**Original Article**

Impact of Symptom Clusters on Quality of Life Outcomes in Patients from Japan with Advanced Nonsmall Cell Lung Cancers

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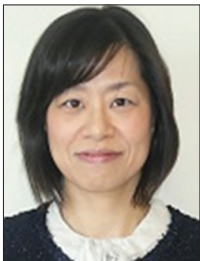
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ABSTRACT

Objective: Identify symptom clusters based on symptoms experienced by patients with advanced nonsmall cell lung cancers (NSCLCs), and examine the relationship between the symptom clusters and impairment in everyday life and quality of life (QOL). **Methods:** Using the M.D. Anderson Symptom Inventory, 9 symptom items and the QOL Questionnaire (QLQ-C-30) evaluation apparatus from the European Organization for Research and Treatment of Cancer, we evaluated symptom severity, interference in daily life, and QOL. Factor analysis and multiple regression analysis techniques were used. **Results:** Sixty patients with advanced NSCLCs seen in pulmonary medicine departments were included in the study. The average age of patients was 64.33 (standard deviation = 11.40).

Thirty-six were male and 24 were female. Three symptom clusters were identified as fatigue/anorexia cluster (dry mouth, altered the sense of taste, drowsiness, fatigue/tiredness, and lack of appetite), pain cluster (anxiety, sadness, and pain), numbness cluster (numbness, leg weakness, and distress). The pain cluster had the strongest influence (adjusted $R^2 = 0.355$) on daily life (emotions) while the numbness cluster most strongly affected walking. The fatigue/anorexia cluster explained 22.7% of role function variance. This symptom clustering may be unique among patients with advanced NSCLCs. **Conclusions:** Each of these clusters affected QOL and everyday life with varying degrees of influence. In clinical screening assessments, focusing on symptom clusters could provide tailored management

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strategies for patients with advanced NSCLCs. These care strategies may improve outcomes specifically for advanced NSCLCs patients.

Introduction

Lung cancer has been the leading cause of cancer-related deaths in Japan, the USA, and Europe, with higher mortality rates than other forms of cancer.[1-3] There are standard chemotherapies and biotherapies effective at prolonging life in patients with nonsmall cell lung cancers (NSCLCs).[4,5] Cancer and these therapies present unique symptom profiles, including a large number of symptoms which can be distressing to the patient and family and negatively impact functionality, quality of life (QOL), and other important outcomes.[6-8] One way to improve the symptoms in patients with advanced lung cancer and patient outcomes may be to gain a better understanding of symptoms occurring concurrently, as in symptom clusters.

Dodd *et al.* proposed the idea of symptom clusters as a way to gain a clearer understanding of symptoms and phenomena that interfere with various everyday activities and impair the QOL.[9] Symptom clusters are defined as two or more symptoms that are manifested simultaneously and affect key patient outcomes such as QOL.[10]

Currently, there is sufficient evidence to support the concept of symptom clusters in patients with cancer generally; however in lung cancer, symptom cluster research is ongoing and no generally accepted cluster symptoms have been determined.[11-18] Chen *et al.* indicated that symptom clusters in lung cancer patients lack quantitative and structural consistency, and demonstrated discrepancies in sample population characteristics and methodologies, such as in the assessment tools and analysis techniques.[19] Specifically, in lung cancer, empirical research studies have identified four symptom clusters comprising 2 to 11 distinct symptoms, and specific symptom clusters have been named [Table 1].[20-26]

To date, the sample sizes of patients with lung cancer enrolled in the published reports of symptom clusters have ranged from 60 to 400. Among these reports, the only study that focused on patient groups of the same kind of NSCLCs[25] included recurrent and secondary lung cancers as well as primary NSCLCs, and 75% of this group received surgical treatment.

While there has been some descriptive work reported for early and unspecified stages of lung cancers, there has been little work examining symptom clusters in exclusively advanced stage (IIIB or IV) lung cancers. In that sample,[20-26] the percentage of patients with advanced stage (IIIB or IV) disease was either unspecified or relatively limited, ranging from 3.0% to 60.0%. Focusing on the group with the same type of advanced stage (IIIB or IV) who received standard therapies (chemotherapy and biotherapy), the most seriously ill NSCLCs patients, with arguably the highest symptom burdens, were underrepresented. The purposes of this study were to identify: (1) symptom clusters, (2) relationships between symptom clusters and the effects on daily life, and (3) relationships between symptom clusters and QOL among advanced stage (IIIB or IV) NSCLCs patients.

Methods

Study sample and procedures

This study is a cross-sectional, descriptive correlation design. As an appropriate sample size for explanatory factor analysis has not been established, it is something that is still being discussed.[27] This study set the sample size as 60 based on previous nursing studies that conducted exploratory factor analysis to examine symptom clusters of advanced lung cancer patients by setting the sample sizes as 60–400.[20-24,26] This study was approved by the Medical University Ethics Committee and the two participating institutions. Using a convenience sampling, patients were recruited from two institutions, a regional university hospital, and a general hospital in the Tokyo metropolitan area. Eligibility criteria are as follows: adult patients (over 20-year-old), with no other diagnosed malignancies, no cognitive impairment, and patients who were being administered standard therapy for advanced (Stage IIIB or IV) primary NSCLCs. Clinicians explained about the access of researchers (nurses) to patients who met the eligibility criteria, and the researchers (nurses) provided information about the study participation orally and in writing to patients who had permitted the access of researchers (nurses).

