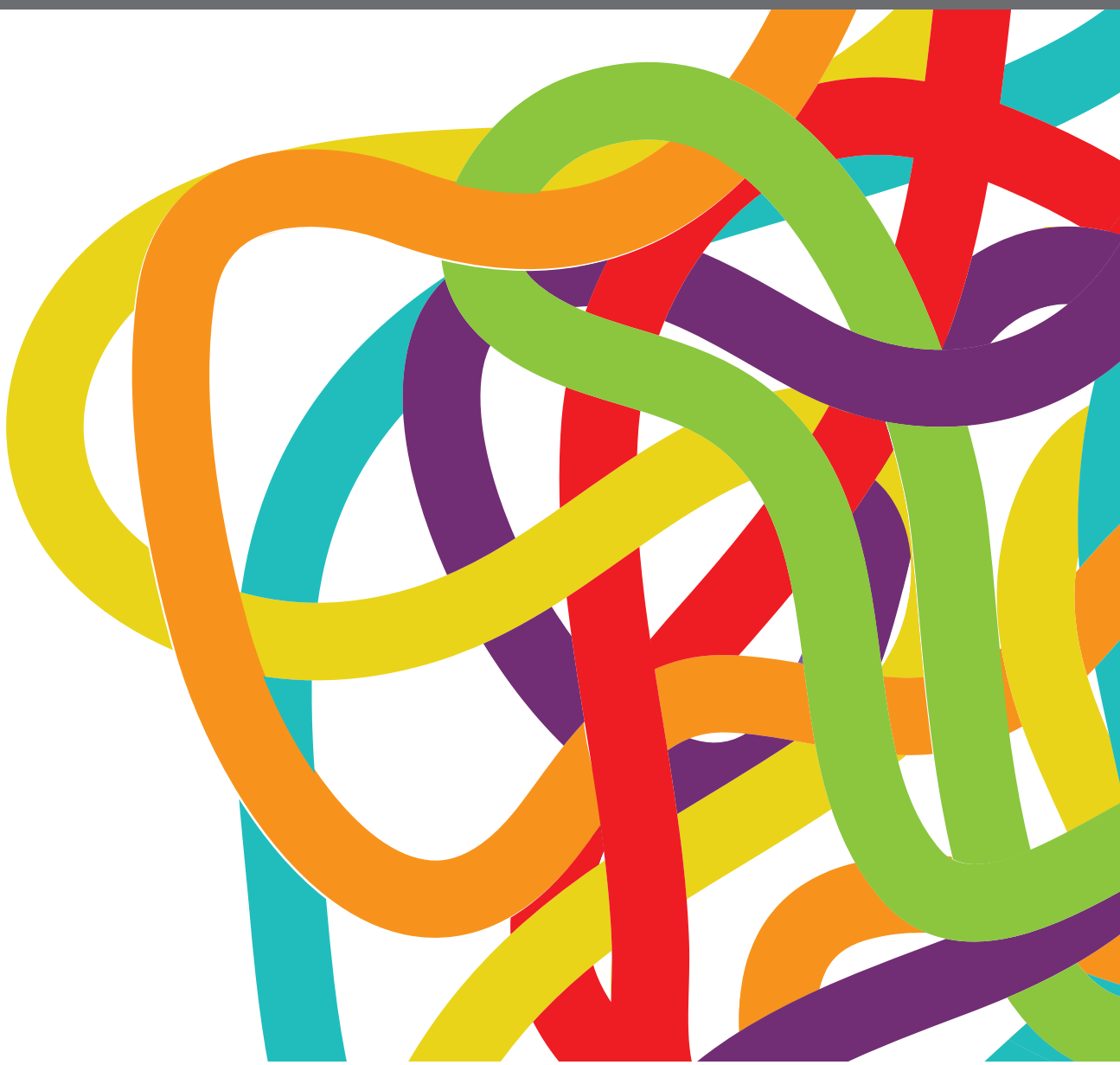
QUALITY OF LIFE AND SIDE EFFECTS MANAGEMENT IN LUNG CANCER TREATMENT

EDITED BY: Alex Molassiotis, Patsy Yates and Janelle Yorke
PUBLISHED IN: Frontiers in Oncology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88966-686-7
DOI 10.3389/978-2-88966-686-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

QUALITY OF LIFE AND SIDE EFFECTS MANAGEMENT IN LUNG CANCER TREATMENT

Topic Editors:
Alex Molassiotis, Hong Kong Polytechnic University, Hong Kong
Patsy Yates, Queensland University of Technology, Australia
Janelle Yorke, The University of Manchester, United Kingdom

Citation: Molassiotis, A., Yates, P., Yorke, J., eds. (2021). Quality of Life and Side Effects Management in Lung Cancer Treatment. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-686-7

Table of Contents

frontiers in Oncology

EDITORIAL
published: 05 March 2021
doi: 10.3389/fonc.2021.651797

Editorial: Quality of Life and Side Effects Management in Lung Cancer Treatment

Alex Molassiotis[1]*, *Patsy Yates*[2] and *Janelle Yorke*[3]

[1] School of Nursing, The Hong Kong Polytechnic University, Kowloon, Hong Kong, [2] Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia, [3] The Christie National Health Service (NHS) Foundation Trust, University of Manchester, Manchester, United Kingdom

Keywords: dyspnea, symptom management, quality of life, symptom cluster, research priorities, lung cancer—diagnosis

Editorial on the Research Topic

Quality of Life and Side Effects Management in Lung Cancer Treatment

Despite significant advances in the treatment of lung cancer, particularly with the evolution of immunotherapies and targeted therapies, the symptom burden is still significant and impact on quality of life for these patients. One-third of lung cancer patients experienced moderate-to-severe symptoms in one study before initial treatment (1), with significantly higher incidence after treatment and as disease progresses (2). The symptom burden in lung cancer patients is, for many symptoms, higher than in other cancer diagnostic groups, as shown in an observational study of more than 120,000 cancer patients (2). Most frequent symptoms include fatigue, pain, psychological distress, breathlessness and cough, while histology and cancer stage differentially affect those symptoms, further affecting multiple domains of quality of life (1, 2). In advanced-stage lung cancer patients, high symptom burden has been significantly associated with overall survival, progression free survival, and objective response rate (3).

It is clear that managing symptoms related to lung cancer and its treatments can positively impact on both quality and quantity of life. Hence, in this Research Topic, we have put together six articles that deal with supportive care topics in the lung cancer population. Half of them focus on breathlessness. Sardaro et al. assessed 80 patients in a prospective study after radiation therapy over a period of 6 months. Their focus was on radiation-induced lung injury (an under-researched topic) and used dyspnea as symptomatic endpoint for lung injury. Parameters of lung volume-dose were strongly correlated with dyspnea, with an increase of 10%. The authors recommended regular assessment of dyspnea to identify early radiation-induced toxicity in the lungs.

The other two studies on breathlessness were randomized trials of non-pharmacological interventions. In a multicenter trial of 144 patients, Yates et al. showed that breathing exercises alongside psychosocial support over 8 weeks was significantly improved in the intervention group in relation to average breathlessness, control over breathlessness and anxiety scores. All these outcomes, however, were secondary outcomes. The primary outcome of "worst" dyspnea, and secondary outcomes for distress from breathlessness, functional status, and depression, did not show an improvement in the intervention group over the control group. This study adds to the limited pool of effective interventions we have to manage breathlessness, and to the consistent literature that breathing retraining and exercises with or without other intervention components can improve this symptom experience. The second trial by Choratas et al. was a small-size feasibility trial of 24 lung cancer patients and 24 of their informal caregivers. The intervention was educational in nature, focusing on teaching patients on aspects of breathlessness and introducing through video

OPEN ACCESS

Edited and reviewed by:
Vamsi Velcheti,
New York University, United States

***Correspondence:**
Alex Molassiotis
alex.molasiotis@polyu.edu.hk

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *11 January 2021*
Accepted: *12 February 2021*
Published: *05 March 2021*

Citation:
Molassiotis A, Yates P and Yorke J (2021) Editorial: Quality of Life and Side Effects Management in Lung Cancer Treatment. Front. Oncol. 11:651797. doi: 10.3389/fonc.2021.651797

clips three interventions, including diaphragmatic breathing, inspiratory muscle training, and the use of a handheld fan. The trial showed that the design of this educational intervention is feasible and suggested improvements in both breathlessness levels and anxiety. However, despite showing some potential effects, a large-scale fully-powered trial is necessary to clarify the effectiveness of this intervention.

The study by Li et al. investigated the experience of symptoms in lung cancer patients receiving chemotherapy in a longitudinal design from before treatment to cycle one to cycle three and above, using latent profile analysis. Two symptom profiles were identified, including those patients with a "Mild" symptom profile and those with "Moderate-severe" one. During the time of assessment, about 41% of those in the mild group moved to have moderate-severe symptoms, whereas only 2% of the latter group moved to the mild symptom group. Eight symptom transition patterns were observed. This study highlights the changing nature of the symptom experience in this group of patients that needs to be considered in the development of interventions to manage the symptom experience.

Another study by Zhang et al. used data from 545 patients to develop a survival prognostic model. The best fit for the model (area under the curve = 0.73) included the following variables: age >/=65, TNM stage, lung lobectomy, chemotherapy type and pretreatment hemoglobin levels. The lack of a validation cohort in this study and its retrospective nature are major limitations but if this model is confirmed in future studies it can provide an easily-calculated prediction of survival in non-small cell lung cancer patients.

Some of our observations during the time we edited this Research Topic were about the poor quality of the submitted studies, limited interest in the topic and the narrow focus of studies. The final article of the Research Topic by Molassiotis et al. highlights research priorities in the field from the perspective of nurses and allied health professionals through an international online survey. The development of interventions, particularly around symptom management, were among the most frequently reported priorities, alongside interventions to improve quality of life and healthcare system issues (such as continuity of care or access to care). The list of priorities may be used by funders to stimulate specific research were there are gaps in the evidence and allow for urgently-needed evidence to be developed and subsequently used to improve the care of patients with lung cancer.

There is a need for more and better quality studies in the field of quality of life and symptom management in lung cancer. While lung cancer patients will live longer with the recent advances in treatments, the majority will still die from the disease, making quality of life, palliative care and end of life care significant priorities, requiring proactive assessment and management of symptoms, and a multidisciplinary care approach.

AUTHOR CONTRIBUTIONS

AM compiled the first draft. PY and JY commented on the draft and had intellectual input. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Mendoza TR, Kehl KL, Bamidele O, Williams LA, Shi Q, Cleeland CS, et al. Assessment of baseline symptom burden in treatment-naïve patients with lung cancer: an observational study. *Support Care Cancer.* (2019) 27:3439–47. doi: 10.1007/s00520-018-4632-0
2. Bubis LD, Davis L, Mahar A, Barbera L, Li Q, Moody L, et al. Symptom burden in the first year after cancer diagnosis: an analysis of patient-reported outcomes. *J Clin Oncol.* (2018) 36:1103–11. doi: 10.1200/JCO.2017.76.0876
3. Pérol M, Winfree KB, Cuyun Carter G, Lin Cui Z, Bowman L, Garon EB. Association of baseline symptom burden with efficacy outcomes: exploratory analysis from the randomized phase III REVEL study in advanced non-small-cell lung cancer. *Lung Cancer.* (2019) 131:6–13. doi: 10.1016/j.lungcan.2019.03.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 20 March 2020
doi: 10.3389/fonc.2020.00362

Development of a Survival Prognostic Model for Non-small Cell Lung Cancer

Yue-Hua Zhang[1,2†], *Yuquan Lu*[3*†], *Hong Lu*[2*] *and Yue-Min Zhou*[3]

[1] Department of Oncology, The First Affiliated Hospital of Henan University, Kaifeng, China, [2] Department of Oncology, Huaihe Hospital of Henan University, Kaifeng, China, [3] International Joint Research Laboratory for Cell Medical Engineering of Henan, Huaihe Hospital of Henan University, Kaifeng, China

Lung cancer is a leading cause of cancer-related death, and >80% of lung cancer diagnoses are non-small-cell lung cancer (NSCLC). However, when using current staging and prognostic indices, the prognosis can vary significantly. In the present study, we calculated a prognostic index for predicting overall survival (OS) in NSCLC patients. The data of 545 NSCLC patients were retrospectively reviewed. Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate the prognostic value of clinicopathological factors. Age (hazard ratio [HR] = 1.25, 95% confidence interval [CI] = 1.02–1.54), TNM stage (III, HR = 1.64, 95% CI = 1.08–2.48; IV, HR = 2.33, 95% CI = 1.48–3.69), lung lobectomy (HR = 1.96, 95% CI = 1.45–2.66), chemotherapy (HR = 1.42, 95% CI = 1.15–1.74), and pretreatment hemoglobin level (HR = 1.61, 95% CI = 1.28–2.02) were independent prognosticators. A prognostic index for NSCLC (PInscl, 0–6 points) was calculated based on age (≥65 years, 1 point), tumor-node-metastasis (TNM) stage (III, 1 point; IV, 2 points), lung lobectomy (no, 1 point), chemotherapy (no, 1 point), and pretreatment hemoglobin level (low, 1 point). In comparison with the "PInscl = 0" subgroup (survival time = 2.71 ± 1.86 years), the "PInscl = 2" subgroup (survival time = 1.86 ± 1.24 years), "PInscl = 3" subgroup (survival time = 1.45 ± 1.07 years), "PInscl = 4" subgroup (survival time = 1.17 ± 1.06 years), "PInscl = 5" subgroup (survival time = 0.81 ± 0.78 years), and "PInscl = 6" subgroup (survival time = 0.65 ± 0.56 years) exhibited significantly shorter survival times. Kaplan-Meier survival analysis showed that patients with higher PInscl scores had poorer OS than those with lower scores (log-rank test: $\chi^2 = 155.82$, $P < 0.0001$). The area under the curve of PInscl for predicting the 1-year OS was 0.73 (95 % CI = 0.69–0.77, $P < 0.001$), and the PInscl had a better diagnostic performance than the Karnofsky performance status or TNM stage ($P < 0.01$). In conclusion, the PInscl, which is calculated from age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin level, significantly predicted OS in NSCLC patients.

Keywords: prognostic model, non-small cell lung cancer, overall survival, hemoglobin, TNM

OPEN ACCESS

Edited by:
Stephen V. Liu, Georgetown University Medical Center, United States

Reviewed by:
Jai Narendra Patel, Levine Cancer Institute, United States
Alex Molassiotis, Hong Kong Polytechnic University, Hong Kong

***Correspondence:**
Yuquan Lu
lll3923@gmail.com
Hong Lu
hhyyluhong@126.com

†These authors share first authorship

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *01 August 2019*
Accepted: *02 March 2020*
Published: *20 March 2020*

Citation:
Zhang Y-H, Lu Y, Lu H and Zhou Y-M (2020) Development of a Survival Prognostic Model for Non-small Cell Lung Cancer. Front. Oncol. 10:362. doi: 10.3389/fonc.2020.00362

INTRODUCTION

Lung cancer is a leading cause of cancer-related death in both men and women (1), and >80% of lung cancer diagnoses are non-small cell lung cancer (NSCLC) (2). To date, the prognosis of NSCLC is mainly based on the tumor-node-metastasis (TNM) staging system (2), histology (2), and predictive biomarker analyses, such as epidermal growth factor (EGFR) mutation (3), anaplastic lymphoma kinase (ALK) translocations (4), c-ros oncogene 1 (*ROS1*) rearrangement (5), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutation (6). However, the prognosis varies significantly even among patients with the same TNM stage, histomorphological characteristics, and mutation status.

A systematic review (7) of 887 articles and our previous study (8) revealed that there are 169 different clinical and laboratory parameters (including pretreatment hemoglobin and carcinoembryonic antigen levels, performance status, sex, weight, metastases, etc.) and molecular prognostic factors that affect survival in NSCLC patients. However, these clinical and laboratory parameters are inconsistent and not commonly used in clinical practice or trial design. Further, assessing molecular prognostic factors such as EGFR, ALK, *ROS1*, *BRAF*, and p53 mutation are not only time-consuming but also expensive. Therefore, a practical prognostic model for predicting overall survival (OS) in NSCLC patients is needed. Many prognostic models incorporating various parameters have been reported. These models include the Glasgow prognostic score (GPS) (9), modified GPS (9), laboratory prognostic index (10), and advanced lung cancer inflammation index (11), all of which use serum parameters assessed in routine laboratory tests, but not clinical parameters. Further, Blanchon et al. assessed the prognostic ability of multiple variables, including age, sex, performance status, histological type, and TNM stage, and developed a validated prognostic index (12) in which performance status and TNM stage played major roles.

In the present study, we retrospectively reviewed data from 545 NSCLC patients and calculated a prognostic index (PInscl) for predicting OS in NSCLC patients based on age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin levels. The prognostic value of the PInscl was evaluated with receiver operating characteristic (ROC) curve analysis and

Abbreviations: NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; BRAF, v-raf murine sarcoma viral oncogene homolog B1; OS, overall survival; GPS, Glasgow prognostic score; ROC, receiver operative characteristic; KPS, Karnofsky performance status; LPHb, low pretreatment hemoglobin; NPHb, high pretreatment hemoglobin; HR, hazard ratio; CI, confidence interval; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; IASLC, International Association for the Study of Lung Cancer.

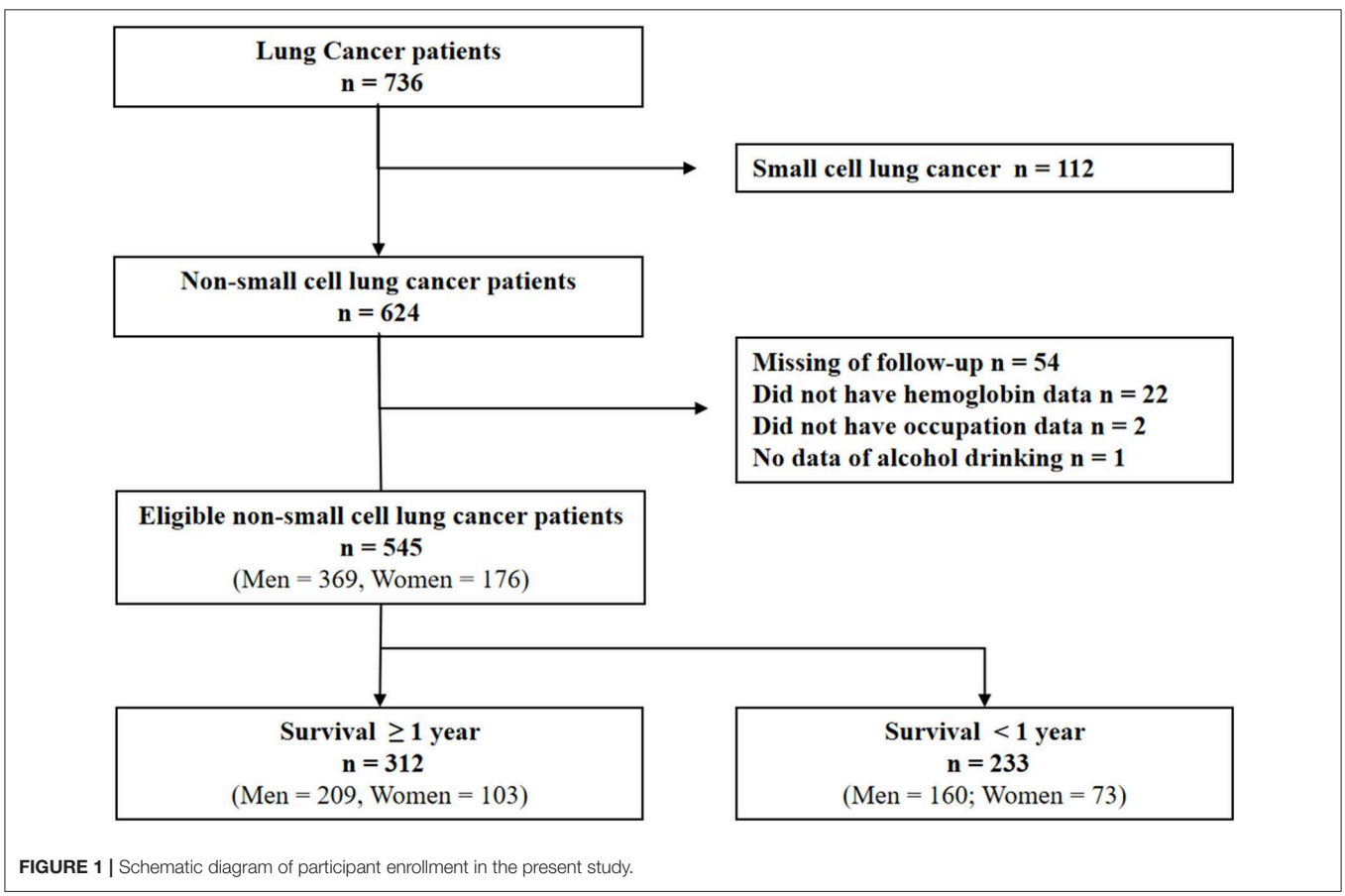


FIGURE 1 | Schematic diagram of participant enrollment in the present study.

compared with those of the Karnofsky performance status (KPS) and TNM stage.

MATERIALS AND METHODS

Patients

All case records of patients with lung cancer admitted to the Huaihe Hospital of Henan University (Henan, China) from May 1, 2010 to June 30, 2017 were analyzed. The inclusion criteria were: (1) NSCLC newly diagnosed at the Huaihe Hospital; (2) histologically or cytologically confirmed NSCLC; and (3) staged according to the TNM staging system (13). Exclusion criteria were: (1) small cell lung cancer; (2) insufficient clinical data; (3) insufficient laboratory data; (4) clinical evidence of active infection or inflammation; (5) hematological disease; (6) pulmonary embolism, acute myocardial infarction, or cerebrovascular accident within 1 month diagnosis. After excluding 191 ineligible patients, 545 patients with NSCLC were selected for the present study (**Figure 1**). This study was carried out in accordance with the recommendations of the Medical Ethics Committee of Huaihe Hospital, Henan University. The protocol was approved by the Medical Ethics Committee of Huaihe Hospital. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Data were retrospectively collected from the patients' case records, including demographic information (age, sex, cigarette smoking, alcohol consumption, and family history of cancer), date of diagnosis and death (obtained from the patients' medical records, local death registration departments, and telephone follow-ups), cancer stage at the time of diagnosis (according to the 8th Edition of the TNM Classification for Lung Cancer) (13), KPS score (≥80 indicated that the patient was able to live and work with mild symptoms or signs and <80 indicated that the patient was unable to live and work normally) (14), therapeutic method (obtained from the patients' medical records), and pretreatment hemoglobin levels [<120 g/L was defined as low pretreatment hemoglobin (LPHb) in men and <110 g/L was defined as LPHb in women according to the normal reference range of hemoglobin in the Chinese population].

Follow-Up

Patients with NSCLC were followed from the date of diagnosis to the date of death or June 25, 2017, whichever came first. OS for each patient was defined as the number of days from the date of diagnosis to the date of death or final follow-up. Person-years were calculated for each subject. Treatments were initiated upon diagnosis and the treatment methods were not exclusive; a patient may have undergone lobectomy, chemotherapy, and radiation simultaneously.

Statistical Analysis

For univariate and multivariate Cox proportional hazards regression analysis, age (<65 vs. ≥65), sex, TNM stage (I-II vs. III-IV), KPS score (≥80 vs. <80), lung lobectomy status, chemotherapy, radiotherapy, smoking status, alcohol consumption, family history of cancer, and pretreatment hemoglobin levels (normal pretreatment hemoglobin (NPHb) vs. LPHb were categorized into the reference group and the observed group, with hazard ratios (HR) and 95% confidence intervals (CI) being calculated to estimate associations between the observed factors and OS in patients with NSCLC. After discarding the insignificant factors in the multivariate analysis, the final Cox model included age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin. Between two prognostic factors, an interaction effect was tested using multivariate analysis. For

TABLE 1 | Clinicopathological and lifestyle factors for patients with non-small cell lung cancer.

		No. of subjects (%)		
		Overall survival <1 year	**Overall survival ≥ 1 year**	***P*-value[a]**
Age (years), median ± SD		63.9 ± 10.7	62.0 ± 9.3	0.036
	<65	113 (48.5)	177 (56.7)	0.057
	≥65	120 (51.5)	135 (43.3)	
Sex				
	Male	160 (68.7)	209 (67.0)	0.678
	Female	73 (31.3)	103 (33.0)	
TNM stage				
	I-II	11 (4.7)	65 (20.8)	< 0.001
	III	84 (36.1)	143 (45.8)	
	IV	138 (59.2)	104 (33.3)	
KPS score				
	≥80	112 (48.1)	212 (68.0)	< 0.001
	<80	121 (51.9)	100 (32.1)	
Lung lobectomy				
	Yes	29 (12.5)	135 (43.3)	< 0.001
	No	204 (87.6)	177 (56.7)	
Chemotherapy				
	Yes	94 (40.3)	188 (60.3)	< 0.001
	No	139 (59.7)	124 (39.7)	
Radiotherapy				
	Yes	29 (12.5)	61 (19.6)	0.027
	No	204 (87.6)	251 (80.5)	
Cigarette smoking				
	No	102 (43.8)	136 (43.6)	0.965
	Yes	131 (56.2)	176 (56.4)	
Alcohol consumption				
	No	186 (79.8)	253 (81.1)	0.713
	Yes	47 (20.2)	59 (18.9)	
Family history				
	No	217 (93.1)	291 (93.3)	0.950
	Yes	16 (6.9)	21 (6.7)	
Hemoglobin, g/L, median ± SD		122.9 ± 20.3	130.3 ± 14.4	< 0.001
	NPHb	158 (67.8)	265 (84.9)	< 0.001
	LPHb	75 (32.2)	47 (15.1)	

Data are presented as n (%) unless otherwise noted.

[a]*Chi square test. SD, standard deviation; TNM, tumor-node-metastasis; KPS, Karnofsky performance status; NPHb, normal pretreatment hemoglobin (men, 120–160 g/L; women, 110–150 g/L); LPHb, low pretreatment hemoglobin (men, <120 g/L; women, ≤110 g/L).*

TABLE 2 | Univariate and multivariate analysis of prognostic factors for patients with non-small cell lung cancer.

Prognostic factor		No. of subjects	Univariate[a]			Multivariate[b]		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Total								
Age	<65	290	1.00			1.00		
	≥65	255	1.42	1.18–1.73	<0.001	1.23	1.00–1.52	0.052
Sex	Male	369	1.00			1.00		
	Female	176	1.00	0.82–1.23	0.972	1.09	0.79–1.50	0.608
TNM Stage	I-II	76	1.00			1.00		
	III	227	2.62	1.81–3.79		1.62	1.06–2.45	0.024
	IV	242	4.39	3.04–6.33	<0.001	2.31	1.45–3.68	<0.001
KPS score	≥80	324	1.00			1.00		
	<80	221	1.85	1.52–2.25	<0.001	1.14	0.92–1.40	0.239
Lung lobectomy	Yes	164	1.00			1.00		
	No	381	3.10	2.44–3.94	< 0.001	1.93	1.42–2.63	<0.001
Chemotherapy	Yes	282	1.00			1.00		
	No	263	1.63	1.34–1.98	<0.001	1.41	1.13–1.76	0.002
Radiotherapy	Yes	90	1.00			1.00		
	No	455	1.31	1.01–1.70	0.044	1.04	0.78–1.38	0.811
Smoking	No	238	1.00			1.00		
	Yes	307	0.98	0.81–1.20	0.870	1.20	0.88–1.63	0.239
Alcohol consumption	No	439	1.00			1.00		
	Yes	106	1.04	0.82–1.32	0.757	1.07	0.82–1.38	0.622
Family history	No	508	1.00			1.00		
	Yes	37	0.91	0.61–1.36	0.638	0.90	0.60–1.36	0.630
Hemoglobin	NPHb	432	1.00			1.00		
	LPHb	122	1.82	1.45–2.27	<0.001	1.54	1.22–1.94	<0.001

[a]*For univariate analysis, Cox proportional-hazards model included survival time (<1 or ≥1 year) and one of the following factors: Age, sex, TNM stage, KPS score, lung lobectomy, chemotherapy, radiotherapy, smoking, alcohol consumption, family history or hemoglobin.* [b]*For multivariate analysis, Cox proportional-hazards model included survival time (<1 or ≥1 year), age, sex, TNM stage, KPS score, lung lobectomy, chemotherapy, radiotherapy, smoking, alcohol consumption, family history, and hemoglobin. HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; KPS, Karnofsky performance status; NPHb, normal pretreatment hemoglobin (men, 120–160 g/L; women 110–150 g/L); LPHb, low pretreatment hemoglobin (men, <120 g/L; women, ≤110 g/L).*

each enrolled item, proportionality was estimated using the Schoenfeld and scaled Schoenfeld residuals.

We developed a PInscl that included age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin based on the results of the final Cox model. Age ≥ 65 years, TNM stage III, not undergoing lung lobectomy, not receiving chemotherapy, and having LPHb were given 1 point; TNM stage IV was given 2 points. The minimum PInscl score was 0 and the maximum PInscl score was 6 (**Supplementary Table 1**). The OS, HR, and 95% CI were calculated for each PInscl score. Associations between PInscl score and OS were evaluated using the Peto-Peto-Prentice test. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was used to examine differences in OS between patients with different PInscl scores.

The discriminatory ability of the PInscl score was tested by assessing the area under the ROC curve (AUC). Further, the AUC of PInscl was compared with those of the KPS and TNM staging using the *DeLong* test (15). In addition, we calculated the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the prognostic score.

All statistical analyses were performed using Stata software version 13 (Stata Corporation, College Station, TX, USA). *P* < 0.05 was considered to indicate a statistically significant difference for all analyses.

RESULTS

Patient Characteristics

Our study included a total of 545 NSCLC patients including 369 men and 176 women. Over half (53.2%) of the patients were <65 years, 59.4% had a KPS score ≥80, 41.7% had stage III disease, and 44.4% had stage IV disease. Approximately a quarter (22.4%) of the patients had LPHb. Treatment methods included lung lobectomy ($n = 164$, 30.1%), chemotherapy ($n = 282$, 51.7%), and radiotherapy ($n = 90$, 16.5%) (**Table 1**).

Univariate Analysis

On univariate Cox proportional hazards regression analysis, a significantly longer survival was observed in patients aged <65 years at diagnosis (HR = 1.42, 95% CI = 1.18–1.73) and who had stage I-II disease (compared to patients with stage III disease, HR = 2.62, 95% CI = 1.81–3.79 or stage IV disease, HR = 4.39, 95% CI = 3.04–6.33). Further, a KPS score ≥80 (HR = 1.85, 95% CI = 1.52–2.25), lung lobectomy (HR = 3.10, 95% CI =

2.44–3.94), chemotherapy (HR = 1.63, 95% CI = 1.34–1.98), radiotherapy (HR = 1.31, 95% CI=1.01–1.70), and NPHb (HR = 1.82, 95% CI = 1.45–2.27) significantly improved prognosis. However, there was no significant association between OS and sex (HR = 1.00, 95% CI = 0.82–1.23), cigarette smoking (HR = 0.98, 95% CI = 0.81–1.20), alcohol consumption (HR = 1.04, 95% CI = 0.82–1.32), or a family history of cancer (HR = 0.91, 95% CI = 0.61–1.36) (**Table 2**).

Multivariate Analysis

Multivariate Cox proportional hazards regression analysis showed that age ≥65 (HR = 1.23, 95% CI = 1.00–1.52), TNM stage (III, HR = 1.62, 95% CI = 1.06–2.45; IV, HR = 2.31, 95% CI = 1.45–3.68), lung lobectomy (HR = 1.93, 95% CI = 1.42–2.63), chemotherapy (HR = 1.41, 95% CI = 1.13–1.76), and LPHb (HR = 1.54, 95% CI = 1.22–1.94) were independently significantly associated with decreased OS (**Table 2**).

The final Cox model indicated that age ≥65 (HR = 1.25, 95% CI = 1.02–1.54), TNM stage (III, HR = 1.64, 95% CI = 1.08–2.48; IV, HR = 2.33, 95% CI = 1.48–3.69), lung lobectomy (HR = 1.96, 95% CI = 1.45–2.66), chemotherapy (HR = 1.42, 95% CI = 1.15–1.74), and LPHb (HR = 1.61, 95% CI = 1.28–2.02) were significantly independent unfavorable prognostic factors of 1-year survival in patients with NSCLC (**Table 3**).

Prognostic Index for Non-small Cell Lung Cancer (PInscl)

In comparison with the "PInscl = 0" subgroup (survival time = 2.71 ± 1.86 years), the "PInscl = 2" subgroup (survival time = 1.86 ± 1.24 years; HR = 2.36, 95% CI = 1.21–4.59), "PInscl

TABLE 3 | Prognostic factors included in the final Cox proportional hazard model for prediction of 1-year survival of 545 patients with non-small cell lung cancer.

Prognostic factor		No. of subjects	HR	95% CI	*P*-value
Age	<65	290	1.00		
	≥65	255	1.25	1.02–1.54	0.030
TNM Stage	I–II	76	1.00		
	III	227	1.64	1.08–2.48	0.020
	IV	242	2.33	1.48–3.69	<0.001
Lung lobectomy	Yes	164	1.00		
	No	381	1.96	1.45–2.66	<0.001
Chemotherapy	Yes	282	1.00		
	No	263	1.42	1.15–1.74	0.001
Hemoglobin	NPHb	423	1.00		
	LPHb	122	1.61	1.28–2.02	<0.001

HR, hazard ratio by multivariate Cox proportional hazards regression; CI, confidence interval; TNM, tumor-node-metastasis; NPHb, normal pretreatment hemoglobin (men, 120–160 g/L; women, 110–150 g/L); LPHb, low pretreatment hemoglobin (men, <120 g/L; women, ≤110 g/L).

TABLE 4 | Combined prognostic effects of age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin levels for 545 patients with non-small cell lung cancer.

PInscl[a]	No. of subjects	Survival time, years (Mean ± SD)	HR	95% CI	*P*-value
Total	545	1.47 ± 1.27			
0	26	2.71 ± 1.86	1.00		
1	59	2.43 ± 1.53	1.48	0.75–2.95	0.261
2	73	1.86 ± 1.24	2.36	1.21–4.59	0.012
3	151	1.45 ± 1.07	4.18	2.23–7.82	<0.001
4	131	1.17 ± 1.06	5.69	3.03–10.66	<0.001
5	80	0.81 ± 0.78	8.75	4.57–16.76	<0.001
6	25	0.65 ± 0.56	13.13	6.32–27.28	<0.001

[a] *PInscl, prognostic index for non-small cell lung cancer (ref.* ***Supplementary Table 1****), P-value for trend, <0.0001 (Peto-Peto-Prentice test). SD, standard deviation; HR, hazard ratio by multivariate Cox proportional hazards regression; CI, confidence interval; NPHb, normal pretreatment hemoglobin (men, 120–160 g/L; women, 110–150 g/L); LPHb, low pretreatment hemoglobin (men, <120 g/L; women, ≤110 g/L).*

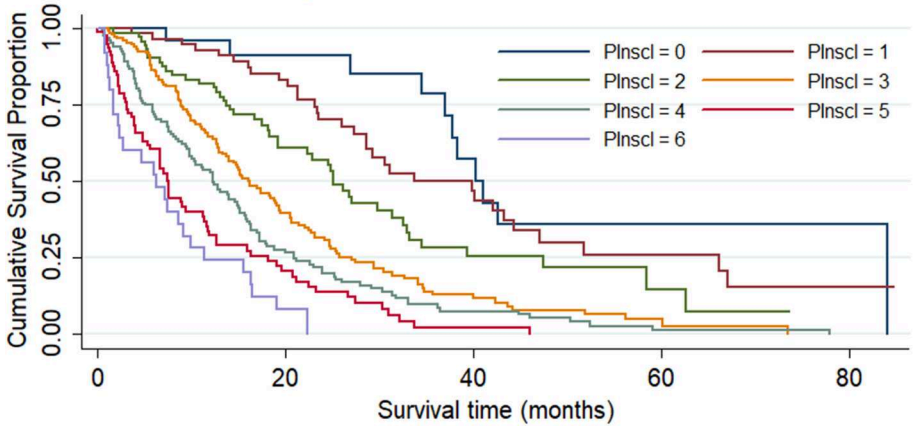


FIGURE 2 | Cumulative survival of patients with non-small cell lung cancer according to the PInscl. Patients with higher PInscl scores (refer to **Supplementary Table**) exhibited a poorer overall survival than those with lower PInscl scores (log-rank test, $\chi^2 = 155.82$; $P < 0.0001$).

