	*30*	201	*15*	80	*6*	1,330
5) Self care	**PF**	1,174	*88*	103	*8*	39	*3*	15	*1*	1,331
6) Limited in work	**RF**	716	*33*	613	*28*	490	*23*	355	*16*	2,174
7) Limited in leisure	**RF**	850	*39*	584	*27*	403	*19*	327	*15*	2,164
8) Dyspnoea	**DY**	972	*30*	1,264	*38*	692	*21*	368	*11*	3,296
9) Pain	**PA**	1,311	*40*	1,079	*33*	605	*18*	308	*9*	3,303
10) Need to rest	**FA**	651	*20*	1,408	*43*	852	*26*	389	*12*	3,300
11) Insomnia	**SL**	1,370	*42*	1,019	*31*	611	*19*	292	*9*	3,292
12) Felt weak	**FA**	938	*28*	1,229	*37*	769	*23*	366	*11*	3,302
13) Appetite loss	**AP**	1,663	*50*	811	*25*	519	*16*	311	*9*	3,304
14) Nausea	**NV**	2,307	*70*	659	*20*	245	*7*	96	*3*	3,307
15) Vomiting	**NV**	2,789	*85*	373	*11*	92	*3*	48	*2*	3,302
16) Constipation	**CO**	2,105	*64*	671	*20*	324	*10*	193	*6*	3,293
17) Diarrhoea	**DI**	2,719	*83*	436	*13*	104	*3*	29	*1*	3,288
18) Felt tired	**FA**	684	*21*	1,489	*45*	801	*24*	325	*10*	3,299
19) Pain interference	**PA**	1,706	*52*	800	*24*	487	*15*	294	*9*	3,287
20) Concentration	**CF**	2,097	*63*	740	*22*	343	*10*	125	*4*	3,305
21) Tension	**EF**	1,168	*35*	1,324	*40*	585	*18*	223	*7*	3,300
22) Worry	**EF**	908	*28*	1,220	*37*	775	*24*	388	*12*	3,291
23) Irritability	**EF**	1,603	*49*	1,143	*35*	415	*13*	117	*4*	3,278
24) Depression	**EF**	1,315	*40*	1,265	*39*	484	*15*	214	*7*	3,278
25) Memory trouble	**CF**	2,003	*61*	949	*29*	263	*8*	76	*2*	3,291
26) Family life	**SF**	1,734	*53*	856	*26*	458	*14*	226	*7*	3,274
27) Social activities	**SF**	1,394	*43*	923	*28*	601	*18*	357	*11*	3,275
28) Financial difficulties	**FI**	2,217	*68*	579	*18*	309	*9*	171	*5*	3,276

		1 (very poor)	2	3	4	5	6	7 (excellent)	Total
29) Overall health	**QL**	115	138	318	573	538	370	130	2,182
		5	*6*	*15*	*26*	*25*	*17*	*6*	
30) Overall quality of life	**QL**	164	217	473	761	767	579	317	3,278
		5	*7*	*14*	*23*	*23*	*18*	*10*	

Appendix 8: Clinical Expert Guidelines for the Management of Cough in Lung Cancer

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REVIEW Open Access

Clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough

Alex Molassiotis[1*], Jaclyn A Smith[2], Mike I Bennett[3], Fiona Blackhall[4], David Taylor[5], Burhan Zavery[6], Amelie Harle[4], Richard Booton[7], Elaine M Rankin[8], Mari Lloyd-Williams[9], Alyn H Morice[10]

Abstract

Background: Cough is a common and distressing symptom in lung cancer patients. The clinical management of cough in lung cancer patients is suboptimal with limited high quality research evidence available. The aim of the present paper is to present a clinical guideline developed in the UK through scrutiny of the literature and expert opinion, in order to aid decision making in clinicians and highlight good practice.

Methods: Two systematic reviews, one focusing on the management of cough in respiratory illness and one Cochrane review specifically on cancer, were conducted. Also, data from reviews, phase II trials and case studies were synthesized. A panel of experts in the field was also convened in an expert consensus meeting to make sense of the data and make clinical propositions.

Results: A pyramid of cough management was developed, starting with the treatment of reversible causes of cough/specific pathology. Initial cough management should focus on peripherally acting and intermittent treatment; more resistant symptoms require the addition of (or replacement by) centrally acting and continuous treatment. The pyramid for the symptomatic management starts from the simpler and most practical regimens (demulcents, simple linctus) to weak opioids to morphine and methadone before considering less well-researched and experimental approaches.

Conclusion: The clinical guidelines presented aim to provide a sensible clinical approach to the management of cough in lung cancer. High quality research in this field is urgently required to provide more evidence-based recommendations.

1. Introduction

Cough is a common symptom in about 23-37% of general cancer patients and 47-86% of lung cancer patients [1]. The first author's data on 100 cancer patients assessed using the Memorial Symptom Assessment Scale from the beginning of cancer treatment to 3, 6 and 12 months showed a prevalence of 42.9%, 39.2%, 35.1% and 36.1% respectively, similarly to the experience of breathlessness, although less distressing than breathlessness [2]; these numbers almost doubled in the lung cancer subgroup analysis. Despite such high prevalence, the management of cough remains suboptimal, with little high quality evidence to guide practice. Much of the current practice on the symptomatic management of cough in lung cancer is experiential and primarily is geared around the use of oral opioids. Current guidelines on the management of cough are often broad and non-specific (suggesting difficulty in making any specific recommendations) and either focus on non-cancer respiratory illnesses with different pathophysiology from cancer-related cough, or provide broad reviews of generally poor quality studies [3-7]. Professional societies that have developed guidelines (non-cancer) include the American College of Chest Physicians (ACCP) [3,8], the European Respiratory Society (ERS) [9] and the British Thoracic Society (BTS) [7].

* Correspondence: alex.molassiotis@manchester.ac.uk
[1]School of Nursing, University of Manchester, UK
Full list of author information is available at the end of the article

Appendix 9:Global rating of change scale

Overall, has there been any change in your <u>cough frequency</u> since you started the new medicine? Please indicate if there has been any change in your symptoms by choosing one of the following options. Are your symptoms:

☐ Worse ☐ About the same ☐ Better

[Patients who state they are better are then asked:]

How much better are your symptoms? Are they:

1. Almost the same, hardly any better at all
2. A little better
3. Somewhat better
4. Moderately better
5. A good deal better
6. A great deal better
7. A very great deal better

[Patients who state they are worse are then asked:]

How much worse are your symptoms? Are they:

8. Almost the same, hardly any worse at all
9. A little worse
10. Somewhat worse
11. Moderately worse
12. A good deal worse
13. A great deal worse
14. A very great deal worse

Overall, has there been any change in your <u>cough severity</u> since you started the new medicine? Please indicate if there has been any change in your symptoms by choosing one of the following options. Are your symptoms:

☐ Worse ☐ About the same ☐ Better

[Patients who state they are better/worse are asked to clarify as above:]