After signing the informed consent documents, participants were provided with a survey form and a reply-paid envelope and instructed to fill in the form; the participants filled in the survey form in the early evening of the same day and posted it back to the research team within 1 week. Researchers (nurses) assisted participants who needed help

Table 1: Studies identifying symptom clusters in lung cancer patients				
Author, year	Instruments	*n*	Percentage of patients with advanced stage lung cancer	Symptom clusters identified

Sarna and Brecht, 1997[20]	SDS (10 items plus 3 items relevant for people with lung cancer)	60	71% NSCLC 84% advanced stage (64% had distant sites of metastasis)	Gastrointestinal distress
				  Nausea frequency, nausea severity, and appetite
				Emotional and physical suffering
				  Pain frequency, pain severity, bowel, appearance, and outlook
				Respiratory distress
				  Insomnia, breathing, and coughing
				Malaise
				  Fatigue, and concentration

Gift *et al.*, 2004[21]	Physical symptoms experience tool (32 items of the original 37 items)	220	Stage III 38.1% Stage IV 21.4%	General Fatigue, weakness, nausea, vomiting, loss of appetite, weight loss, and altered sense of taste

Wang *et al.*, 2006[22]	MDASI (13 items plus cough and sore throat)	64	Stage III 97% Stage IV 3%	Pattern 1
				  Sore throat and pain
				Pattern 2
				  Nausea and vomiting
				Pattern 3
				  Lack of appetite, drowsiness, fatigue, sleep disturbance, dry mouth, and distress
				Pattern 4
				  Difficulty remembering, coughing, numbness, sadness, and shortness of breath

Wang *et al.*, 2008[23]	MDASI, Taiwanese (13 items)	108	Stage IV 19.4%	General
				  Pain, fatigue, sleep disturbance, distress, lack of appetite, drowsiness, dry mouth, sadness, and numbness
				Gastrointestinal
				  Nausea and vomiting

Henoch *et al.*, 2009[24]	SDS (11 items of the original 15 items) EORTC QLQ-C30 (11 items) QLQ-LC13 (only the item assessing coughing was used)	400	85% NSCLC Stage IIIB 19% Stage IV 41%	Pain
				  Bowel, pain, nausea, appetite loss, and fatigue
				Mood
				  Mood, outlook, concentration, and insomnia
				Respiratory
				  Dyspnea and coughing

Brown *et al.*, 2011[25]	Lung Cancer Symptom Scale (six symptoms) symptom query questionnaire (five symptoms) CES-D (depressed mood)	196	100% NSCLC Local or regional 80% Metastasis 20%	Fatigue Shortness of breath Coughing Pain Poor appetite

Khamboon *et al.*, 2015[26]	Memorial symptom assessment scale (32 symptoms)	300	97.3% NSCLC Stage III 18% Stage IV 82%	Emotional-elimination discomfort
				  Feeling irritable, feeling drowsy, feeling bloated, dizziness, problems with urination, constipation, and changes in skin
				Anorexia-related
				  Dry mouth, change in the way food tastes, and lack of appetite
				Treatment-related gastrointestinal and other
				  Nausea, vomiting, and hair loss
				Neurological and body image
				  Numbness/tingling in hands/feet, "I don't like myself," pain, worrying, weight loss
				Respiratory and sleep disturbance
				  Shortness of breath, coughing, and difficulty in sleeping

SDS: Symptom Distress Scale, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire-Core 30, MDASI: M.D. Anderson Symptom Inventory, CES-D: Center for Epidemiologic Studies Depression Scale, NSCLC: Nonsmall cell lung cancers

with completing the survey form due to numbness in the hands, by reading out the answer choices at the interview, and indicating the choice by circling the corresponding number. The participants sealed and posted the envelopes by themselves.

Analytical instruments

The survey included input from the M.D. Anderson Symptom Inventory (MDASI), a brief measure of the severity and impact of cancer-related symptoms.

The MDASI is in English and is a self-rating multiple symptom assessment scale comprising 13 symptom items and 6 interference items.[28] The scale utilized in this study was created by combining the 13-item Japanese version of the MDASI (MDASI-J)[29] plus an advanced NSCLCs symptom scale comprising nine symptom items (altered sense of taste, weight loss, leg weakness, cough, rash, impaired concentration, irritability, anxiety, and depression), developed by the authors based on a preliminary study of symptoms experienced by patients

with advanced NSCLCs. Impairment in everyday life was evaluated using the 6-item MDASI-J system in the same order as in the MDASI.

With the MDASI-J and the NSCLCs symptom modules, the participants rate the severity of symptoms during the previous 24 h by circling a number between 0 and 10, where 0 stands for "not present" and 10 is "as bad as can be imagined." The responses in the advanced NSCLCs symptom module are reported in the same manner. Cronbach's alpha values were 0.87 for this study population, 0.88 for the MDASI-J, 0.83 for the advanced NSCLCs symptom module, and 0.92 for the combined total of 22 categories.

For the QOL scale, we employed the Japanese version of the Core QOL Questionnaire (QLQ-C30), with permission from the European Organization for Research and Treatment of Cancer (EORTC).[30,31] We analyzed five functions (physical, role, cognitive, emotional, and social) and global QOL. Data, including age, gender, disease, and treatment details, including diagnosis (tissue type), cancer stage (tumor, node, metastasis classification), comorbidities, current treatment regimen, time since diagnosis (in days), use of analgesic medications (yes/no), and the Eastern Cooperative Oncology Group Performance Status (ECOG PS),[32] were extracted from electronic medical records. Participants were also asked to fill in a demographic background form providing details such as educational level, work history, marital state, and persons they are living together with.

Statistical analysis

Regarding the inconsistencies in the symptom clusters identified in lung cancer patients in different studies, Chen *et al.*[19] pointed out the inconsistency in the analytical methods to identify symptom clusters. Henoch *et al.*[24] suggest that a factor analysis is the most suitable tool for the empirical exploration of potential symptom clusters. Five (71%)[20-24,26] among previous studies shown in Table 1 used factor analysis and evaluated Cronbach's alpha and Pearson's correlation.[25] Therefore, we assumed that identification of symptom clusters by factor analysis would be effective to overcome the problem of inconsistency in the study method and determined to use factor analysis in this study. We also used the Promax rotation method that describes correlations between factors, assuming that there are correlations between symptom clusters.

Following the definition of Kim *et al.*[10] that there is a better correlation between symptom items in the symptom clusters, we determined symptoms with significant correlations

within a factor for the factors belonging to a symptom cluster. Therefore, this study identified symptom clusters by estimating the number of factors through an exploratory factor analysis (principal factor analysis: Promax rotation). The magnitude of a factor pattern was set to 0.3 or higher based on Gift *et al.*,[21] who reported at least one factor. Cronbach's alpha was calculated for each factor, along with the number of clustered symptoms, and Pearson's correlation coefficients between symptoms to evaluate the internal consistency of symptom clusters identified.