= 3" subgroup (survival time = 1.45 ± 1.07 years; HR = 4.18, 95% CI = 2.23–7.82), "PInscl = 4" subgroup (survival time = 1.17 ± 1.06 years; HR = 5.69, 95% CI = 3.03–10.66), "PInscl = 5" subgroup (survival time = 0.81 ± 0.78 years; HR = 8.75, 95% CI = 4.57–16.76), and "PInscl = 6" subgroup (survival time = 0.65 ± 0.56 years; HR = 13.13, 95% CI = 6.32–27.27) had a significantly shorter survival time (**Table 4**). Kaplan-Meier survival curve analysis showed that patients with higher PInscl scores had a poorer OS than those with lower scores (log-rank test, $\chi^2 = 155.82$; $P < 0.0001$) (**Figure 2**).

The AUC for the PInscl for predicting 1-year OS was 0.73 (95% CI = 0.69–0.77, $P < 0.001$) (**Figure 3**). Comparisons of the AUCs between the PInscl and the KPS or the TNM stage showed that the PInscl had a better diagnostic performance than either the KPS or the TNM stage (**Table 5**). The sensitivity, specificity, NPV, and PPV for the PInscl index were 71.2, 62.7, 71.8, and 61.9%, respectively.

DISCUSSION

The results of the present study highlighted the importance of prognostic models in estimating prognosis in NSCLC patients. Our prognostic model, the PInscl, was based on age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin level. The PInscl had a statistically significant discriminative ability to predict OS. Further, the PInscl had a statistically better diagnostic performance than the KPS score or the TNM stage for 1–5 year OS (**Table 5**). This might be because the PInscl included other factors, making it more comprehensive and sensitive.

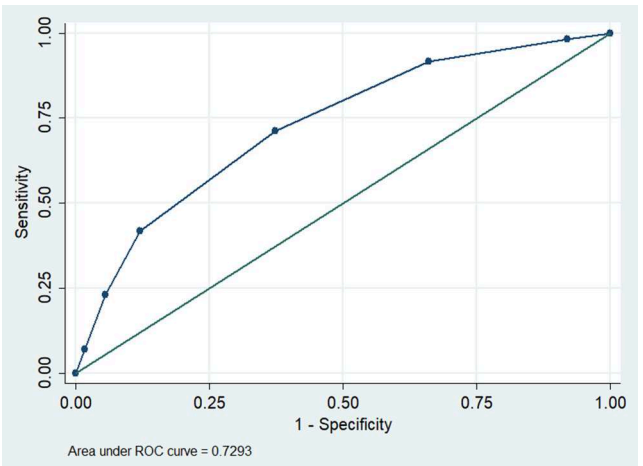


FIGURE 3 | Discriminatory power for PInscl predicting 1-year overall survival (OS). The area under the curve (AUC) was 0.73 (95 % confidence interval = 0.69–0.77, $P < 0.0001$).

In previous studies, age has been recognized as a prognostic factor for NSCLC using cut-off values of 80, 75, 70, and even 50 years (16–19). In the present study, age <65 years was associated with a longer survival time in both univariate (HR = 1.42, 95% CI = 1.18–1.73) and multivariate (HR = 1.23, 95% CI = 1.00–1.52) analyses. We also analyzed age as a continuous variable, but it was not significantly correlated with OS.

The TNM staging system, which classifies cancer according to the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases, is frequently used in clinical practice to predict prognosis (20). Its reliability has been fully established through the IASLC (International Association for the Study of Lung Cancer) study (21). In our present study, stage III (HR = 1.64, 95% CI = 1.08–2.48) and stage IV (HR = 2.33, 95% CI = 1.48–3.69) disease were indicative of a poorer prognosis (**Table 3**). However, as the coefficient of the TNM stage was not more than two times those of other factors in multivariate analysis (data not shown), we did not emphasize it in our model, as Blancoon et al. did (12).

Anemia is linked to prognosis, and hemoglobin has long been recognized as a prognostic factor for NSCLC patients (22–25). We found that hemoglobin <120 g/L in men and <110 g/L in women was associated with a shorter OS (HR = 1.62, 95% CI = 1.29–2.03).

In many cases, lung lobectomy is still the most effective treatment method for NSCLC (26). The impact of minimally invasive lobectomy and thoracotomy lobectomy on survival has also been assessed (27). However, lobectomy will be applied according to the clinical situation for NSCLC patients (28). In the present study, surgical resection was not recommended for stage IV patients. Therefore, although we found that lung lobectomy was an independent prognostic factor for NSCLC patients, we cannot say whether a physical condition suitable for lobectomy, lobectomy itself, or both contributed favorably to OS. Regardless, lung lobectomy was an independent prognostic factor in the model.

Chemotherapy is another major treatment method for NSCLC (29), and more chemotherapies have become

TABLE 5 | Discriminatory power of the PInscl, KPS, and TNM for overall survival of non-small cell lung cancer patients.

	Area under the curve (AUC)				
Overall survival	**1-year**	**2-year**	**3-year**	**4-year**	**5-year**
PInscl	0.73 ± 0.02 (0.69–0.77)	0.73 ± 0.02 (0.68–0.77)	0.77 ± 0.03 (0.71–0.83)	0.75 ± 0.04 (0.66–0.83)	0.83 ± 0.06 (0.72–0.94)
KPS	0.64 ± 0.02 (0.59–0.68)**	0.59 ± 0.03 (0.54–0.64)**	0.63 ± 0.03 (0.57–0.7)**	0.600± 0.05 (0.49–0.7)**	0.76 ± 0.06 (0.64–0.87)**
TNM	0.67 ± 0.02 (0.63–0.71)**	0.67 ± 0.03 (0.62–0.73)**	0.70 ± 0.03 (0.64–0.77)**	0.66 ± 0.05 (0.55–0.76)*	0.69 ± 0.08 (0.54–0.85)**

*PInscl, prognostic index for non-small cell lung cancer; KPS, Karnofsky performance status; TNM, tumor-node-metastasis stage. *p<0.05, **p<0.01.*

clinically available (30). We found that chemotherapy was an independent prognostic factor in both univariate and multivariate analysis. This result was in line with those of previous studies (8, 31) However, patients received both cisplatin- and paclitaxel-based chemotherapies, and we did not divide the patients into subgroups, which may have affected the results. Chemotherapy, particularly cisplatin-based adjuvant chemotherapy, might also improve survival among patients with completely resected NSCLC (32). Although we could not exclude its potential long-term influence, we did not find a significant synergistic effect of chemotherapy and lung lobectomy (data not shown).

This study has several strengths. First, the PInscl can be simply calculated and used in almost all NSCLC patients. Data on age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin are easy to obtain and do not require exhaustive testing and complicated biological examination. Second, it is practicable. We could predict OS simply by the PInscl score, which is meaningful for patients, their families, and clinicians. ROC curve analysis showed that the PInscl score was a fairly predictable index and was more sensitive than the KPS and TNM score. However, the study also has limitations. First, selection bias may be a concern due to the monocentric design of the study and the absence of random sampling, even though exhaustive inclusion of consecutive cases over 5-years should alleviate the bias. Second, the discriminative power of the PInscl was not assessed in a population with features different from that in which it was derived. Third, the model does not include mutational information (e.g., EGFR/ALK mutations). Fourth, the lack of a validation cohort might weaken the power of the present study. Therefore, whether it is suitable to be expostulated to other NSCLC populations needs further verification.

By developing this simple prognostic index, we suggest that the PInscl, which is calculated from age, TNM stage, lung lobectomy, chemotherapy, and pretreatment hemoglobin level, might significantly predict OS in NSCLC patients.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to Yuquan Lu (lll3923@gmail.com).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Henan University, Huaihe Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Y-HZ made substantial contributions to data collection and was a major contributor in writing the manuscript. YL analyzed and interpreted the data contributed to manuscript preparation and revision and gave final approval for the version to be published. HL was responsible for the acquisition of data and institutional review board application, conducted data interpretation, and gave final approval for the version to be published. Y-MZ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This work was supported by the Program of Kaifeng Science and Technology Development Plan (2020).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00362/full#supplementary-material

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* (2019) 69:7–34. doi: 10.3322/caac.21551
2. Ettinger DS, Aisner DL, Wood DE, Akerley W, Bauman J, Chang JY, et al. NCCN guidelines insights: non-small cell lung cancer, version 5.2018. *J Natl Compr Canc Netw.* (2018) 16:807–21. doi: 10.6004/jnccn.2018.0062
3. Yao ZH, Liao WY, Ho CC, Chen KY, Shih JY, Chen JS, et al. Real-world data on prognostic factors for overall survival in EGFR mutation-positive advanced non-small cell lung cancer patients treated with first-line gefitinib. *Oncologist.* (2017) 22:1075–83. doi: 10.1634/theoncologist.2016-0331
4. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* (2010) 363:1693–703. doi: 10.1056/NEJMoa1006448
5. Shaw AT, Ou SH, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med.* (2014) 371:1963–71. doi: 10.1056/NEJMoa1406766
6. Sacher AG, Dahlberg SE, Heng J, Mach S, Janne PA, Oxnard GR. Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer. *JAMA Oncol.* (2016) 2:313–20. doi: 10.1001/jamaoncol.2015.4482
7. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. *Chest.* (2002) 122:1037–57. doi: 10.1378/chest.122.3.1037
8. Zhang YH, Lu Y, Lu H, Zhang MW, Zhou YM, Li XL, et al. Pre-treatment hemoglobin levels are an independent prognostic factor in patients with non-small cell lung cancer. *Mol Clin Oncol.* (2018) 9:44–9. doi: 10.3892/mco.2018.1628
9. Fan H, Shao ZY, Xiao YY, Xie ZH, Chen W, Xie H, et al. Comparison of the Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS) in evaluating the prognosis of patients with operable and inoperable non-small cell lung cancer. *J Cancer Res Clin Oncol.* (2016) 142:1285–97. doi: 10.1007/s00432-015-2113-0
10. Ulas A, Turkoz FP, Silay K, Tokluoglu S, Avci N, Oksuzoglu B, et al. A laboratory prognostic index model for patients with advanced non-small cell lung cancer. *PLoS ONE.* (2014) 9:e114471. doi: 10.1371/journal.pone.0114471
11. Ozyurek BA, Ozdemirel TS, Ozden SB, Erdogan Y, Ozmen O, Kaplan B, et al. Does advanced lung inflammation index (ALI) have prognostic significance in metastatic non-small cell lung cancer? *Clin Respir J.* (2018) 12:2013–9. doi: 10.1111/crj.12768
12. Blanchon F, Grivaux M, Asselain B, Lebas FX, Orlando JP, Piquet J, et al. 4-year mortality in patients with non-small-cell lung cancer: development

and validation of a prognostic index. *Lancet Oncol.* (2006). 7:829–36. doi: 10.1016/S1470-2045(06)70868-3
13. Kay FU, Kandathil A, Batra K, Saboo SS, Abbara S, Rajiah P. Revisions to the tumor, node, metastasis staging of lung cancer 8th edition: rationale, radiologic findings and clinical implications. *World J Radiol.* (2017) 9:269–79. doi: 10.4329/wjr.v9.i6.269
14. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol.* (1984) 2:187–93. doi: 10.1200/JCO.1984.2.3.187
15. deLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. (1988) 44:837–45. doi: 10.2307/2531595
16. Pawlak K, Gabryel P, Kujawska A, Kasprzyk M, Piwkowski C, Kuffel B, et al. Long-term results of surgical treatment of non-small cell lung cancer in patients over 75 years of age. *Kardiochir Torakochirurgia Pol.* (2018) 15:65–71. doi: 10.5114/kitp.2018.76470
17. Lara MS, Brunson A, Wun T, Tomlinson B, Qi L, Cress R, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a california cancer registry analysis. *Lung Cancer.* (2014) 85:264–9. doi: 10.1016/j.lungcan.2014.04.007
18. Kim TH, Park B, Cho JH, Kim HK, Choi YS, Kim KM, et al. Pneumonectomy for clinical stage i non-small cell lung cancer in elderly patients over 70 years of age. *Korean J Thorac Cardiovasc Surg.* (2015) 48:252–7. doi: 10.5090/kjtcs.2015.48.4.252
19. Hsu CL, Chen JH, Chen KY, Shih JY, Yang JC, Yu CJ, et al. Advanced non-small cell lung cancer in the elderly: the impact of age and comorbidities on treatment modalities and patient prognosis. *J Geriatr Oncol.* (2015) 6:38–45. doi: 10.1016/j.jgo.2014.09.178
20. Choi HS, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH, et al. Application of the new 8th TNM staging system for non-small cell lung cancer: treated with curative concurrent chemoradiotherapy. *Radiat Oncol.* (2017) 12:122. doi: 10.1186/s13014-017-0848-2
21. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Goldstraw P, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol.* (2015) 10:1515–22. doi: 10.1097/JTO.0000000000000673
22. Motoishi M, Sawai S, Hori T, Yamashita N. The preoperative HbA1c level is an independent prognostic factor for the postoperative survival after resection of non-small cell lung cancer in elderly patients. *Surg Today.* (2018) 48:517–24. doi: 10.1007/s00595-017-1612-9
23. Gauthier I, Ding K, Winton T, Shepherd FA, Livingston R, Johnson DH, et al. Impact of hemoglobin levels on outcomes of adjuvant chemotherapy in resected non-small cell lung cancer: the JBR.10 trial experience. *Lung Cancer.* (2007) 55:357–63. doi: 10.1016/j.lungcan.2006.10.021
24. Aoe K, Hiraki A, Maeda T, Katayama H, Fujiwara K, Tabata M, et al. Serum hemoglobin level determined at the first presentation is a poor prognostic indicator in patients with lung cancer. *Intern Med.* (2005) 44:800–4. doi: 10.2169/internalmedicine.44.800
25. Watine J. Blood hemoglobin as an independent prognostic factor in surgically resected stages I and II non-small cell lung cancer patients. *Ann Thorac Surg.* (2002) 73:2034–5. doi: 10.1016/S0003-4975(02)03475-6
26. Deslauriers J, Gregoire J. Surgical therapy of early non-small cell lung cancer. *Chest.* (2000) 117:104S−9. doi: 10.1378/chest.117.4_suppl_1.104S
27. Paul S, Isaacs AJ, Treasure T, Altorki NK, Sedrakyan A. Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. *BMJ Clin Res.* (2014) 349:g5575. doi: 10.1136/bmj.g5575
28. Vansteenkiste J, Crino L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO consensus conference on lung cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol.* (2014). 25:1462–74. doi: 10.1093/annonc/mdu089
29. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small cell lung cancer collaborative group. *BMJ.* (1995). 311:899–909. doi: 10.1136/bmj.311.7010.899
30. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* (2002) 346:92–8. doi: 10.1056/NEJMoa011954
31. Shaverdian N, Veruttipong D, Wang J, Kupelian P, Steinberg M, Lee P. Pretreatment anemia portends poor survival and nonlocal disease progression in patients with stage I non-small cell lung cancer treated with stereotactic body radiation therapy. *J Thorac Oncol.* (2016) 11:1319–25. doi: 10.1016/j.jtho.2016.04.030
32. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med.* (2004) 350:351–60. doi: 10.1056/NEJMoa031644

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 02 September 2020
doi: 10.3389/fonc.2020.01366

Developing and Assessing the Effectiveness of a Nurse-Led Home-Based Educational Programme for Managing Breathlessness in Lung Cancer Patients. A Feasibility Study

Aristides Choratas[1], Evridiki Papastavrou[1], Andreas Charalambous[1,2] and Christiana Kouta[1]*

[1] Nursing Department, Cyprus University of Technology, Limassol, Cyprus, [2] Nursing Department, University of Turku, Turku, Finland

OPEN ACCESS

Edited by:
Patsy Yates, Queensland University of Technology, Australia

Reviewed by:
Vanessa Nicole Brunelli, Queensland University of Technology, Australia
Jane Louise Phillips, University of Technology Sydney, Australia

***Correspondence:**
Aristides Choratas
2006aris@cytanet.com.cy

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *28 October 2019*
Accepted: *29 June 2020*
Published: *02 September 2020*

Citation:
Choratas A, Papastavrou E, Charalambous A and Kouta C (2020) Developing and Assessing the Effectiveness of a Nurse-Led Home-Based Educational Programme for Managing Breathlessness in Lung Cancer Patients. A Feasibility Study. Front. Oncol. 10:1366. doi: 10.3389/fonc.2020.01366

Introduction: Breathlessness is the most common and refractory symptom in lung cancer patients. Even though various educational programmes have been developed, only a few were intended for implementation in the home setting for its management.

Aim: Feasibility of a study for implementing a nurse-led educational programme for breathlessness management of lung cancer patients at home.

Method: A randomized feasibility study was undertaken between February 2017 and October 2018. Patients were recruited through referral from oncologists from two oncology centers in Cyprus under certain inclusion and exclusion criteria. Patients were randomized in the intervention or control group via a computer programme, and their named family caregivers (f.c.) were allocated in the same group. Participants were not blinded to group assignment. The intervention consisted of a PowerPoint presentation and implementation of three non-pharmacological interventions. The control group received usual care. Patients were assessed for breathlessness, anxiety, and depression levels, whereas f.c. were assessed for anxiety, depression, and burden levels. F.c. also assessed patients' dyspnea level. The duration of the study process for both the intervention and control group was over a period of 4 weeks.

Results: Twenty-four patients and their f.c. ($n = 24$) were allocated equally in the intervention and control group. Five patients withdrew, and the final sample entered analysis was 19 patients and 19 family caregivers. In the intervention group $n = 11 + 11$, and in the control group $n = 8 + 8$. In the intervention group patients' breathlessness and anxiety levels showed improvement and their f.c.s in the anxiety and burden levels. Major consideration was the sample size and the recruitment of the patients by the referring oncologists. Attrition was minor during the study process. No harm was recorded by the participants of the study.

Conclusions: The study provided evidence of the feasibility of the implementation of the educational programme. For the future definitive study major consideration should be patients' recruitment method in order to achieve adequate sample size. Moreover, qualitative data should be collected in relation to the intervention and the involvement of f.c. The feasibility study was registered to the Cyprus Bioethics Committee with the registration number 2016/16. There was no funding of the study.

Keywords: breathlessness, home care, educational programme, lung cancer, nurse

INTRODUCTION

Breathlessness is a common symptom in patients with cancer (1, 2) and is the commonest amongst patients with lung cancer (3) and among patients in need of palliative care or advanced cancer (4). As classified by the American Thoracic Society in 1999 (5, p. 322), breathlessness is a subjective experience of difficulty in breathing that consists of qualitative distinctive sensations that differ in intensity. Breathlessness is caused by multiple physiological, psychological, environmental, and social factors, and simultaneously it can be exacerbated by such factors (4–6). It is a symptom that possesses great challenges for health care professionals when it comes to its effective management, especially for patients with cancer in terminal stages. With evidence showing that breathlessness increases significantly in the last 6 months of life, its frequent assessment is crucial in order for therapy to be accustomed (7). Furthermore, assessment is important for the anxiety of both the patient and their family to be identified and addressed (7).

At home, the family often undertakes the role of the caregiver for the patient, helping monitor and manage symptoms and becoming the contact person between the patient and the health care professionals (8). Family caregivers can offer limited care in relation to breathlessness management with related problems evolving, in comparison to the care offered at the hospital (9). This is mainly because family caregivers have no or limited knowledge and experience in managing breathlessness but also because of the high level of skills required to effectively manage these (9, 10). Poor management at home creates complications in patients' care affecting their quality of life and increasing admissions to the hospital. Moreover, it burdens family caregivers mainly during the end of life period of the patient, when the disease has progressed (11).

Despite the fact that the comprehensive and effective management of breathlessness remains a challenge, various strategies for managing breathlessness have been developed including pharmacological and non-pharmacological methods. For the pharmacological management of breathlessness due to cancer and the accompanying problems (e.g., anxiety, air hunger, and panic) the standard treatment is the administration of opioids with other drugs being of controversial benefit like benzodiazepines, phenothiazines, antidepressants, and steroids (12–17). There is no evidence of the effectiveness of oxygen therapy for cancer patients with dyspnea at home. Oxygen use is encouraged when saturation drops below 90% (at rest), in order to achieve improvement of functional capacity and quality of life and reduce the effects of breathlessness and mortality. However, there is the risk for patients to develop dependence (18–20).

The non-pharmacological methods include breathing techniques which assist in improving the effectiveness of the breathing cycle such as diaphragmatic breathing, inspiratory and/or expiratory muscle training, pursed-lip breathing, respiratory muscle stretching calisthenics, breathing exercises, or exercise training (stretching, walking, stairs climbing, upper, and lower aerobic) (21–25) psychoeducation, normal activities achieving training, relaxation techniques training, and psychological support (12, 15, 20, 26). The effectiveness of resistance inspiratory muscle training (IMT) was demonstrated in a two-arm, non-blinded, randomized controlled, proof-of-principle study in Cyprus and the United Kingdom in the home setting (27). The use of fans, preferably hand-held fans, directed to the face was also found to be effective (12, 15, 20, 28). Other methods include the use of mechanical ventilation techniques, e.g., CPAP, BiPAP, neuroelectrical stimulation, and chest vibration (14). Inspiratory muscle training will be used in the present study because it has already been tested for inpatient lung cancer patients in Cyprus (27). Diaphragmatic breathing technique will also be used as an already effective method (21–25) and the handheld fan, apart from its efficacy as mentioned above, because it is an economic and easy to use method for patients at home (29).

There is limited research on the effectiveness of home-based educational programmes for breathlessness and even less when is related to cancer. Olivier et al. (25) state that such programs are feasible and safe for cancer patients, so they should be assessed in association with all health care offered to cancer patients at home (if exists) in order to establish complete, holistic, and personalized home care. This was based on their study of lung or mesothelioma cancer patients undergoing chemotherapy who were offered pulmonary rehabilitation (PR) at home with exercise training, therapeutic education, and psychosocial support. The existing limited research shows that nurse-led educational programs have positive effect on patients with breathlessness due to Chronic Obstructive Pulmonary Disease (COPD), lung cancer, and heart failure (21–25, 30, 31). In the above studies the educational programs consisted of different methods of breathing retraining, pulmonary exercises, exercises for strengthening physical strength, psychosocial therapy, daily activities management training, and information in relation to the patient's disease and symptoms and their management either general for all patients or patient tailored (21–25, 30, 31).

The effectiveness of an educational intervention at home was shown in the study by Eui-Geum (30), where both the intervention and the control group received the educational programme. The intervention group received a pulmonary rehabilitation programme and the control group an educational support, and both groups showed improvement in breathlessness (30). Health related quality of life, functionality, or self-efficacy were assessed in some studies and showed improvement among the participants in the intervention group (21–23, 30, 31) except from one study (24). In the study by Olivier et al. (25), no significant improvement was shown in the breathlessness level from the intervention but did not worsen. In the study by Hermiz et al. (31) no differences among the intervention (patient tailored verbal and written education and support) and control groups (normal care) in presentation or admission to hospital or in overall functional status were noted.

The results of the above studies showed significant benefits for the intervention group in improving breathlessness not only in relation to the baseline assessment but also compared to a control group. Even though Pulmonary Function Test appeared to have no change, arterial blood gases improved and consequently breathlessness improved (23, 30). This improvement was due to the desensitization of dyspnea, the increase in vital capacity of the lungs and the decrease in the level of partial pressure of arterial carbon dioxide ($PaCo_2$) (23). According to Akinci et al. (23) home-based educational programmes are preferable where no pulmonary rehabilitation programs exist at hospital level and because there is higher performance by patients as they are at home. Moreover, as Eui-Geum (30) stated, as the intensity of the program was controlled by patients, the sense of self-efficacy might improve leading to better adherence to the practical aspects of the programme. Symptom management was also improved by increasing motivation and self-care through the implementation of a nurse-led programme (21). The educational advice given on the effective breathing methods also might be the reason for improvement in breathlessness levels (22, 30). Padula et al. (30) reported that the inability to achieve secondary aims might be due to the chosen assessment tools, whereas Olivier et al. (25) stated that high attrition might have been the reason for not achieving study goals.

For the use of pharmacological and non-pharmacological methods in managing breathlessness and supporting patients and their family caregivers, nurses have the most important role either independently or as a member of a multidisciplinary team (20). Continuous nursing support is vital in the successful implementation of home care, offering the possibility to patients and family caregivers to have all the support and information when it is needed (32, 33).

In Cyprus the new cases of patients diagnosed with lung cancer are increasing every year, $n = 198$ in 2008 and $n = 321$ in 2013 (34, 35). However, no research data exist for the implementation of any programme for the management of breathless patients (due to cancer or any other disease) within or outside the hospital setting in the country.

Depending on the results of the present study, the intervention can be considered for application in a future bigger study to a broader health care area of breathless cancer patients in the home setting, for possible implementation as the first non-pharmacological intervention in the country (36). By the implementation of the programme the role of nurses in home care is expected to be enhanced and patients and family caregivers are expected to be strengthened in self-managing breathlessness at their own home setting.

The aim of the present feasibility study was the development of a nurse-led home-based educational programme for the management of breathlessness in lung cancer patients, the implementation of the programme, and the evaluation of its effectiveness to patients and their family care.

MATERIALS AND METHODS

This was a feasibility randomized control trial that took place between February 2017 and October 2018, with an intervention group receiving the educational programme and the usual care and a control group receiving during the period of assessment only the usual care. Usual care consisted of the pharmacological management by oncologists which was prescribed to patients experiencing breathlessness, including oxygen therapy. The intervention group had a baseline assessment followed by the implementation of the educational programme. Within 2 weeks there was a reassessment and repetition of the programme, and on the 4th week the final assessment was carried out. The control group had the same assessments over the same period of time. Based on the principle of fairness, the intervention was offered to the patients that were randomized to control group following the completion of the study without any measurements recorded. Family caregivers, as named by their participating patients, were also included in the study. Together with their patients they either received the intervention or were part of the control group. Family caregivers completed their own assessment tools at the same period of time as the patients (**Figure 1**).

Sample

Lung cancer patients with medium to severe breathlessness (rating 3–6 on the mBorg scale), according to an assessment from their oncologist from the two largest oncology centers in Cyprus, were eligible to participate in the study and were referred to the researcher. Other criteria for patients to be eligible for referral and inclusion in the study were (a) not to be receiving during the study period active treatment for their cancer, (b) not to be at the end of life stage in order to be able to complete the study within the 4 weeks of the study as judged by the referring oncologist, and (c) to be able to speak and understand Greek language in order to be able to understand the intervention. The last criterion was that the patient had to have a family caregiver they could name, in order to participate. Previous research studies and the number of lung cancer patients within the country were used for power analysis and calculation of the desired sample size ($n = 45$). After commencing the study doctors were unable to identify enough eligible patients to participate. Thus, the criterion for not receiving active treatment for cancer was dismissed, and patients under active chemotherapy became eligible for inclusion in the study. Moreover, it was decided to complete the study by October 2018 as a priori and regardless of the sample size.

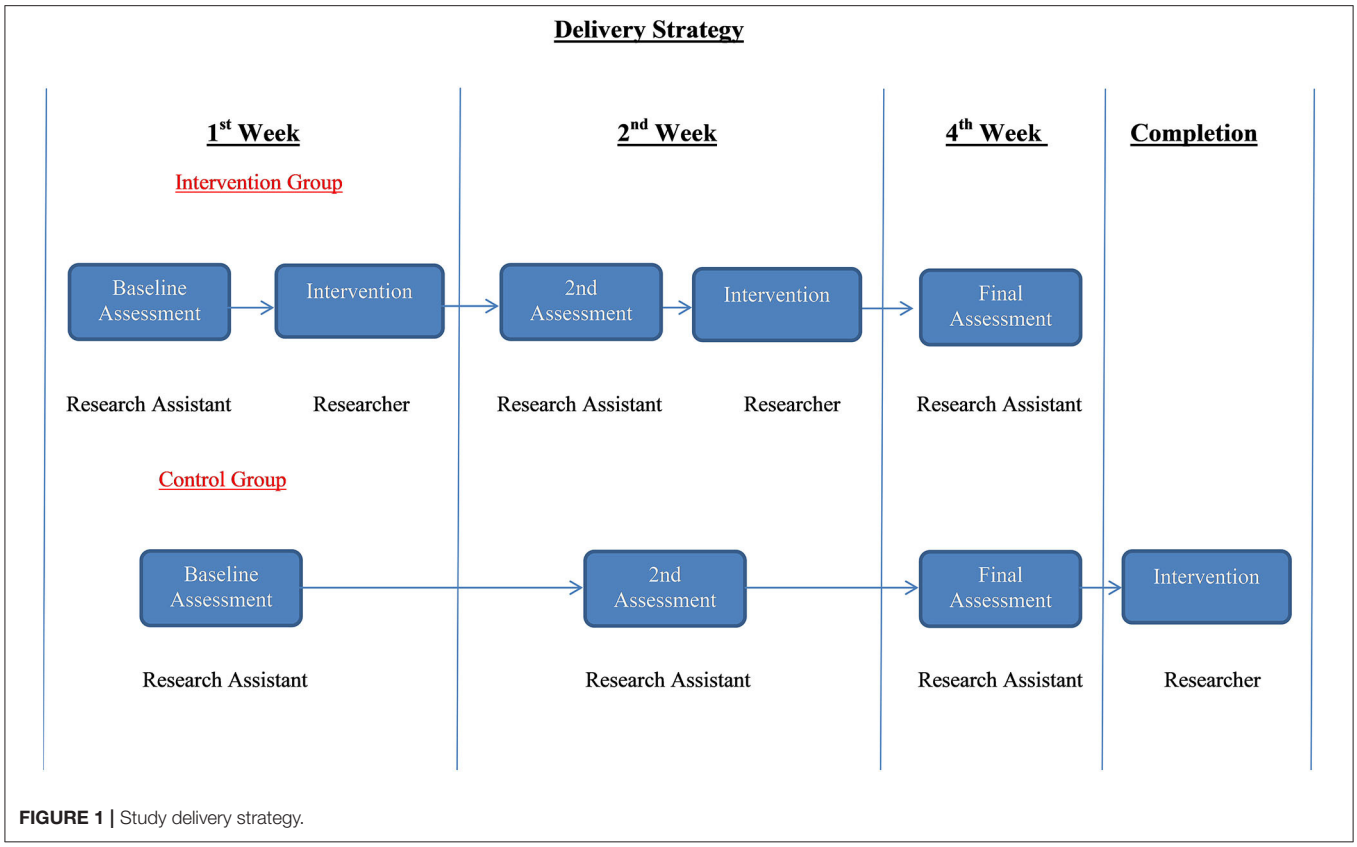


FIGURE 1 | Study delivery strategy.

Patients, after being informed by their oncologist about the study, if interested had to call the researcher in order to receive information about the study and give oral consent and their contact information. Participating patients had to name their family caregivers who would join them and participate in the study giving also consent, but also needed to be able to comprehend the educational material. No geographical restrictions were set. Randomization was performed allocating participants alternatively in the control or the intervention group through a computerized method by a research associate. He then contacted a specially trained research fellow, who is an experienced nurse working with patients with breathlessness, who was carrying out the assessments at patients' home setting. Participants in the study were not blinded to group assignment due to the nature of the intervention of the study. The researcher was involved in the process only for applying the intervention after being informed by the research associate carrying out measurements.

INTERVENTION

The intervention was designed through extensive literature review, discussions with clinical experts and the research group, and was based on the Prepared Family Caregiver model (COPE) developed by Houts et al. (37). COPE is a prescriptive problem solving model directed toward the care, information, and training family caregivers should receive in order to provide the best care at home, empowering both the patient and family caregivers (37). The educational programme included a PowerPoint presentation incorporating two video recordings and a practical exercise. The PowerPoint presentation consisted of information about the definition, causes, and clinical picture of breathlessness and its effects on patients and family caregivers. The two videos showed the effect of breathlessness on patients and the proper use of a handheld fan. The videos were used in Breathlessness Intervention Service in a hospital in UK together with an informational booklet, and their effectiveness was shown in various studies conducted for this purpose (38–40). The practical part consisted of three non-pharmacological methods for managing breathlessness and explanation of their effectiveness. Those were diaphragmatic breathing, inspirational muscle training (IMT), and use of a handheld fan. The choice for using the PowerPoint presentation was to offer complete one time information and explanation with a way that was visually interesting to the patient and which was of short duration. At the end the trainer/researcher answered questions from the participants. The educational programme lasted about 30–50 min according to patient's and family caregiver's needs. The implementation of the educational activity was undertaken by the researcher, an oncology nurse having extensive knowledge and experience in teaching patients and nurses for more than 25 years.

The educational programme was applied twice to the intervention group after the 1st and 2nd assessment and once

to the control group after completing the final assessment (**Figure 1**).

Data Collection

For assessing the effect of the intervention on breathlessness, data for patients were collected using the Modified Borg Scale (mBorg scale) and the Visual Analog Scale (VAS)-Breathlessness. Lung Function (FCV, FEV1) was assessed using spirometry and Hospital Anxiety and Depression Scale (HADS) was used for assessing the effect of breathlessness on patients. Data were collected for the intervention group before the intervention (baseline assessment), in 2 weeks' time and in 4 weeks' time. At all times all assessments were performed assessing the breathlessness levels, the lung function, and anxiety and depression. The same assessment tools were used to collect data from the control group at the same time intervals, in 4 weeks' time, and then the intervention was implemented to the patients in this group. Family caregivers gave data on the level they assessed their own patient's breathlessness using the mBorg scale. Also on the effect of the educational programme on them, at the same time interval as their patients, using the HADS scale for anxiety and depression and the Zarit Burden Interview (ZBI) scale for the burden they experienced. The data were collected by a specially trained research fellow.

The mBorg scale is a categorical scale which is considered the most frequently used instrument for measuring breathlessness (dyspnea) (41, 42). It requires the identification of the experienced breathlessness on a 12 point scale from 0 (no breathlessness) to 10 (very, very severe). The VAS-Breathlessness scale assesses the experienced Breathlessness at Worst and at Best and the Distress caused by the symptom. All 3 subscales rate Breathlessness or its burden from 0 (no Breathlessness) to 10 (extreme Breathlessness) over the last 24 h (43). According to Gerlach et al. (42) the VAS scales and the mBorg scale are preferred for assessing the intensity of the symptom, the quality of the sensation of breathlessness, and the related to breathing dysfunction. They support this as the scales showed concurrent validity and test/retest reliability, Cronbach's a. 0.54 (VAS) and 0.45 (mBorg) and correlations >0.8 (for both) compared to other tools (42). The choice of the above scales has taken in consideration the criteria on the choice of the appropriate tools for measuring cancer related breathlessness by Dorman et al. (44) which included among others relevance and feasibility to participants and sensitivity to changes of the symptom.

The Hospital Anxiety and Depression Scale (HADS) consists of 14 multiple choice questions assessing anxiety and depression. The questionnaire was translated into the Greek language (45) and shows internal consistency (0.87–0.85) and validity (0.722–0.749). It has been used in Cypriot cancer patients' population for assessing anxiety and depression levels (27). The same scale was used for assessing the anxiety and depression of family caregivers in a study assessing the effectiveness of a breathlessness management service (40).

The Zarit Burden Interview (ZBI) consists of 22 items, is self-completed, and assesses the burden family caregivers' experience by the caring process (46). It has been used in assessing the burden family caregivers experience during the care of patients with breathlessness due to lung cancer (47, 48). It was translated in Greek language and used in the Cypriot population showing validity and high internal reliability (Cronbach a = 0.94) (46, 49, 50). The items of the questionnaire are nine for personal strain, seven for role strain, four for relationship deprivation, and two for management of care (49). They are rated on a 5 point Likert scale from 0 (*never*) to 4 (*nearly always*). The higher the score from the sum of the items, ranging from 0 to 88, indicates greater burden (48–50).

Collection of any information on harms was not included in the study design. However, participants were informed on the consent form of the possible side effects of spirometry as well as the medical conditions restrictive of applying spirometry. Moreover, during the 4 weeks period that IMT was implemented by the intervention group participants, they were guided to report any problems faced to the researcher in order to be recorded and resolved. Patients in either group were offered support by the researcher after completion of the study for as long as they wished.

No changes in measurements took place after commencing the pilot study as the research associate did not identify any problems or difficulties during the process.

Data Analysis

A test for equivalence of demographic characteristics of the Control and Intervention groups was performed, using chi-square test. Testing for equivalence of the Control and Intervention groups regarding the clinical characteristics of the patients (FCV, FEV1) and the level of the scales assessing Breathlessness and Anxiety/Depression and Burden for patients and family caregivers was performed using the statistic Welsch *t*-test. Measurement of the level of correlation between the clinical characteristics and the Breathlessness and Anxiety/Depression scales of the patients at baseline was performed with Pearson linear correlation. The same correlation measurement was performed for the Breathlessness, Anxiety/Depression and Burden scales of the family caregivers. The effect of the intervention on the clinical characteristics and at the level of the scales used, was performed with the statistical analysis Repeated Measures ANOVA (RM ANOVA). Specifically, the statistical significance of the Group-Time interaction coefficient for its effect on the level of clinical measurements and scales was studied. The data included in the analysis were only the data from the participants from all groups that completed the whole study.

The analysis was performed in SPSS v.21 and statistical significance was set at 0.05.

Ethical Approval

Approval for conducting the research was granted by the Cyprus National Bioethics Committee, which is the only authorizing body for studies to be conducted in the country, with an authorization No: 2016/16. Approval was also obtained for accessing doctors and patients from the Cyprus Ministry of Health for the public hospital and the Bank of Cyprus Oncology Center. The Office of the Commissioner for Protection of Personal Data of the country gave permission for keeping records for the purpose of the study.

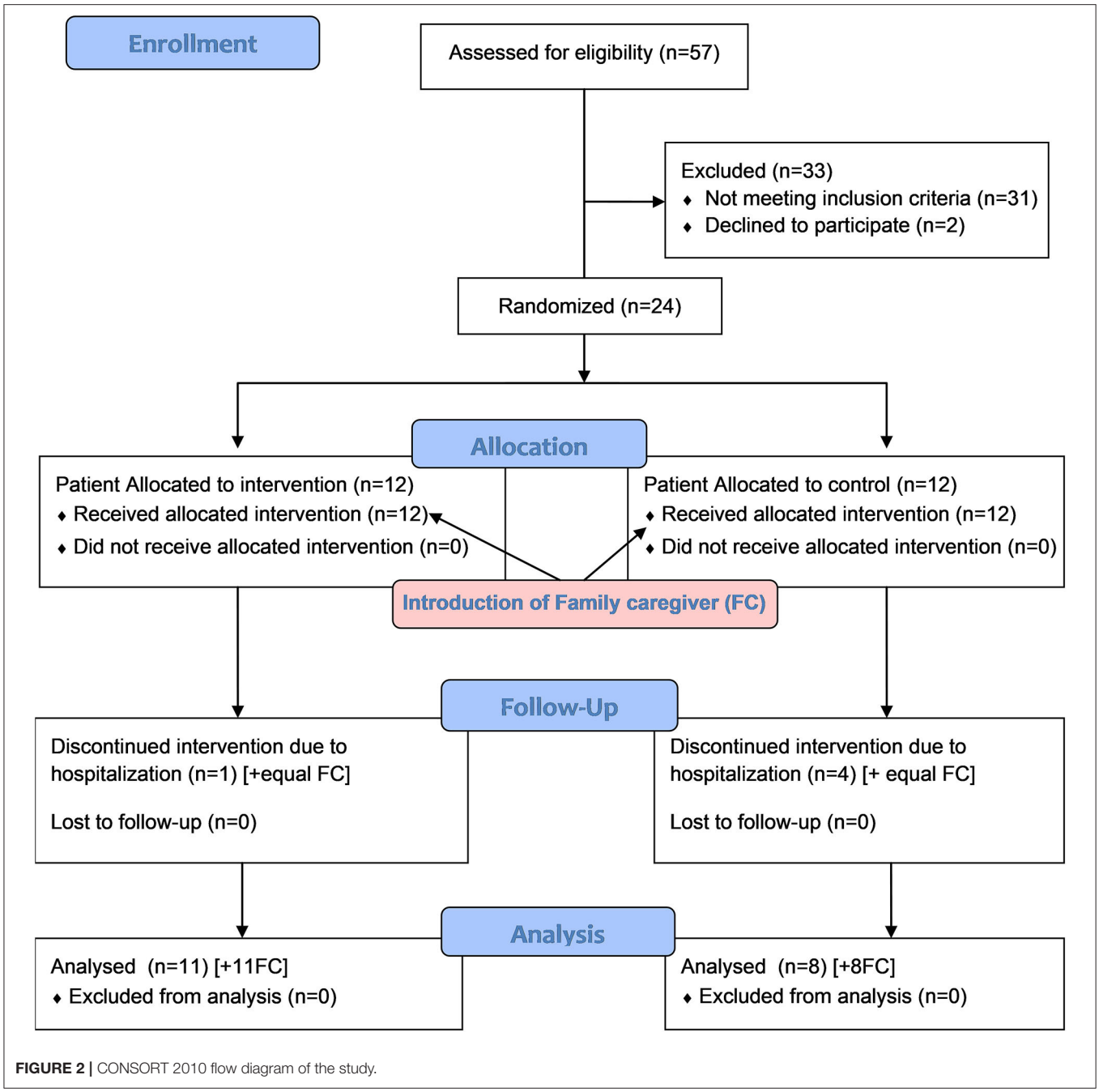


FIGURE 2 | CONSORT 2010 flow diagram of the study.

A written informed consent was signed by all the participants in the study (patients and family caregivers) at the first meeting with the research fellow conducting the assessments.

RESULTS

Twenty-six ($n = 26$) eligible patients were referred and two refused to participate. From the 24 participating patients five ($n = 5$) withdrew from the study during the process due to hospitalization (hospice or hospital). The reason for hospitalization was deterioration of the general condition of the patients requiring inpatient care and was not related to the implementation of the intervention or participation in the study. Finally 19 patients completed the study either in the intervention group ($n = 11$) or the control group ($n = 8$). Consequently their named family caregivers were allocated in the same groups: $n = 11$ in the intervention group and n = 8 in the control group. No family caregiver expressed willingness to leave the study (**Figure 2**).

TABLE 1 | Demographic data of the two groups.

		Intervention group ($n = 11$)		Control group ($n = 8$)		Total ($n = 19$)		*p*-value
		N	%	*N*	%	*N*	%	
Gender	Female	2	18	3	38	5	26	0.345
	Male	9	82	5	63	14	74	
Age	46–60	0	0	1	13	1	5	0.425
	61–74	9	82	5	63	14	74	
	75+	2	18	2	25	4	21	
Family	Widow	1	9	1	13	2	11	0.351
Condition	Divorced	0	0	1	13	1	5	
	Married	10	91	5	63	15	79	
	Single	0	0	1	13	1	5	
Nationality	Cypriot	9	82	8	100	17	89	0.202
	Other	2	18	0	0	2	11	
Educational	Lyceum/technical school graduate	1	9	2	25	3	16	0.504
Level	Gymnasium graduate	6	55	5	63	11	58	
	Elementary graduate	2	18	0	0	2	11	
	No elementary graduate/ No grammatical knowledge	2	18	1	13	3	16	
Smoking		7	64	5	63	12	63	0.96
Receiving drugs for breathlessness		3	27	1	13	4	21	0.435
Oxygen use		6	55	5	63	11	58	0.729

Demographics

In the study the majority of the participants were male patients ($n = 14$, 74%) and between the ages of 61 and 74 ($n = 14$, 74%). Seventy-nine percent ($n = 15$) were married and 89% were Cypriots by nationality. Only $n = 3$ patients (16%) had no grammatical knowledge and the majority $n = 11$ (58%) were Gymnasium graduates (3 years in secondary school). In relation to smoking 63% ($n = 12$) of participants in both groups were smoking regardless of the gender or age group **(Table 1)**.

There was no statistically important difference in the demographic characteristics among the participants of the intervention and the control group either among the patients or the family caregivers ($p > 0.05$).

Usual Care

Even though 21% of patients ($n = 4$) were receiving drugs for managing breathlessness, more than half (58%) ($n = 11$) were taking oxygen therapy for managing breathlessness at home. There was no statistically important difference in relation to the usual care that was received by the intervention or the control group ($p > 0.05$).

Among family caregivers 63% ($n = 12$) were females, 74% ($n = 14$) over the age of 61, and 68% ($n = 13$) were spouse/partners.

Baseline Assessment

In the baseline assessment, for breathlessness, of both groups of patients ($n = 19$) using the mBorg scale (0–10), the median breathlessness score was 5.7 ($\pm$1.4) with a range from 3 (lowest) to 9 (highest). The median "Breathlessness at best" by the use of the VAS- Breathlessness (0–10) scale on this first assessment was 2.5 ($\pm$1.3) with 0 as the lowest and five as highest, whereas "Breathlessness at worst" of the same scale was 7.4 ($\pm$1.4) ranging from 4 to 9. Patients rated their ≪Distress due to Breathlessness≫ at 6.5 ($\pm$ 1) on this first assessment of the VAS-Breathlessness scale (0–10) ranging from 3 (lowest) to 10 (highest). The median Anxiety levels of the patients' baseline assessment using the HADS scale (0–21) was 8.9 ($\pm$3.7) and the median Depression levels (on the same scale) was 9.5 ($\pm$5.6) (**Table 2**).

Comparing the results of the baseline assessment between the Intervention and the Control group, there were no statistically important differences among the groups in relation to the parameters of Lung Function (FCV, FEV1), the breathlessness levels as assessed by the two scales and of the Anxiety and Depression levels ($P > 0.05$). However, in the assessment of the VAS-Distress by Breathlessness, the distress expressed by the participants was higher in the intervention group (7.4 $\pm$ 1.5) in relation to the control group (5.4 $\pm$ 1.9) ($p = 0.03$).

Linear correlations of all the variables of patients' first assessment were performed. High positive correlation was shown between patients assessment of Breathlessness (mBorg scale) and Breathlessness at Worst (VAS-Breathlessness) ($r = 0.523$, $p < 0.01$) whereas moderately positive correlation was shown between the former and Breathlessness at Best (VAS-Breathlessness) ($r = 0.34$, $p = 0.154$). Breathlessness as assessed by patients (mBorg scale) showed also high positive correlation with Distress by Breathlessness ($r = 0.423$, $p = 0.071$), moderately positive correlation with Anxiety ($r = 0.384$, $p = 0.105$), and low positive correlation with Depression ($r = 0.279$, $p = 0.247$). Moreover, Distress by Breathlessness showed high

TABLE 2 | Baseline assessments' median of intervention and control group.

Group	Both groups ($n = 19$)		Intervention ($n = 11$)		Control ($n = 8$)		
	Median	St. D.	Median	St. D.	Median	St. D.	*p*-value
FCV	1.9	0.5	1.96	0.54	1.78	0.3	0.373
FEV1	1.3	0.4	1.3	0.39	1.38	0.37	0.645
Breathlessness (mBorg Scale)	5.7	1.4	5.9	1.6	5.5	1.2	0.529
Breathlessness at best (VAS- Breath.)	2.5	1.3	2.8	1.6	2.1	0.8	0.239
Breathlessness at worst (VAS- Breath.)	7.4	1.4	7.6	1.2	7	1.7	0.381
Distress by breathlessness (VAS-Breath.)	6.5	1.9	7.4	1.5	5.4	1.9	0.03
Anxiety (HADS)	8.9	3.7	10.4	2.6	7	4.2	0.071
Depression (HADS)	9.5	5.6	11.3	4.5	7.1	6.3	0.472

TABLE 3 | Pearsons' linear correlations of patient's baseline assessment.

	FCV	FEV1	Breath. mBorg scale	Breath. at best	Breath. at worst	Distress by breath.	Anxiety
FCV	1						
FEV1	,608**	1					
Breath. (mBorg scale)	−0,043	−0,26	1				
Breath. at best	−0,225	−,518*	0,34	1			
Breath. at worst	−0,24	−0,41	,523*	,559*	1		
Distress by breath.	−0,02	−0,18	0,423	,658**	,716**	1	
Anxiety	0,13	−0,277	0,384	0,342	,535*	,554*	1
Depression	0,098	−0,378	0,279	,498*	,483*	,503*	,706**

positive correlation both with Anxiety ($r = 0.554$, $p < 0.01$) and Depression ($r = 0.503$, $p < 0.01$) (**Table 3**).

Family caregivers assessed the levels of breathlessness they believed their spouse/partner experienced with a median of 4.8 (±1.8) on the mBorg scale ranging from 2 to 9. Their median Anxiety levels at baseline assessment using the HADS scale (0–21) was 7.9 (±4.3) and the median Depression levels was 7.2 (±4.4). The burden of family caregivers was rated at 31.7 (±11.9) on the ZBI scale (0–88). Comparing the results of the intervention and the control group at baseline there is statistically important difference $p < 0.05$ in the Anxiety and Burden that family caregivers experience (**Table 4**).

Effect of the Intervention

Breathlessness as assessed by patients, using both scales (mBorg, VAS-Breathlessness), improved between baseline and final assessment in the intervention group whereas it deteriorated in the control group. Likewise this appeared when measuring the Distress due to Breathlessness and the Anxiety of patients where in the intervention group improved by 1.4 in both assessments and in the control group deteriorated by 1.6 and 3.3, respectively. Depression levels deteriorated during time and between the two assessments in both groups by +0.7 in the intervention group and by +1.7 in the control group. Comparing the Spirometry measurements of the two groups' Lung Function, the results in the intervention group did not show changes over the three assessments (FCV: 0.95–0.96, FEV1: 1.3–1.32) whereas in the control group the measurements appeared to show minor improvement (FCV: 1.78–1.92, FEV1: 1.38–1.5) (**Table 5**).

The statistical analysis from patients data also showed that the interaction factor Group X Time was statistically important for the Distress due to Breathlessness ($F = 9.87$, $p < 0.001$) and for the Anxiety ($F = 5.9$, $p = 0.027$) (**Table 6**).

Family caregivers' assessments showed improvement in patient's Breathlessness assessment in the intervention group (−0.6) compared to the control group (+1.5). Anxiety and Depression in the intervention group remained steady whereas it deteriorated in the control group. Burden was also deteriorated in the control group in the final assessment, but it improved in the intervention group (**Table 7**).

The interaction factor Group X Time for family caregivers' measurements was statistically important in all measurements: level of Breathlessness ($p = 0.017$), Anxiety ($p = 0.001$), Depression ($p = 0.038$), and Burden ($p = 0.002$).

The results of the study also show that there is a high positive correlation in the measurements of Breathlessness, using the mBorg scale, between the patients and the family caregivers assessments ($r = 0.619$, $p < 0.01$). This states that a high or low score in the self-assessment of breathlessness by patients relates to the same high or low score in the assessment made by their family caregiver. Moreover, it is important to note that the median level of self-assessment by the patients (5.7 + 1.14) is by one point (on the scale) higher than the assessment made by the family caregiver (4.8 + 1.8) ($t = 1.8$, $p = 0.072$). Moreover, there is

TABLE 4 | Family caregivers baseline assessments' median intervention and control group.

Group	Both groups ($n = 19$)		Intervention (n=11)		Control (n=8)		p-value
	Median	St. D.	Median	St. D.	Median	St. D.	
Patients' breathlessness (mBorg Scale)	4.8	1.8	5.2	1.9	4.3	1.6	0.259
Anxiety	7.9	4.3	9.9	3.3	5.3	4.2	0.023
Depression	7.2	4.4	7.8	4.1	6.3	4.9	0.472
Burden	31.7	11.9	37.4	11.7	24	7	0.007

TABLE 5 | Patients' measurements at baseline assessment and final assessment.

	Intervention ($n = 11$)		Control ($n = 8$)		
	Median	St. Dev.	Median	St. Dev.	p-value
FCV					
Baseline assessment	1.95	0.54	1.78	0.3	0.373
4th week	1.96	0.62	1.92	0.6	0.889
FEV1					
Baseline assessment	1.3	0.39	1.38	0.37	0.645
4th week	1.32	0.43	1.5	0.69	0.523
Breathlessness (mBorg scale)					
Baseline assessment	5.9	1.6	5.5	1.2	0.529
4th week	5.1	2.6	6.4	1.8	0.228
Breathlessness at best (VAS-breath.)					
Baseline assessment	2.8	1.6	2.1	0.8	0.239
4th week	2.6	2.2	3.1	2.6	0.675
Breathlessness at worst (VAS-breath.)					
Baseline assessment	7.6	1.2	7	1.7	0.381
4th week	6.6	1.9	7.4	1.8	0.404
Distress by breathlessness (VAS-breath.)					
Baseline assessment	7.4	1.5	5.4	1.9	0.03
4th week	6	2.3	7	1.5	0.267
Anxiety					
Baseline assessment	10.4	2.6	7	4.2	0.071
4th week	9	4.8	10.3	3.7	0.532
Depression					
Baseline assessment	11.3	4.5	7.1	6.3	0.472
4th week	12	6.4	9.8	5.8	0.439

TABLE 6 | Time X Group interaction for the possible effect of the educational programme to the intervention group- patients.

Measure	Type III sum of squares	df	Mean square	F	Sig.
FCV	0,048	1,179	0.04	0,306	0.624
FEV	0,028	1,125	0.025	0,236	0.661
Breathlessness (mBorg Scale)	6,807	1,585	4.294	2,688	0.097
Breathlessness at best (VAS-Breath.)	3,81	1,584	2.406	1,315	0.279
Breathlessness at worst (VAS-Breath.)	4,431	1,909	2.321	1,999	0.153
Distress by breathlessness (VAS-breath.)	20,707	1,954	10.599	9,876	**<0.001**
Anxiety	49,293	1	49.293	5,9	**0.027**
Depression	8,34	1	8.34	1,181	0.292

TABLE 7 | Family caregivers' measurements at baseline assessment and final assessment.

	Intervention ($n = 11$)		Control ($n = 8$)		
	Median	St. Dev.	Median	St. Dev.	p-value
Patients' breathlessness (mBorg Scale)					
Baseline assessment	5.2	1.9	4.3	1.6	0.259
4th week	4.6	2.7	5.8	2	0.228
Anxiety					
Baseline assessment	9.9	3.3	5.3	4.2	0.023
4th week	9.5	3.5	8.8	3.1	0.647
Depression					
Baseline assessment	7.8	4.1	6.3	4.9	0.472
4th week	7.9	4.3	8.6	4.2	0.72
Burden					
Baseline assessment	37.4	11.7	24	7	0.007
4th week	35.1	10	34.8	6.3	0.928

high positive correlation between the anxiety patients and family caregivers experience ($r = 0.521$, $p < 0.05$) and low positive correlation in relation to depression ($r = 0.268$, $p = 0.266$).

No unintended effects or harms were recorded during the study period by any of the participants (patients or family caregivers) and regardless of the groups they were allocated to.

DISCUSSION

The results of this feasibility control trial and taking under consideration the small sample size revealed that the introduction of the educational program in the patients' intervention group had a moderate effect on breathlessness, on the distress due to the symptom, and to their anxiety level. Moreover, the high correlations in the first assessment between the above suggest that attempting to manage breathlessness would influence positively the distress patients experience and consequently their anxiety.

With the implementation of the educational program improvement was shown in the level of breathlessness experienced by the patients through their self-assessment. Total breathlessness level as assessed using the mBorg scale improved in the intervention group almost by one point in the 10 point scale whereas in the control group it deteriorated by the same degree. The same also happened when assessing their worst breathlessness experience. This is in line with the effect of educational interventions in managing breathlessness in previous studies either applied in the home setting (21–24) or in outpatient breathlessness clinics (38–40, 51, 52).

The implementation of the educational program did not show improvement in lung function since no significant change was identified in FCV and FEV1 measurements in the intervention group. On the contrary there was an improvement in functional capacity in the control group. These findings are in line with those reported by preceding studies by Akinci and Olgun (23) and Eui-Geum (30) regarding the results in the intervention group. However, the findings with regards to the point of improvement in the control group show it is an infrequent finding (30) and needs further study in the following larger scale study and mainly as to the possible effect of family caregiver's involvement in the process. Moreover, in the present study the influence of family caregivers in the implementation of the practical aspects of the intervention was not assessed and needs to be included in the future studies.

In addition, the distress due to breathlessness and anxiety of patients showed improvement by the intervention implemented. Respiratory distress improved in the intervention group compared to the control group which agrees with the findings of previous studies (21–24, 30, 31). Anxiety levels improvement in the intervention group is in line with the results of Olivier et al. (25) study where there was a significant improvement in stress levels. Patients' experienced depression, as assessed, does not appear to decrease during the study in both the control and the intervention groups. This is consistent with the study by Olivier et al. (25) and may be correlated with the diagnosis and treatment itself or other problems patients experience in general and not exclusively due to the process of the implementation of the educational program for managing breathlessness.

It can be argued that the confounding variables (use of oxygen and/or medication as usual care) might be the reason for the improvement of patient's breathlessness. However, as both groups received the usual care and no statistically important difference was shown between the two groups in relation to the above, the implementation of the intervention is suggestive of being the influencing component for the results of the present study.

In the present study, breathlessness appears to have a moderate to low positive association with anxiety and depression in patients, whereas discomfort due to breathlessness has a high positive correlation with both anxiety and depression. From the assessment of the respiratory distress experienced by patients, it suggests that the reported degree reflects the worst level of breathlessness experience. The above can lead to the conclusion that the consequences of the symptom and not the symptom itself are the lead causes for the patients' experienced anxiety and depression together with other factors like the diagnosis, treatment, prognosis, etc. (53, 54). Consequently if the symptom can't be managed effectively, by targeting its effects, the health care professional might be able to reduce or even prevent patient's feelings of anxiety and depression. This must be taken into consideration in the future planning of larger scale studies and explored further to lead to conclusive results, thus designing self-management home-based interventions that target both the symptom and the consequent effects.

The high positive correlation between the assessment of breathlessness by the patients and their family caregiver might have an important implication in the clinical area and the home care setting. This can be argued despite the fact that the experience is subjective and as Hui et al. (55) and Moody and McMillan (56) support, family caregivers can give accurate information to health care professionals about the status of the symptom for their patient, thus helping its management.

The low correlation of the level of breathlessness with anxiety and depression of family caregivers might imply that the degree of the symptom does not have any effect on them. On the other hand the high correlation they showed with burden might suggest that the higher the burden, the higher the anxiety and depression family caregivers experience.

The high correlation of the anxiety experienced by patients with the anxiety of family caregivers is very important for health care professionals because it implies that for every intervention applied to patients in relation to managing anxiety, family caregivers must be involved as they experience anxiety as well (57). However, the results of the present study in relation to the correlation between patients and family caregivers experience of depression, is in discrepancy with the results of the study by Li et al. (57) where there is high positive correlation in the presence of depression. This needs further study in the large research as might be due to the limitations of the present study or other factors like the culture of Cypriot cancer patients and their family caregivers.

Even though there are no data from research in the home care setting to compare the effectiveness of such an intervention on family caregivers' anxiety, depression, and burden, comparisons with studies in the palliative care setting show agreement in the improvement of the burden experienced (58, 59). However, the differences between the studies with the present in the changes shown for anxiety and depression might be due to the period characterizing palliative care (58, 59).

This feasibility study showed that the application of the educational program in the home care setting for supporting patients can be successful. Thus, should proceed with the implementation of a larger scale study taking into consideration all the problems that were faced during the present effort. The implementation of the intervention should be taken into consideration in developing health care programs for cancer patients in the community in the future. Clinical application of the educational program has potential as an adjuvant therapy, along with medication regimens for managing breathlessness for lung cancer patients and also in rehabilitation (24). Cancer nurses

or home care nurses by providing the educational program might be able to achieve, through providing accurate information, support, practical advice, verbal persuasion, and gentle coaxing, the trusting environment that can be helpful to patients (24). Moreover, they need to be careful during the implementation of any supportive exercise intervention because as stated by Olivier et al. (25), in their study with cancer patients, if patients are left alone they do not adhere to the physical exercise programme due to lack of motivation. However, even by the presence of a nurse patients' anxiety can be reduced as stated by Khajian Gelogahi et al. (60) and Osterman et al. (61). In the present study, no qualitative data were collected, thus motivational issues should be taken under consideration in the future studies in order to assess whether patients were lacking motivation to practice the non-pharmacological interventions and whether family caregivers were present during the implementation of the intervention in order to help adhesion. Moreover, it needs further study in relation to the culture of the Cypriot people and family.

The measurements used for both the patients and the family caregivers appear to be suitable for the purpose of the study, and no negative issues were raised by the research associate administering them. The 4 weeks' duration for the implementation of the study, even though it did not give any negative effect, could be prolonged to 6–8 weeks. However, this could be done with caution as it might consequently lead to increased attrition due to either deterioration of patients' condition or loss of motivation by patients or family caregivers.

The positive results of the present study can be utilized for the development of a bigger scale study aiming to establish the benefit for patients with breathlessness due to lung cancer and their family caregivers, through the implementation of this educational programme. In future studies referrals by doctors and nurses of patients from other health care settings, e.g., hospice or hospital, who are going to be transferred at home, can be included in the study as well as patients in the palliative care setting.

The ultimate goal of the researchers is the implementation of the intervention as the first evidence based practice for managing breathlessness, which will be established in cancer home care nursing in the country. Moreover, the intervention might be able to expand and examine its effectiveness with breathless patients due to other chronic diseases (with the necessary modifications) like Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure.

The implementation of this educational program is a step toward achieving breathlessness self-management for patients with lung cancer. This comes in line with the results of previous studies with COPD patients which promoted self-management through various interventions and resulted in improvement in breathlessness and reductions in respiratory-related hospital admissions (62).

In general the development and implementation of educational programmes for the patients and the family caregivers suggests that these can be effective, opening a new area for health care professionals (63–65).

Study Limitations

The main limitation of the study was the small sample size preventing the generalization of the results. Despite the fact that the number of eligible patients that refused to participate was very low ($n = 2$) and the time frame of the study was prolonged to 21 months, it was very difficult to achieve a satisfactory level of participating patients.

Another major limitation of the study was the inevitable inclusion of participants that received medication for breathlessness and/or oxygen therapy. This was due to the fact that in Cyprus non-pharmacological methods are not used regularly in practice by health care professionals in order to help patients deal with breathlessness at home. In the future studies the inclusion or exclusion of patients receiving pharmacological interventions should be carefully decided by researchers. Moreover, due to the nature of the disease and of the symptom, other inclusion or exclusion criteria might be considered more carefully in order to give possibility for increasing the sample size.

CONCLUSION

The results indicate that the implementation of an educational program at home for the management of breathlessness can be of benefit to cancer patients leading to the achievement of improvement in their daily living. Moreover, by establishing such educational programs, health care professionals, and mainly nurses can achieve self-management of symptoms by patients. Nurses and especially home care nurses can make the difference in addressing the problem of breathlessness encountered by patients at home and reduce unnecessary hospitalizations. They are in the ideal position to motivate patients despite the negativeness that exists due to the detrimental effects of the diagnosis and the symptom of breathlessness. It is obvious that not every patient manages to address breathlessness successfully and not every intervention is going to be beneficial for the patients; thus, careful and individualized planning is required, as stated by Akinci and Olgun (23). Moreover, it is not expected that the structured intervention will resolve the problem of breathlessness without effort by patients so there are definitely negative consequences during the process.

Nurse educators and nurse managers need to be more aware of the new era of directing nursing care into the community and into home care and should do their best to support nurses and student nurses to develop and enhance this role. This can be achieved by redesigning the systems of care implementing evidence based home care and developing nurse leaders (66).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cyprus National Bioethics Commitee Independent Body by Cyprus Legislation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ACho: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. CK, ACha, and EP: substantial contributions to the design of the work and revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The videos were kindly offered by the Breathlessness Intervention Service of the Addenbrooke's hospital in Cambridge, England, and the threshold IMT by the George Petrou LTD (Philips Respironics). Thanks to Dr. Ioannides, Dr. Orfanos, Dr. Kyriakou, and the Cyprus Anticancer Society.

REFERENCES

1. Booth S, Silvester S, Todd C. Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. *Palliat Support Care.* (2003) 1:337–44. doi: 10.1017/S1478951503030499
2. Peoples AR, Bushunow PW, Garland SN, Heckler CE, Roscoe JA, Peppone LL, et al. Buspirone for management of dyspnea in cancer patients receiving chemotherapy: a randomized placebo-controlled URCC CCOP study. *Support Care Cancer.* (2016) 24:1339–47. doi: 10.1007/s00520-015-2903-6
3. Wooho B, Jong ML, Jick HH, Chang DY, Hyeon HK, Chin KR, et al. Dyspnea as a prognostic factor in patients with non-small cell lung cancer. *Yonsei Med J.* (2016) 57:1063–9. doi: 10.3349/ymj.2016.57.5.1063
4. Meriggi F. Dyspnea in cancer patients: a well-known and neglected symptom. *Rev Recent Clin Trials.* (2018) 13:84–8. doi: 10.2174/1574887113666180326112116
5. Dyspnea: mechanisms, assessment and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med.* (1999) 159:321–40. doi: 10.1164/ajrccm.159.1.ats898
6. Dorman S, Jolley S, Abemethy A, Currow D, Johnson M, Farquhar M, et al. Researching breathlessness in palliative care: consensus statement of the national cancer research institute palliative care breathlessness subgroup. *Palliat Med.* (2009) 23:213–27. doi: 10.1177/0269216309102520
7. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ. Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. *Palliat Med.* (2010) 24:777–86. doi: 10.1177/0269216310378785
8. Longacre LM, Weber-Raley L, Kent EE. Toward engaging caregivers: inclusion in care and receipt of information and training among caregivers for cancer patients who have been hospitalized. *J Cancer Educ.* (2020). doi: 10.1007/s13187-019-01673-5
9. Malik AF, Gysels M, Higginson JI. Living with breathlessness: a survey of caregivers of breathless patients with lung cancer or heart failure. *Palliat Med.* (2013) 27:647–56. doi: 10.1177/0269216313488812
10. Ullgren H, Tsitsi Th, Papastavrou E, Charalambous A. How family caregivers of cancer patients manage symptoms at home: a systematic review. *Int J Nurs Stud.* (2018) 85:68–79. doi: 10.1016/j.ijnurstu.2018.05.004
11. Bee EP, Barnes P, Luker AK. A systematic review of informal caregivers' needs in providing home-based end-of-life care to people with cancer. *J Clin Nurs.* (2008) 18:1379–93. doi: 10.1111/j.1365-2702.2008.02405.x
12. Cachia E, Ahmedzai HS. Breathlessness in cancer patients. *Eur J Cancer.* (2008) 44:1116–23. doi: 10.1016/j.ejca.2008.03.004
13. Kloke M, Cherny N. Treatment of dyspnoea in advanced cancer patients: ESMO clinical practice guidelines. *Ann Oncol.* (2015) 26 (Suppl. 5):v169–73. doi: 10.1093/annonc/mdv306
14. Navigante AH, Cerchietti LCA, Castro MA, Lutteral MA, Cabalar ME. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnoea perception in patients with advanced cancer. *J Pain Symptom Manag.* (2006) 31:38–47. doi: 10.1016/j.jpainsymman.2005.06.009
15. Huhmann M, Camporeale J. Supportive care in lung cancer: clinical update. *Semin Oncol Nurs.* (2012) 28:e1–10. doi: 10.1016/j.soncn.2012.03.009
16. Di Salvo WM, Joyce MM, Tyson LB, Culkin AE, Mackay K. Putting evidence into practice: evidence-based interventions for cancer-related dyspnea. *Clin J Oncol Nurs.* (2008) 12:341–52. doi: 10.1188/08.CJON.341-352
17. German Guideline Program in Oncology. *Evidence-Based Guideline: Palliative care for patients with incurable cancer. Short version1:1.* (2015). AWMF-Registration number: 128/001.
18. Griner GJ. Ambulatory home oxygen: what is the evidence for benefit, and who does it help? *Respir Care.* (2013) 58:48–64. doi: 10.4187/respcare.01918
19. Booth S, Anderson H, Swannick M, Wade R, Kite S, Johnson M. The use of oxygen in the palliation of breathlessness. *Respir Med.* (2004) 98:66–77. doi: 10.1016/j.rmed.2003.08.008
20. Moore S, Plant H, Bredin M. Dyspnea. In Kearney N, Richardson A, editors. *Nursing Patients with Cancer. Principles and Practice. Ion.* Athens: Ellin Publications. (2011).
21. Özkaptan B, Kapucu S. Home nursing care with the self-care model improves self-efficacy of patients with chronic obstructive pulmonary disease. *Japan J Nurs Sci.* (2016) 13:365–77. doi: 10.1111/jjns.12118
22. Kagaya H, Takahashi H, Sugawara K, Kasai C, Kiyokawa N, Shioya T. Effective home-based pulmonary rehabilitation in patients with restrictive lung disease. *Tohoku J Exp Med.* (2009) 218:215–9. doi: 10.1620/tjem.218.215
23. Akinci AC, Olgun N. The effectiveness of nurse-led, home-based pulmonary rehabilitation in patients with COPD in Turkey. *Rehabil Nurs.* (2011) 36:159–64. doi: 10.1002/j.2048-7940.2011.tb00084.x
24. Padula CA, Yeaw E, Mistry S. A home-based nurse-coached inspiratory muscle training intervention in heart failure. *Appl Nurs Res.* (2009) 22:18–25. doi: 10.1016/j.apnr.2007.02.002
25. Olivier C, Grosbois JM, Cortot B.A, Peres S, Heron C, Delourme J. Real-life feasibility of home-based pulmonary rehabilitation in chemotherapy treated patients with thoracic cancers: a pilot study. *Bio Med Central Cancer.* (2018) 18:178–86. doi: 10.1186/s12885-018-4102-6
26. Bailey CD, Wagland R, Dabbour R. An integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses. *BMC Pulm Med.* (2010) 10:63. doi: 10.1186/1471-2466-10-63
27. Molassiotis A, Charalambous A, Taylor P, Stamataki Z, Summers Y. The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial. *Supportive Care Cancer.* (2015) 23:1637–45. doi: 10.1007/s00520-014-2511-x
28. Thongkhamcharoen R, Breaden K, Agar M, Hamzah E. Dyspnea management in palliative home care: a case series in Malaysia. *Indian J Palliat Care.* (2012) 18:128–33. doi: 10.4103/0973-1075.100835
29. Luckett T, Phillips J, Johnson MJ, Farquhar M, Swan F, Assen T, et al. Contributions of a hand-held fan to self-management of chronic breathlessness. *Eur Respir J.* (2017) 50:1700262 doi: 10.1183/13993003.00262-2017
30. Eui-Geum O. The effects of home-based pulmonary rehabilitation in patients with chronic lung disease. *Int J Nurs Stud.* (2003) 40:873–9. doi: 10.1016/S0020-7489(03)00071-3