Following the definition of Kim *et al.*,[10] we evaluated the influence of symptom clusters on important outcomes of patients, everyday life, and QOL. Correlations between the symptom clusters and impairment in daily life and QOL were analyzed by calculating Pearson's *r* correlation coefficients for the average scores for each symptom within the cluster, average scores on the 6-point MDASI-J everyday life impairment inventory, the EORTC QLQ-C30 five-function scale (physical, role, cognitive, emotional, and social), and the average global QOL scores.

To determine the impact on outcomes, we performed a stepwise multiple regression analysis. The independent variables were the symptom cluster base score. The variables were demographic (age and education status) and clinical (ECOG PS, comorbid conditions, and time since diagnosis) entered simultaneously into the regression analyses. The score for each identified symptom cluster was converted to a symptom cluster base score to generate an independent variable.[33,34] The dependent variables were the MDASI-J (impairment of everyday life score), and the standardized scores for the EORTC QLQ-C30 five functions and the global QOL. A higher score of these standardized scores (range, 1–100) indicates a better QOL.[35] There was no multicollinearity effect (minimum tolerance of 0.2) as per Yanai and Ogata.[36]

The level of statistical significance was set at 0.05. Descriptive statistics was used to evaluate sample characteristics. All statistical analyses were performed using SPSS®, version 19.0 (IBM®, New York, NY, USA).

Results

Participant characteristics

Patients were recruited from April to November 2010. Of the 67 potential participants who met the eligibility criteria, 61 agreed to participate. The participants were asked to complete a written questionnaire. Complete responses were received from sixty participants and were used as the data in the analysis. As shown in Table 2, the average age of

the sixty participants was 64.33 years, (standard deviation [SD] =11.40 years). The median ECOG PS was 1.0. For standard therapies, 88.3% of the participants received a combination therapy of platinum (cisplatin or carboplatin), a maintenance therapy, gefitinib, or erlotinib at the baseline of the study. Six (10%) were not undergoing chemotherapy because they were in a follow-up period between the previous treatment and being evaluated for progressive disease. Further, one participant (1.7%) was under palliative radiotherapy proceeding to a chemotherapy period. Fifty-five percent of the participants were outpatients who filled in the survey themselves while 45.0% asked the researchers to fill in the survey in an interview setting due to neuropathy limiting the ability to write.

The average symptom severities (ranked in order) were 3.77 (fatigue/tiredness, SD = 3.02), 3.12 (drowsiness, SD = 2.62), and 3.05 (lack of appetite, SD = 2.91). The prevalence (%) was highest for both fatigue/tiredness and drowsiness, at approximately 80.0%. Over 30.0% of participants experienced all symptoms excluding the lowest two as shown in Figure 1. The two least severe symptoms – rash (average severity 0.83, SD = 1.63) and vomiting (average severity 0.80, SD = 1.98) – were excluded

due to low reliability. Analyses were based on the scores for the remaining twenty symptoms.

As shown in Table 3, the average impairment scores (ranked in order) were 3.71 (enjoyment of life, SD = 3.10), 3.37 (life in general, SD = 3.11), and 3.35 (walking, SD = 2.94). The averages of the standardized scores for the EORTC QLQ C-30 five functions (ranked in order) that patients reported as poorest were 57.78 (role, SD = 32.25), 67.66 (physical, SD = 22.99), 74.16 (social, SD = 25.93), and 49.58 (global QOL, SD = 24.52).

Factor analysis

The Promax rotation principal factor analysis identified five factors from the scores of the twenty symptoms: Factor A includes impaired concentration, irritability, depression, weight loss, difficulty in remembering, and shortness of breath. Factor B includes dry mouth, altered sense of taste, drowsiness, fatigue/tiredness, and lack of appetite. Factor C includes Anxiety, sadness, and pain. Factor D includes sleep disturbance, nausea, and cough. Factor E includes numbness, leg weakness, and distress. As shown in Table 4, Cronbach's alpha coefficients for the five factors were in the range of 0.73–0.84.
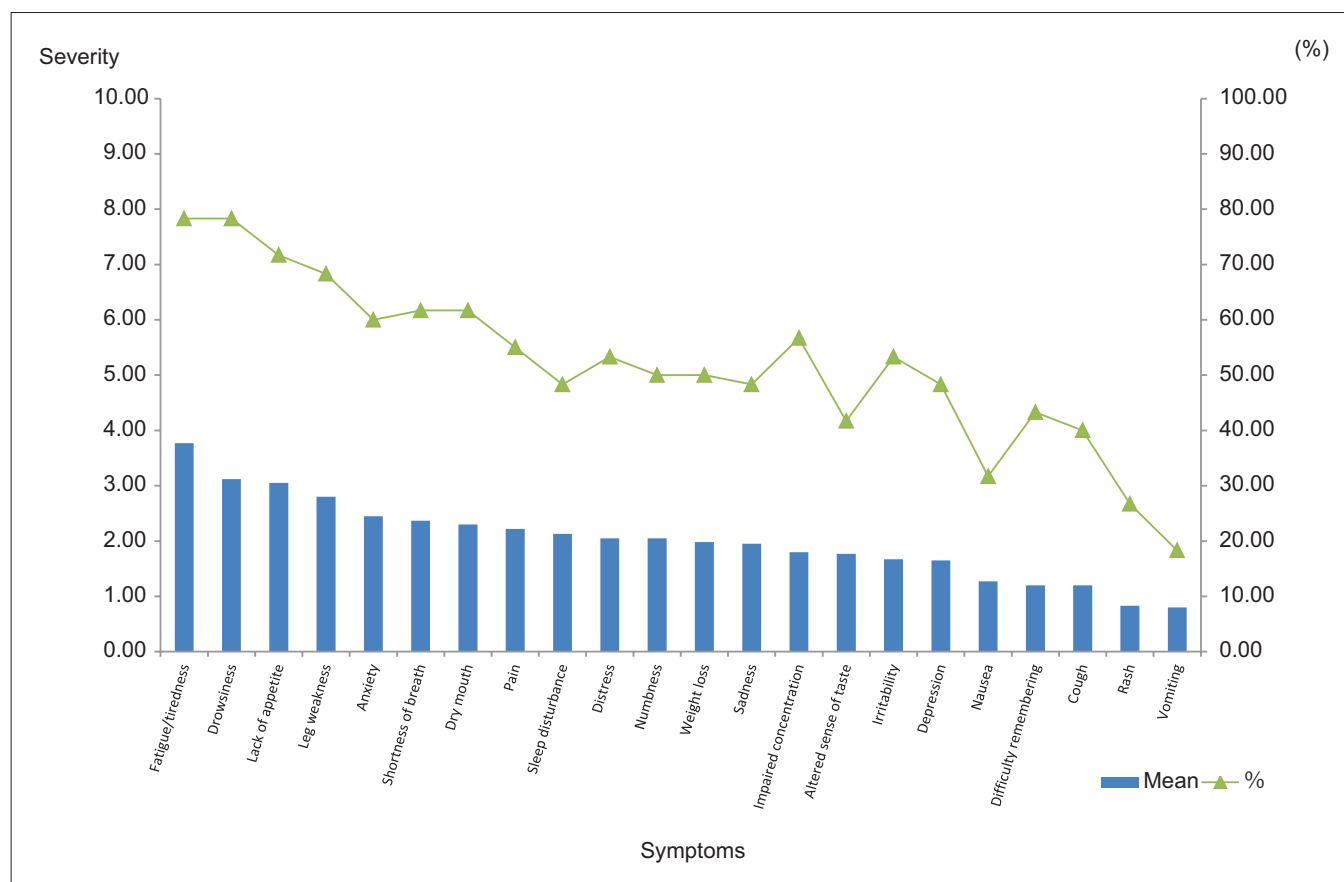