31. Hermiz O, Comino E, Marks G, Daffurn K, Wilson S, Harris M. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. *Br Med J.* (2002) 325:938–42. doi: 10.1136/bmj.325.7370.938
32. Wilkes L, White K, O'Riordan L. Empowerment through information: supporting rural families of oncology patients in palliative care. *Austr J Rural Health.* (2000) 8:41–6. doi: 10.1046/j.1440-1584.2000.81258.x
33. Oldham L, Kristjanson L. Development of a pain management programme for family carers of advanced cancer patients. *Int J Palliat Nurs.* (2004) 10:91–9. doi: 10.12968/ijpn.2004.10.2.12455
34. Cyprus Cancer Registry. Progress Report. *Cyprus Ministry of Health.* (2011). Avaliable online at: https://www.moh.gov.cy/MOH/MOH.nsf/All/8CC3E402600EFBCDC22579CA0042F7F4/$file/Cyprus%20Canser%20Registry%20-%20Progress%20Report%20for%202011%20(Data%202006-2008).pdf
35. Cyprus Cancer Registry. *Progress Report Cyprus Ministry of Health.* (2016). Available online at: https://www.moh.gov.cy/moh/moh.nsf/All/A0B4FEC0AC7BB073C22579C7002A9683/$file/%CE%88%CE%BA%CE%B8%CE%B5%CF%83%CE%B7%20%CE%A0%CF%81%CE%BF%CF%8C%CE%B4%CE%BF%CF%85%20%CE%91%CF%81%CF%87%CE%B5%CE%AF%CE%BF%CF%85%20%CE%9A%CE%B1%CF%81%CE%BA%CE%AF%CE%BD%CE%BF%CF%85,%CE%91%CF%8D%CE%B3%CE%BF%CF%85%CF%83%CF%84%CE%BF%CF%82%202016,%20(%CE%A3%CF%84%CE%BF%CE%B9%CF%87%CE%B5%CE%AF%CE%B1%202011-2013).pdf
36. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol.* (2010) 10:1–10. doi: 10.1186/1471-2288-10-1
37. Houts PS, Nezu AM, Nezu CM, Bucher JA. The prepared family caregiver: a problem-solving approach to family caregiver education. *Patient Educ Couns.* (1996) 27:63–73. doi: 10.1016/0738-3991(95)00790-3
38. Booth S, Moffat C, Farquhar M, Higginson IJ, Bausewein C, Burkin J. Developing a breathlessness service for patients with palliative and supportive care needs, irrespective of diagnosis. *J Palliat Care.* (2011) 27:28–36. doi: 10.1177/082585971102700106
39. Bausewein C, Jolley C, Reilly C, Lobo P, Kelly J, Bellas H, et al. Development, effectiveness and cost-effectiveness of a new out-patient breathlessness support service: study protocol of a phase III fast-track randomized controlled trial. *BMC Pulm Med.* (2012) 12:58. doi: 10.1186/1471-2466-12-58
40. Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? findings of a mixed-method randomised controlled trial. *BMC Med.* (2014) 31:194. doi: 10.1186/s12916-014-0194-2
41. Boshuizen CR, Vincent DA, van den Heuvel MM. Comparison of modified Borg scale and visual analog scale dyspnea scores in predicting re-intervention after drainage of malignant pleural effusion. *Support Care Cancer.* (2013) 21:3109–16. doi: 10.1007/s00520-013-1895-3
42. Gerlach Y, Williams MT, Coates AM. Weighing up the evidence–a systematic review of measures used for the sensation of breathlessness in obesity. *Int J Obesity.* (2013) 37:341–9. doi: 10.1038/ijo.2012.49
43. Corner J, O' Driscol M. Development of a breathlessness assessment guide for use in palliative care. *Palliat Med.* (1999) 13:375–84. doi: 10.1191/026921699674958656
44. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? a systematic review. *Palliat Med.* (2007) 21:177–91. doi: 10.1177/0269216307076398
45. Michopoulos I, Douzenis A, Kalkavoura C, Christodoulou C, Michalopoulou P, Kalemi G, et al. Hospital Anxiety and Depression Scale (HADS): validation in a Greek general hospital sample. *Ann Gen Psychiatry.* (2008) 7:4 doi: 10.1186/1744-859X-7-4
46. Papastavrou E, Kalokerinou-Anagnostopoulou A, Alevizopoulos G, Papacostas S, Tsangari H, Sourtzi P. The validity and reliability of the Zarit burden interview in Greek Cypriot carers of patients with dementia. *Nosileftiki.* (2006) 45:439–49.
47. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol.* (2010) 63:535–42. doi: 10.1016/j.jclinepi.2009.06.014
48. Belgacem B, Auclair C, Fedor MC, Brugnon D, Blanquet M, Tournlihac O, Gerbaud. A caregiver educational program improves quality of life and burden for cancer patients and their caregivers: a randomized clinical trial. *Eur J Oncol Nurs.* (2013) 17:870–6. doi: 10.1016/j.ejon.2013.04.006
49. Papastavrou E, Andreou P, Middleton N, Papacostas S, Georgiou-Kyriakou I. Factors associated with quality of life among family members of patients with dementia in Cyprus. *Int Psychogeriatr.* (2014) 26:443–52. doi: 10.1017/S104161021300224X
50. Papastavrou E, Charalambous A, Tsangari H, Karayiannis G. The burdensome and depressive experience of caring what cancer, schizophrenia, and Alzheimer's disease caregivers have in common. *Cancer Nurs.* (2012) 35:187–94. doi: 10.1097/NCC.0b013e31822cb4a0
51. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med.* (2014) 2:979–87. doi: 10.1016/S2213-2600(14)70226-7
52. Chan WLW, Ng CW, Lee C, Cheng P, Cheung KW, Siu KS, et al. Effective management of breathlessness in advanced cancer patients with a program-based, multidisciplinary approach: the "SOB program" in Hong Kong. *J Pain Symptom Manag.* (2016) 51:623–7. doi: 10.1016/j.jpainsymman.2015.10.022
53. Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol.* (2013) 20:1941–8. doi: 10.1245/s10434-012-2793-5
54. Bužgová R, Jarošová D, Hajnová E. Assessing anxiety and depression with respect to the quality of life in cancer inpatients receiving palliative care. *Eur J Oncol Nurs.* (2015) 19:667–72. doi: 10.1016/j.ejon.2015.04.006
55. Hui D, Morgado M, Vidal M, Withers L, Nguyen Q, Chisholm G, et al. Dyspnea in hospitalized advanced cancer patients: subjective and physiologic correlates. *J Palliat Med.* (2013) 16:274–80. doi: 10.1089/jpm.2012.0364
56. Moody L, cMillan S. Dyspnea and quality of life indicators in Hispanic patients and their caregivers. *Health Qual Life Outcomes.* (2003) 1:9 doi: 10.1186/1477-7525-1-9
57. Li Q, Lin Y, Xu Y, Zhou H. The impact of depression and anxiety on quality of life in Chinese cancer patient family caregiver dyads, a cross-sectional study. *Health and Quality of Life Outcomes.* (2018) 16:230. doi: 10.1186/s12955-018-1051-3
58. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin.* (2010) 60:317–39. doi: 10.3322/caac.20081
59. Becqué YN, Rietjens JA, van Driel AG, van der Heide A, Witkamp E. Nursing interventions to support family caregivers in end-of-life care at home: a systematic narrative review. *Int J Nurs Stud.* (2019) 97:28–39. doi: 10.1016/j.ijnurstu.2019.04.011
60. Khajian Gelogahi Z, Aghebati N, Mazloum SR, Mohajer S. Effectiveness of nurse's intentional presence as a holistic modality on depression, anxiety, and stress of cardiac surgery patients. *Holistic Nurs Pract.* (2018) 6:296. doi: 10.1097/HNP.0000000000000294
61. Osterman LCP, Schwartz-Barcott D, Asselin M. An exploratory study of nurses' presence in daily care on an oncology unit. *Nurs Forum.* (2010) 45:197–205. doi: 10.1111/j.1744-6198.2010.00181.x
62. Zwerink M, Brusse-Keizer M, van der Valk DLPM.P, Zielhuis A.G, Monninkhof M.E, van der Palen J, et al. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* (2014) 3. doi: 10.1002/14651858.CD002990.pub3
63. Kuo LM, Huang HL, Liang J, Kwok YT, Hsu WC, Su PL, et al. A randomized controlled trial of a home-based training pro-gramme to decrease depression in family caregivers of persons with dementia. *J Adv Nurs.* (2017) 73:585–98. doi: 10.1111/jan.13157

64. Kwom JH. Overcoming barriers in cancer pain management. *J,Clin Oncol.* (2014) 32:1727–33. doi: 10.1200/JCO.2013.52.4827
65. Kizza BI, Muliira KJ. The influence of a home-based education intervention on family caregivers' knowledge and self-efficacy for cancer pain management in adult patients within a resource-limited setting. *J Cancer Educ.* (2019) 34:1150–9. doi: 10.1007/s13187-018-1421-x
66. Jarrín FO, Pouladi AF, Madigan AE. International priorities for home care education, research, practice, and management: qualitative content analysis. *Nurse Educ Today.* (2019) 83–7. doi: 10.1016/j.nedt.2018.11.020

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 14 October 2020
doi: 10.3389/fonc.2020.522407

Distinct Subgroups of Patients With Lung Cancer Receiving Chemotherapy: A Latent Transition Analysis

Nannan Li[1], Lili Hou[2] and Shu Li[3]*

[1] School of Nursing, Shanghai Jiao Tong University, Shanghai, China, [2] Department of Nursing, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3] Department of Nursing, Shanghai Seventh People's Hospital, Shanghai, China

Objectives: To identify subgroups of patients with lung cancer receiving chemotherapy based on the severity dimension of symptom experience, and to examine changes in membership between these subgroups over time.

Methods: Patients who were scheduled to receive chemotherapy completed the Chinese version of the MD Anderson Symptom Inventory and the revised lung cancer module with a total of 19 symptom items. Data were collected at three time points: two weeks before chemotherapy (T1), after chemotherapy cycle 1 (T2), and after chemotherapy cycle 3 or above (T3). The latent profile analysis and latent transition analysis were used to identify underlying subgroups and describe changes in subgroup membership over time.

Results: From the total sample (*N* = 195), 160 patients completed the symptom assessment at T1, T2, and T3. Two distinct latent symptom profiles of patients could be identified at T1, T2, and T3, which were classified as "Mild" and "Moderate-Severe" profiles. From T1 to T2 and T3, members in the Mild profile were more likely to move to the Moderate-Severe profile. Chemotherapy protocols, prior surgery treatment, and level of education can predict the transitions.

Conclusion: Results provide a better understanding of the patient's different symptom experiences and characteristics. These could help clinicians to anticipate symptom patterns and develop interventions in lung cancer patients who were scheduled to receive chemotherapy for the first time.

Keywords: lung cancer patients, symptom experience, chemotherapy, latent transition analysis, symptom profile

OPEN ACCESS

Edited by:
Patsy Yates,
Queensland University of Technology, Australia

Reviewed by:
Jichuan Wang,
George Washington University, United States
Sangchoon Jeon,
Yale University, United States

****Correspondence:***
Lili Hou
pisces_liz@126.com

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *22 December 2019*
Accepted: *14 August 2020*
Published: *14 October 2020*

Citation:
Li N, Hou L and Li S (2020) Distinct Subgroups of Patients With Lung Cancer Receiving Chemotherapy: A Latent Transition Analysis. Front. Oncol. 10:522407. doi: 10.3389/fonc.2020.522407

INTRODUCTION

Individuals with lung cancer experience multiple symptoms, which are frequently associated with disease and side effects of treatment (1). A number of physical and psychological symptoms were reported during the chemotherapy trajectory (2, 3). An early study has shown that symptoms are related to each other and appear simultaneously, and this phenomenon is described as "symptom

cluster" (4). Compared with single symptoms, clusters may have more deleterious influences on patient outcomes, such as quality of life, functional status, and survival (5). Identifying symptom clusters with validity is paramount for developing targeted interventions aimed at improving clinical outcomes of patients.

Two conceptual approaches to symptom cluster analysis have been demonstrated in the current research. The first common approach was categorizing symptoms, which is a "variable-oriented" approach that focused on symptom variables (6). Most common statistical analysis, such as principal components analysis (PCA) (7), factor analysis (FA) (8), and cluster analysis (9) were used to identify symptom clusters in patients with lung cancer. Emotional or psychological and gastrointestinal symptom clusters were commonly identified. However, individual variability may not have been considered in prior studies. In addition, symptom cluster patterns may change over time (10). The statistical methods mentioned above are advantages in dealing with the cross-sectional data, but for some longitudinal data, they are limited to tracking individual trajectories of symptom experiences over the course of a disease or treatment.

Another approach focused on being "person-oriented" and grouped patients by their symptom patterns. Latent class analysis (LCA) can provide a model-based method to grouping patients using categorical variables (11, 12), and members in each latent class have similar symptom experiences. Latent class analysis is called latent profile analysis (LPA) when using continuous variables (12). Latent transition analysis (LTA) is an extension of LCA that identifies changes in latent class membership using longitudinal data. It can estimate the transition probability of individuals who move from one latent class to another at different time points (11, 12). These analytical methods have received growing attention in cancer symptom cluster research over recent years. A few cross-sectional studies (13–15) classified patients into subgroups using LCA, but a limited number of studies used longitudinal data. Four studies explored subgroups of patients prior and after chemotherapy based on symptom occurrence or severity in a heterogeneous sample (16, 17) or specific cancer type of patients (18, 19). Different distinct subgroups, transition status, and patient characteristics were identified using LCA and LTA.

Previous studies have provided a deep understanding of grouping patients and their changes over time. To our knowledge, there has been no research conducted in patients with lung cancer. To better understand the interindividual variability among patients with lung cancer, this study aims to identify the latent profiles based on the severity dimension of symptom experience, to compare the characteristics of different group patients, and to examine the changes in subgroup membership over time.

MATERIALS AND METHODS

Patient Selection and Study Design

A total of 195 participants were recruited using convenience sampling. Inclusion criteria included: being older than 18 years; able to read and speak Chinese; a diagnosis of lung cancer; scheduled to receive chemotherapy for the first time; chemotherapy protocols were platinum-containing a two-drug combination; and without cognitive impairment.

This study was a prospective, longitudinal study. Data were collected at three time points: two weeks before chemotherapy (T1), within one week after chemotherapy cycle 1, and after cycle 3 or above (T2 and T3). This study was approved by the hospital ethics committee.

Measures

Demographic and Medical Characteristics

Demographic variables included age, gender, educational level, and income. Medical characteristics included prior treatment, comorbidities, cancer stage, and chemotherapy protocols.

Chinese Version of the MD Anderson Symptom Inventory

The MD Anderson Symptom Inventory (MDASI) was used to evaluate the severity of symptoms and symptom interference with daily life (20). It consists of 13 core symptom items and six symptom interference items. Each item was measured using a 0 (not present) to 10 (as bad as can imagine) numeric rating scale. The MDASI has been translated into a Chinese version (MDASI-C), which has good internal consistency (Cronbach's α ranges from 0.84 to 0.90) (21). For this study, the 13 symptom items of the MDASI-C were used.

Revised Lung Cancer Module of the MDASI

The lung cancer module of the MDASI was developed from the MDASI, which consists of cough, constipation, and sore throat (22). Researchers revised this module to measure the symptom burden of Chinese patients with lung cancer (23). The revised version of the lung cancer module consists of cough, expectoration, hemoptysis, chest tightness, constipation, and weight loss. It has an acceptable internal consistency reliability (0.773) and content validity (0.944) (23).

Statistical Analysis

Data were analyzed using Mplus 7.4 and SPSS version 21.0. The LPA and LTA were conducted to identify subgroups of patients with lung cancer and explore transitions in subgroup membership over time, using the symptom severity data. To have a sufficient number of patients with each symptom in LPA and LTA, symptoms that occurred in less than 40% of patients at three time points were excluded from the analysis, and were not used in these studies (17, 24).

First, separate LPAs were performed to identify latent profiles of patients with distinct symptom patterns at three time points. The number of latent profiles for each LPA was determined by model comparison. Several statistical fit indices, including the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC) values, and the sample-size-adjusted BIC (Adj.BIC), were applied to compare the models, with smaller BIC, AIC, and Adj.BIC indicating a better-fitting model (25). Lo–Mendell–Rubin (LMR) adjusted likelihood ratio and the bootstrapped likelihood ratio test (BLRT) were used to compare

the fit of the k and the k − 1 profile model. The significant p value ($p < 0.05$) in these tests would indicate that the k profile model fits data better than the k − 1 profile model (11). The entropy value indicates the profile classification accuracy, and the higher the entropy the better the model is.

After identifying the optimal latent profile model at each time point, we extended the LPA models to LTA to examine the transitions in membership between latent profiles over time. The log-likelihood was used for model comparison and confirmation. To ensure that the maximum likelihood solution can be identified for LTA models, 100 sets of random starting values were used to examine the percentage of potential solutions that converged to the maximum likelihood solution. A higher percentage represents the model was sufficiently well identified (26). In LTA, the possible transitions of latent profiles from T1 → T2 → T3 were estimated. The latent profile membership and transitions were saved as "observed" categorical variables for further analysis. Descriptive statistics in each profile, such as patients' demographics, medical characteristics, and symptom severity, were analyzed and compared using SPSS version 21.0. Logistic regression was used to examine if participant characteristics predict the latent profile transitions.

Before LTA, we tested a longitudinal measurement invariance across time. Measurement invariance assumes that all the measurement parameters are equal across all the time points and the meanings of profiles are the same at each time point, thus the model can be interpreted meaningfully (27). A fixed sequence of model comparison was conducted, which involved configural invariance, weak invariance, strong invariance, strict invariance, invariant factor variances, and invariant factor covariances models with restrictive constraints imposed (28). The chi-square difference test and a change (Δ) in CFI (comparative fit index) were used to compare those six nested models. A non-significant chi-square difference test indicates the current model was more suitable than the previous one; a value of ΔCFI smaller than −0.01 indicates that the hypothesis of invariance should not be rejected. The change in CFI are superior to chi-square difference tests due to their stability (29).

RESULTS

Latent Profile Analyses

In total, 160 patients completed the symptom assessment at T1, T2, and T3. A total of four out of the 19 symptoms (pain, numbness, hemoptysis, and weight loss) that occurred in less than 40% at all three time points were excluded in the LPA. Separate LPAs were performed at each time point. **Supplementary Table 1** provides the fit statistics for models ranging from one to five latent profiles. At T1, the two-profile model had lower AIC, BIC, and Adj.BIC values than the one-profile model, and the LMR and BLRT statistics were significant for the two-profile model, indicating that the two-profile model fits data better than the one-profile model. Although the three-, four-, and five-profile models had lower AIC, BIC, and Adj.BIC values in comparison to the two-profile model, the LMR statistics were not significant. Thus, the two-profile model fits data well. At T2 and T3, similar LPA models were found. The two-profile model was selected as the best fit model at each time point. The entropy value was 0.98, 0.913, and 0.937 at T1, T2, and T3, respectively.

Longitudinal Measurement Invariance

The results of longitudinal measurement invariance across time are presented in **Supplementary Table 2**. Chi-square difference test showed that model 2 is significantly different from model 1, but the change in CFI ($\Delta CFI < 0.01$) supported model 2's constraining equal factor loadings. Other results were based on non-significant chi-square difference tests ($p > 0.05$) and the change in CFI ($\Delta CFI < 0.01$) between models, suggesting that there is evidence of strong, strict, factor variances, and factor covariances being invariant. Thus, equal restrictions were imposed on measurement parameters across time.

Latent Transition Analysis

Latent transition analysis was done using longitudinal data from three time points of measurement. Models with different numbers of latent profiles were compared (**Supplementary Table 3**). Results showed that models with four or more profiles were unidentified because of not converging. The two-profile model had a higher percentage of solutions that converged to the maximum likelihood solution. Additionally, combined with the results of LPAs determined above, we selected the two-profile model (entropy value = 0.953) as the best fit model. According to the mean score of symptom severity at each time point, profile 1 was classified as "Mild," and profile 2 was classified as "Moderate-Severe." **Supplementary Figure 1** shows the mean scores of multiple symptoms by profile from the LTA model.

Differences in Sample Characteristics Among the Two Profiles

Supplementary Table 4 presents the differences in demographic and medical characteristics. At T1, there were significant differences in gender between the Mild and Moderate-Severe profiles. Patients in the Moderate-Severe profile were more likely to be female.

Transitions Between Latent Profiles and Predictors

In LTA, the transition probabilities of latent profiles between three time points were estimated (**Supplementary Table 5**). Members in the Mild profile at T1 were more likely to transition. About 59.1% of them remained at T2, while 40.9% transitioned to the Moderate-Severe profile. Members in the Moderate-Severe profile at T1 were relatively stable; only two patients transitioned to the Mild profile at T2. From T2 to T3, members in two profiles were both relatively stable, with 88.8 and 95.5% of them remaining in the Mild and Moderate-Severe profile. Only 11.2% in the Mild profile moved to the Moderate-Severe profile. 0.5% in the Moderate-Severe profile moved to the Mild profile. From T1 to T3, 53.9% of patients in the Mild profile remained at T3, while 46.1% transitioned to the Moderate-Severe profile. Among patients in the Moderate-Severe profile at T1, 75% of them remained at T3, while 25% transitioned to the Mild profile.

Given the two latent profiles at each time point, there are eight transition patterns from T1 → T2 → T3. As shown in **Supplementary Table 5**, pattern 1 (patients in the Mild profile at T1 remained over time) and pattern 4 (patients in the Mild profile at T1 transitioned to the Moderate-Severe profile at T2 and T3) were the most common transition patterns, accounting for 86.88% of all transitions. Logistic regression revealed that the chemotherapy protocol can predict pattern 1; prior surgery treatment and level of education can predict pattern 4 (see **Supplementary Table 6**).

DISCUSSION

This study is the first to identify subgroups of patients with lung cancer using LPA and LTA. We identified two distinct subgroups of patients based on the severity of 15 symptoms from prior to and following chemotherapy. Patient characteristics among subgroups and the transitions in patients over time were reported. These results provided evidence for the person-oriented method on symptom cluster research.

Two Latent Profiles at Each of the Three Time Points

In this population, two latent symptom profiles could be identified at T1, T2, and T3. Profile 1 was classified as "Mild" and had a relatively low symptom score. Profile 2 was classified as "Moderate-Severe" and had a moderate to severe score for multiple symptoms. This classification based on symptom scores is consistent with symptom control practice guidelines (30, 31). Similar grouping results were found in children undergoing chemotherapy, which were defined as "less severe symptoms" and "severe symptoms" (18). A previous LTA study (17) identified three latent classes (low, moderate, high) using symptom occurrence in oncology (including lung cancer) outpatients, which differs from our findings. This is possibly due to the small sample size, or the different symptom dimension used.

Differences Patient Characteristics Among Two Profiles

There were significant differences in gender among the two profiles before chemotherapy. Patients in the Moderate-Severe profile were more likely to be female. This finding was similar to a prior study (32) which found that females experienced higher levels of physical and psychological symptoms. Although there are relatively fewer females than males in the lung cancer population, more attention and support should be given them.

Transitions Between Latent Profiles and Predictors

In our study, the most common transition between latent profiles occurred in the Mild profile at T1. Among 152 patients, about half of them remained over time, and patients who were receiving the GP protocol were more likely to remain in the Mild profile than those receiving AP protocol. However, the toxic reaction of AP and GP protocols revealed no difference in patients with non-small-cell lung cancer (33). This is mainly because most patients were receiving the AP protocol in this study. Half transitioned to the Moderate-Severe profile after chemotherapy cycles. This finding suggests that some patients experienced a worsening symptom burden after chemotherapy cycle 1, and these symptom experiences may persist during chemotherapy. As reported by Wang et al., this phenomenon may be a predictor of overall survival (34).

Our study showed that patients who had surgery treatment and had low education levels before chemotherapy were more likely to transition to the Moderate-Severe profile over the course of chemotherapy cycles than patients who had no surgery treatment and had high education levels. These predictors were also reported in previous results (32, 35). Thus, symptom support should be given to these patients. Additionally, membership in the two profiles were both relatively stable during chemotherapy cycles. This result has not been reported in patients with lung cancer, but was consistent with the previous report that used LTA to examine the changes in profile status among children patients, which revealed that subgroup membership remains relatively stable from the start to the mid-way cycle of chemotherapy (18).

Implications for Practice

This study focuses on patients receiving chemotherapy for the first time, characterizing patients into "Mild" and "Moderate-Severe" subgroups based on multiple symptom experience. Importantly, patient characteristics between groups were observed and were shown to have great significance for clinical practice. The tailored severity-based symptom intervention strategies can be developed for specific populations. According to our findings, the majority of transitions were found in the "Mild" group, in which patients moved to the "Moderate-Severe" group. This provides a better understanding toward the change in symptom experience over the course of chemotherapy. The predictive factors of transitions may help clinicians to pay more attention to patients who had surgery treatment and had low education levels when implementing interventions. It is important to promote positive transitions in lung cancer patients receiving chemotherapy.

LIMITATIONS AND CONCLUSION

Several limitations should be considered. The relatively small sample size may have limited the number of distinct categories grouping patients. A small group (N = 8) of patients were identified prior to chemotherapy, thus, this classification needs to be further verified. Additionally, we did not evaluate symptoms through the consecutive cycles and after completion of chemotherapy. Finally, four symptoms with occurrence rates of less than 40% were excluded in LPA and LTA, and the effects of these symptoms may be ignored.

In conclusion, we identified the Mild and Moderate-Severe subgroups in patients with lung cancer prior to and following their cycles of chemotherapy. Two distinct symptom patterns were observed in symptom scores. Patients in the Mild profile

were more likely to move to the Moderate-Severe profile after the cycles of chemotherapy. These findings could help clinicians to anticipate symptom patterns and develop interventions in lung cancer patients who were scheduled to receive chemotherapy for the first time.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of Shanghai Seventh People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH provided guidance for the design of the study and revised the manuscript. NL and SL collected the data. NL analyzed the data and wrote the manuscript. All authors contributed significantly and were in agreement with the content of the manuscript.

ACKNOWLEDGMENTS

We express our profound gratitude to all patients that participated to this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.522407/full#supplementary-material

REFERENCES

1. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *J Pain Symptom Manage*. (2000) 19:137–53. doi: 10.1016/s0885-3924(99)00150-5
2. Genc F, Tan M. Symptoms of patients with lung cancer undergoing chemotherapy and coping strategies. *Cancer Nurs*. (2011) 34:503–9. doi: 10.1097/ncc.0b013e31820b7024
3. Silvoniemi M, Vasankari T, Loyttyniemi E, Valtonen M, Salminen E. Symptom assessment for patients with non-small cell lung cancer scheduled for chemotherapy. *Anticancer Res*. (2016) 36:4123–8.
4. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum*. (2001) 28:465–70.
5. Gift AG, Jablonski A, Stommel M, Given CW. Symptom clusters in elderly patients with lung cancer. *Oncol Nurs Forum*. (2004) 31:202–12. doi: 10.1188/04.ONF.202-212
6. Miaskowski C, Aouizerat B, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessments in patients with cancer. *JNCI Monographs*. (2007) N37:39–46. doi: 10.1093/jncimonographs/lgm003
7. Henoch I, Ploner A, Tishelman C. Increasing stringency in symptom cluster research: a methodological exploration of symptom clusters in patients with inoperable lung cancer. *Oncol Nurs Forum*. (2009) 36:E282–92. doi: 10.1188/09.ONF.E283-E292
8. Wong ML, Cooper BA, Paul SM, Levine JD, Conley YP, Wright F, et al. Differences in symptom clusters identified using ratings of symptom occurrence versus severity in lung cancer patients receiving chemotherapy. *J Pain Symptom Manage*. (2017) 54:1–10. doi: 10.1016/j.jpainsymman.2017.04.005
9. Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC. Symptom clusters and relationships to symptom interference with daily life in Taiwanese lung cancer patients. *J Pain Symptom Manage*. (2008) 35:258–66. doi: 10.1016/j.jpainsymman.2007.03.017
10. Kirkova J, Walsh D, Aktas A, Davis MP. Cancer symptom clusters: old concept but new data. *Am J Hosp Palliat Care*. (2010) 27:282–8. doi: 10.1177/1049909110364048
11. Nylund K, Bellmore A, Nishina A, Graham S. Subtypes, severity, and structural stability of peer victimization: what does latent class analysis say? *Child Dev*. (2007) 78:1706–22. doi: 10.2307/4620733
12. Collins LM, Lanza ST. *Latent Class and Latent Transition Analysis: With Applications in the Social, Behavioral, and Health Science*. Hoboken, NJ: John Wiley & Sons. (2010). p. 8–14.
13. Doong SH, Dhruva A, Dunn LB, West C, Paul SM, Cooper BA, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. *Biol Res Nurs*. (2015) 17:237–47. doi: 10.1177/1099800414550394
14. Illi J, Miaskowski C, Cooper B, Levine JD, Dunn L, West C, et al. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine*. (2012) 58:437–47. doi: 10.1016/j.cyto.2012.02.015
15. Miaskowski C, Cooper BA, Melisko M, Chen LM, Mastick J, West C, et al. Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. *Cancer*. (2014) 120:2371–8. doi: 10.1002/cncr.28699
16. Jeon S, Sikorskii A, Given BA, Given CW, Redeker NS. Latent transition analysis of the symptom experience of cancer patients undergoing chemotherapy. *Nurs Res*. (2019) 68:91–8. doi: 10.1097/NNR.0000000000000332
17. Miaskowski C, Cooper BA, Aouizerat B, Melisko M, Chen LM, Dunn L, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. *Eur J Cancer Care*. (2017) 26:1–12. doi: 10.1111/ecc.12437
18. Wang JC, Jacobs S, Dewalt DA, Stern E, Gross H, Hinds PS. A longitudinal study of promis pediatric symptom clusters in children undergoing chemotherapy. *J Pain Symptom Manage*. (2017) 55:359–67. doi: 10.1016/j.jpainsymman.2017.08.021
19. Dirksen SR, Belyea MJ, Wong W, Epstein DR. Transitions in symptom cluster subgroups among men undergoing prostate cancer radiation therapy. *Cancer Nurs*. (2016) 39:3–11. doi: 10.1097/NCC.0000000000000236
20. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients the M. D. Anderson symptom inventory. *Cancer*. (2000) 89:1634–46. doi: 10.1002/1097-0142(20001001)89:7<1634::aid-cncr29>3.0.co;2-v
21. Wang XS, Wang Y, Guo H, Mendoza TR, Hao XS, Cleeland CS. Chinese version of the M. D. Anderson symptom inventory: validation and application of symptom measurement in cancer patients. *Cancer*. (2004) 101:1890–901. doi: 10.1002/cncr.20448
22. Mendoza TR, Wang XS, Lu C, Palos GR, Liao ZX, Mobley GM, et al. Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson symptom inventory. *Oncologist*. (2011) 16:217–27. doi: 10.1634/theoncologist.2010-0193
23. Zhang LL, Zang Y. Revision and evaluation of the lung cancer module of the MD Anderson symptom inventory. *Tumor*. (2013) 33:441–5.
24. Miaskowski C, Dunn L, Ritchie C, Paul SM, Cooper B, Aouizerat BE, et al. Latent class analysis reveals distinct subgroups of patients based on symptom

occurrence and demographic and clinical characteristics. *J Pain Symptom Manage*. (2015) 50:28–37. doi: 10.1016/j.jpainsymman.2014.12.011
25. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a monte carlo simulation study. *Struct Equ Modeling*. (2007) 14:535–69. doi: 10.1080/10705510701575396
26. Lanza ST, Bray BC. Transitions in drug use among high risk women: an application of latent class and latent transition analysis. *Adv Appl Stat Sci*. (2010) 3:203. doi: 10.1021/jp900614a
27. Nylund KL. *Latent Transition Analysis: Modeling Extensions and an Application to Peer Victimization*. Los Angeles, CA: University of California. (2007).
28. Wang M, Elhai JD, Dai X, Yao S. Longitudinal invariance of posttraumatic stress disorder sympt oms in adolescent earthquake survivors. *J Anxiety Disord*. (2012) 26:263–70. doi: 10.1016/j.janxdis.2011.12.009
29. Cheung GW, Rensvold RB. Evaluating goodness-of-fit indices for testing measurement invariance. *Struct Equ Model*. (2002) 9:233–55. doi: 10.1207/s15328007sem0902_5
30. Grossman SA, Benedetti C, Brock C, Cleeland C, Coyle N, Dube JE, et al. NCCN practice guidelines for cancer pain. *Oncology*. (2000) 14:135–50.
31. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology*. (2000) 14:151–61.
32. Akin S, Can G, Aydiner A, Ozdilli K, Durna Z. Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. *Eur J Oncol Nurs*. (2010) 14:400–9. doi: 10.1016/j.ejon.2010.01.003
33. Zhu YM, Gan YL, Xu HY, Chen WH, Dai HP. Clinical effectiveness of pemetrexed combined with cisplatin chemotherapy for advanced and maintenance treatment for patients with non-small-cell lung cancer. *Eur Rev Med Pharmacol Sci*. (2018) 22:1943–7.
34. Wang XS, Shi QL, Lu C, Basch EM, Johnson VE, Mendoza TR, et al. Prognostic value of symptom burden for overall survival in patients receiving chemotherapy for advanced non small cell lung cancer. *Cancer*. (2010) 116:137–45. doi: 10.1002/cncr.24703
35. Wong ML, Paul SM, Cooper BA, Dunn LB, Hammer MJ, Conley YP, et al. Predictors of the multidimensional symptom experience of lung cancer patients receiving chemotherapy. *Support Care Cancer*. (2017) 25:1931–9. doi: 10.1007/s00520-017-3593-z

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 26 October 2020
doi: 10.3389/fonc.2020.591799

Nursing and Allied Health Research Priorities in the Care of Patients With Thoracic Malignancies: An International Cross-Sectional Survey

Alex Molassiotis[1], Anne Fraser[2], Melissa Culligan[3], Pippa Labuc[4], Degi L. Csaba[5] and Andreas Charalambous[6]*

[1] School of Nursing, The Hong Kong Polytechnic University, Hong Kong, Hong Kong, [2] Blood and Cancer Service, Auckland City Hospital, Auckland, New Zealand, [3] School of Medicine, University of Maryland Medical Center, Baltimore, MD, United States, [4] Department of Occupational Therapy, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [5] Faculty of Sociology and Social Work, Babeş-Bolyai University, Cluj-Napoca, Romania, [6] Nursing Department, Cyprus University of Technology, Limassol, Cyprus

OPEN ACCESS

Edited by:
Ibiayi Dagogo-Jack, Massachusetts General Hospital Cancer Center, United States

Reviewed by:
Lara Traeger, Massachusetts General Hospital Cancer Center, United States
Melina Elpi Marmarelis, University of Pennsylvania, United States

***Correspondence:**
Alex Molassiotis
alex.molasiotis@polyu.edu.hk

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *05 August 2020*
Accepted: *05 October 2020*
Published: *26 October 2020*

Citation:
Molassiotis A, Fraser A, Culligan M, Labuc P, Csaba DL and Charalambous A (2020) Nursing and Allied Health Research Priorities in the Care of Patients With Thoracic Malignancies: An International Cross-Sectional Survey. Front. Oncol. 10:591799. doi: 10.3389/fonc.2020.591799

Background: There is currently no evidence of research priorities from nurses and allied health professionals working in the field of thoracic malignancies, which could provide strategic directions for funders, policy makers, and researchers.

Objective: The aim of this study is to identify the priorities for lung cancer and other thoracic malignancies research and practice in nurses and allied health professionals.

Methods: Descriptive cross-sectional web-based international survey conducted through international societies' membership lists.

Results: Participants included 152 nurses and allied health professionals. Key priority categories were related to developing and evaluation interventions; symptom management interventions; health care system issues; treatment-related research (immunotherapy; targeted therapies); persistent/late effects management (fatigue; pulmonary toxicity); risk reduction, and screening research. The specific topic with the highest endorsement (80.9%) was the development of interventions to improve quality of life. Symptom management interventions, particularly for pain, dyspnea, and fatigue, were also highly endorsed. Health care system topics were related to delivery of care and included nurse-/allied health-led care (67.5%), working with the multidisciplinary team (67.5%), continuity of care (69.2%), and access to care (67.5%). Topics around screening/early detection research were highly endorsed too.

Conclusion: A clear focus (and need) for research in interventions to improve quality of life and symptom management, particularly for pain, dyspnea, and fatigue was also established, alongside healthcare system issues and screening research.

Implications for practice: International societies and funding bodies could consider these topics in their funding decisions and in shaping their strategic directions in the care of patients with thoracic malignancies.

Keywords: lung cancer, research priorities, nursing, allied health professionals, thoracic malignancies, quality of life, symptoms, interventions

INTRODUCTION

Shifts in cancer care have seen the introduction of more effective treatments such as precision medicine, targeted therapies, and immunotherapy. These novel agents have led to improvements in survival, clinical outcomes, and more focus on prevention, early detection, survivorship, supportive and palliative care. As cancer care changes, so may be the impact of these changes on the patients and their families, creating new or different unmet needs. Nurses and Allied Health professionals need to continue developing new knowledge and addressing clinical unmet needs in order to provide dynamically efficient and patient-centred care. Information on research priorities can provide strategic directions for a particular area of care, highlight a gap in the current knowledge, can be a resource for researchers, policy makers and funding agencies, and potentially can increase the likelihood of research findings influencing clinical practice, care policies, and education. Furthermore, such surveys setting research agendas can elevate the voices of nurses and allied health professionals to shape innovations in care, add value and impact in such innovations by delivering data, creates engaged professionals and allows them to be advocates for their patients, and families' issues of importance.

Identifying research priorities is often carried out by national or international societies and organisations. For example, the Oncology Nursing Society in USA is conducting research priority surveys almost every four years for the past three decades. Its latest report highlights the priority areas being around patient adherence, screening in minority groups, symptom control, managing late effects, and delivery of survivorship care (1). Other reports focus on specific cancers or specific pathways of care. For example, research in young adults with haematological cancers (n = 80) has identified clinical medicine and psychosocial care as research areas of the highest priority (2). A nurse-patient collaboration project supported by the United Kingdom Oncology Nursing Society (n = 50 nurses and 18 patients) showed a high level of consensus on research related to prevention, screening, early diagnosis, and psychological care across the cancer trajectory (3). Research needs and priorities have been identified in the area of breast cancer (4), kidney research (5), expert panels, or caregivers (6), and prostate cancer survivorship (7) through Delphi consensus. In lung cancer care there is only a small-scale (n = 42) survey of health professionals in Australia, highlighting that reducing the time from presentation of symptoms to diagnosis and treatment was the highest priority while other priorities included timely referral to palliative care or unmet needs in vulnerable populations (8). Another interesting approach to measuring priorities has been the Stakeholder Engagement in quEstion Development and Prioritization (SEED) Method, which is a multi-stakeholder methodology that uses principles of community engagement and causal modelling to develop health research questions that reflect the priorities of patients, clinicians, and other community stakeholder (9). According to the findings of the latter study, the resulting research agenda poses questions on how a broad range of topics including access to care, support systems and coping mechanisms, social determinants of health, and quality of care impacts lung cancer outcomes (9).

The management of lung cancer and other thoracic malignancies has seen significant changes over the past decade with the development of novel therapies, improvements in palliative and supportive care, and earlier diagnosis (5). Also, there is currently no evidence on research priorities from nurses and allied health professionals, which could reflect unmet needs in lung cancer care across the cancer continuum. Hence, the overall aim of the current study is to identify the priorities for lung cancer care research and practice in nurses and allied health professionals. The results from this study can be used to inform the development of lung cancer care-specific research priorities in the wider lung cancer nursing and allied health community and contexts.

METHODS

Design

This study is a cross-sectional international web-based survey. Survey participants were recruited from the email membership lists of international societies, such as nursing and allied health membership of the International Association for the Study of Lung Cancer (IASLC), International Thoracic Oncology Nursing Forum (ITONF), European Oncology Nursing Society (EONS), Multinational Association of Supportive Care in Cancer (MASCC), and the UK National Lung Cancer Forum (UKNLCF). Individuals participating could have forwarded the survey link to other individuals in their network or even to their national society, as requested through the survey's information letter. We have also used social media, with the survey being disseminated through Twitter, Facebook, and Linkedin. The survey information letter asked individuals to complete the survey only if they worked exclusively or mostly with lung cancer patients. For nursing, most of the societies were lung cancer specific and hence it was expected that all nursing participants would be working most of their time with lung cancer patients. For allied health professionals, while we left this to be self-defined, we restricted the types of professionals that could participate to a few only by disseminating the survey in societies for occupational and physical therapy, social work, and psycho-oncology only as those work more closely with cancer patients albeit acknowledging this would be a small part of their workload with the exception of psycho-oncology. The sample represents diverse backgrounds in academic and practice settings. The term "lung cancer" in this study reflects patients with any thoracic malignancy. The term "care" includes care provided across the disease trajectory.

Data Collection

The survey questionnaire on research priorities developed by the Oncology Nursing Society (ONS) (1) was the basis for the questionnaire of this study. Permission was obtained from ONS and the questionnaire was adapted to reflect specific areas of lung cancer care not reflected in the original ONS

questionnaire. Questionnaire adaptation was done through discussions with lung cancer care experts and literature on the topic and resulted only in the addition of items not covered in the original ONS survey under the same domains. Six experts (4 nurses, 1 occupational therapist, and 1 psycho-oncologist) also commented on the content, clarity of the questions posed, or wording through two rounds of comments. The web survey was developed through an in-house e-survey platform. The final questionnaire included a section on the participants' characteristics (sex, age group, society membership, country of residence, professional discipline, years of experience, highest degree, and primary work setting). Questions on research priorities were then broken down into categories/sections, including developing and evaluating interventions (50 statements which also include items on developing interventions for nearly 30 symptoms and 20 complementary therapies), screening research (3 statements), reducing social inequalities in lung cancer care (3 statements), symptom management interventions (with specific focus on 28 symptoms and 3 more general symptom statements), treatment- and diagnosis-related research (14 statements), persistent and late effects (list of 19 late effects), risk reduction in cancer patients and survivors (10 statements), survivorship issues (5 statements), healthcare systems (26 statements), and caregivers issues (12 statements). All statements were rated on a 4-point scale, with "1" representing highest priority and "4" representing not at all of a priority. Participants were then additionally asked to select from a list of 28 symptoms the three most difficult symptoms to manage and the three most distressing symptoms for lung cancer patients. Ethical approval for the conduct of the study was obtained from the Human Research Ethics Review Committee of the Hong Kong Polytechnic University. Email lists were used through society administrators after permission was obtained from the respective chair/president/board. Society members received an email invitation with a letter explaining the purpose of the study, the anonymous nature of the survey, the societies involved, and ethical approval, asking their voluntary participation and stating that completion of the questionnaire would imply consent. A reminder email was sent to the same email lists after 3–4 weeks. The survey was open for four months until late 2019. There was no clear information from most of the societies on the specific number of nurses and allied health professionals, as membership included many different disciplines, and hence no response rate could be calculated. Although there was no predetermined sample size calculation as the population size was not known, as a rule of thumb we expected to have at least 100 responses in order to have any meaningful results.

Data Analysis

Data analysis was primarily based on descriptive statistics. Frequencies and percentages were calculated for each item of each domain of the survey tool. A rank order of these frequencies was tabulated. The percentage scores refer to proportions of participants who rated the item at a specific priority score (i.e. score 1 for "high priority" to score 4 "low/no priority"). Comparisons were made with regards to education (degree holders or lower vs. postgraduate education) and work setting (inpatient/outpatient/ambulatory setting vs. home care/palliative care vs. educational setting) without the use of any formal statistics.

RESULTS

Sample Characteristics

The sample included 152 participants, most of whom (n = 136) were from the nursing discipline. They had an average of 13.4 (SD = 9.8) years of experience working with patients with thoracic malignancies. Most were coming from the USA, UK or other European countries and were members of IASLC, EONS, or ITONF providing an international reach to the required sample. More details are presented in **Table 1**.

Research Priorities

Out of the top twenty priorities, the categories of developing and evaluating interventions, symptom management interventions and health care system topics had four specific items selected each. Persistent/late effects, treatment-related research, risk reduction in cancer patients and survivors and screening research had two items selected as priorities each. As the two topics selected in persistent/late effects included symptoms, this combined with the category of symptom management interventions makes the symptoms research as the top priority area. Also, development of interventions in different categories included primarily interventions for symptom control, containing also self-management symptom interventions (69.7%). Looking at specific items selected as top priorities, the highest priority was on interventions to improve quality of life (80.9%). The next two priorities with 78.8 and 73% each were related to interventions for the management of dyspnea and pain, respectively. Other key symptoms that were in the top twenty priority list included fatigue management, and managing pulmonary toxicity and depression (with anxiety management being the 21st topic selected with 61.3%). Palliative care interventions were high in the priority list (72.4%) as was research related to immunotherapy and targeted therapies (around 70%). Health care system topics of high priority included continuity of care, access to care, nurse-led care, and working with the multidisciplinary team. Risk reduction through smoking cessation approaches and screening/early detection, particularly in undeserved and/or uninsured people, accounted for the remaining top priorities. A detailed description of the top twenty priorities is presented in **Table 2**.

The lowest priority (all <20%) was related to all 15 statements about research in different types of complementary and alternative medicine. Other low priority areas, selected by less than 30% of participants, included social support and counselling interventions (30%), interventions that use technology to address symptoms (29.6%), spiritual care (29.6%), bereavement research

TABLE 1 | Sample characteristics (n = 152).

		N	%
Gender	Male	24	15.8
	Female	128	84.2
Age group	20–29	9	5.92
	30–39	38	25
	40–49	41	26.97
	50–59	48	31.58
	>60	16	10.53
Country of residence	USA	30	19.7
	UK	21	13.9
	Ireland	14	9.3
	Iceland	9	5.9
	Greece	8	5.3
	Australia	8	5.3
	Cyprus	7	4.6
	Turkey	7	4.6
	Sweden	7	4.6
	Belgium	5	3.3
	Canada	5	3.3
	Europe (other)	19	12.3
	Asia	8	5.3
	Africa	4	2.6
Society membership*	IASLC	47	30.9
	EONS	42	27.6
	ITONF	27	17.8
	NLCFN	9	5.9
	Other society or multiple society membership	49	32.2
Professional discipline	Nursing	136	89.5
	Physiotherapy/Occupational therapy	5	3.3
	Social Work/Psychology	3	1.95
	Others (Speech therapy, Doctor, Pharmacy, Program director, Advocate, Oncocoach)	8	5.25
Highest degree	Associate degree/Diploma	11	7.2
	Bachelor degree	29	19.1
	Master's degree	72	47.4
	DNP/Professional doctorate	6	3.9
	Doctoral degree (PhD)	34	22.4
Primary place of work	Inpatient care	35	23
	Ambulatory/outpatient care	55	36
	Hospice/palliative care	16	10
	University/College	34	22.1
	Others (research center, home care, day-care, medical center, advocacy, cancer society, government cancer control	12	7.90

*Participants could choose more than one option, hence percentage in higher than 100%
IASLC, International Association for the Study of Lung Cancer; EONS, European Oncology Nursing Society; ITONF, International Thoracic Oncology Nursing Forum; NLCFN, National Lung Cancer Forum for Nurses (UK).*

(28.9%), bio-informatics (25%), and non-medical prescribing (24.8%). In relation to the list of 28 symptoms, the item with the lowest endorsement was unexplained weight loss (38.2%), while cough research was endorsed by 54% of participants.

Table 3 presents the top ten most difficult to manage symptoms and the most distressing symptoms for patients. Pain, dyspnea, and fatigue were the top three symptoms identified both in terms of difficulty in managing and being distressing for patients. Interestingly, cough, being a common symptom in lung cancer, was 9th in the list of difficult symptoms to manage in the current study, but was recognized as the 4th most distressing symptom for patients.

Endorsement of topics was also assessed in terms of highest degree held (Bachelor degree holders and below vs those having postgraduate education) and the work place (inpatient/outpatient/ambulatory setting versus homecare/hospice/palliative care versus university/college setting). Regarding education level, the key priorities were consistent between the two groups, with symptom management and quality of life being the common priorities. The group with baccalaureate education and below was further concerned on access to care, whereas those with postgraduate education highlighted research in immunotherapy as a key priority for them. In terms of priority endorsement based on work setting, symptom management interventions and interventions to improve quality of life were also common across all three groups. However, the hospital-based group prioritized other clinical topics (i.e. management of pain and dyspnea and immunotherapy research), the community/palliative care group had additional emphasis on psychosocial adjustment, while the education-based group had additional emphasis on self-management interventions and health care system aspects such as continuity of care and access to care (**Table 4**).

DISCUSSION

This is the first survey of nursing and allied health professionals focusing on their research priorities in the field of thoracic malignancies. Key priorities were about developing interventions to improve quality of life, symptom management, and palliative care. Endorsements of high priority also included health care system-related research reflecting issues around the delivery of care, treatment-related research (immunotherapy and targeted therapy), persistent/late effects management of pulmonary toxicity and fatigue, smoking cessation as a way to reduce risk in patients and screening/early detection research. Pain, dyspnea, and fatigue were the highest ranked symptoms both in terms of difficulty in managing them and the distress impacting upon patients.

The focus on development and evaluation of interventions to improve quality of life and symptom management reflects the significant unmet needs of patients with lung cancer, who are often diagnosed at a late stage experiencing at the same time a complex array of supportive care needs, while our knowledge on how to manage these needs is fairly fragmented (10). This is also an area of care that has produced new challenges as a result of the introduction of newer treatments with complex and difficult symptoms to manage (11). Pain was endorsed as the most difficult symptom to manage, perhaps reflecting more complex pain syndromes in largely palliative care patients where the evidence-base is limited and the research investment minimal. Dyspnea has received more research attention over the years, but still our knowledge is not adequate to provide complete relief to patients. However significant efforts in finding new interventions continue and new approaches are developed (12, 13). Managing (refractory) fatigue is a topic featuring at the top of complex, distressing and difficult to manage symptoms for decades now across cancer groups, and was also identified as the most difficult

TABLE 2 | Top 20 Research priorities in lung cancer care.

Rank	Theme	Specific focus	High priority = 1	2	3	Not at all = 4	Mean*	SD
1	Develop and evaluate interventions	Interventions to improve quality of life	123 (80.9%)	25 (16.4%)	3 (2%)	1 (0.7%)	1.22	0.5
2	Symptom management interventions	Dyspnea/Shortness of breath	108 (78.8%)	23 (16.8%)	5 (3.6%)	1 (0.7%)	1.26	0.56
3	Symptom management interventions	Pain (e.g., Chest pain, bone pain)	100 (73%)	32 (23.4%)	4 (2.9%)	1 (0.7%)	1.31	0.56
4	Develop and evaluate interventions	Assistance with management of symptoms	101 (72.4%)	37 (24.3%)	2 (1.3%)	1 (0.7%)	1.29	0.52
4	Develop and evaluate interventions	Palliative care interventions (home/community-based and hospital-based)	110 (72.4%)	37 (24.3%)	2 (1.3%)	1 (0.7%)	1.42	0.67
6	Treatment- and diagnosis-related research	Immunotherapy	92 (71.9%)	30 (23.4%)	6 (4.7%)	0	1.33	0.56
7	Develop and evaluate interventions	Self-management interventions to improve symptom control	86 (69.7%)	36 (23.7%)	7(4.6)	3 (2)	1.39	0.67
8	Treatment- and diagnosis-related research	Targeted therapies	89 (69.5%)	33 (25.8%)	6 (4.7%)	0	1.35	0.57
9	Health care systems	Continuity of care	81 (69.2%)	28 (23.9%)	12 (10.3%)	1 (0.9%)	1.38	0.61
10	Risk reduction in cancer patients and survivors	Smoking cessation	83 (68.6%)	28 (23.1%)	7 (5.8%)	3 (2.25%)	1.42	0.72
11	Health care systems	Access to care	79 (67.5%)	28 (23.9%)	10 (8.5%)	0	1.41	0.64
11	Health care systems	Work with the multi-disciplinary team	79 (67.5%)	28 (23.9%)	7 (6%)	3 (2.6%)	1.44	0.72
11	Health care systems	Nurse-led/AHP-led care	79 (67.5%)	28 (23.9%)	5 (4.3%)	5 (4.3%)	1.45	0.77
14	Persistent and late effects	Fatigue	82 (67.2%)	31 (25.4%)	8 (6.6%)	1 (0.8%)	1.41	0.65
15	Symptom management interventions	Fatigue	91 (66.4%)	41 (29.9%)	5 (3.6%)	0	1.37	0.55
15	Persistent and late effects	Pulmonary toxicity	81 (66.4%)	38 (31.1%)	2 (1.6%)	1 (0.8%)	1.37	0.56
17	Risk reduction in cancer patients and survivors	Screening/early detection	78 (64.5%)	29 (24%)	12 (9.9%)	2 (1.7%)	1.49	0.74
18	Symptom management interventions	Depression	88 (64.2%)	40 (29.2%)	8 (5.8%)	1 (0.7%)	1.43	0.64
19	Screening research	Screening and early detection for lung cancer in underserved and/or underinsured individuals	92 (62.6%)	34 (23.1%)	16 (10.9%)	5 (3.4%)	1.55	0.82
20	Screening research	Screening for lung cancer in at-risk individuals	95 (62.5%)	37 (24.3%)	12 (7.9%)	3 (2%)	1.48	0.73

**Lower mean scores represent higher priority (1 = highest priority, 4 = lowest priority).*

TABLE 3 | Top ten most difficult symptoms to manage and most distressing symptoms for lung cancer patients.

	Difficult to manage symptoms		Distress from symptoms	
	%	Rank order	%	Rank order
Pain (e.g., Chest pain, bone pain)	53.7	1	49.8	1
Dyspnea/Shortness of breath	43.5	2	47.8	2
Fatigue	43.1	3	26.3	3
Functional impairment	16.7	4	17.6	5
Depression	14.9	5	10.8	8
Anxiety	13	6	16.6	6
Cachexia	13	6	5.9	10
Peripheral neuropathy	13	6		
Cough	10.2	9	20.6	4
Cognitive dysfunction	9.3	10		
Sleep/wake disturbances			14.7	7
Immunosuppression-related symptoms			6.6	9

symptom to manage and the most distressing for patients in the ONS 2013 survey (1). A number of interventions, primarily non-pharmacological ones, have shown promising results for several symptoms (14, 15), although the uptake of such approaches in clinical practice is often less than optimal. Pulmonary toxicity has received high endorsement as a key research area, not only reflecting perhaps the frustration of clinicians in managing this difficult symptom but also as an example where a multidisciplinary effort is needed in order to provide optimal care, connected with the health care systems related topic in the survey.

Cough is a symptom that 57–67% of patients with lung cancer experience (16) and is severe enough to require treatment in as many as 62% of them (17). The complexity of its treatment is also highlighted in the most recent clinical guidelines developed by the American College of Chest Physicians (18). However, it was not endorsed by our sample as a key research priority on symptoms, although it was recognized as the fourth most distressing symptom for patients. A possible interpretation of this finding lies in the fact that lung cancer-related cough is an important unmet clinical need for which morbidity and distress are often underestimated by health professionals (16). This discrepancy needs to be elucidated a little more clearly in the future.

Psychosocial care topics received low endorsement generally, including coping, psychosocial adjustment, bereavement care, and spiritual care, with the exception of managing depression. Only those participants working in the community and palliative care settings endorsed these higher than the rest of the participants. Psychosocial care is key to improving quality of life, and often a high priority area in many past surveys (1–3). It would be useful in the future, perhaps with qualitative research, to explore this discrepancy further in the lung cancer field.

Delivery of care and health care system-related issues have been the focus of nursing and allied health for a couple of decades with the identification and evaluation of service provision, service models and early palliative care, reviewed elsewhere (11). The changing face of cancer care is an area where the specialized roles

TABLE 4 | Differences and similarities in research priorities based on education and work setting.

Participants with BSc/Diploma	N (%)	Participants with MSc, DNP, PhD	N (%)
Interventions to manage Pain (e.g., Chest pain, bone pain)	27 (87.1%)	Interventions to improve quality of life	94 (83.9%)
Interventions to manage Dyspnea/Shortness of breath	25 (80.6%)	Intervention to manage Dyspnea/Shortness of breath	79 (79.8%)
Pulmonary effects	19 (79.2%)	Intervention to manage Pain (e.g., Chest pain, bone pain)	74 (74.7%)
Access to care	19 (82.6%)	Assistance with management of symptoms interventions	81 (73%)
Interventions to improve quality of life	32 (80%)	Immunotherapy	64 (69.6%)

Participants from inpatient/ outpatient/ambulatory care	N (%)	Participants from homecare/ hospice/palliative care	N (%)	Participants from universities/ colleges	N (%)
Interventions to improve quality of life	74 (82.2%)	Intervention to manage pain	14 (93.3%)	Continuity of care	23 (76.7%)
Intervention to manage Dyspnea/ Shortness of breath	63 (79.7%)	Persistent and late effects (Pulmonary)	11 (91.7%)	Assistance with management of symptoms interventions	23 (69.7%)
Intervention to manage pain	59 (74.7%)	Psychological adjustment and coping	10 (90.9%)	Access to care	22 (73.3%)
Immunotherapy	52 (73.2%)	Assistance with management of symptom interventions	15 (88.2%)	Self-management interventions to improve symptom control	26 (76.5%)
Assistance with management of symptoms interventions	63 (70.8%)	Interventions to improve quality of life	14 (82.4%)	Interventions to improve quality of life	25 (73.5%)

across nurses and allied healthcare professionals become pivotal (19). The rise of new treatments and consequently of new and often complex adverse events (e.g. irAEs) requires specialized training and skills in order to timely diagnose, treat, and monitor over time (20). Furthermore, as the needs of patients change there are also opportunities to deliver care in a more patient-centred and optimal way. Novel targeted therapies have led to increased survival in some of the lung cancer population, opening the discussions around survivorship care in this population. To achieve appropriate delivery of often complex care in lung cancer, three issues from the health care system topics that ranked the highest are important to consider, including a) nurse/allied health-led care, b) continuity of care rather than fragmented care as we currently see in many places (11, 21) and c) the role of the multidisciplinary team. Access to care continues to be of concern, similarly to other nursing surveys (1). Some topics in this category received low endorsement, such as non-medical prescribing, which may not be necessarily related to lack of research interest but rather with the perception that the topic has been covered already and there is enough data on evidence or delivery issues and further work may not be a priority at this stage. Furthermore, treatment-related research was identified in this sample of high priority, including immunotherapy and targeted therapies. These therapies are changing the treatment field in lung cancer and hence provide hope for many and the participants recognized that more research in optimising these novel treatments is necessary.

An interesting finding was the lowest priority attributed to all the 15 statements about research in different types of complementary and alternative medicine. This finding comes in contrast to studies that demonstrate an uprising in the numbers of patients with cancer (including lung cancer patients) who choose to utilize CAM and CAM use is reported in 42% of lung cancer patients (22). The frequent use of CAM within the lung cancer context is notable and there is a need for obtaining information on their use, particularly in controlled clinical trials, to prospectively document it.

There is a strong case for more research in screening/early detection for lung cancer (23). However, specifically for nursing, in a recent systematic review it was demonstrated that only a small fraction of studies was attributed to this field of care across cancer types (20). As most patients with lung cancer are diagnosed at a late stage, where cure is not an option, the participants emphasized that screening and early detection alongside with smoking cessation to reduce risk is highly desirable. Screening/early detection in at risk populations such as minorities and underserved and uninsured populations in the wider cancer filed were also the third and fifth highest priorities in the ONS 2013 survey too (1). Promising work in the field of early detection highlights that such approaches may be linked with enhanced clinical outcomes and potentially be cost-effective (24, 25).

Strengths of this survey include efforts to represent international perspectives; adaptation of an existing established survey as a base; intended breadth and inclusiveness of survey items by including multiple facets of care; and unique focus on lung cancer specifically. Limitations of this survey are similar to any web-based surveys, including difficulty in establishing a representative sample and difficulties with reach. While a response rate for this survey was not established due to the lack of separate categories available in email lists of large international societies, response rates in similar surveys are typically very small. Indeed the ONS 2013 survey (1) had a response rate of 11%, similar to previous ONS surveys. While every effort was made to encourage allied health professionals to participate and several related societies were approached, either there was no response from the societies or minimal response from their members (who often do not work exclusively in cancer care), leading to a very small number of allied health professionals participating. Hence, there was lack of specificity in "nursing" and "allied health professional" inclusion criteria and the data from this survey reflect more the views and priorities of nurses. In the future, more targeted sampling for allied health professionals will be necessary. Finally, there was lack of differentiation between individual survey items; this may have led to some confusion or difficulty in the interpretation of the items by the respondents, although the domain title for each of these items, which was visible to respondents, provided some context for them to consider before replying.

CONCLUSIONS

There is strong support from the data presented that future research should focus on the development and evaluation of interventions to improve quality of life and symptom management, particularly for pain, dyspnea, and fatigue. Palliative care interventions also had strong endorsement. Screening and early detection research should be a priority. It was interesting to see that practice location and highest degree obtained changed the research priorities, which highlights the value of this study since research priorities are often determined by doctors or PhD holders and not other allied-health professionals who have substantial patient-care experience. Of equal importance was what survey respondents did not think should be a research priority, some of which have been the focus of substantial research efforts such as technology to address symptoms and counseling interventions. International societies and funding bodies could consider these topics in their funding decisions and in shaping their strategic directions in the care of patients with lung cancer. These results can also be used as a guide for researchers when thinking about developing research in lung cancer care in a patient-centred research agenda.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was reviewed and approved by The Hong Kong Polytechnic University ethics committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM contributed study conception, development of protocol, data analysis, writing paper. AF, MC, PL, DLC, AC contributed to study design and data collection, and provided critical comments to paper drafts.. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank the following societies for supporting this study and distributing the survey through their email lists: International Association for the Study of Lung Cancer, Multinational Association for Supportive Care in Cancer, European Oncology Nursing Society, International Thoracic Oncology Nursing Forum and the UK National Lung Cancer Nursing Forum.

REFERENCES

1. LoBiondo-Wood G, Brown CG, Knobf MT, Lyon D, Mallory G, Mitchell SA, et al. Priorities for oncology nursing research: the 2013 national survey. *Oncol Nurs Forum* (2014) 41(1):67–76. doi: 10.1188/14.ONF.67-76
2. Clinton-McHarg T, Paul C, Sanson-Fisher R, D'Este C, Williamson A. Determining research priorities for young people with haematological cancer: a value-weighting approach. *Eur J Cancer* (2010) 46(18):3263–70. doi: 10.1016/j.ejca.2010.06.013
3. Cox A, Arber A, Gallagher A, MacKenzie M, Ream E. Establishing Priorities for Oncology Nursing Research: Nurse and Patient Collaboration. *Oncol Nurs Forum* (2017) 44(2):192–203. doi: 10.1188/17.ONF.192-203
4. Cardoso F, Harbeck N, Barrios CH, Bergh J, Cortés J, El Saghir N, et al. Research needs in breast cancer. *Ann Oncol* (2017) 28(2):208–17. doi: 10.1093/annonc/mdw571
5. Jones GS, Baldwin DR. Recent advances in the management of lung cancer. *Clin Med* (2018) 18(Suppl 2):s41–6. doi: 10.7861/clinmedicine.18-2-s41
6. Lambert SD, Ould Brahim L, Morrison M, Girgis A, Yaffe M, Belzile E, et al. Priorities for caregiver research in cancer care: an international Delphi survey of caregivers, clinicians, managers, and researchers. *Supp Care Cancer* (2019) 27(3):805–17. doi: 10.1007/s00520-018-4314-y
7. Ralph N, Green A, Sara S, McDonald S, Norris P, Terry V, et al. Prostate cancer survivorship priorities for men and their partners: Delphi consensus from a nurse specialist cohort. *J Clin Nurs* (2020) 29:265–73. doi: 10.1111/jocn.15096
8. McGregor D, Rankin N, Butow P, York S, White K, Phillips J, et al. Closing evidence-practice gaps in lung cancer: Results from multi-methods priority setting in the clinical context. *Asia Pac J Clin Oncol* (2017) 13(1):28–36. doi: 10.1111/ajco.12499
9. Rafie CL, Zimmerman EB, Moser DE, Cook S, Zarghami F. A lung cancer research agenda that reflects the diverse perspectives of community stakeholders: process and outcomes of the SEED method. *Res Involv Engagem* (2019) 5:3. doi: 10.1186/s40900-018-0134-y
10. Maguire R, Papadopoulou C, Kotronoulas G, Simpson MF, McPhelim J, Irvine L. A systematic review of supportive care needs of people living with lung cancer. *Eur J Oncol Nurs* (2013) 17:449–64. doi: 10.1016/j.ejon.2012.10.013
11. Molassiotis A, Uyterlinde W, Hollen PJ, Sarna L, Palmer P, Krishnasamy M. Supportive care in lung cancer: milestones over the past 40 years. *J Thorac Oncol* (2015) 10(1):10–8. doi: 10.1097/JTO.0000000000000407
12. Molassiotis A, Charalambous A, Taylor P, Stamataki Z, Summers Y. The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial. *Supp Care Cancer* (2015) 23(6):1637–45. doi: 10.1007/s00520-014-2511-x
13. Yorke J, Lloyd-Williams M, Smith J, Blackhall F, Harle A, Warden J, et al. Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial. *Supp Care Cancer* (2015) 23(11):3373–84. doi: 10.1007/s00520-015-2810-x
14. Henshall CL, Allin L, Aveyard H. A Systematic Review and Narrative Synthesis to Explore the Effectiveness of Exercise-Based Interventions in Improving Fatigue, Dyspnea, and Depression in Lung Cancer Survivors. *Cancer Nurs* (2019) 42(4):295–306. doi: 10.1097/NCC.0000000000000605
15. Simoff MJ, Lally B, Slade MG, Goldberg WG, Lee P, Michaud GC, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* (2013) 143(5 Suppl):e455S–97S. doi: 10.1378/chest.12-2366
16. Harle A, Molassiotis A, Buffin O, Burnham J, Smith J, Yorke J, et al. A cross sectional study to determine the prevalence of cough and its impact in patients with lung cancer: a patient unmet need. *BMC Cancer* (2020) 20(1):9. doi: 10.1186/s12885-019-6451-1
17. Harle ASM, Blackhall FH, Molassiotis A, Yorke J, Dockry R, Holt KJ, et al. Cough in Patients With Lung Cancer: A Longitudinal Observational Study of Characterization and Clinical Associations. *Chest* (2019) 155(1):103–13. doi: 10.1016/j.chest.2018.10.003
18. Molassiotis A, Smith JA, Mazzone P, Blackhall F, Irwin RS. CHEST Expert Cough Panel. Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report. *Chest* (2017) 151 (4):861–74. doi: 10.1016/j.chest.2016.12.028

19. Kelly D, Charalambous A. Recognising the impact and future potential of cancer nursing: The RECaN project and beyond. *Eur J Oncol Nurs* (2017) 29: A1–2. doi: 10.1016/j.ejon.2017.06.004
20. Charalambous A, Wells M, Campbell P, Torrens C, Östlund U, Oldenmenger W, et al. A scoping review of trials of interventions led or delivered by cancer nurses. *Int J Nurs Stud* (2018) 86:36–43. doi: 10.1016/j.ijnurstu.2018.05.014
21. Lowe M, Molassiotis A. A longitudinal qualitative analysis of the factors that influence patient distress within the lung cancer population. *Lung Cancer* (2011) 74(2):344–8. doi: 10.1016/j.lungcan.2011.03.011
22. Bismark RS, Chen H, GK D, Gage-Bouchard EA, Mahoney MC. Complementary and alternative medicine use among patients with thoracic malignancies. *Supp Care Cancer* (2014) 22(7):1857–66. doi: 10.1007/s00520-014-2144-0
23. Bade BC, Brasher PB, Luna BW, Silvestri GA, Tanner NT. Reviewing Lung Cancer Screening: The Who, Where, When, Why, and How. *Clin Chest Med* (2018) 39(1):31–43. doi: 10.1016/j.ccm.2017.09.003
24. Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. *Health Technol Assess* (2018) 22(69):1–276. doi: 10.3310/hta22690
25. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* (2016) 20(40):1–146. doi: 10.3310/hta20400

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 01 December 2020
doi: 10.3389/fonc.2020.591610

A Randomized Controlled Trial of a Non-pharmacological Intervention for Cancer-Related Dyspnea

Patsy Yates[1], Janet Hardy[2], Alexandra Clavarino[3], Kwun M. Fong[4], Geoffrey Mitchell[5], Helen Skerman[1], Vanessa Brunelli[1] and Isabella Zhao[1]*

[1] Queensland University of Technology, Cancer & Palliative Outcomes Center, Kelvin Grove, QLD, Australia, [2] Mater Health Services, Mater Research—The University of Queensland, Brisbane, QLD, Australia, [3] The University of Queensland, School of Pharmacy, Brisbane, QLD, Australia, [4] The University of Queensland Thoracic Research Center, The Prince Charles Hospital, Brisbane, QLD, Australia, [5] The University of Queensland, School of Clinical Medicine, Brisbane, QLD, Australia

Objectives: To evaluate the efficacy of a brief tailored non-pharmacological intervention comprising breathing retraining and psychosocial support for managing dyspnea in cancer patients.

Design: Multicenter, single blinded, parallel group, randomized controlled trial.

Setting: Four major public hospitals, Brisbane, Australia.

Participants: One hundred and forty four cancer patients, including 81 who received an 8-week tailored intervention and 63 who received standard care.

Inclusion Criteria: Diagnosis of small or non-small cell lung cancer, mesothelioma or lung metastases; completed first line therapy for the disease; average dyspnea rating >2 on (0–10) rating scale in past week; anticipated life expectancy ≥3 months.

Outcomes: The primary outcome measure was change in "worst" dyspnea at 8 weeks compared to baseline. Secondary outcomes were change in: dyspnea "at best" and "on average"; distress; perceived control over dyspnea; functional status, psychological distress; and use of non-pharmacological interventions to manage dyspnea at 8 weeks relative to baseline.

Results: The mean age of participants was 67.9 (SD = 9.6) years. Compared to the control group, the intervention group demonstrated a statistically significant: (i) improvement in average dyspnea from T1($M = 4.5$, SE = 0.22) to T3 ($M = 3.6$, SE = 0.24) vs. ($M = 3.8$, SE = 0.24) to ($M = 4.1$, SE = 0.26); (ii) greater control over dyspnea from T1 ($M = 5.7$, SE = 0.28) to T3 ($M = 7.5$, SE = 0.31) vs. ($M = 6.8$, SE = 0.32) to ($M = 6.6$, SE = 0.33); and (iii) greater reduction in anxiety from T1 ($M = 5.4$, SE = 0.43) to T3 ($M = 4.5$, SE = 0.45) vs. ($M = 4.2$, SE = 0.49) to ($M = 4.6$, SE = 0.50). This study found no intervention effect for best and worst dyspnea, distress from breathlessness, functional status, and depression over time.

Conclusions: This study demonstrates efficacy of tailored non-pharmacological interventions in improving dyspnea on average, control over dyspnea, and anxiety for cancer patients.