Figure 1: Twenty two symptoms, symptom severity score and prevalence

Table 2: Participant demographic characteristics and medical characteristics (*n*=60)

Characteristics	*n* (%)	Mean (SD)	Range	Median
Age (years)		64.33 (11.40)	24-83	64.00
Sex				
Female	24 (40)			
Male	36 (60)			
Marital status				
Married	50 (73.3)			
Single, divorced, or widowed	10 (16.7)			
Employment status				
Employed	18 (30.0)			
Unemployed or retired	42 (70.0)			
Education (years)				
University, graduate school, or junior college (>12)	24 (40.0)			
Senior high school (≦12)	29 (48.3)			
Junior high school (≦9)	6 (10.0)			
Elementary school (≦6)	1 (1.7)			
Time since diagnosis (days)		483.98 (639.64)	6-2607	276.50
ECOG PSR		1.1 (0.6)	0-3	1.0
0	7 (11.7)			
1	41 (68.3)			
2	10 (16.7)			
3	2 (3.3)			
Histological types of cancer				
Adenocarcinoma	53 (88.3)			
Squamous cell carcinoma	6 (10.0)			
Adenocarcinoma + squamous cell carcinoma	1 (1.7)			
Cancer stage				
III B	17 (28.3)			
IV	43 (71.7)			
Current treatment				
Chemotherapy	53 (88.3)			
CBDCA + PTX	9 (15.0)			
Gefitinib	10 (16.7)			
CDDP + MTA	4 (6.6)			
CBDCA + MTA	3 (5.0)			
MTA	7 (11.7)			
DOC	6 (10.0)			
GEM + UFT	4 (6.6)			
CDDP + VNR	3 (5.0)			
CBDCA + GEM	2 (3.3)			
GEM	1 (1.7)			
VNR	1 (1.7)			
Erlotinib	2 (3.3)			
CBDCA + PTX + bevacizumab	1 (1.7)			
Palliative RT	1 (1.7)			
None	6 (10.0)			
Number of comorbidities				
0	25 (41.7)			
1 or more	35 (58.3)			
Current analgesics usage				
Yes	23 (38.3)			
No	37 (61.7)			

ECOG PSR: Eastern Cooperative Oncology Group performance status rating, CDDP: Cisplatin, CBDCA: Carboplatin, PTX: Paclitaxel, MTA: Pemetrexed, DOC: Docetaxel, GEM: Gemcitabine, UFT: Tegafur uracil, VNR: Vinorelbine, RT: Radiotherapy, SD: Standard deviation

Table 3: Impairment scores and standardized European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 scores (*n*=60)

Activity	Score	
	Mean	SD
Daily life interference		
Life in general	3.37	3.11
Emotions	2.68	2.81
Work (including housework)	3.34	3.59
Interpersonal relationships	1.88	2.67
Walking	3.35	2.94
Enjoyment of life	3.71	3.12
EORTC QLQC-30 five functions and global QOL		
Physical	67.66	22.99
Role	57.78	32.25
Cognitive	79.16	19.32
Emotional	80.28	16.45
Social	74.16	25.93
Global QOL	49.58	24.52

SD: Standard deviation, QOL: Quality of life, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

Table 4: Factor analysis of twenty symptoms (*n*=60)

Row cluster	Factor loading	Cronbach's alpha
Factor A		
Impaired concentration	0.874	0.83
Irritability	0.736	
Depression	0.721	
Weight loss	0.566	
Difficulty remembering	0.564	
Shortness of breath	0.311	
Factor B		
Dry mouth	0.779	0.84
Altered sense of taste	0.668	
Drowsiness	0.580	
Fatigue/tiredness	0.534	
Lack of appetite	0.482	
Factor C		
Anxiety	0.685	0.74
Sadness	0.516	
Pain	0.508	
Factor D		
Sleep disturbance	0.786	0.73
Nausea	0.715	
Cough	0.394	
Factor E		
Numbness	0.877	0.78
Leg weakness	0.490	
Distress	0.400	

Factor extraction method: Principal factor analysis; rotation method: Promax with Kaiser normalization

Peason's correlation coefficients among symptoms within a factor

As Table 5 shows, three of the factors showed statistically significant correlations ($P < 0.05$) between all the

Table 5: Pearson's correlation coefficient between symptoms within each factor (n=60)

Factor A

Symptom	Impaired concentration	Irritability	Depression	Weight loss	Difficulty remembering	Shortness of breath
Impaired concentration	1.00					
Irritability	0.58**	1.00				
Depression	0.59**	0.73**	1.00			
Weight loss	0.44**	0.55**	0.48**	1.00		
Difficulty remembering	0.52**	0.27*	0.44**	0.32*	1.00	
Shortness of breath	0.32*	0.38**	0.52**	0.45**	0.13	1.00

Factor B

Symptom	Dry mouth	Altered sense of taste	Drowsiness	Fatigue/tiredness	Lack of appetite
Dry mouth	1.00				
Altered sense of taste	0.59**	1.00			
Drowsiness	0.60**	0.40**	1.00		
Fatigue/tiredness	0.48**	0.55**	0.54**	1.00	
Lack of appetite	0.54**	0.49**	0.36**	0.53**	1.00

Factor C

Symptom	Anxiety	Sadness	Pain
Anxiety	1.00		
Sadness	0.63**	1.00	
Pain	0.41**	0.42**	1.00

Factor D

Symptom	Sleep disturbance	Nausea	Cough
Sleep disturbance	1.00		
Nausea	0.58**	1.00	
Cough	0.59**	0.23	1.00

Factor E

Symptom	Numbness	Leg weakness	Distress
Numbness	1.00		
Leg weakness	0.63**	1.00	
Distress	0.51**	0.49**	1.00

*P<0.05, **P<0.01

Table 6: Step-wise regression analysis of the three clusters and daily life interference coefficients (n=60)

Variable	Daily life interference (life in general)			Daily life interference (emotions)			Daily life interference (work including housework)			Daily life interference (interpersonal relationships)			Daily life interference (walking)			Daily life interference (enjoyment of life)		
	β	P	Adjusted R²	β	P	Adjusted R²	β	P	Adjusted R²	β	P	Adjusted R²	β	P	Adjusted R²	β	P	Adjusted R²
Fatigue/anorexia cluster	0.206	0.128	-	0.160	0.199	-	0.081	0.561	-	−0.065	0.666	-	0.306	0.022*	0.052	0.372	0.002**	0.076
Pain cluster	0.484	<0.001**	0.249	0.563	<0.001**	0.355	0.424	0.001**	0.208	0.357	0.005**	0.112	−0.008	0.957	-	0.330	0.008**	0.333
Numbness cluster	−0.037	0.788	-	0.180	0.162	-	0.221	0.121	-	0.155	0.320	-	0.364	0.007**	0.281	−0.182	0.165	-
Model F	11.635**	-	-	19.834**	-	-	10.797**	-	-	8.446**	-	-	15.727**	-	-	17.101**	-	-

*P<0.05, **P<0.01. All the models are adjusted for age, education, comorbidity, ECOG PSR and time since diagnosis. Fatigue/anorexia cluster: Dry mouth, altered sense of taste, drowsiness, fatigue/tiredness, lack of appetite, Pain cluster: Anxiety, sadness, pain, Numbness cluster: Leg weakness, numbness, distress, ECOG PSR: Eastern Cooperative Oncology Group Performance Status Rating

Table 7: Step-wise regression analysis of the three clusters and quality of life coefficients ($n=60$)

Variable	Physical function			Role function			Cognitive function			Emotional function			Social function			Global QOL		
	β	P	Adjusted R^2	β	P	Adjusted R^2	β	P	Adjusted R^2	β	P	Adjusted R^2	β	P	Adjusted R^2	β	P	Adjusted R^2
Fatigue/anorexia cluster	−0.205	0.136	-	−0.490	<0.001**	0.227	−0.448	<0.001**	0.191	0.061	0.663	-	0.064	0.641	-	−0.363	0.004**	0.117
Pain cluster	−0.432	<0.001**	0.178	−0.101	0.473	-	−0.024	0.865	-	−0.499	<0.001**	0.236	−0.409	0.001**	0.204	−0.190	0.204	-
Numbness cluster	−0.199	0.151	-	0.084	0.552	-	−0.030	0.834	-	−0.101	0.483	-	0.019	0.893	-	0.062	0.683	-
Model F	15.444**		-	18.304**		-	9.878**		-	19.197**		-	12.198**		-	8.794**		-

**P<0.01. All the models are adjusted for age, education, comorbidity, ECOG PSR and time since diagnosis. Fatigue/anorexia cluster: Dry mouth, altered sense of taste, drowsiness, fatigue/tiredness, lack of appetite, Pain cluster: Anxiety, sadness, pain, Numbness cluster: Leg weakness, numbness, distress, QOL: Quality of life, ECOG PSR: Eastern Cooperative Oncology Group Performance Status Rating

constituent symptoms. Based on these results, it was determined that three symptom clusters could be identified fatigue/anorexia cluster (dry mouth, altered sense of taste, drowsiness, fatigue/tiredness, and lack of appetite), pain cluster (anxiety, sadness, and pain), and numbness cluster (numbness, leg weakness, and distress).

Effects of symptom clusters on outcomes (interference of daily life and quality of life)

As seen in Table 6, the three symptom clusters explained 5.2%–35.5% of the variance in impairment of everyday life quality. The pain cluster is the only cluster influencing all five subscales of the impairment in everyday life (excluding walking). It is more likely that the fatigue/anorexia cluster and the pain cluster only influenced enjoyment of life, but did not impair other aspects of everyday life. The pain cluster had the strongest influence on the emotion parameter with the adjusted $R^2 = 0.355$. The numbness cluster had the strongest influence on the walking parameter, with the adjusted $R^2 = 0.281$.

As Table 7 shows, multiple regression analysis suggested that fatigue/anorexia and pain clusters alone explained 11.7%–23.6% of the variance in QOL. Fatigue/anorexia and pain clusters influenced three subscales of the QOL score. Particularly, it is more likely that fatigue/anorexia cluster influenced three subscales of the QOL (excluding the physical, emotion, and social functions). It is also more likely that the pain cluster only influenced physical, emotion, and social function, but not any of the other subscales of the QOL. Fatigue/anorexia cluster had the strongest influence on the role function (adjusted $R^2 = 0.227$), with the pain cluster the strongest influence on the emotional function (adjusted $R^2 = 0.236$).