OPEN ACCESS

Edited by:
Meng Xu Welliver, The Ohio State University, United States

Reviewed by:
Jose Gilberto Bazan, Ohio State University Hospital, United States
Valerio Gristina, University of Palermo, Italy

****Correspondence:***
Patsy Yates
p.yates@qut.edu.au

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: *05 August 2020*
Accepted: *16 September 2020*
Published: *01 December 2020*

Citation:
Yates P, Hardy J, Clavarino A, Fong KM, Mitchell G, Skerman H, Brunelli V and Zhao I (2020) A Randomized Controlled Trial of a Non-pharmacological Intervention for Cancer-Related Dyspnea. Front. Oncol. 10:591610. doi: 10.3389/fonc.2020.591610

Clinical Trial Registration: The trial is registered at the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au). The registration number is ACTRN12607000087459.

Keywords: dyspnea, non-pharmacological interventions, nurse-led interventions, randomized controlled trial, anxiety

INTRODUCTION

Dyspnea is a common and distressing symptom experienced by many people with advanced cancer. Estimates of the prevalence of dyspnea range from 29 to 74% in adults in palliative care settings, increasing in the last weeks of life (1). Compared to other cancer types, dyspnea is most common and most severe in primary lung cancer patients, affecting 90% of this patient group (2). Causes of dyspnea in advanced disease are complex and multifactorial, including obstructions or restrictions directly related to lung or pleural involvement or its treatments, factors indirectly related to the disease such as infections, anemia, or respiratory muscle weakness from cachexia, and from comorbid conditions that may be unrelated to the primary presenting problem, such as underlying chronic obstructive pulmonary disease or heart failure (3, 4). Treatment for dyspnea in this population has been medically focused and centered on addressing the underlying causes, with radiotherapy, chemotherapy and pharmacological interventions, and the drainage of effusions most commonly being used to achieve some reduction in this symptom (5–7). However, dyspnea is an especially complex symptom to assess and treat in practice, as the threshold of perception varies widely, with the severity of disease not always directly related to the intensity of breathing discomfort (8).

Dyspnea is a subjective experience of breathing discomfort that derives from interactions among multiple physiological, social, and environmental factors, and can induce secondary physiological and behavioral responses (8). For some patients, dyspnea remains unrelieved despite the use of currently available intervention strategies (6). The multidimensional nature of the dyspnea experience suggests a range of non-pharmacological methods used as adjuncts to medical management offers some potential in reducing the impact of the symptom. Systematic reviews have reported benefits of non-pharmacological interventions for dyspnea management (9–12). The systematic review conducted by Zhao and Yates examined the influence of various intervention components, delivery methods, and clinical contexts on outcomes of non-pharmacological interventions for breathlessness management in participants with lung cancer (10). On the basis of the five eligible studies included in this review, it was concluded that participants with better functional status may be more likely to benefit from the interventions, and that multi-component strategies that are tailored to the participants' individual needs are likely to be more effective.

The primary hypothesis for this study was that, compared to participants who receive standard education for managing dyspnea, participants who receive a non-pharmacological intervention for managing dyspnea delivered using evidence-based psycho-educational strategies will report greater improvement in "worst" dyspnea at 8 weeks. A secondary aim of this study was to examine the relative effectiveness of this intervention over time by comparing change in dyspnea "at best" and "on average," and change in distress caused by dyspnea, as well as change in participant's perceived control over dyspnea, functional status and psychological distress, and use of non-pharmacological interventions to manage dyspnea at 8 weeks.

METHODS

Trial Design and Participants

The study involved a multicenter, single blind, parallel group, randomized controlled trial conducted in four major public hospitals in Brisbane, Australia. This project was funded by the National Health & Medical Research Council (NHMRC) and registered with Australian New Zealand Clinical Trials Registry (ACTRN12607000087459). Each site was granted ethical approval from its local research ethics committee. Participants who met the following criteria were invited to participate in the study: (1) a diagnosis of small cell or non-small cell lung cancer, mesothelioma or lung metastases; (2) completed first line therapy for the disease; (3) an average dyspnea rating >2 on an 11 point (0–10) numeric rating scale in the past week; and (4) an anticipated life expectancy of at least 3 months. Participants who had cognitive impairment that would prevent them from responding to a survey questionnaire or who had a life expectancy of <3 months at the time of screening were not eligible. Written informed consent was obtained from participants and/or their careers.

Intervention

Participants allocated to the intervention group received a face to face instructional session of about 60 min, followed by weekly phone calls for 3 weeks, to reinforce the strategies (**Figure 1**). The intervention combined breathing re-training with individualized psychosocial support and was delivered using evidence-based psycho-educational strategies (**Box 1**). The timing and application of the strategies in the multi-component intervention were tailored to the individual, based on the nurses' assessment, although all components and delivery strategies listed might be used with each participant. The instruction was supplemented by a range of resources to reinforce intervention delivery and promote self-management, including audio recordings, printed fact sheets, an individualized management plan, and a referral prompt sheet. While both groups received education on principles for managing dyspnea, the intervention group differed from the control group in

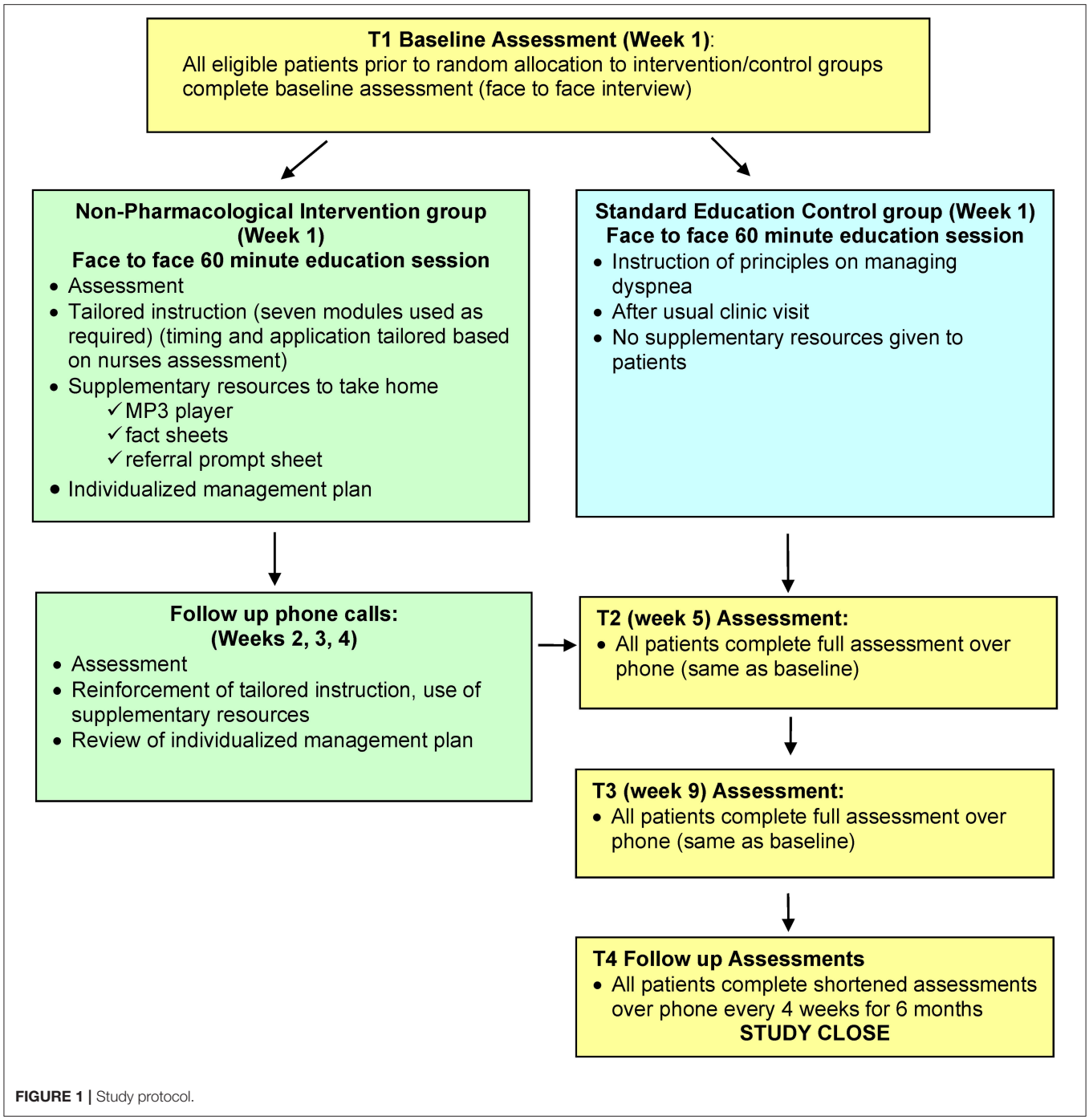


FIGURE 1 | Study protocol.

that they also received additional supplementary materials designed to reinforce learning, promote confidence and self-management, and thus enhance intervention outcomes. In addition, participants in both groups continued to receive standard care and other usual supportive care measures, including routine clinic visits, anti-cancer treatments, and other supportive drug therapy or interventions.

Nurses with experience in working with lung cancer patients were employed to deliver the interventions. The nurses underwent an extensive training program to facilitate a skilled and consistent approach to intervention delivery. The training program included learning activities that aimed to develop advanced knowledge and skills in dyspnea management, supportive communication, and the use of the evidence-based psycho-educational strategies. An intervention protocol was developed to provide the nurse with a framework to tailor intervention techniques to specific dyspnea needs of each participant and to facilitate standardization of the intervention.

BOX 1 | Components of the non-pharmacological intervention for dyspnea.

Component	Timing
Detailed assessment of • dyspnea • its meaning • factors that ameliorate or exacerbate it	Week 1—Incorporated into face to face session
• its impact	Weeks 2, 3, 4—Incorporated into telephone follow up
Delivering tailored information on ways of managing dyspnea	Week 1—Face to face session (app. 60 min) delivered by trained nurse
Instruction incorporates a selection of seven modules on the principles managing dyspnea: • Understanding and managing factors contributing to dyspnea • Improving breathing efficiency • Reducing distress • Relaxing • Activity pacing • Strategies for the caregiver • Recognizing when to seek support	Weeks 2, 3, 4—Reinforcement of instruction through telephone follow up sessions (~15 min)
Training in breathing control techniques, progressive muscle relation, and distraction	Week 1—Incorporated into face to face session Weeks 2, 3, 4—Incorporated into telephone follow up
Goal setting to complement breathing and relaxation exercise, to help manage function and social activities	Week 1—Incorporated into face to face session
Development of an individualized plan documenting: • Triggers to breathlessness • Specific strategies to be implemented for reducing these triggers, including development of daily activity plans	Weeks 2, 3, 4—Incorporated into telephone follow up
Supporting the family caregiver	Week 1—Incorporated into face to face session
Involvement of family caregiver where possible in training programs	Weeks 2, 3, 4—Incorporated into telephone follow up
Early recognition of problems warranting medical intervention	Week 1—Incorporated into face to face session
• Prompt sheet for participant and family caregiver to use record referral points, and to facilitate discussion with health care professionals on dyspnea	Weeks 2, 3, 4—Incorporated into telephone follow up

Adapted from Corner et al. (13).

The quality of the intervention and compliance with study protocols were monitored by investigators who reviewed tape recordings of some sessions selected at random.

Outcomes

The primary outcome measure of this study was change in "worst" dyspnea at 8 weeks in participants in the intervention group compared to the standard care group. Secondary endpoints were change in dyspnea "at best" and "on average," and change in distress caused by dyspnea, as well as change in participant's perceived control over dyspnea, functional status, psychological distress, and use of non-pharmacological interventions to manage dyspnea at 8 weeks from the commencement of the intervention, in the intervention group compared to the standard care group. In addition, relevant clinical information was assessed at each time point to enable comparison of intervention and control groups on key clinical and treatment variables that might influence the effectiveness of the intervention or the outcomes of interest to this study.

Perceptions of Dyspnea

Five 11-point (0–10) numeric rating scales (NRS) were used to rate dyspnea at best, at worst and on average, distress caused by dyspnea, and control over dyspnea. The NRS has good test-retest reliability (14) and is recognized as an effective measure for patients who are experiencing symptoms such as dyspnea, as it is easily rated by patients who have varying degrees of physical and psychological incapacity (15). One point change on an 11-point numerical rating scale is accepted in recent methodological papers as being a clinically important difference for chronic refractory breathlessness (16).

Psychological Distress

Level of psychological distress was assessed using the Hospital Anxiety and Depression Scale (17), which has been widely used as a screening tool for anxiety and depression in cancer patients and has been recommended to be routinely administered to palliative care patients (17, 18). Higher scores indicate higher levels of anxiety and depression. A clinically important difference is indicated by a one-point change on the 11-point numerical rating scale (19).

Functional Status

The ECOG Performance Rating scale is widely used to assess how the disease affects the daily living abilities of the patient (20). Scores range from 0 (fully active) to 4 (completely disabled). Functional status was rated by the research nurse from participant responses.

Use of Non-pharmacological Interventions

A scale to assess the extent to which participants used the various component strategies was developed in our pilot study. A total of 13 strategies were recommended based on the four modules developed for the non-pharmacological intervention, which could reflect strategies to improve breathing efficiency, reduce distress, relaxation, and activity pacing. Content validity of the items was determined by matching items to components of the intervention, as well as the items included in the breathlessness assessment guide developed in the UK (13). A count was made of the number of recommended non-pharmacological interventions utilized.

Sample Size

Sample size was calculated using the potential effect size and standard deviation of the primary outcome measure (worst breathlessness) informed by our pilot study (21). In order to detect a 1.6-point mean difference in outcome between groups with a standard deviation of 3.0, a two-sided 5% significance level

and 90% power, we required a sample size of 71 participants per group at T3 (8 weeks). Allowing 30% for attrition and 20% for contingencies and potential confounding, the estimated sample size was 214 (107 per arm).

Randomization

Randomization on a 1:1 basis was by a computer-generated table of random numbers for each site prepared by an investigator with no clinical involvement in the trial. After the research nurse had obtained the participant's consent, a contact independent of the recruitment process at the Institute of Health and Biomedical Innovation (IHBI) at Queensland University of Technology was telephoned for allocation consignment. Participants allocated to the intervention group were aware of the allocated arm, however outcome assessors and data analysts were kept blind to the allocation.

Statistical Methods

Descriptive statistics and frequency distributions were calculated for participants' demographic and clinical characteristics. The hypotheses were tested using the pooled data from all sites and analyses were done on an intention-to-treat basis. Outcomes were assessed on a priori hypotheses, with each endpoint being considered separately in the analysis. Change in continuous outcome variables over time were examined using Linear Mixed Models (LMMs) and time by group interaction effects. Estimation of the effect of the intervention on breathlessness ratings, anxiety, and depression was based on the mean difference between the intervention and standard care groups at T3 relative to T1. Functional status was coded as a dichotomous variable, so the impact of the intervention on functional status over time was assessed using Generalized Estimating Equations (GEE) and binary logistic regression, assuming an independent correlations matrix. Statistical analyses were performed using SPSS version 18 (SPSS for Windows, Release 18.0; SPSS, Chicago, IL). A 1.6-unit change in breathlessness ratings was considered a clinically important difference. Statistical significance was determined at the conventional level of 5% or less (two-tailed hypothesis tests). Means or odds ratios and 95% confidence intervals (CI) are presented, relevant to the data type. Selected results from these analyses were previously reported in abstract form (22).

RESULTS

From March 2008 through January 2011, a total of 144 participants were recruited at four hospitals and randomized (**Figure 2**). The attrition rate at 8 weeks was 19% (27 participants); of these, 18 intervention and 9 control participants were lost to follow up. The main reason for withdrawal was that participants were too unwell or deceased. Those lost to follow up did not differ significantly on baseline demographic or medical information from those who remained in the study, except that those lost to follow-up were more likely to have a primary cancer diagnosis of "other" cancers with lung metastases.

Of the 144 participants, 81 were randomly assigned to the intervention group and 63 to the control group. Overall, the mean age was 67.9 (SD = 9.6) years and more than 60% of the participants were male, married or de facto, and lived with a spouse or partner (**Table 1**). The majority of participants had non-small cell lung cancer as their primary diagnosis (62.6%) and 42.4% of participants had distant metastases at study entry (**Table 2**). Approximately half of all participants had COPD and one quarter reported having five co-morbid conditions in addition to the primary cancer (**Table 2**). The proportion of participants who underwent radiotherapy and/or chemotherapy was similar (17.9 and 17.1%, respectively). Baseline demographic, clinical characteristics and medications of the groups are presented in **Tables 1**, **2**.

Changes in Dyspnea Severity Ratings Between Groups Over Time

For the primary outcome of worst dyspnea, there was no statistically significant difference in change over time between the groups ($p = 0.70$) (**Table 3**). Relative to T1, the change in worst dyspnea, indicated by the mean difference between the intervention and control groups was −0.38 (95% CI: −1.30 to 0.53) at 8 weeks (**Table 3**, **Figure 3**).

Analysis of secondary outcomes revealed significant differences between the groups in average dyspnea. Dyspnea on average improved only for the intervention group ($p = 0.018$) (**Table 3**, **Figure 3**). Similarly, for other dimensions of the dyspnea experience, significant improvement in perceived control over dyspnea at 8 weeks was observed for the intervention group when compared to the control group ($p = 0.001$) (**Table 3**). The intervention group perceived increased control over dyspnea from T1 to T3, compared to the control group that showed worsening control over dyspnea from T1 to T3 (**Figure 4**). Analysis of the other secondary outcomes did not reach statistical significance between the groups over time. For dyspnea at best, the group by time interaction effect was close to significance ($p = 0.06$) (**Table 3**). In the intervention group, dyspnea at best improved from T1 to T3, but worsened in the control group over time (**Figure 3**). Similarly, the group by time interaction effect in distress caused by dyspnea was not significant ($p = 0.07$) (**Table 3**, **Figure 4**). Relative to T1 and the control group, the greater improvement in dyspnea-related distress in the intervention group at 8 weeks (mean difference = −1.40, 95% CI: −2.60 to −0.21) was statistically significant.

Change in Anxiety and Depression Between Groups Over Time

There was a significant change in anxiety between groups and over time ($p = 0.025$). Anxiety level decreased in the intervention group from T1 to T3, but increased in the control group from T1 to T2 and T3 (**Figure 5**). Relative to T1 and the control group, there was a greater and statistically significant reduction in anxiety in the intervention group at 8 weeks (mean difference = −1.3; 95% CI: −2.38 to −0.25) (**Table 3**). However, there was no statistically significant difference in depression between the groups over time ($p = 0.20$) (**Table 3**).

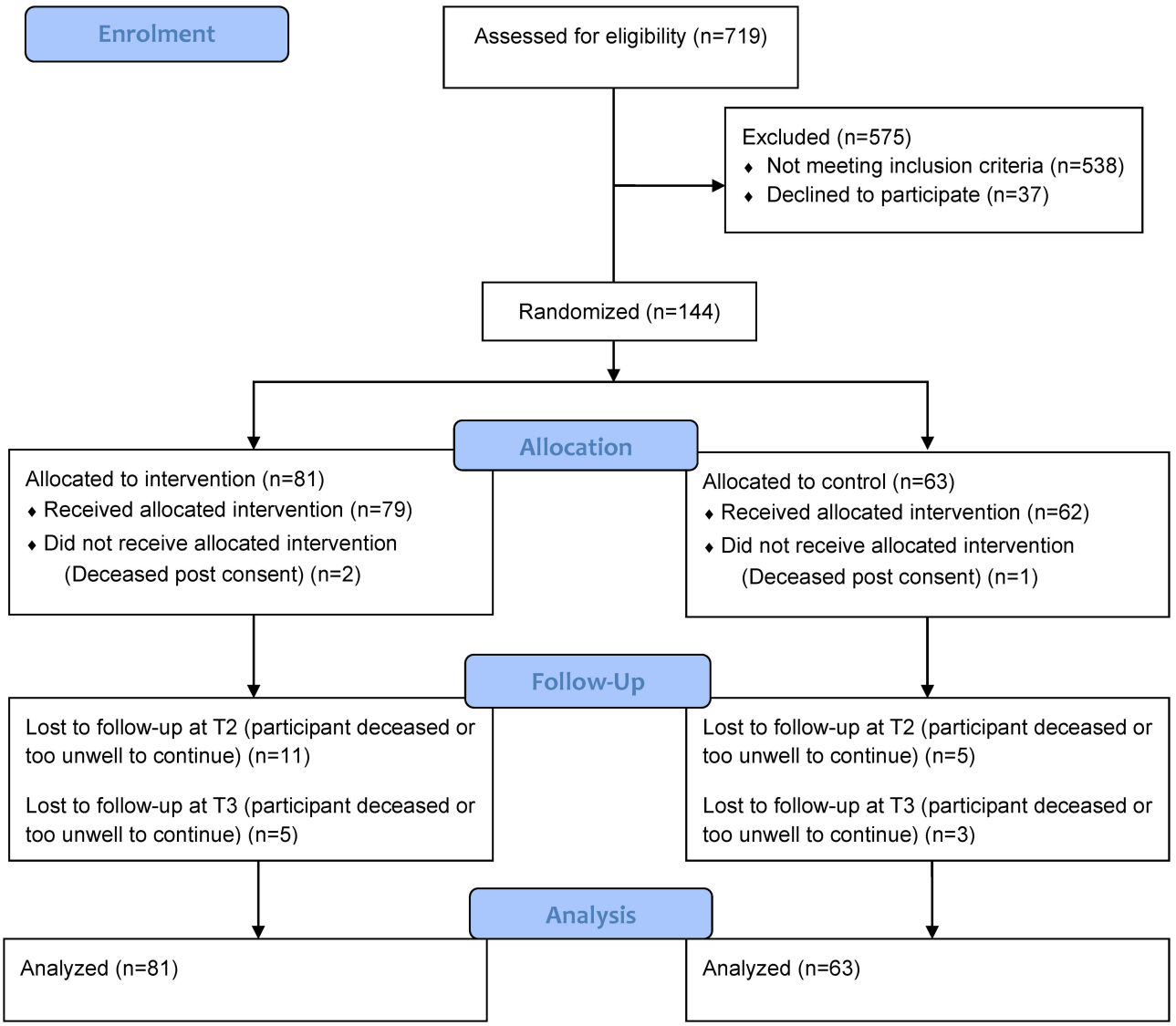


FIGURE 2 | Participant screening and randomization.

Change in Functional Status Between Groups Over Time

The two groups did not differ significantly in functional status over time ($p = 0.41$). Relative to T1 and the control group, there was no statistically significant change in functional status in the intervention group at 8 weeks (OR: 0.87; CI [0.53–1.41]) (**Table 3**).

Change in Use of Non-pharmacological Interventions Between Groups Over Time

For the number of non-pharmacological interventions used to manage dyspnea, there was a significant difference between groups and over time ($p = 0.014$). Relative to T1 and the control group, the greater use of non-pharmacological interventions by the intervention group at 8 weeks was statistically significant (mean difference = 1.25; 95% CI: 0.82 to 1.68) (**Table 3**).

DISCUSSION

Previous studies of non-pharmacological interventions for dyspnea associated with cancer have reported benefits from intensive interventions involving several weeks of face-to-face contact with specially trained health professionals. This multicenter randomized controlled study evaluated a brief tailored non-pharmacological intervention delivered by nurses for managing dyspnea. While no significant effects were demonstrated for the primary outcome "dyspnea at worst," our findings show that participants receiving the brief self-management focused intervention supplemented by a

TABLE 1 | Demographic information of study participants ($n = 144$).

	All ($n = 144$)		Intervention group ($n = 81$)		Control group ($n = 63$)	
	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)
Age[a]	67.9 (9.6)		67.7 (9.1)		68.1 (10.3)	
Gender		53 (36.8)		28 (34.6)		24 (38.1)
Female						
Male		91 (63.2)		53 (65.4)		39 (61.9)
Marital status[b]						
Single/divorced/ separated/widowed		42 (29.2)		23 (28.4)		19 (30.2)
Married/de facto		96 (66.7)		54 (66.7)		42 (66.7)
Living arrangements[c]						
Lives alone		31 (21.5)		16 (19.8)		15 (23.8)
With spouse/partner		93 (64.6)		53 (65.4)		40 (63.5)
With children or other		13 (9.0)		7 (8.6)		6 (9.5)
Highest level of education[d]						
Did not complete/completed primary school		27 (18.8)		16 (21.6)		11 (17.5)
Completed year 10/certificate		56 (38.9)		29 (35.8)		27 (42.9)
Completed year 12		12 (8.3)		7 (8.6)		5 (7.9)
Vocational training		26 (18.1)		16 (19.8)		10 (15.9)
Tertiary qualification		11 (7.6)		6 (7.4)		5 (7.9)

[a] $n = 131$.
[b] $n = 138$.
[c] $n = 137$.
[d] $n = 132$.

TABLE 2 | Baseline medical information of study participants ($n = 144$).

	All ($n = 144$)	Intervention ($n = 81$)	Control ($n = 63$)
Primary cancer diagnosis[a]			
Small cell lung cancer	19 (13.2)	11 (13.6)	8 (12.7)
Non-small cell lung cancer	87 (60.4)	47 (58.0)	40 (63.5)
Mesothelioma	13 (9.0)	7 (8.6)	6 (9.5)
Other	20 (13.9)	12 (14.8)	8 (12.7)
Extent of disease at study entry[b]			
Localized	30 (20.8)	18 (22.2)	12 (19.0)
Locally advanced	27 (18.8)	16 (19.8)	11 (17.5)
Distant metastases	42 (29.2)	23 (28.4)	19 (30.2)
COPD[c]			
Yes	69 (47.9)	40 (49.4)	29 (46.0)
No	70 (48.6)	38 (46.9)	32 (50.8)
Severity of COPD[d]			
Mild	20 (29.0)	12 (30.0)	8 (27.6)
Moderate	14 (20.3)	8 (20.0)	6 (20.7)
Severe	21 (30.4)	13 (32.5)	8 (27.6)
Radiotherapy/chemotherapy[e]			
Nil	39 (27.1)	17 (21.0)	22 (34.9)
Radiotherapy	25 (17.4)	18 (22.2)	7 (11.1)
Chemotherapy	24 (16.7)	15 (18.5)	9 (14.3)
Both	52 (36.1)	28 (34.6)	24 (38.1)
Number of co-morbidities[f]			
0	14 (9.7)	8 (9.9)	6 (9.5)
1	24 (16.7)	10 (12.3)	14 (22.2)
2	22 (15.3)	16 (19.8)	6 (9.5)
3	19 (13.2)	12 (14.8)	7 (11.1)
4	26 (18.1)	14 (17.3)	12 (19.0)
5	35 (24.3)	18 (22.2)	17 (27.0)
Medication[g]			
Bronchodilators/anti-spasms	46 (31.9)	24 (29.6)	22 (34.9)
Steroid	27 (18.8)	18 (22.2)	9 (14.3)
NSAIDS	18 (12.5)	10 (12.3)	8 (12.7)
Diuretic	10 (6.9)	5 (6.2)	5 (7.9)
Analgesics	74 (51.4)	41 (50.6)	33 (52.4)
Anti-hypertensive/cardiac drug	69 (47.9)	37 (45.7)	32 (50.8)
Anti-depression/anti-anxiety	55 (38.2)	33 (40.7)	22 (34.9)
Antibiotics	13 (9.0)	5 (6.2)	8 (12.7)
Oxygen	0 (0.0)	0 (0.0)	0 (0.0)
Other respiratory agents	4 (2.8)	2 (2.5)	2 (3.2)
Other drugs	117 (81.3)	66 (81.5)	51 (81.0)

[a] $n = 139$.
[b] $n = 99$.
[c] $n = 139$.
[d] $n = 55$.
[e] $n = 140$.
[f] $n = 140$.
[g] $n = 138$.
All data presented in number (%).

range of technology enhanced delivery strategies resulted in improvements in dyspnea on average and perceived control over dyspnea, and a reduction in anxiety at 8 weeks, compared to participants receiving standard care. The intervention group also demonstrated increased uptake of the recommended non-pharmacological strategies to manage dyspnea, suggesting the effectiveness of the intervention on reducing breathlessness. On the 0–10 NRS, the levels of improvement in average dyspnea and control over dyspnea at T3 in the intervention group relative to T1 and the control group were more than 1 unit (1.15 and 1.92, respectively). This one point change on an 11-point numerical rating scale is accepted in methodological papers as being a clinically important difference for chronic refractory breathlessness (16). Additionally, the reduction in anxiety level at T3 in the intervention group relative to T1 and the control group was 1.32, indicating clinical significance (19).

We had chosen dyspnea at worst as the primary outcome for this study to be consistent with the initial study of non-pharmacological interventions for breathlessness upon which this intervention was based. While no significant improvement was identified for this primary outcome, the consistent improvements identified for other dyspnea severity measures provide some confidence in the efficacy of this intervention. Indeed, dyspnea on average, is an important indicator of the overall rating of the symptom experienced by the participants, as it takes all situations into consideration and

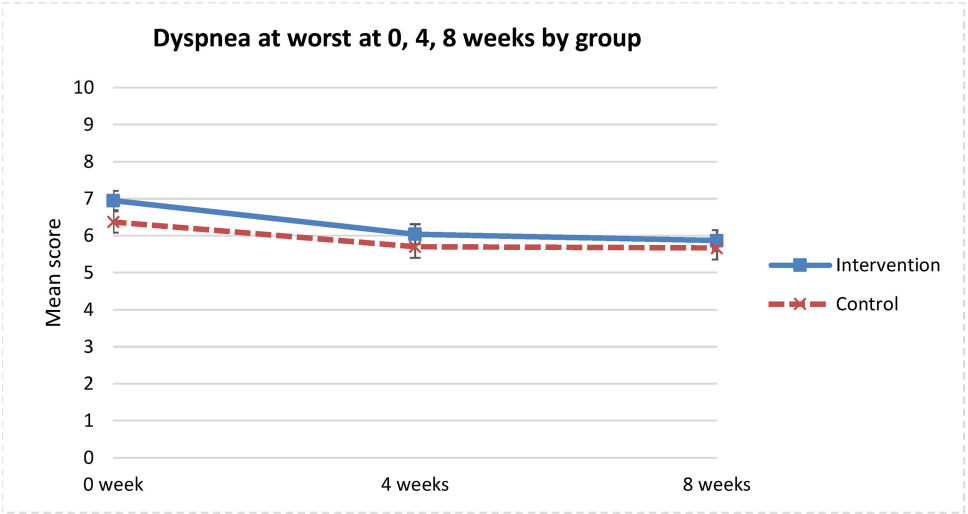
TABLE 3 | Changes in outcome measures over time by intervention and control groups.

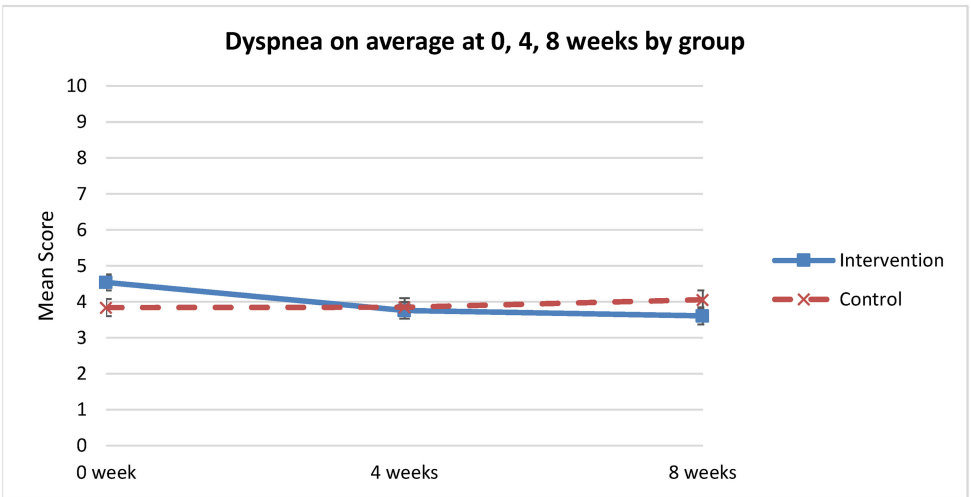
		Intervention	Control	Group* time	Intervention	Control		Effect size	
		Mean (SE)	Mean (SE)	*P*-value	Mean difference (SD) relative to T1	Mean difference (SD) relative to T1	Mean difference (SD) relative to T1 and the control group	Mean difference between groups/SD	95% CI
Dyspnea at worst	T1	6.95 (0.26)	6.37 (0.29)	0.70					
	T2	6.04 (0.27)	5.70 (0.30)		−0.91 (2.27)	−0.67 (2.27)	−0.23 (2.27)	−0.11	[−0.97; 0.51]
	T3	5.87 (0.28)	5.67 (0.31)		−1.08 (2.27)	−0.7 (2.28)	−0.38 (2.28)	−0.17	[−1.30; 0.53]
Dyspnea on average	T1	4.54 (0.22)	3.84 (0.24)	0.018					
	T2	3.76 (0.23)	3.85 (0.25)		−0.78 (1.93)	0.01 (1.89)	−0.80 (1.91)	−0.41	[−1.48; −0.12]
	T3	3.61 (0.24)	4.06 (0.26)		−0.93 (1.93)	0.22 (1.90)	−1.15 (1.92)	−0.60	[−1.98; −0.31]
Dyspnea at best	T1	3.03 (0.22)	2.52 (0.25)	0.06					
	T2	2.44 (0.23)	2.64 (0.26)		−0.59 (1.93)	0.12 (1.97)	−0.71 (1.95)	−0.36	[−1.41; −0.02]
	T3	2.28 (0.24)	2.66 (0.27)		−0.75 (1.93)	0.14 (1.98)	−0.89 (1.95)	−0.46	[−1.70; −0.08]
Distress caused by dyspnea	T1	4.68 (0.33)	3.39 (0.38)	0.069					
	T2	3.44 (0.36)	2.90 (0.39)		−1.24 (2.95)	−0.49 (2.97)	−0.75 (2.96)	−0.25	[−1.83; 0.32]
	T3	3.04 (0.37)	3.15 (0.40)		−1.64 (2.93)	−0.24 (2.97)	−1.40 (2.95)	−0.47	[−2.60; −0.21]
Control over dyspnea	T1	5.72 (0.28)	6.77 (0.32)	0.001					
	T2	7.06 (0.30)	7.03 (0.33)		1.34 (2.48)	0.26 (2.51)	1.08 (2.49)	0.43	[0.17; 1.99]
	T3	7.49 (0.31)	6.62 (0.33)		1.77 (2.48)	−0.15 (2.48)	1.92 (2.48)	0.78	[0.93; 2.92]
Anxiety	T1	5.39 (0.43)	4.16 (0.49)	0.025					
	T2	4.44 (0.44)	4.30 (0.49)		−0.95 (3.73)	0.14 (3.78)	−1.09 (3.76)	−0.29	[−1.98; −0.21]
	T3	4.51 (0.45)	4.60 (0.50)		−0.88 (3.71)	0.44 (3.77)	−1.32 (3.74)	−0.35	[−2.38; −0.25]
Depression	T1	5.56 (0.42)	5.39 (0.48)	0.202					
	T2	4.99 (0.44)	5.50 (0.49)		−0.57 (3.69)	0.11 (3.74)	−0.68 (3.71)	−0.18	[−1.59; 0.23]
	T3	4.85 (0.45)	5.77 (0.49)		−0.71 (3.66)	0.38 (3.70)	−1.09 (3.68)	−0.30	[−2.34; 0.15]
Number of interventions used	T1	7.37 (0.27)	7.10 (0.31)	0.014					
	T2	8.48 (0.29)	7.15 (0.32)		1.11 (1.81)	0.05 (1.82)	1.06 (1.81)	0.59	[0.74; 1.38]
	T3	8.51 (0.30)	6.99 (0.32)		1.14 (2.39)	−0.11 (2.40)	1.25 (2.40)	0.52	[0.82; 1.68]
ECOG*	T1	1.23 (0.09)	1.26 (0.11)	0.537					
	T2	1.24 (0.10)	1.35 (0.11)		0.01 (0.81)	0.09 (0.85)	−0.08 (0.83)	0	
	T3	1.31 (0.10)	1.42 (0.11)		0.08 (0.80)	0.16 (0.84)	−0.08 (0.82)	0	

**ECOG performance status (16), with higher scores indicating worse performance status.*

asks the participants to do an overall assessment of dyspnea experienced in the past seven days. As such, our findings reflect important outcomes from the patient's perspective. On the other hand, dyspnea at best and worst is at the extremes of a scale reflecting special and extreme events that only happen rarely. The intervention also did not improve depression compared to standard care. There are a number of predictors for depression in lung cancer patients, including functional impairment, physical symptom burden, and fatigue (23). This brief intervention might not be sufficiently intense to impact this complex symptom, and a more comprehensive approach may be required. The two groups also remained very similar in performance status (ECOG) through the study period. A focus on other concurrent symptoms that impact on functional status, such as fatigue, might be required to have a greater impact on this outcome.