Discussion

This study uniquely identified three symptom clusters comprised three to five symptoms each from a broad range of symptoms experienced, although the severity was mild and reported at one point in time among patients with exclusively advanced stage (IIIB or IV) NSCLCs. Further, participants in the study by Wang *et al.*[23] were comprised a wide range of cancers including Stages I and II, the number of participants who were at Stage III among the 108 participants was not reported, and only 21 participants (19.4%) were at the advanced stage (IV). This is different from the present study that focuses exclusively on advanced stage ($n = 60$; 28.3% Stage IIIB and 71.7% Stage IV) patients. The differences will be smaller if Wang *et al*. had analyzed only the patients with cancers in the

advanced Stages III and IV (*n* = 64; 97% Stage III and 3% Stage IV).[22]

Fatigue/anorexia cluster comprises lack of appetite, drowsiness, fatigue/tiredness, altered sense of taste, and dry mouth. This cluster is similar to the pattern 3 (lack of appetite, drowsiness, fatigue, sleep disturbance, dry mouth, and distress) reported by Wang *et al*.[22] Okuyama *et al.* established an explanatory model for this symptom clustering, suggesting that malnutrition could precipitate the lack of appetite, identified as one of the causes of malaise in outpatients with advanced lung cancer.[37] Dry mouth and altered sense of taste may lead to lack of appetite and malnutrition, causing malaise, and associated drowsiness in a clustering phenomenon.

The pain cluster comprises pain, anxiety, and sadness. Pain is experienced by many lung cancer patients,[38] and Hopwood and Stephens report that the physiological response to pain can lead to psychological symptoms of anxiety and sadness.[39] In the USA, 32% of advanced lung cancer patients assessed with MDASI reported moderate to severe pain symptom levels.[40] With the MDASI-J, 11% of the sample with Japanese cancer patients (*n* = 252) reported moderate (5–6), and 12% severe (≥ 7) pain levels.[29] These are lower pain levels than the USA samples where 19% report moderate pain and 15% of the sample report severe pain (*n* = 527).[28]

This research project may have more (proportionally) advanced stage (Stage IV: 71.7%) lung cancer patients who received more attention to palliative care needs and symptoms.[41] This attention may have alleviated the severity in the pain. There may be differences in the symptom expression of pain severity expressed among the Japanese patients with cancer reported by Okuyama *et al*.[29] This research project is significant because it shows that patients with advanced NSCLCs during the treatment period have experienced symptom clusters although the severity of the pain is mild. Therefore, if alleviation care is not provided actively through monitoring and communication focusing on symptom clusters for patients with advanced NSCLCs in the treatment period, it is not possible to alleviate pain effectively. Specifically, for this Japanese population, this trend may be seen to provide an accurate explanation.

The pain scores may be influenced by a phenomenon like the finding in previous research documenting that Japanese respondents avoid polar categories and tend to choose middle range responses.[42] Further, thinking about the origin of the word "pain," the English origin contains "penalty" and "punishment." However, "pain" (Itami in Japanese)

implies "a condition of the extent to which somebody or something experiences distress," and the word is used to express an extreme physical, material, or mental condition. The word "Itami" originally does not include the meaning of punishment.[43] On this account, efforts of health-care professionals to encourage patients to report symptoms may be insufficient in Japan compared to those in European and American countries where reporting of symptoms is encouraged to receive potential medications striving for alleviation. According to a study that investigated the illness perceptions and QOL of Japanese and Dutch patients with NSCLCs, it is suggested that Japanese patients are more strongly aware of the therapeutic efficacy in controlling illness and more strongly believe in the effectiveness of medical care for lung cancer than Dutch patients.[44] Further, patients with lung cancer are reported to harbor hopes of being cured.[45] For the above reasons, for patients with the most advanced stages of NSCLCs like in this study, suffering pain may arouse doubts about the effectiveness of the medical care for their lung cancer, and reduce the efficacy of the medical care due to a perceived mismatch between their expectations and their physical condition, resulting in the passive-sounding report of the pain. Thus, the pain cluster identified in this study may be unique to the Japanese patients with advanced NSCLCs under standard chemotherapy. As Gift *et al*.[21] have pointed out, it is necessary to examine whether groups of different racial background with different cultural background experience report similar symptom intensities.

The numbness cluster comprises numbness, leg weakness, and distress. Again, Wang *et al*. report different results from their study, including all stages of patients with lung cancer, probably resulting from the inclusion of earlier stage patients not receiving chemotherapy.[23] Numbness is a form of peripheral neuropathy (sensory) associated with taxane chemotherapy (paclitaxel and docetaxel) and platinum (cisplatin and carboplatin) agents commonly used in conjunction with standard therapy for patients with advanced NSCLCs.[4,46] Numbness was reported by 48.4% of the participants in the study here. It is plausible that the numbness decreased ease of ambulation and was a cause of the resultant distress.

The second aim of the study here was to identify relationships between symptom clusters and the functional status and interference in daily life. The pain cluster contributed to five areas of daily life interference ranked in the order of emotions, life in general, work including housework, interpersonal relationships, and enjoyment of life (respectively β = 0.563, β = 0.484, β = 0.424, β = 0.357, and β = 0.330).

The fatigue/anorexia cluster explained 7.6% of the daily life interference (enjoyment of life) variance and 5.2% of (walking) variance while the pain cluster explained 35.5% of the pain cluster variance, which is the highest value. Therefore, it was suggested that the pain cluster showed a stronger influence on daily life interference (emotions) than the fatigue/anorexia cluster. Our study results agree with two other studies.[8,9] Put differently, it became clear that the pain cluster has a negative impact on the functional status which is important for daily life. It seems clear that the pain cluster had an adverse effect on all five areas of daily life interference (ranked in the order: Emotions, life in general, work including housework, interpersonal relationships, and enjoyment of life). Further, as the numbness cluster explained 28.1% of daily life interference (walking), this could be an important symptom cluster to which health-care professionals (nurses) should give special attention to maintain walking ability. Therefore, it is necessary in the nursing to give consideration to the interference of numbness in daily life. In addition, nurses could consider that all of the identified symptom clusters may influence the functional status and daily life.

The third aim of the study was to identify the relationship between symptom clusters and QOL. The fatigue/anorexia cluster explained 11.7% of only one global QOL variance. In addition, the fatigue/anorexia cluster influenced 3 functional areas in QOL, and compared with 2 areas of everyday life interference, it seemed to have a negative impact on QOL. This implies that it is important for health-care professionals to monitor the fatigue/anorexia cluster to prevent deterioration of QOL. Further, the fatigue/anorexia cluster showed a stronger influence on QOL (role function) while the pain cluster showed a stronger influence on QOL (emotional function). Further, the pain cluster was more likely to influence emotional, physical, and social functions. As described above, considering that the fatigue/anorexia cluster influenced only 3 functional areas in QOL while the pain cluster daily life interference influenced 5 areas, it is suggested that difficulty in daily life due to the pain cluster occurs earlier than the influence on QOL. This suggests that the pain cluster may be a precursor to the fatigue/anorexia cluster. In this study, QOL was not influenced by the numbness cluster. These findings agree with those of fox where fatigue was significantly but only mildly correlated with QOL.[47] In the fox study, pain was not significantly correlated with QOL because many patients had completed active treatment.

As described above, the pain cluster affects physical, emotional, and social functions of QOL, whereas the fatigue/anorexia cluster affects role and cognitive functions,

affecting different areas. For the pain cluster, as patients cannot look after themselves and have difficulty in doing housework when they are in pain, it becomes difficult to avoid deterioration in physical and social functions. In addition, pain may cause psychological symptoms of anxiety and sadness.[39] When patients experience such negative feelings, emotional functions deteriorate as patients avoid going out and talking with others due to the worry about life with lung cancer, feeling death to be close, and even feeling fear.[48] Therefore, the pain cluster can affect three areas: physical, emotional, and social areas. For the fatigue/anorexia cluster, this symptom cluster includes drowsiness. Therefore, patients may be aware of deterioration of cognitive functions, having difficulty in concentrating on watching TV and reading books. Further, fatigue, which there is no effective way to cope with, makes it difficult to continue work and activities of daily living and also hinders hobbies and leisure activities.[8] Therefore, the fatigue/anorexia cluster can affect the role and cognitive functions.

Although three symptom clusters were identified, the symptom item severity is lower than mild (< 4) among the participants reported here. Regardless of severity, it is a universal desire to improve QOL and mitigate symptoms in patients with advanced NSCLCs. Symptom clusters are important for an understanding of global QOL because the clustering of the symptoms allows the clinician to appreciate the burden of a group of symptoms and the likelihood that symptoms may be occurring together. Treating one symptom without considering the symptom cluster may result in a greater symptom burden and poorer QOL. Nursing care based on individual tendencies suggested by focusing on symptom clusters as well as monitoring and assessing daily life interference may facilitate personalized intervention and contribute to improvement of QOL in a life-extending period as treatment outcomes.

Limitations

First, this study has several limitations due to it being a convenience sample of patients with advanced NSCLCs undergoing standard therapy (*n* = 60). Second, it can no more than suggest the existence and influence of the three symptom clusters based on data at one point in time (the time of participation in the study) in a group of patients with advanced NSCLCs undergoing standard therapy (*n* = 60). This limits the extent to which we can generalize from the findings of this study. Third, it is not possible to rule out selection bias. Fourth, this study used a cross-sectional design, with no consideration of changes over time due to the therapeutic regimen, the disease stage,

patient age, and changes in performance status in relation to the symptom clusters in patients with advanced NSCLCs undergoing standard therapy. Fifth, this study has not sufficiently examined the influence of various background factors, such as comorbidity and medication other than pain medications, known as potential factors to play roles in the experience of symptoms. Future studies need to employ a longitudinal design to determine whether the symptom clustering identified here is present across the lung cancer treatment trajectory.

Implications for future research and practice

By illustrating the existence of symptom clusters that influence key patient outcomes, the results of this study may prove useful in the design of ongoing screening assessment procedures. In this Japanese sample, almost 73.0% of patients reported pain severity scores below mild (< 4) lower than the higher levels reported in a USA sample. Because Japanese patients are not likely to express more symptom distress, providing interventions that target specific symptoms based on the standards used in the USA[49] may not be generally helpful for Japanese patients.

Conclusion

We identified three symptom clusters, each comprising three to five specific symptoms that influence QOL outcomes to different degrees. The knowledge gap that this paper addresses provides important information for nurses to understand and take into account to personalize the assessment and education of patients and families with advanced (IIIB or IV) NSCLCs. In the care of patients with advanced (IIIB or IV) NSCLCs undergoing standard therapy, clinicians must tailor clinical guidelines to prevent underestimation and intervention delays in the management of complex symptom clusters for patients like the group here with a high rate of mortality.

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Conflicts of interest

There are no conflicts of interest.

References

1. The Editorial Board of the Cancer Statistics in Japan EDS. Cancer Statistics in Japan 2014th edition. Available from: http://www.ganjoho.jp/data/reg_stat/statistics/brochure/2014/cancer_statistics_2014_fig_E.pdf. [Last accessed on 2015 Aug 11].

2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics. CA Cancer J Clin 2011;61:212-49.

3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, *et al.* Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-403.

4. Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, *et al.* Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-23.

5. Gridelli C, de Marinis F, Pujol JL, Reck M, Ramlau R, Parente B, *et al.* Safety, resource use, and quality of life in paramount: A phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol 2012;7:1713-21.

6. Tishelman C, Petersson LM, Degner LF, Sprangers MA. Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. J Clin Oncol 2007;25:5381-9.

7. Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y. Prevalence and screening of dyspnea interfering with daily life activities in ambulatory patients with advanced lung cancer. J Pain Symptom Manage 2002;23:484-9.

8. Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y. Impact of dyspnea, pain, and fatigue on daily life activities in ambulatory patients with advanced lung cancer. J Pain Symptom Manage 2002;23:417-23.

9. Dodd M, Miaskowski C, Paul S. Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum 2001;28:465-70.

10. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: Concept analysis and clinical implications for cancer nursing. Cancer Nurs 2005;28:270-82.

11. National Institutes of Health State-of-science Panel. State-of-science conference on symptom management in cancer: Pain, depression, and fatigue. J Natl Cancer Inst Monogr 2004;32:17-21.