Our results contrast to those of Bredin et al. (24), on which this study was based, who found significant improvement for breathlessness at best, performance status, and levels of depression at 8 weeks in the intervention group (24). There are a number of possible explanations for these differences. Firstly, in Bredin's study, missing data due to the withdrawal of participants from the study were imputed according to a method suggested by Gould (25). This approach has been controversial with the development of multiple imputations; and some studies questioned the validity of the application of multiple imputations (26, 27). Our study did not impute any missing data. We selected LMM as this approach could fully accommodate all of the data available for a subject even if some data were missing (28). Secondly, in Bredin's study, changes in outcome measures between baseline and 8 weeks were calculated and analyzed. This method of analysis assumed that all participants were able to show a change in either direction on the rating scales, as acknowledged by the authors. However, participants whose baseline measurements were at the extremes of a scale would only show change in one direction. From this perspective, LMM





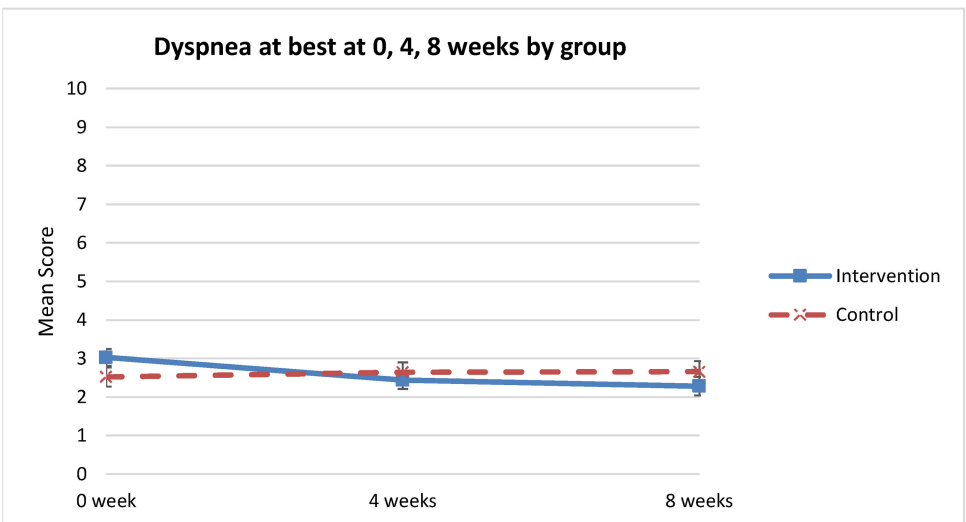
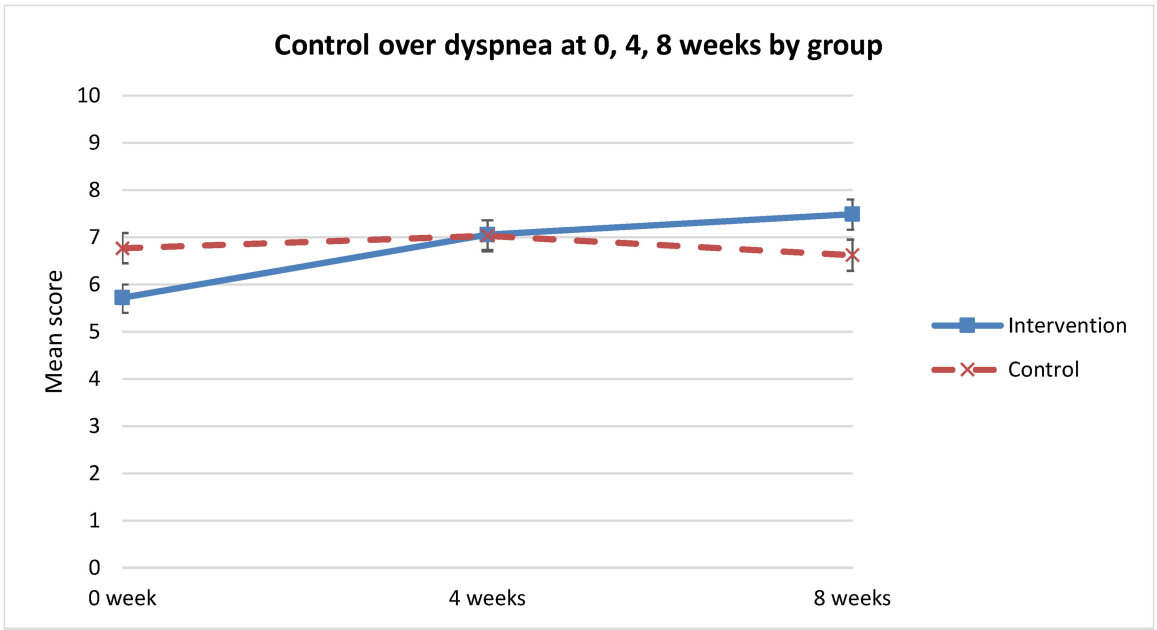


FIGURE 3 | Dyspnea NRS ratings at worst, best and on average over time (0 week, 4 weeks, 8 weeks).



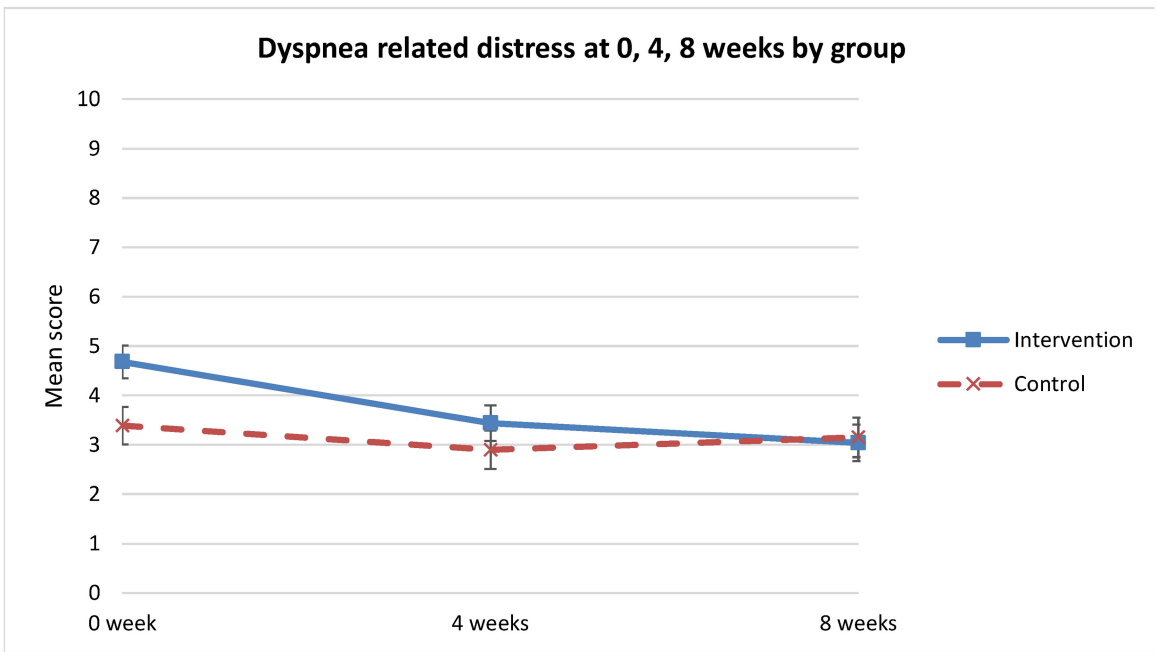


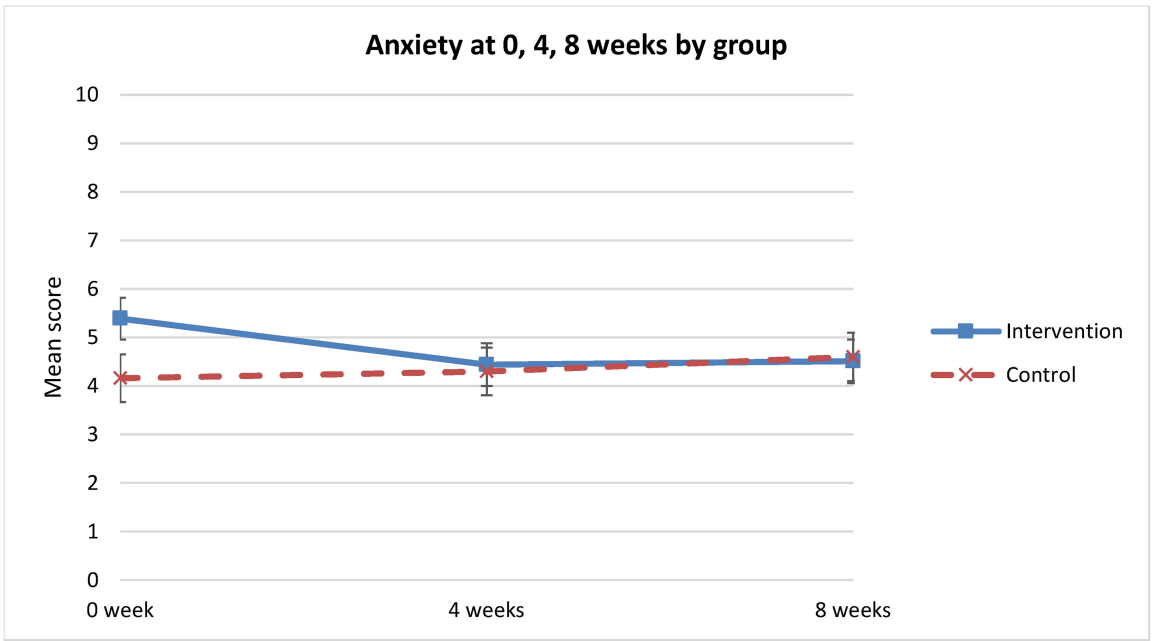
FIGURE 4 | Change in "control over dyspnea" & "dyspnea-related distress" over time (0 week, 4 weeks, 8 weeks).

is a preferred approach to analyze all three time points, so was selected as the analysis model in our study.

A key focus of our brief intervention was promoting the patient's confidence in self-management of dyspnea. Our findings that patients report a greater sense of control over dyspnea reflect improvement in an important patient-centered outcome. The increased uptake of non-pharmacological interventions reflects the greater confidence in self-management of dyspnea in the intervention group.

Strengths and Limitations

This multicenter, single blind randomized controlled trial was conducted to evaluate the efficacy of a brief tailored non-pharmacological intervention comprising breathing retraining and psychosocial support for managing dyspnea in lung cancer participants. The success of the nurse led interventions further supports the inclusion of experienced nurses at all stages of care to support participants and carers, as recommended in the most updated National Institute for Health and Clinical Excellence



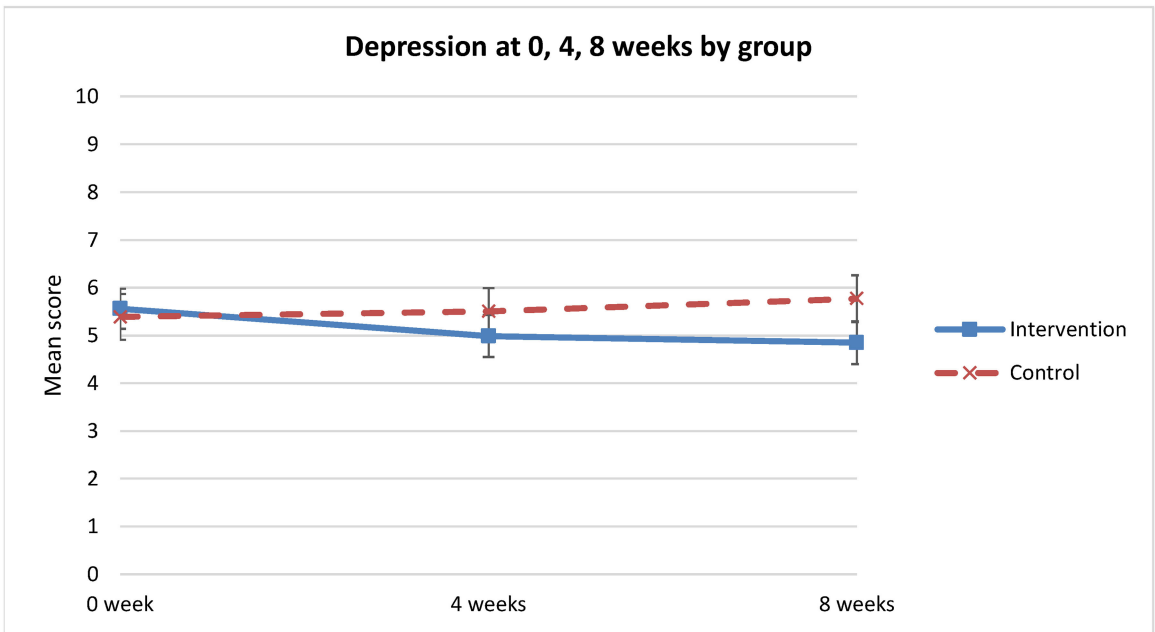


FIGURE 5 | HADS scores over time (0 week, 4 weeks, 8 weeks).

(NICE) guidance (29). The study is novel in that it applies best available evidence about methods for delivering psycho-educational interventions for people with cancer to optimize the delivery of non-pharmacological intervention strategies with proven efficacy. The tailored instructions offered in the first education session were reinforced by telephone calls, weekly for 3 weeks. This reinforcement using flexible health service delivery options is promising. The intervention required minimal clinic time, with different forms of support materials (e.g., booklets, electronic recordings) for participants to use at their own pace and individual situations rather than in a more structured or formal way. The intervention evaluated in this study can be readily incorporated into routine clinical practice to manage the symptom and practitioners could use these guidelines for targeting intervention strategies more appropriately to participants' clinical status and personal goals.

Despite the strengths of this study, the results might not generalize to a wider population. As the participants were recruited from major hospitals in a metropolitan area and the majority of the participants lived in the metropolitan or

surrounding areas, their characteristics might be different from those in rural and remote areas. The supplementary take-home materials and telephone follow metropolitan communities.

This is one of the largest randomized controlled trials of non-pharmacological interventions for dyspnea. Despite this, we recorded an imbalance in the number of participants in intervention and control groups most likely due to the use of simple 1:1 randomization at each study site, rather than blocked randomization. The minimum sample size of 71 in each group was not achieved in the control group due to difficulties with recruitment, despite an extended study timeframe. This resulted in slightly <90% power in the analyses. We also did not observe significant differences between groups for the primary outcome, dyspnea at worst. Our targeted sample size was calculated based on change in "worst" dyspnea between groups at week 4 (mean = 1.63, SD = 3.0) in the pilot study (21), which was greater than the mean difference achieved in this trial. The small number of participants in the pilot study ($n = 30$) could have contributed to the larger variation by chance in that study. Despite these statistical limitations, the significant improvements observed across several secondary outcome measures provide some confidence that the intervention has great potential for improving dyspnea management for patients with cancer.

Potential bias should be acknowledged. For example, drop-out bias could have occurred as the attrition rate at 8 weeks was 19%. The main reason for withdrawal was that participants were too unwell or were deceased. However, comparison between the drop-outs and those who remained in the study showed no statistical difference on baseline demographic or medical information, except that those lost to follow-up were more likely to have a primary cancer diagnosis of "other" cancers with lung metastases. Time-related bias should also be considered due to the extended recruitment from March 2008 through January 2011. Despite the time since study completion, the applicability of these findings to contemporary practice remains, given that dyspnea continues to be a significant problem for cancer patients and that no significant advances in non-pharmacological interventions have occurred since this time.

CONCLUSION

This multicenter randomized controlled study to evaluate brief tailored non-pharmacological interventions delivered by nurses for managing dyspnea confirm that participants receiving such interventions showed improvement in dyspnea on average, greater control over dyspnea, and a reduction in anxiety over time. The intervention evaluated in this study builds on recent evidence about the importance of tailoring interventions to patient's needs and concerns and demonstrates the value of such approaches in promoting self-management of dyspnea.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Queensland University of Technology Human Research Ethics Committee; Mater Health Services Human Research Ethics Committee; Princess Alexandra Hospital Human Research Ethics Committee; The Prince Charles Hospital and Health Service District Human Research Ethics Committee; Royal Brisbane & Women's Hospital Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PY was the guarantor and has contributed to the planning, conduct, and the reporting of the work. JH, AC, KF, and GM have contributed to the planning and conduct of the work and the review of the manuscript. HS has contributed to the planning, analysis, and reporting of the work. VB has contributed to the conduct of the work and the review of the manuscript. IZ has contributed to the conduct, analysis, and reporting of the work. All authors acknowledge and appreciate the contribution from the study participants.

FUNDING

This work was supported by National Health and Medical Research Council Australia, Project Grant No. 443237.

REFERENCES

1. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. *Palliat Med*. (2007) 21:177–91. doi: 10.1177/0269216307076398
2. Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax*. (1993) 48:339–43. doi: 10.1136/thx.48.4.339
3. Lok CW. Management of breathlessness in patients with advanced cancer: a narrative review. *Am J Hosp Palliat Care*. (2016) 33:286–90. doi: 10.1177/1049909114554796
4. Kvale PA. Chronic cough due to lung tumors. *Chest*. (2006) 129(1 Suppl.):147S−53S. doi: 10.1378/chest.129.1_suppl.147S
5. Cairns L. Managing breathlessness in patients with lung cancer. *Nurs Stand*. (2012) 27:44–9. doi: 10.7748/ns2012.11.27.13.44.c9450
6. Bailey CD, Wagland R, Dabbour R, Caress A, Smith J, Molassiotis A. An integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses. *BMC Pulm Med*. (2010) 10:63. doi: 10.1186/1471-2466-10-63
7. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. *Nat Clin Pract Oncol*. (2008) 5:90–100. doi: 10.1038/ncponc1034
8. American Thoracic Society. Mechanisms, assessment and management: a consensus statement. *Am J Respir Crit Care Med*. (1999) 159:321–40. doi: 10.1164/ajrccm.159.1.ats898

9. Yates P, Schofield P, Zhao I, Currow D. Supportive and palliative care for lung cancer patients. *J Thorac Dis*. (2013) 5(Suppl. 5):S623–8. doi: 10.3978/j.issn.2072-1439.2013.10.05
10. Zhao I, Yates P. Non-pharmacological interventions for breathlessness management in patients with lung cancer: a systematic review. *Palliat Med*. (2008) 22:693–701. doi: 10.1177/0269216308095024
11. Rueda J, Solà I, Pascual A, Subirana Casacuberta M. Non-invasive interventions for improving well-being and quality of life in patients with lung cancer. *Cochrane Database Syst Rev*. (2011) 2011:CD004282. doi: 10.1002/14651858.CD004282.pub3
12. Bausewein C, Booth S, Gysels M, Higginson IJ. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev*. (2008) 2:CD005623. doi: 10.1002/14651858.CD005623.pub2
13. Corner J, O'Driscoll M. Development of a breathlessness assessment guide for use in palliative care. *Palliat Med*. (1999) 13:375–84. doi: 10.1191/026921699674958656
14. Wilcock A, Crosby V, Clarke D, Tattersfield A. Repeatability of breathlessness measurements in cancer patients. *Thorax*. (1999) 54:375. doi: 10.1136/thx.54.4.374b
15. Ahmedzai S. Palliation of respiratory symptoms. In: Doyle D, Hanks G, McDonald N, editors. *Oxford Textbook of Palliative Medicine*. Oxford: Oxford Medical Publications (1993), 349–78.
16. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage*. (2013) 46:957–63. doi: 10.1016/j.jpainsymman.2013.01.011
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
18. Holtom N, Barraclough J. Is the Hospital Anxiety and Depression Scale (HADS) useful in assessing depression in palliative care? *Palliat Med*. (2000) 14:219–20. doi: 10.1191/026921600675483740
19. Puhan MA, Frey M, Buchi S, Schunemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. (2008) 6:46. doi: 10.1186/1477-7525-6-46
20. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. (1982) 5:649–55. doi: 10.1097/00000421-198212000-00014
21. Yates P, White E, Skerman H. Evaluating alternate approaches for delivering non-phamacological interventions for dyspnea in patients with lung cancer. *Oncol Nurs Forum*. (2007) 34:551.
22. Yates P, Hardy J, Kwun F, Brunelli V, Zhao I, Skerman H, et al. A randomised controlled trial of a non-pharmacological intervention for dyspnoea. *Asia-Pacific J Clin Oncol*. (2011) 7(Suppl. 4):82. doi: 10.1111/j.1743-7563.2011.01477.x
23. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol*. (2000) 18:893–903. doi: 10.1200/JCO.2000.18.4.893
24. Bredin M, Corner J, Krishnasamy M, Plant H, Bailey C, A'Hern R. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ*. (1999) 318:901–4. doi: 10.1136/bmj.318.7188.901
25. Gould AL. A new approach to the analysis of clinical drug trials with withdrawals. *Biometrics*. (1980) 36:721–7. doi: 10.2307/2556126
26. Meng XL. Multiple-imputation inferences with uncongenial sources of input. *Stat Sci*. (1994) 9:538–58. doi: 10.1214/ss/1177010269
27. Fay RE, Schafer JL, Skinner C, Zaslavsky AM, Meng XL. Multiple-imputation inferences with uncongenial sources of input—comment. *Stat Sci*. (1994) 9:558–73. doi: 10.1214/ss/1177010270
28. West BT. Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Eval Health Prof*. (2009) 32:207–28. doi: 10.1177/0163278709338554
29. National Institute for Health and Care Excellence. *Lung Cancer: Diagnosis and Management*. (2019). Available online at: https://www.nice.org.uk/guidance/ng122 (accessed August 6, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 23 December 2020
doi: 10.3389/fonc.2020.594590

Dyspnea in Patients Receiving Radical Radiotherapy for Non-Small Cell Lung Cancer: A Prospective Study

Angela Sardaro[1,2], Fiona McDonald[1,3], Lilia Bardoscia[4], Konstantin Lavrenkov[1,5], Shalini Singh[1,6], Sue Ashley[1], Daphne Traish[1], Cristina Ferrari[2], Icro Meattini[1,7], Artor Niccoli Asabella[2] and Michael Brada[1,3,8]*

[1] Lung Research Unit, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom, [2] Interdisciplinary Department of Medicine, Nuclear Medicine Unit and Section of Radiology and Radiation Oncology, University of Bari Aldo Moro, Bari, Italy, [3] Academic Radiotherapy Unit, The Institute of Cancer Research, Sutton, United Kingdom, [4] Radiation Therapy Unit, Department of Oncology and Advanced Technology, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [5] Department of Oncology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel, [6] Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Department of Radiotherapy, Lucknow, India, [7] Department of Biomedical, Experimental, and Clinical Sciences, University of Florence, Radiation Oncology Unit - Oncology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, [8] Department of Radiation Oncology, University of Liverpool and Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom

OPEN ACCESS

Edited by:
Alex Molassiotis,
Hong Kong Polytechnic University,
Hong Kong

Reviewed by:
Pasquale Pisapia,
University of Naples Federico II, Italy
Zhongxing Liao,
University of Texas MD Anderson Cancer Center, United States

***Correspondence:**
Lilia Bardoscia
liliabardoscia@gmail.com

Specialty section:
This article was submitted to Thoracic Oncology, a section of the journal Frontiers in Oncology

Received: 20 August 2020
Accepted: 18 November 2020
Published: 23 December 2020

Citation:
Sardaro A, McDonald F, Bardoscia L, Lavrenkov K, Singh S, Ashley S, Traish D, Ferrari C, Meattini I, Asabella AN and Brada M (2020) Dyspnea in Patients Receiving Radical Radiotherapy for Non-Small Cell Lung Cancer: A Prospective Study. Front. Oncol. 10:594590. doi: 10.3389/fonc.2020.594590

Background and Purpose: Dyspnea is an important symptomatic endpoint for assessment of radiation-induced lung injury (RILI) following radical radiotherapy in locally advanced disease, which remains the mainstay of treatment at the time of significant advances in therapy including combination treatments with immunotherapy and chemotherapy and the use of local ablative radiotherapy techniques. We investigated the relationship between dose-volume parameters and subjective changes in dyspnea as a measure of RILI and the relationship to spirometry.

Material and Methods: Eighty patients receiving radical radiotherapy for non-small cell lung cancer were prospectively assessed for dyspnea using two patient-completed tools: EORTC QLQ-LC13 dyspnea quality of life assessment and dyspnea visual analogue scale (VAS). Global quality of life, spirometry and radiation pneumonitis grade were also assessed. Comparisons were made with lung dose-volume parameters.

Results: The median survival of the cohort was 26 months. In the evaluable group of 59 patients there were positive correlations between lung dose-volume parameters and a change in dyspnea quality of life scale at 3 months (V_{30} p=0.017; V_{40} p=0.026; V_{50} p=0.049; mean lung dose p=0.05), and a change in dyspnea VAS at 6 months (V_{30} p=0.05; V_{40} p=0.026; V_{50} p=0.028) after radiotherapy. Lung dose-volume parameters predicted a 10% increase in dyspnea quality of life score at 3 months (V_{40}; p=0.041, V_{50}; p=0.037) and dyspnea VAS score at 6 months (V_{40}; p=0.027) post-treatment.

Conclusions: Worsening of dyspnea is an important symptom of RILI. We demonstrate a relationship between lung dose-volume parameters and a 10% worsening of subjective

dyspnea scores. Our findings support the use of subjective dyspnea tools in future studies on radiation-induced lung toxicity, particularly at doses below conventional lung radiation tolerance limits.

Keywords: non-small cell lung cancer, radiotherapy, dyspnea, dose-volume parameters, radiation-induced lung injury

INTRODUCTION

Radical radiotherapy (RT), with or without chemotherapy has an established role as an alternative to surgery in medically inoperable, localized and locally advanced non-small cell lung cancer (NSCLC) (1, 2). In particular, chemoradiation represents the standard of care for locally advanced disease (3–5). The disappointing survival rates following radical conventionally fractionated RT have been the impetus behind application of advanced RT techniques with the aim of increasing radiation dose intensity without additional toxicity (6–9).

Radiation-induced lung injury (RILI) remains a significant limiting factor to dose escalation. Knowledge of the effect of radiation on lung is imperative for optimization and comparison of the relative merits of different RT plans. The risk of radiation pneumonitis (RP), an interstitial pulmonary inflammatory process usually developing within 6 months of RT, is the predominant endpoint used to quantify RILI, forming the basis of recommended RT dose-volume constraints obtained by lung dose volume histogram (DVH) in conventional RT (10). However, the grading of RP is challenging as the most frequently used scoring systems, including the Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) system, have a small number of broad categories combining symptomatic, functional, and radiological criteria in addition to indication of medical intervention. In addition, the incidence of clinically significant RP is low and therefore, it is not discriminatory at doses below conventional tolerance defined by incidence of RP.

Arguably, the most clinically relevant endpoint for patients is the worsening of symptoms, particularly dyspnea. A more discriminating measure of the effect of radiation on dyspnea may be useful for weighing up the potential risks and benefits of a RT plan at doses below conventional tolerance defined by the incidence of RP. We carried out an explorative, prospective assessment of dyspnea based on the hypothesis that RILI below conventional tolerance may be detected and quantifiable where dyspnea assessment may offer a more discriminatory and objective measure.

MATERIALS AND METHODS

Patient Population

Between February 2003 and January 2011, patients were invited to participate in a prospective observational study following approval by the institution's Committee for Clinical Research and Local Research Ethics Committee. The trial was conducted in accordance with European Union guidelines for Good Clinical Practice and signed informed consent was obtained from participants. All patients scheduled to receive radical RT to a dose of 64 Gray (Gy) in 32 daily fractions were eligible for study entry if they fulfilled the following criteria: histological or radiological diagnosis of localized medically inoperable or unresectable locally advanced NSCLC (AJCC 6th edition stages I-III, excluding T4 lesions associated with pleural effusion), baseline forced expiratory volume in 1 s (FEV1) greater than 40% of predicted normal value and World Health Organization (WHO) performance status 0-2.

Radiotherapy Planning and Delivery

A planning helical computed tomography (CT) scan of the thorax was acquired with the patient positioned on a chest board either in free breathing or breath-hold using the active breathing control (ABC) device with 2.5–3 mm slice thickness (11, 12). RT planning was performed using the Pinnacle^3 planning software (Philips Medical Systems Madison, WI). The extent of the gross tumor volume (GTV) was defined using CT lung windows (Width=1600, Length=-300) with reference to diagnostic imaging. The clinical target volume (CTV) was considered the same as the GTV. In patients treated in free breathing, a margin of 1.5 cm was added cranio-caudally with axially 1 cm for central disease and 1.5 cm for peripheral disease added to the CTV to create the planning target volume (PTV). In patients treated with ABC, an isotropic margin of 1 cm was added from CTV to PTV. Conformal plans were created to ensure adequate coverage of the PTV in accordance with International Commission on Radiation Units (IRCU) 50 and 62 recommendations, whilst maintaining the constraints for organs at risk. Treatment was delivered in a single phase to a dose of 64 Gy in 32 daily fractions prescribed to the 100% isocenter using a linear accelerator (Elekta, Crawley, UK).

Radiotherapy Lung DVH Parameters

Both lungs were considered together as a single paired organ and contoured on the planning scan using CT lung windows. Care was taken to ensure inclusion of the whole lung tissue from apices to bases including regions of collapse or consolidation. The extent of the GTV/CTV, trachea and proximal bronchial tree were excluded from the volume. The total mean lung dose (MLD) was recorded for each patient in addition to the percentage of the total lung volume at threshold doses of radiation in Gy (V_{dose}) ranging from 20 Gy to 60 Gy in 10 Gy increments (V_{20}, V_{30}, V_{40}, V_{50}, V_{60}). All plans met the dose constraints of a V_{20} ≤30% and a MLD of ≤18 Gy.

Pre-Treatment and Follow-Up Assessments and Dyspnea Scales

Dyspnea, pneumonitis, spirometry and quality of life (QoL) were prospectively assessed at baseline prior to treatment, at 3, 6, 9, and 12 months after completion of RT and then 6 monthly until disease progression or death. Patients were imaged with chest radiograph or CT scan at follow-up time-points. At baseline patients were asked to complete the Adult Comorbidity Evaluation 27 questionnaire (ACE-27) (13). At each scheduled study appointment patients were assessed clinically and the physician-scored pneumonitis grade (CTCAE) was recorded (14). Patients were asked to complete the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire including the lung module (QLQ-LC13) (15, 16). Dyspnea was assessed using the breathlessness section of QLQ-LC13 and from patients' marking the dyspnea visual analogue scale (VAS), a 100 mm long vertical line, to indicate their degree of breathlessness (17). Each VAS was separately recorded without reference to previous reading. Pulmonary function tests (PFT) consisted in FEV1 and forced vital capacity (FVC) measured using an Alpha III spirometer (Vitalograph, Lenexa, KS) and were recorded as the percentage of the predicted value. Ventilation parameters were chosen for correlative analysis because strictly representative for respiratory function and capacity, unlike perfusion parameters possibly affected by confounding factors, such as cardiac and/or hematological comorbidities.

Statistical Analysis

A sample size of at least 30 lung cancer patients was arbitrary defined, since this was an explorative, prospective study and no similar study designs to compare with for accrual evaluation have ever been reported in literature. Statistical analysis will eventually be descriptive for future findings and data integration.

Survival analysis from the start of radiation treatment was performed using the Kaplan-Meier method. As the primary objective was to assess changes in dyspnea and other measures of lung function due to radiation, patients with progressive disease were censored for dyspnea assessment at the time of disease progression. Median follow-up, progression free survival (PFS) and overall survival (OS) were calculated with 95% confidence intervals (CI).

Data were taken from the 3 QoL questions related to breathlessness (**Table 1**) and the calculated dyspnea QoL score was normalized to a 100 point scale (16). The dyspnea VAS was assessed and attributed a score from 0 to 10 to the nearest millimeter. The global QoL score was calculated from 0 to 100. The pneumonitis grade and the percentage of predicted normal values for FEV_1 and FVC were documented.

Changes in dyspnea QoL, dyspnea VAS, global QoL, FEV1, and FVC from the baseline pre-RT measurement were detected for individual patients at each post-irradiation time-point. A positive change indicated a worsening of dyspnea QoL, dyspnea VAS and global QoL and an improvement in FEV1 and FVC. Comparisons between the mean changes and the corresponding baseline values for the cohort were performed with 95% CI at each post-RT time-point and correlations with lung DVH parameters at 3, 6, and 12 months post-RT were assessed using rank correlation coefficients. The association between the rate of ≥ grade 2 RP at 3 months after RT and lung DVH parameters was calculated using a rank correlation coefficient. The rate of RP at other time-points was considered too much low for further correlation assessments.

Where a significant correlation at the 5% level was observed between lung DVH parameters and changes from baseline post-RT, the Mann Whitney test was performed to test for correlation of lung DVH parameters with a clinically relevant worsening of dyspnea or pulmonary function. For the purposes of statistical analysis, a clinically relevant worsening was defined as follows: 10% increase in dyspnea QoL compared to baseline, 10% increase in dyspnea VAS compared to baseline, and 10% decrease in FEV1 or FVC compared to baseline. Exploratory receiver operator curve (ROC) analyses were also carried out to assess for an optimal cut-off to predict worsening of dyspnea or pulmonary function following treatment.

TABLE 1 | EORTC QLQ-LC13 dyspnea QoL assessment.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Were you short of breath when you rested?	1	2	3	4
Were you short of breath when you walked?	1	2	3	4
Were you short of breath when you climbed stairs?	1	2	3	4

RESULTS

Patient Population, Follow-Up and Disease Outcome

Eighty consecutive patients during the study period fitted the selection criteria and accepted to participate to the study. Among these, 21 patients were excluded from further analysis: five had missing pre-RT dyspnea assessment, one did not complete RT due to pulmonary embolism, eight had missing 3-month post-RT dyspnea assessment and seven developed disease progression prior to 3-month post-RT assessment. Data from the remaining 59 patients were analyzed for the study purpose. The characteristics of the population in study are summarized in **Table 2**. In particular, 34 (57.6%) patients suffered from cardiac and/or hematological comorbidities, and 54 (91.5%) of them reported smoke habit.

With a median follow-up of 20 months (range 0 to 78), the median progression free survival was 16 months (95% CI: 10–23) and the median overall survival was 26 months (95% CI: 14–38) (**Figure 1**).

Baseline Measurements and Compliance

The mean baseline dyspnea QoL, dyspnea VAS, global QoL, FEV1 and FVC and lung dose-volume data for the cohort are summarized

TABLE 2 | Patient and disease characteristics.