12. Barsevick AM. The elusive concept of the symptom cluster. Oncol Nurs Forum 2007;34:971-80.

13. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. J Natl Cancer Inst Monogr 2007;37:39-46.

14. Xiao C. The state of science in the study of cancer symptom clusters. Eur J Oncol Nurs 2010;14:417-34.

15. Molassiotis A, Lowe M, Blackhall F, Lorigan P. A qualitative exploration of a respiratory distress symptom cluster in lung cancer: Cough, breathlessness and fatigue. Lung Cancer 2011;71:94-102.

16. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nurs 2012;35:E1-20.

17. Franceschini J, Jardim JR, Fernandes AL, Jamnik S, Santoro IL. Relationship between the magnitude of symptoms and the quality of life: A cluster analysis of lung cancer patients in Brazil. J Bras Pneumol 2013;39:23-31.

18. Lin S, Chen Y, Yang L, Zhou J. Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients. J Clin Nurs 2013;22:1281-90.

19. Chen E, Nguyen J, Cramarossa G, Khan L, Leung A, Lutz S, *et al.* Symptom clusters in patients with lung cancer: A literature review. Expert Rev Pharmacoecon Outcomes Res 2011;11:433-9.

20. Sarna L, Brecht ML. Dimensions of symptom distress in women with advanced lung cancer: A factor analysis. Heart Lung 1997;26:23-30.

21. Gift AG, Jablonski A, Stommel M, Given CW. Symptom clusters in elderly patients with lung cancer. Oncol Nurs Forum 2004;31:202-12.

22. Wang XS, Fairclough DL, Liao Z, Komaki R, Chang JY, Mobley GM, *et al.* Longitudinal study of the relationship between chemoradiation therapy for non-small-cell lung cancer and patient symptoms. J Clin Oncol 2006;24:4485-91.

23. 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.

24. 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.

25. Brown JK, Cooley ME, Chernecky C, Sarna L. A symptom cluster and sentinel symptom experienced by women with lung cancer. Oncol Nurs Forum 2011;38:E425-35.

26. Khamboon T, Pongthavornkamol K, Olson K, Wattanakitkrileart D, Viwatwongkasem C, Lausoontornsiri W. Symptom experiences and symptom cluster across dimensions in Thais with advanced lung cancer. Pac Rim Int Nurs Res 2015;19:330-44.

27. Arrindell W, Ende J. An empirical test of the utility of the observations-to-variables-ratio in factor and components analysis. Appl Psychol Meas 1985;9:165-78.

28. 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.

29. Okuyama T, Wang XS, Akechi T, Mendoza TR, Hosaka T, Cleeland CS, *et al.* Japanese version of the MD Anderson Symptom Inventory: A validation study. J Pain Symptom Manage 2003;26:1093-104.

30. 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;85:365-76.

31. Kobayashi K, Takeda F, Teramukai S, Gotoh I, Sakai H, Yoneda S, *et al.* A cross-validation of the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) for Japanese with lung cancer. Eur J Cancer 1998;34:810-5.

32. Common Toxicity Criteria, Version 2.0 Publish Date 30 April, 1999. Available from: http://www.ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf [Last accessed on 2016 Aug 11].

33. Wang Y, O'Connor M, Xu Y, Liu X. Symptom clusters in Chinese patients with primary liver cancer. Oncol Nurs Forum 2012;39:E468-79.

34. Kim HJ, Barsevick AM, Tulman L. Predictors of the intensity of symptoms in a cluster in patients with breast cancer. J Nurs Scholarsh 2009;41:158-65.

35. Fayers PM, Aaronson NK, Bjordai K, Groenvold M, Curran D, Bottomley A, On Behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organization for Research and Treatment of Cancer; 2001.

36. Yanai H, Ogata H. SPSS statistical data analysis – Introduction to statistics with examples from health care, nursing, biology and psychology. Kyoto. Gendai-Sugakusha 2006. p. 230-45.

37. Okuyama T, Tanaka K, Akechi T, Kugaya A, Okamura H, Nishiwaki Y, *et al.* Fatigue in ambulatory patients with advanced lung cancer: Prevalence, correlated factors, and screening. J Pain Symptom Manage 2001;22:554-64.

38. Kim E, Dodd M, Aouizerat B, Jahan T, Miaskowski C. A review of the prevalence and impact of multiple symptoms in oncology patients. J Pain Symptom Manage 2009;37:715-36.

39. Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: Implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. Br J Cancer 1995;71:633-6.

40. Mendoza TR, Wang XS, Lu C, Palos GR, Liao Z, 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.

41. Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: A meta-analysis. J Thorac Oncol 2007;2:845-53.

42. Yoshino R. Reconstruction of trust on a cultural manifold: Sense of trust in longitudinal and cross-national surveys of national character. Behaviormetrika 2009;36:115-47.

43. Hoka S. Listen to the voice of pain – Think through pains seen in culture and literature. Pains and Culture. Ch. 1. Tokyo: Kokuseido Shuppan; 2008. p. 24-9.

44. Kaptein AA, Yamaoka K, Snoei L, Kobayashi K, Uchida Y, van der Kloot WA, *et al.* Illness perceptions and quality of life in Japanese and Dutch patients with non-small-cell lung cancer. Lung Cancer 2011;72:384-90.

45. Hoogerwerf MA, Ninaber MK, Willems LN, Kaptein AA. "Feelings are facts": Illness perceptions in patients with lung cancer. Respir Med 2012;106:1170-6.

46. Gelmon K. The taxoids: Paclitaxel and docetaxel. Lancet 1994;344:1267-72.

47. Fox SW, Lyon DE. Symptom clusters and quality of life in survivors of lung cancer. Oncol Nurs Forum 2006;33:931-6.

48. Maguire R, Stoddart K, Flowers P, McPhelim J, Kearney N. An interpretative phenomenological analysis of the lived experience of multiple concurrent symptoms in patients with lung cancer: A contribution to the study of symptom clusters. Eur J Oncol Nurs 2014;18:310-5.

49. National Comprehensive Cancer Network. NCCN Guidelines Distress Management Version 1. 2014. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. [Last accessed on 2016 Aug 11].