Patient characteristics	N = 59	%	Mean (SD)
Gender			
Male	35	59	
Female	24	41	
Age in years			69 (10)
Performance status (WHO)			
0	19	32	
1	38	64	
2	2	4	
Co-morbidity score			
0	13	22	
1	15	26	
2	17	29	
3	12	20	
Missing	2	3	
Smoking status			
Current	54	92	
Never smoker or ex-smoker	5	8	
Disease characteristics			
Histological diagnosis			
Squamous cell carcinoma	24	41	
Adenocarcinoma	14	24	
Other	5	8	
Missing	16	27	
Disease stage (AJCC 6th ed)			
I	14	24	
II	7	12	
IIIA	19	32	
IIIB	18	30	
Neoadjuvant chemotherapy	24	41	
Prior lobectomy	3	5	

WHO, World Health Organization; AJCC, American Joint Committee on Cancer.

TABLE 3 | Baseline assessment and normal lung DVH data.

Measurement	Mean	95% CI
Dyspnea QoL (n=59)	26	21–31
Dyspnea VAS (n=59)	2.2	1.5–2.8
Global QoL (n=58)	67	63–72
FEV1% of predicted (n=56)	69	64–74
FVC % of predicted (n=55)	86	80–91
MLD (Gy) (n=59)	12	11–13
V20 (%) (n=59)	23	20–26
V30 (%) (n=59)	18	15–21
V40 (%) (n=59)	13	11–16
V50 (%) (n=59)	9	7–12
V60 (%) (n=59)	6	4–9

QoL, quality of life; VAS, visual analogue scale; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MLD, mean lung dose; V_{dose}, percentage of the total lung volume at threshold doses of radiation in Gy.

in **Table 3**. All 59 patients had clinical assessments at baseline and 3 months post-RT. Taking withdrawal of patients from further follow-up due to disease progression and death into account, 2/48 (4%), 16/39 (41%), 1/35 (3%) had missing follow-up assessments at 6, 9, and 12 months, respectively, with no missing assessments but few surviving patients at 18 months post-RT excluded from further analysis, data attributable to the prognosis of the percentage of patients with IIIA and IIIB disease stage.

Change in Dyspnea Quality of Life, Dyspnea VAS, Global Quality of Life, FEV 1 and FVC from Baseline, and Rate of Radiation Pneumonitis

The mean dyspnea QoL score of the cohort increased by 4 (95% CI: -2–10) at 3 months after irradiation. Twenty-nine patients (49%) had worse dyspnea QoL with a mean increase in score of 22 (95% CI: 17–27); 20 patients (34%) had improved dyspnea QoL with a mean decrease in score of 20 (95% CI: 15–26) and 10 patients (17%) had no change in QoL score. The mean change from baseline at follow-up time-points is displayed in **Table 4**. Changes in dyspnea QoL from baseline at different time-points by classifying patients as those who initially improved, remained stable, or worsened between baseline and 3 months post-RT are displayed in **Figure 2**. The mean change in dyspnea VAS, global QoL, FEV1, and FVC from baseline at the follow up time-points is reported in **Table 4**. At 3 months post-RT eight (14%), two

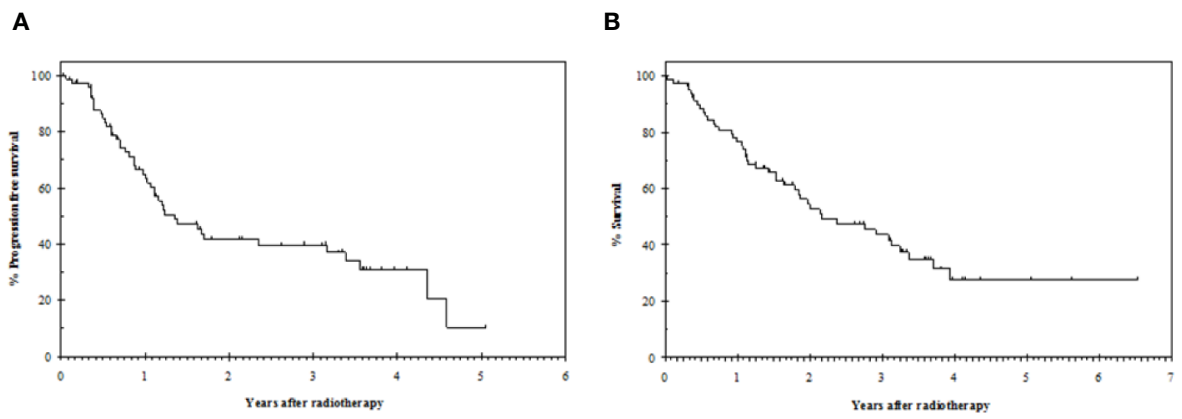


FIGURE 1 | **(A)** PFS and **(B)** OS in a cohort of 80 patients treated with radical RT.

TABLE 4 | Mean change from baseline of dyspnea QoL, dyspnea VAS, global QoL, and percentage of predicted FEV1 and FVC at time-points post-RT with 95% CI in parentheses.

Time post-RT (months)	Mean change in % dyspnea scores (range)				
	3	6	9	12	18
Dyspnea QoL score	4 (-2 to 10)	7 (0 to15)	2 (-4 to 8)	11 (3 to 20)	15 (5 to 26)
Dyspnea VAS score	1.0 (0.2 to 1.8)	1.7 (0.8 to 2.7)	1.3 (0.3 to 2.3)	1.7 (0.5 to 2.8)	2.1 (0.8 to 3.5)
Global QoL score	1 (-5 to 7)	-6 (-14 to 3)	-10 (-21 to 2)	-8 (-16 to 0)	-5 (-16 to 6)
% of predicted FEV1	2 (-1 to 4)	1 (-3 to 6)	2 (-5 to 8)	0 (-5 to 6)	2 (-4 to 8)
% of predicted FVC	2 (-3 to 8)	-2 (-6 to 2)	3 (-7 to 12)	-1 (-7 to 6)	2 (-6 to 9)

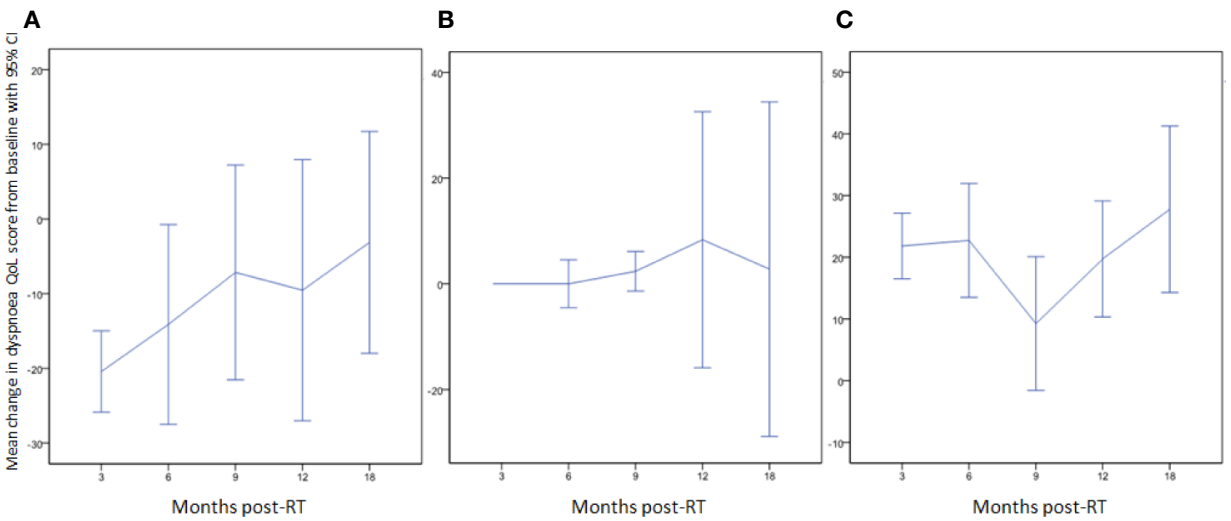


FIGURE 2 | Change in dyspnea QoL from baseline at different time-points by classifying patients as those who **(A)** initially improved (QoL score decreased: 20/59; 34%), **(B)** remained stable (10/59; 17%), or **(C)** initially worsened (QoL score increased: 29/59; 49%) between baseline and 3 months post-RT.

(3%), and two (3%) patients had grade 1, grade 2, and grade 3 RP, respectively. At 6 months after the treatment, three (7%), one (3%), and one (3%) patients had grade 1, grade 2, and grade 3 RP, respectively.

Relationship Between Lung DVH and Measures of Lung Function

Table 5 shows the relationship between dyspnea and lung function measures including dyspnea QoL, dyspnea VAS, FEV1, FVC, and incidence of RP. Change in dyspnea QoL score at 3 months correlated with the lung V_{30}, V_{40}, V_{50}, and MLD (p=0.017, p=0.026, p=0.049, and p=0.05, respectively). There was no significant correlation between lung DVH parameters and change in dyspnea VAS, global QoL, FEV1, FVC, and rate of ≥ grade 2 RP at 3 months. Change in dyspnea VAS score at 6 months correlated with the lung V_{30}, V_{40}, and V_{50} (p=0.05, p=0.026 and p=0.028, respectively). No significant correlation between lung DVH parameters and change in dyspnea QoL, global QoL, FEV1 or FVC was demonstrated at 6 months. At 12 months there was a significant negative correlation between the change in FVC and the lung V_{40} and V_{60} (p=0.043 and p=0.046, respectively) and between the change in FEV1 and lung V_{40}, V_{50}, and V_{60} (p=0.016, p=0.011, and p=0.005, respectively).

ROC Analysis for Lung Damage Post-Radiotherapy

Lung damage defined by a 10% increase in dyspnea QoL score at 3 months correlated with the lung V_{40} and V_{50} with an area under the curve (AUC) of 0.66 (p=0.041) and 0.66 (p=0.037), respectively (**Figure 3**). Lung damage defined by a 10% increase in dyspnea VAS score at 6 months correlated to the lung V_{40} with an AUC of 0.69 (p=0.027) (**Figure 3**). A cut off of 11% for the V_{40} was associated with a sensitivity of 76% and a specificity of 53% for predicting worsening of dyspnea by a 10% increase in dyspnea QoL score at 3 months, and a sensitivity of 83% and a specificity of 61% by a 10% increase in dyspnea VAS score at 6 months post-RT. ROC analysis demonstrated that no DVH parameter significantly predicted clinically relevant lung damage defined by a 10% decrease in FVC or FEV1 (% of predicted) at 12 months post-RT compared to baseline.

DISCUSSION

Worsening of dyspnea is a characteristic feature of clinically relevant RILI (18). Our study aimed to prospectively evaluate

TABLE 5 | Rank correlation between normal lung DVH parameters and lung function.

DVH Parameter Correlations		Change in Dyspnea QoL			Change in Dyspnea VAS			Change in Global QoL			Change in FVCas % of predicted			Change in FEV1as % of predicted			Rate of ≥ grade 2 RP
		3m	6m	12m	3m	6m	12m	3m	6m	12m	3m	6m	12m	3m	6m	12m	3m
N		59	44	30	59	45	33	57	44	32	52	38	29	52	39	29	4
V20	Co	0.22	0.15	0.00	0.18	0.18	0.17	-0.12	-0.06	0.27	-0.09	-0.23	-0.24	-0.05	-0.15	-0.15	0.45
	Sig	0.088	0.340	0.995	0.180	0.247	0.335	0.378	0.688	0.139	0.540	0.169	0.205	0.745	0.373	0.432	0.553
V30	Co	0.31	0.27	0.19	0.21	0.29	0.22	-0.20	-0.15	-0.03	-0.06	-0.23	-0.31	-0.08	-0.19	-0.29	0.89
	Sig	**0.017**	0.074	0.327	0.107	**0.050**	0.220	0.145	0.336	0.879	0.659	0.172	0.097	0.585	0.247	0.129	0.106
V40	Co	0.29	0.20	0.18	0.17	0.33	0.31	-0.17	-0.12	-0.05	0.00	-0.13	-0.38	-0.85	-0.17	-0.45	0.89
	Sig	**0.026**	0.184	0.351	0.207	**0.026**	0.080	0.194	0.438	0.798	0.979	0.442	**0.043**	0.549	0.309	**0.016**	0.106
V50	Co	0.26	0.232	0.12	0.13	0.33	0.22	-0.17	-0.10	0.05	0.06	-0.14	-0.35	-0.05	-0.22	-0.47	0.45
	Sig	**0.049**	0.13	0.539	0.335	**0.028**	0.229	0.217	0.530	0.807	0.669	0.400	0.062	0.728	0.185	**0.011**	0.553
V60	Co	0.13	0.15	-0.02	0.11	0.28	0.17	-0.08	0.02	0.14	0.13	-0.08	-0.37	-0.04	-0.27	-0.50	0.00
	Sig	0.327	0.333	0.915	0.402	0.060	0.348	0.549	0.879	0.452	0.346	0.625	**0.046**	0.799	0.099	**0.005**	1.000
MLD	Co	0.26	0.06	-0.22	0.05	0.11	-0.03	-0.14	-0.01	0.16	-0.14	-0.20	-0.34	-0.22	-0.09	-0.23	0.45
	Sig	**0.050**	0.688	0.240	0.717	0.476	0.858	0.285	0.939	0.396	0.342	0.234	0.069	0.123	0.590	0.222	0.553

m, months; N, number of patients; Co, correlation coefficient; Sig, 2-tailed significance.
Significant correlations shown in bold.

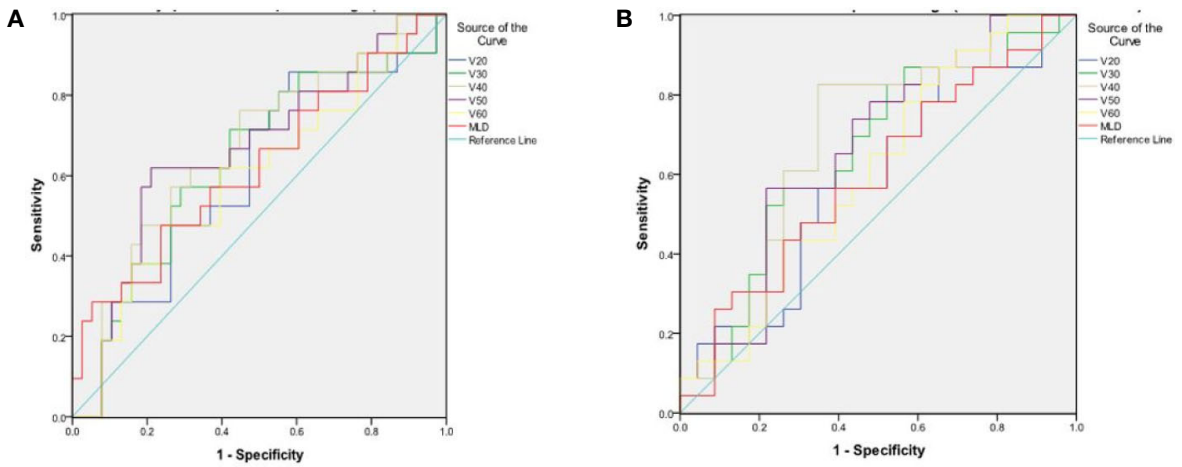


FIGURE 3 | Receiver Operator Curve **(A)** for 10-point change in dyspnea QoL between baseline and 3 months post-RT **(B)** for 1-point change in dyspnea VAS between baseline and 6 months post-RT.

subjective dyspnea changes following radical RT for NSCLC as a measure of potential lung toxicity when treating to disease below radiation tolerance of the lung.

The study demonstrated a significant correlation between lung DVH parameters and change in dyspnea post-RT using two different patient-completed dyspnea tools. Three months post-RT, a change in dyspnea QoL score significantly correlated with lung DVH parameters (V_{30} p=0.017; V_{40} p=0.026; V_{50} p=0.049; MLD p=0.05). Six months post-RT, a change in dyspnea VAS score significantly correlated with lung DVH parameters (V_{30} p=0.05; V_{40} p=0.026; V_{50} p=0.028). Lung DVH parameters were significantly predictive for a 10% increase in dyspnea QoL score 3 months post-RT (V_{40}; p=0.041, V_{50}; p=0.037) and dyspnea VAS score 6 months after the treatment (V_{40}; p=0.027), respectively.

The observed rate of ≥ grade 2 RP at 3 and 6 months post-RT was low (6%) with no correlation observed between rate of ≥ grade 2 RP and lung DVH parameters. This low rate of RP is to be expected given that the lung dose-volume constraints were met for all RT plans. Despite a significant negative correlation at 12 months between any change in the percentage of predicted FVC and lung V_{40} and V_{60}, respectively, and between any change in percentage of predicted FEV1 and lung V_{40}, V_{50}, and V_{60}, respectively, no lung DVH parameters were significant predictors of a clinically relevant worsening of FVC or FEV1, defined in this study by a 10% reduction in percentage of predicted values.

Dyspnea in patients with NSCLC is multi-factorial and is affected by respiratory and cardiac comorbidity (18, 19). While dyspnea is the predominant symptom in classical RP, the clinical diagnosis of RP is challenging due to confounding cardio-respiratory conditions affecting the lung cancer patient population (20). In addition, baseline respiratory function/dyspnea can be an additional risk factor for RILI (21).

Dyspnea is a subjective symptom not easily validated with objective tests. Nevertheless, it is of primary importance to the patient and in the absence of RP may provide a more sensitive measure of small changes to lung function and arguably a more appropriate measure for monitoring the patterns and severity of dyspnea over time. This study explored the relationship between lung dose-volume information and patient-recorded changes in dyspnea following irradiation. Measurement of relative dyspnea compared to baseline pre-RT values was performed to account for comorbidities as a confounding factor. However, given the complexity of dyspnea as a symptom, two tools were used to permit both a unidimensional dyspnea assessment with the VAS (17) and a lung cancer specific dyspnea assessment tool derived from the EORTC QOL questionnaire (15, 16). Such an approach to assessment of dyspnea had been suggested in a systematic review of the available tools (22) and a 10% change from baseline values is a reasonable measure of a clinically meaningful change (23). The dyspnea scales used in this study were demonstrated as a valid and reliable tool in a range of cancer patient populations, including lung cancer patients, and confirmed to reflect the common symptoms and treatment-related toxicities underlying radio(chemo)therapy (24). Another limitation of the study is the multiple testing in a small number of patients and the associated increased potential for Type I error in the results. Therefore, our results require validation in a larger cohort of patients.

Advances in planning software and delivery techniques permitted increasing flexibility when adjusting RT plans to spare normal tissue while maintaining target coverage. Distilling lung 3-dimensional dose-volume distribution data down to a threshold metric for risk of RILI produce a range of thresholds for various metrics in the RP literature (25–38). This is likely to be due to the gradual increase in lung damage with radiation dose (18). However, recommended thresholds for MLD and lung V_{20} with conventional fractionation remain widely used as normal tissue dose-constraints and are considered useful to aid assessment and optimization of different RT plans (10, 39). In this series, we recorded MLD 11% to 13% Gy and V_{20} 20% to 26%, in line with the accepted thresholds to minimize the risk of RILI (40). While the relatively small numbers in this study limited the statistical power of the results, ROC curve analyses suggested that the percentage volume of lung receiving 40 Gy (V_{40}) may be predictive for an increase in subjective dyspnea following conventionally fractionated RT. A lung V_{40} threshold of 11% may be a useful additional constraint and warrants validation in a larger cohort of patients.

We report the first radiotherapy study to describe the relationship between lung DVH parameters and self-assessed dyspnea scores. There have been studies of physician scored dyspnea which is recognized to suffer from investigator bias. Lung DVH parameters have shown no correlation with a change in physician-scored dyspnea score in stage I NSCLC patients receiving stereotactic RT (41). The evolution of dyspnea following radical RT for stage I-III NSCLC has also been studied in 197 patients using the physician-scored CTCAE classification (dyspnea grades 0–4) with worsening dyspnea in 17% to 27% of patients. The investigators highlighted the need for assessing dyspnea at more than one time-point post-RT (42).

To date, radiobiological parameters, rather than subjective dyspnea tools, have gained increasing interest in preventing RILI for thoracic irradiation. Recent publications argue in favor of NTCP model as a possible way to optimize treatment plans according to the probability of RP (18), and a multinomial NTCP has been proposed as possibly predictive for dyspnea grade with high accuracy (43). The need for intensification of local treatment to achieve better local control and improve survival rates for NSCLC without additional toxicity has also given rise to several, promising, dose escalation studies in United Kingdom, based on prespecified and mean lung dose constraints to increase tumor control probability without worsening normal tissue complication probability (NTCP) (44–49).

Radiotherapy dose-independent clinical factors impact on the risk of RILI (18, 50) and include age and comorbidity (50), smoking status (51), tumor location (52), systemic therapy (53, 54) and target therapies (18). The risk of RILI can also be affected by dose-dependent factors related to the irradiation of the heart rather than lung (55). Development of multi-factorial models including clinical and dosimetric factors for prediction of risk of RILI is important. Such a model was developed using a physician assessed dyspnea score (CTCAE version 3.0 (14)) as the endpoint (56). Addition of clinical factors to dosimetric factors improved the performance of the model in predicting for severe dyspnea post-RT. The use of patient-scored dyspnea assessments may further improve the performance of such models. However, these are only appropriate at doses close to or beyond conventional accepted tolerance limits and do not provide information on the effect of radiation at doses below tolerance limits.

In conclusion, dyspnea is a prominent symptom of RILI, which remains an important limitation for radical treatment of NSCLC with RT. Monitoring changes in dyspnea as an endpoint for multi-factorial predictive models of lung toxicity is important to increase the efficacy of radio(chemo)therapy without compromising treatment safety. Given the subjective nature of the symptom, patient-completed tools may be more sensitive and subject to less bias than physician grading. We have demonstrated that lung dose-volume parameters predict for a 10% worsening of dyspnea QoL at 3 months and dyspnea VAS at 6 months post-RT. A constraint of 11% of the lung volume receiving 40 Gy, if validated, may be useful in limiting the proportion of patients who experience ≥10% increase in dyspnea score following conventional RT. Further estimates, including competing risk analysis, will be needed to define the complex relationship among dyspnea, lung cancer and RILI in detail, also taking into account the rate of locally advanced disease stage. Our findings support the use of subjective dyspnea tools in future studies on lung RT toxicity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors only after the authorization of the Study Coordinator (MB).

AUTHOR CONTRIBUTIONS

FM, DT and AS collected and managed the data, and wrote the manuscript together with MB. FM developed the project, analyzed the data together with SA, and edited the manuscript. LB reviewed the literature and edited the manuscript. KL and SS interpreted the data. CF edited the manuscript. IM collected, managed, and analyzed the data, and wrote the manuscript. AA edited the manuscript. MB developed the project, peformed data integrity check and data analysis accuracy check, and edited the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

This work was undertaken in The Royal Marsden NHS Foundation Trust, which received a proportion of its funding from the NHS Executive. The views expressed in this publication are those of the authors and not necessarily those of the NHS Executive. This work was supported by The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, and The National Institute for Health Research Senior Investigator Awards and Cancer Research UK Section of Radiotherapy grant number C46/A2131. We acknowledge NHS funding to the NIHR Biomedical Research Centre.

REFERENCES

1. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* (2010) 28:2181–90. doi: 10.1200/JCO.2009.26.2543
2. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* (2010) 303:1070–6. doi: 10.1001/jama.2010.261
3. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2017) 28(suppl_4):iv1–iv21. doi: 10.1093/annonc/mdx222
4. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. *World J Clin Oncol* (2017) 8(1):1–20. doi: 10.5306/wjco.v8.i1.1
5. National Comprehensive Cancer Network® NCCN. Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-small Cell Lung Cancer Version 3.2020. (2020). Available at: https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.
6. van Baardwijk A, Bosmans G, Boersma L, Wanders S, Dekker A, Dingemans AMC, et al. Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. *Int J Radiat Oncol Biol Phys* (2008) 71:1394–401. doi: 10.1016/j.ijrobp.2007.11.070
7. De Ruysscher D, Wanders R, van Haren E, Hochstenbag M, Geraedts W, Pitz C, et al. HI-CHART: a phase I/II study on the feasibility of high-dose continuous hyperfractionated accelerated radiotherapy in patients with inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2008) 71:132–8. doi: 10.1016/j.ijrobp.2007.09.048
8. Thirion P, Holmberg O, Collins CD, O'Shea C, Moriarty M, Pomeroy M, et al. Escalated dose for non-small-cell lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. *Radiother Oncol* (2004) 71(2):163–6. doi: 10.1016/j.radonc.2003.09.006
9. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* (2006) 66:126–34. doi: 10.1016/j.ijrobp.2006.04.034
10. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* (2010) 76(3 Suppl):S70–6. doi: 10.1016/j.ijrobp.2009.06.091
11. McNair HA, Brock J, Symonds-Tayler JR, Ashley S, Eagle S, Evans PM, et al. Feasibility of the use of the Active Breathing Co ordinator (ABC) in patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC). *Radiother Oncol* (2009) 93:424–9. doi: 10.1016/j.radonc.2009.09.012
12. Brock J, McNair HA, Panakis N, Symonds-Tayler R, Evans PM, Brada M. The use of the Active Breathing Coordinator throughout radical non-small-cell lung cancer (NSCLC) radiotherapy. *Int J Radiat Oncol Biol Phys* (2011) 81:369–75. doi: 10.1016/j.ijrobp.2010.05.038
13. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* (2004) 291(20):2441–7. doi: 10.1001/jama.291.20.2441
14. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* (2003) 13(3):176–81. doi: 10.1016/S1053-4296(03)00031-6
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* (1993) 85(5):365–76. doi: 10.1093/jnci/85.5.365
16. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer* (1994) 30A:635–42. doi: 10.1016/0959-8049(94)90535-5
17. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. *Rehabil Nurs* (1989) 14:323–5. doi: 10.1002/j.2048-7940.1989.tb01129.x
18. Giuranno L, Ient J, De Ruysscher D, Vooijs MA. Radiation-Induced Lung Injury (RILI). *Front Oncol* (2019) 9:877. doi: 10.3389/fonc.2019.00877
19. Nalbantov G, Kietselaer B, Vandecasteele K, Oberije C, Berbee M, Troost E, et al. Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients. *Radiother Oncol* (2013) 109:100–6. doi: 10.1016/j.radonc.2013.08.035
20. Kocak Z, Evans ES, Zhou SM, Miller KL, Folz RJ, Shafman TD, et al. Challenges in defining radiation pneumonitis in patients with lung cancer. *Int J Radiat Oncol Biol Phys* (2005) 62:635–8. doi: 10.1016/j.ijrobp.2004.12.023
21. Kong FM, Wang S. Nondosimetric risk factors for radiation-induced lung toxicity. *Semin Radiat Oncol* (2015) 25(2):100–9. doi: 10.1016/j.semradonc.2014.12.003
22. Bausewein C, Farquhar M, Booth S, Gysels M, Higginson IJ. Measurement of breathlessness in advanced disease: a systematic review. *Respir Med* (2007) 101:399–410. doi: 10.1016/j.rmed.2006.07.003
23. Booth S. Report of 'Improving research methodology in breathlessness' meeting held by MRC Clinical Trials Unitand Cicely Saunders Foundation. *Palliat Med* (2006) 20:219–20. doi: 10.1191/0269216306pm1132xx
24. Schröder C, Engenhart-Cabillic R, Vorwerk H, Schmidt M, Huhnt W, Blank E, et al. Patient's quality of life after high-dose radiation therapy for thoracic carcinomas: Changes over time and influence on clinical outcome. *Strahlenther Onkol* (2017) 193(2):132–40. doi: 10.1007/s00066-016-1068-7
25. Bradley JD, Hope A, El Naqa I, Apte A, Lindsay PE, Bosch W, et al. A nomogram to predict radiation pneumonitis, derived from a combined analysis of RTOG 9311 and institutional data. *Int J Radiat Oncol Biol Phys* (2007) 69:985–92. doi: 10.1016/j.ijrobp.2007.04.077
26. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* (1999) 45:323–9. doi: 10.1016/S0360-3016(99)00183-2
27. Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, Das SK, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* (2001) 51:650–9. doi: 10.1016/S0360-3016(01)01685-6
28. Hope AJ, Lindsay PE, El Naqa I, Alaly JR, Vicic M, Bradley JD, et al. Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters.

Int J Radiat Oncol Biol Phys (2006) 65:112–24. doi: 10.1016/j.ijrobp.2005.11.046
29. Kim TH, Cho KH, Pyo HR, Lee JS, Zo JI, Lee DH, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. *Radiology* (2005) 235(1):208–15. doi: 10.1148/radiol.2351040248
30. Kong FM, Hayman JA, Griffith KA, Kalemkerian GP, Arenberg D, Lyons S, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. *Int J Radiat Oncol Biol Phys* (2006) 65:1075–86. doi: 10.1016/j.ijrobp.2006.01.051
31. Kwa SL, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. *Int J Radiat Oncol Biol Phys* (1998) 42:1–9. doi: 10.1016/S0360-3016(98)00196-5
32. Kwa SL, Theuws JC, Wagenaar A, Damen EM, Boersma LJ, Baas P, et al. Evaluation of two dose-volume histogram reduction models for the prediction of radiation pneumonitis. *Radiother Oncol* (1998) 48:61–9. doi: 10.1016/S0167-8140(98)00020-6
33. Martel MK, Ten Haken RK, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. *Int J Radiat Oncol Biol Phys* (1994) 28:575–81. doi: 10.1016/0360-3016(94)90181-3
34. Rancati T, Ceresoli GL, Gagliardi G, Schipani S, Cattaneo GM. Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. *Radiother Oncol* (2003) 67:275–83. doi: 10.1016/S0167-8140(03)00119-1
35. Seppenwoolde Y, De Jaeger K, Boersma LJ, Belderbos JS, Lebesque JV. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2004) 60:748–58. doi: 10.1016/j.ijrobp.2004.04.037
36. Wang S, Liao Z, Wei X, Liu HH, Tucker SL, Hu CS, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). *Int J Radiat Oncol Biol Phys* (2006) 66(5):1399–407. doi: 10.1016/j.ijrobp.2006.07.1337
37. Yorke ED, Jackson A, Rosenzweig KE, Merrick SA, Gabrys D, Venkatraman ES, et al. Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* (2002) 54(2):329–39. doi: 10.1016/S0360-3016(02)02929-2
38. Yorke ED, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. *Int J Radiat Oncol Biol Phys* (2005) 63:672–82. doi: 10.1016/j.ijrobp.2005.03.026
39. Palma AD, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-Analysis. *Int J Radiat Oncol Biol Phys* (2013) 85(2):444–50. doi: 10.1016/j.ijrobp.2012.04.043
40. Seppenwoolde Y, Lebesque JV, de Jaeger K. Comparing different NTCP models that predict the incidence of radiation pneumonitis. *Int J Radiat Oncol Biol Phys* (2003) 55:724–35. doi: 10.1016/S0360-3016(02)03986-X
41. Paludan M, Traberg Hansen A, Petersen J, Grau C, Hoyer M. Aggravation of dyspnea in stage I non-small cell lung cancer patients following stereotactic body radiotherapy: Is there a dose-volume dependency? *Acta Oncol* (2006) 45:818–22. doi: 10.1080/02841860600915314
42. De Ruysscher D, Dehing C, Yu S, Wanders R, Ollers M, Dingemans AMC, et al. Dyspnea evolution after high-dose radiotherapy in patients with non-small cell lung cancer. *Radiother Oncol* (2009) 91:353–9. doi: 10.1016/j.radonc.2008.10.006
43. Defraene G, Schuit E, De Ruysscher D. Development and internal validation of a multinomial NTCP model for the severity of acute dyspnea after radiotherapy for lung cancer. *Radiother Oncol* (2019) 136:176–84. doi: 10.1016/j.radonc.2019.03.034
44. van Baardwijk A, Wanders S, Boersma L, Borger J, Ollers M, Dingemans AMC, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. *J Clin Oncol* (2010) 28:1380–6. doi: 10.1200/JCO.2009.24.7221
45. Hatton MQF, Hill R, Fenwick JD, Morgan SA, Wilson PC, Atherton PJ, et al. Continuous Hyperfractionated Accelerated Radiotherapy - Escalated Dose (CHART-ED): A Phase I Study. *Radiother Oncol* (2016) 118(3):471–7. doi: 10.1016/j.radonc.2015.11.015
46. Landau DB, Hughes L, Baker A, Bates AT, Bayne MC, Counsell N, et al. "IDEAL-CRT: a phase 1/2 trial of isotoxic dose-escalated radiation therapy and concurrent chemotherapy in patients with stage II/III non-small cell lung cancer". *Int J Radiat Oncol Biol Phys* (2016) 95:1367–77. doi: 10.1016/j.ijrobp.2016.03.031
47. Fenwick JD, Landau DB, Baker AT, Bates AT, Chinnamani E, Garcia-Alonso A, et al. Long-Term Results From the IDEAL-CRT Phase 1/2 Trial of Isotoxically Dose-Escalated Radiation Therapy and Concurrent Chemotherapy for Stage II/III Non-small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* (2020) 106(4):733–42. doi: 10.1016/j.ijrobp.2019.11.397
48. I-START Study ISRCTN: 74841904. A phase I/II trial of isotoxic accelerated radiotherapy in the treatment of patients with non-small cell lung cancer. (2018). (NCT01537991). Available at: http://www.isrctn.com/ISRCTN74841904; https://clinicaltrials.gov/ct2/show/NCT01537991.
49. Haslett K, Franks K, Hanna GG, Harden S, Hatton M, Harrow S, et al. Protocol for the isotoxic intensity modulated radiotherapy (IMRT) in stage III non-small cell lung cancer (NSCLC): a feasibility study. *BMJ Open* (2016) 6:e010457. doi: 10.1136/bmjopen-2015-010457
50. Vogelius IR, Bentzen SM. A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis. *Acta Oncol* (2012) 51:8,975–983. doi: 10.3109/0284186X.2012.718093
51. Jin H, Tucker SL, Liu HH, Wei X, Yom SS, Wang S, et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. *Radiother Oncol* (2009) 91(3):427–32. doi: 10.1016/j.radonc.2008.09.009
52. Vinogradskiy Y, Tucker SL, Liao Z, Martel MK. Investigation of the Relationship Between Gross Tumor Volume Location and Pneumonitis Rates Using a Large Clinical Database of Non-Small-Cell Lung Cancer Patients. *Int J Radiat Oncol Biol Phys* (2012) 82(5):1650–8. doi: 10.1016/j.ijrobp.2011.02.009
53. Onishi H, Kuriyama K, Yamaguchi M, Komiyama T, Tanaka S, Araki T, et al. Concurrent two-dimensional radiotherapy and weekly docetaxel in the treatment of stage III non-small cell lung cancer: a good local response but no good survival due to radiation pneumonitis. *Lung Cancer* (2003) 40:79–84. doi: 10.1016/S0169-5002(02)00532-9
54. Tsujino K, Hirota S, Kotani Y, Kado T, Yoden E, Fujii O, et al. Radiation pneumonitis following concurrent accelerated hyperfractionated radiotherapy and chemotherapy for limited-stage small-cell lung cancer: Dose-volume histogram analysis and comparison with conventional chemoradiation. *Int J Radiat Oncol Biol Phys* (2006) 64(4):1100–5. doi: 10.1016/j.ijrobp.2005.09.025
55. Huang EX, Hope AJ, Lindsay PE, Trovo M, El Naqa I, Deasy JO, et al. Heart irradiation as a risk factor for radiation pneumonitis. *Acta Oncol* (2010) 50(1):51–60. doi: 10.3109/0284186X.2010.521192
56. Dehing-Oberije C, De Ruysscher D, van Baardwijk A, Yu S, Rao B, Lambin P. The importance of patient characteristics for the prediction of radiation-induced lung toxicity. *Radiother Oncol* (2009) 91:421–6. doi: 10.1016/j.radonc.2008.12.002

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership