Managing Symptoms in Patients with Advanced Lung Cancer During Radiotherapy: Results of a Psychoeducational Randomized Controlled Trial

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Abstract

Context. Breathlessness, fatigue, and anxiety are distressing symptoms for patients with advanced lung cancer. Usually managed as isolated symptoms, they often can occur simultaneously. Previous research often has addressed management of discrete symptoms rather than considering them as a cluster, which, in reality, is the situation faced by patients.

Objectives. This study aimed to examine the effectiveness of a psychoeducational intervention (PEI) on the symptom cluster of anxiety, breathlessness, and fatigue, compared with usual care.

Methods. A pretest/post-test, two-group, randomized, controlled trial was conducted. Education on symptom management and coaching in the use of progressive muscle relaxation were delivered to patients one week prior to commencing radiotherapy (RT), and repeated three weeks after beginning RT. Symptom data were collected at four time points: prior to the intervention, three weeks, six weeks, and 12 weeks postintervention.

Results. One hundred forty lung cancer patients receiving palliative RT were recruited from a publicly funded hospital in Hong Kong. Doubly multivariate analysis of variance revealed a significant difference (time × group interaction effect, \(P = 0.003\)) over time between the PEI and usual care control group on the pattern of change of the symptom cluster. Significant effects on the patterns of changes in breathlessness (\(P = 0.002\)), fatigue (\(P = 0.011\)), anxiety (\(P = 0.001\)), and functional ability (\(P = 0.000\)) also were found.

Conclusion. PEI is a promising treatment for relieving the symptom cluster and each of the individually assessed symptoms. More effort needs to be directed at...
Introduction

Lung cancer is the leading cancer diagnosis for both genders in Hong Kong.1 The majority of patients with lung cancer either presents with advanced disease or develops metastases soon after the initial diagnosis. Although radiation therapy (RT) can manage endobronchial or extrinsic lesions of lung cancer and lengthen a patient’s life,2 it also can cause severe side effects that compromise quality of life. Patients with advanced lung cancer undergoing RT are particularly vulnerable to the symptoms of breathlessness, fatigue, and anxiety3, which impact on patient function.6–8 Patients with lung cancer often experience symptoms concurrently and they usually have overlapping and interactive effects.9,10 A symptom cluster is defined as three or more concurrent symptoms that are moderately correlated with each other.11 Providing an intervention aimed at treating a symptom cluster as a whole could lead to greater effectiveness and efficiency, which potentially maximizes the use of clinicians’ and patients’ efforts.

Although the concept of symptom clusters is now acknowledged to be at the cutting edge of science in symptom management,12,13 few published accounts of intervention trials attempt to treat symptoms together as a cluster. Early in 1995, Lenz et al.14 published a theory of unpleasant symptoms that focused on explaining the impact of experiencing multiple symptoms. This theory laid a foundation for the current trend to investigate the treatment of multiple symptoms simultaneously. Given et al.’s8 study demonstrated the “value-added” role of a psychoeducational intervention (PEI) in reducing the overall symptom burden of 12 common symptoms. In 2004, Given et al.15 conducted a similar study demonstrating the positive effect of a PEI on 15 symptoms. However, these studies did not test or define the multiple symptoms as a cluster; in other words, the association and concurrent existence of these symptoms were not tested.

A recent review indicated that the intensity of a symptom cluster comprising breathlessness, fatigue, and anxiety worsens during RT, and these symptoms cluster together in patients treated with RT.5,16 There are several studies that demonstrate correlations and similarities between breathlessness, fatigue, and anxiety.16–18 For instance, stress is identified as a common trigger for all these symptoms.19 The episode of breathlessness, fatigue, and anxiety usually begins with a trigger, which is either physical or emotional stress.5,16–19 Physical stress includes pain and labored breathing, whereas emotional stress may include fear, worry, and anger.

PEIs intend to prepare patients for the symptom experience, to clarify misconceptions, to alleviate stress and negative affects, to enhance a sense of control over the illness, and to promote self-care practice.5,8,15 In the last few decades, large numbers of studies evaluating PEIs in patients with cancer have been conducted.12 Progressive muscle relaxation (PMR) appears to be the most prevalent intervention to be studied, followed by patient education. Although PEI has been advocated to manage cancer symptoms, breathlessness and fatigue appear to be neglected and understudied symptoms. Despite the reported benefits of PEI in the management of anxiety, there have been fewer studies of PEI in patients with lung cancer, in contrast to other cancers.19 In addition, no research has been reported to date on the impact of a PEI on the intensity and distress generated by these symptoms when considered as a cluster.

Reduced patient functioning is considered a common outcome of symptom experience, as supported by several theories and...
models,9,10 and by empirical evidence.7,11 An important research question is whether relief of symptom clusters promotes patients’ function. Researchers have recommended that function be studied as an outcome of interventions directed at a symptom cluster, and have emphasized the desirability of conducting symptom cluster research on homogeneous samples and in a particular culture.7,20

The aim of this study was to examine the effectiveness of a PEI combining patient education and PMR for relief of a symptom cluster involving anxiety, breathlessness, and fatigue in patients with advanced lung cancer receiving palliative radiotherapy (RT), compared with a usual care control group. The study evaluated the hypothesis that there would be a significant difference over time in the pattern of the symptom cluster of anxiety, breathlessness, and fatigue between lung cancer patients receiving the PEI and those receiving usual care.

**Methods**

**Setting and Subjects**

A pretest/post-test, two-group, randomized, controlled trial was conducted in an outpatient RT unit of a publicly funded hospital in Hong Kong. All patients attending the RT Department were approached to consider participating and to assess eligibility. A total of 140 subjects were recruited and consented to the study.

Anxiety was selected as a major outcome for the purpose of sample estimation, as anxiety (effect size ranging from 0.3 to 0.8) is the most frequently measured variable for determining the efficacy of PMR and PEI.21 A medium effect size was used to calculate the sample size. Given an estimated attrition rate of 10% and based on the original sample estimate of 64, the sample size needed per group was 70. Patients were randomized by lucky draw method to either an intervention group or control group.

Inclusion criteria were as follows: 1) age 16 years or older; 2) Stage 3 or 4 lung cancer and scheduled to receive palliative RT of an average of 4.5 Gy/fraction; 3) the ability to communicate in Chinese; 4) signed informed consent; 5) an Abbreviated Mental Test score of 8 or above indicating normal cognitive ability; and 6) A Karnofsky Performance Status score of 60% or above, indicating the patient was capable of some self-care and not bedridden. Exclusion criteria included patients with known psychiatric morbidity and/or involvement in other clinical trials.

**Primary Outcome Measures**

**Breathlessness.** Patients’ subjective experience of the intensity of breathlessness was assessed using a 100 mm visual analogue scale (VAS). A VAS has been used in previous studies and has shown to be a sensitive tool through which to assess the subjective experience of breathlessness.6

**Fatigue.** The intensity subscale of the revised Piper Fatigue Scale22 consists of 23 items directed at measuring intensity of fatigue. Reliability and validity have been established.22 The instrument has been translated into Chinese and found to be valid and reliable (0.97 alpha coefficient).23

**Anxiety.** The Chinese version of the A-state scale of the State-Trait Anxiety Inventory24 was used to assess state anxiety. The A-state scale consists of 20 items for measuring immediate feelings of apprehension, nervousness, and worry, and has an established internal consistency of 0.90.25

**Secondary Outcome Measure**

**Functional Ability.** The functional ability subscale of the Chinese version (HK) of the SF-36 Health Survey26 was used. The subscale includes a multi-item scale measuring four dimensions: 1) physical functioning; 2) role limitation because of physical problem; 3) role limitation because of emotional problem; and 4) social functioning. The SF-36 has been shown to be a valid measure to assess the effectiveness of PEI.26

Baseline demographic/disease/treatment data were obtained from patients and their medical records. Patients’ previous experiences with PEI or complementary therapies also were assessed.

**Intervention**

Breathlessness, fatigue, and anxiety are multifaceted symptoms that comprise cognitive, psychological, and behavioral components, suggesting that a combination of education and relaxation may produce a more holistic
Development of the PEI in this study was informed by previous research on breathlessness, fatigue, and anxiety in cancer patients, and the literature on PEIs. PEI alters patients’ perceptions and sensations of symptoms through stress reduction; clarification of misconceptions; and the adoption of adaptive behaviors. The aim of the current intervention was to manage the three symptoms together (as a cluster), based on the symptoms’ commonality in that stress could aggravate each one of them. Patients were enabled to adopt adaptive behaviors to delay the intensification of symptoms through the following components: preparatory information; discussion of symptom experience; exploration of meanings of, and goals associated with, symptoms; advice on self-care strategies; and training and practice in PMR (Fig. 1).

A 40-minute educational package plus coaching of PMR was delivered to patients within one week prior to the beginning of the course of RT, and reinforced three weeks after commencing RT. The education package consisted of leaflets and discussion on the selected symptoms and their self-care management (Appendix). The intervention was delivered by registered nurses with two years of clinical experience. A two-day training session was given to the intervention nurses, focusing on the educational package and the practice of PMR.

An audiotape in Chinese and educational leaflets were provided to patients. Patients were encouraged to practice PMR daily and as required. Patients in the intervention group were given a telephone reminder at the end of the second week to enhance participation in the Week 3 sessions.

Usual Care
The usual care of this study comprised a mandatory individual briefing of the RT procedure and about a five to seven minute discussion of side effects focusing on skin care by a therapy radiographer. Patients also were invited to attend an optional group talk given by a registered nurse and a medical social worker about general care before and/or after the commencement of RT. Patients in both intervention and control groups were offered this usual care.

Patient Adherence and Participation in the Intervention

**Intervention Activity Log.** An intervention activity log was set up in which the research assistant (RA) recorded, at each session, problems encountered during implementation of the intervention. The RA also recorded patients’ general involvement, such as attention span and ability to follow instruction.

**Diary.** Adherence to the relaxation exercise was recorded in a simple health diary (calendar) by patients for 12 consecutive weeks. Health diaries are commonly used in clinical research and have been shown to be a practical and sensitive tool to record health actions over time.

**Data Collection Procedure**
Data were collected by an RA who was blinded to group allocation. Subjects were asked to complete all outcome measures before RT commenced and prior to randomization (T0), and then at Week 3 (T1), Week 6 (T2), and at three months (T3). For maximum effect of PMR, regular daily practice for three to six weeks is necessary. To detect the full effect of the intervention and changes in the intensity of symptoms (expected to become gradually worse as RT progressed, with a peak at around Weeks 3–6) and the longer term effects of the intervention some months after RT had finished, a repeated-measure
design was adopted to detect the patterns of change over time.

Data Analysis

Doubly multivariate analysis of variance (MANOVA) was performed to examine the effect of the PEI on the symptom cluster, referred to as a composite outcome comprising the vector of means on the transformed scores of breathlessness, fatigue, and anxiety across time. Scores of all three symptoms at all time points were positively skewed; therefore, the original scores of breathlessness, fatigue, and anxiety were transformed by square root transformations to achieve the best distribution of normality. Mixed between-within subjects analysis of variance (ANOVA) compared scores on functional ability between study groups across time. Missing data at T1, T2, and T3 were imputed by a carry-forward method based on intention-to-treat analysis. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 13.0 for Windows (SPSS Inc., Chicago, IL).

The analyses of changes in outcome variables between T0 and T2 were the main focus; data relating to changes between T0 and T3 were only assessed in an exploratory manner to examine longer-term effects.

Results

During the study period, 255 patients with advanced lung cancer were assessed for eligibility. Fifty-nine patients (23%) did not meet the eligibility criteria, mainly because of poor scores on the Karnofsky scale and Abbreviated Mental Test. Fifty-six patients (21%) declined to participate because they were not interested in the study, or because they felt they were too tired and/or too ill to participate. The remaining 140 eligible patients consented to participate. The overall attrition rate was 4% at Week 3 (T1), 9% at Week 6 (T2), and 27% at Week 12 (T3). Patients in the control group (42%) experienced higher attrition than the intervention group (11%) at T3. At all time points, the sole reason for attrition was death.

Baseline Characteristics of the Study Sample

The majority of patients were male (83%), married (87%), and retired (54%). Patients’ mean scores on the Abbreviated Mental Test (9.43 of 10) and Karnofsky scores (84 of 100) were high. Less than half of the patients had distant metastasis (46%), comorbidty (40%), or concurrent treatment with chemotherapy (18%). Patients’ mean duration of cancer illness was 4.4 months. The chest and mediastinum were the major sites of RT.

The majority of patients (75%–80%) had no history of practicing relaxation exercise, or of using complementary therapies or other supportive services. Less than half (33%) attended the usual care group talk that was offered to all study patients. At baseline, all patients had a low intensity for breathlessness (mean = 15.81, range 0–100), whereas their fatigue (mean = 3.41, range 0–10) and anxiety (mean = 42.04, range 20–80) intensity scores were low to moderate. They had an overall low-to-moderate functional score (mean = 25.14–66.41, range 0–100). Patients in the control group had a significantly more advanced stage of cancer ($\chi^2 = 4.13$, $P < 0.05$) when compared with the intervention group. Table 1 shows mean symptom scores and functional ability for each study group from baseline to Week 12.

Correlations Among Outcome Variables

Significant and moderate positive intercorrelations among breathlessness, fatigue, and anxiety at T0, T1, T2, and T3 were found ($P < 0.01$) and all pairs of variables’ associations had correlations of less than 0.07. This supports the use of the MANOVA test as MANOVA performs best for variables with moderate strength correlations. This also underlines the clustering of these symptoms. In addition to the significant intercorrelations between these outcome variables, each of the baseline outcome variables also related significantly to their respective post-test measurements. These relationships suggest there was a need to consider not only the three outcome variables, but also the repeated time factor as multivariate, so the effect of the intervention came to be analyzed by doubly MANOVA.

Outcome Evaluation From T0 to T2

Because of the baseline difference of cancer stage between the study groups, stage of cancer was entered into the model for analysis. All subsequent analyses included both stage of cancer and study groups as independent variables. The nonsignificant effects of the interaction
terms time × stage \((P > 0.05)\) and time × group × stage \((P > 0.05)\) show that stage of cancer did not appear to affect the pattern of change on the symptom cluster and each individual variable and the time × group interaction was not different by stage of cancer across T0−T3.

Results in Table 2 show that the pattern of change of the composite outcome across the study period T0−T2 was found to be significantly different between the two study groups (time × group interaction effect, \(P = 0.003\)). According to Cohen,\(^{34}\) the strength of eta-squared values (0.14) can be interpreted as a large intervention effect.

As a significant result on the multivariate test of significance of the composite outcome was found, further investigations (univariate tests) in relation to each of the dependent variables of breathlessness, fatigue, and anxiety were conducted. To reduce the possibility of a Type I error, the original alpha level of 0.05 was divided by 3, giving a new alpha level of 0.017.\(^{35}\)

Univariate tests on breathlessness showed a significant difference \((P = 0.002)\) in the pattern of change in breathlessness between the two study groups across T0−T2 (time × group effect), with small effect (partial eta-squared = 0.04). There was a significant
difference ($P = 0.011$) in the pattern of change in fatigue, with a small effect size (partial eta-squared = 0.033). In terms of anxiety, again there was a significant difference ($P = 0.001$) in the pattern of change, with small effect size (partial eta-squared = 0.051) (Table 3).

Mixed between-within subjects ANOVA compared scores on functional ability between study groups across T0—T2. Results in Table 4 show that there was a statistically significant effect for time × group interaction ($P = 0.000$), suggesting there was a significant difference in the pattern of change in scores of functional ability from T0 to T2 for the two groups, with moderate effect size (0.11).

Long-Term Effect of PEI

Because of the high attrition rate (27%) at Week 12, the examination of the effect of PEI at Week 12 (T3) was only exploratory in nature. The pattern of change of the composite outcome across the study period T0—T3 was significantly different between the two study groups (time × group interaction effect) ($P = 0.004$).

Univariate tests showed that there was a significant difference in the pattern of change (time × group effect) in breathlessness ($P = 0.001$) and anxiety ($P = 0.005$) between the two study groups across T0—T3, with a small effect size (partial eta-squared = 0.043 and 0.035, respectively). No significant difference was found in the pattern of change in fatigue across T0—T3 ($P = 0.034$).

Mixed between-within subjects ANOVA shows there was a significant difference in the pattern of change in scores of functional ability over 12 weeks for the two groups (time × group interaction $P = 0.002$).
Patients’ Adherence to and Participation in the Intervention

Ninety-four percent of subjects in the intervention group completed the intervention in full as measured by the intervention log. The majority demonstrated high attention and interest in the intervention. On average, subjects practiced four to five sessions of PMR/week. Over 60% of subjects both read the leaflets and listened to the audiotape.

Discussion

Published research on managing symptom clusters in patients with cancer is scant. The present study provides support for the management of breathlessness, fatigue, and anxiety together as a symptom cluster. Results suggest that PEIs provide a promising approach for the simultaneous treatment of multiple symptoms within a cluster.

Meta-analyses of previous trials of PEI in cancer patients report effect sizes ranging from small to moderate, depending on the symptom under investigation and the type of intervention. Comparisons among effect sizes are difficult to make because of the diversity of interventions and study designs. Nevertheless, a major strength of the present study was that the three target symptoms were combined into a single composite outcome (consisting of the vector of the means on the scores of breathlessness, fatigue, and anxiety). The composite outcome, namely the symptom cluster, was designed to capture the totality of effectiveness of the PEI. The total difference in symptom intensity between the intervention and control groups might go undetected if each dependent variable were to be examined separately. Weinfurt suggests that comparing differences in the composite outcome is a more sensitive approach to detecting intervention effects than comparing individual outcomes. An additional strength of measuring this composite outcome was to reduce the risk of Type 1 error, likely to occur when multiple comparisons with the same group of patients are conducted.

Another strength is that the study used three independent instruments to measure the intensity of the three selected symptoms. This allows for the performance of multivariate tests (to meet the assumption of singularity). Previous studies using combined symptom severity scores as the outcome measure were not suited to multivariate testing and unable to identify the effect of the intervention on individual symptoms. The present study is one of the few PEI studies conducted in an Asian population with cancer. As evidenced by patients’ lack of previous experience in using psychosocial-oriented interventions, and conclusions drawn from previous reviews, the application of PEI in this context can be considered novel. The low attendance at the usual care session indicates a need for a change to the current service and its delivery mode. The PEI was found to be an acceptable and feasible intervention and appeared to cause no harmful effects to patients, even at their advanced stage of disease. Future developments may consider incorporating PEI as a usual component of practice and evaluating its clinical effects through a Phase IV study.

In view of the generally poor health status of the subjects, it was important that outcome measures were concise so as not to overburden patients. Therefore, the present study focused on symptom intensity; other dimensions, such as distress and the impact of symptom cluster on patients’ overall quality of life, were not measured. These could be important aspects of outcome measurement in symptom studies. In future studies, using a VAS to measure the distress from dyspnea and other symptoms rather than just intensity may be an option. However, researchers need to take a balanced view combining scientific interest with patient assessment burden.

Cost effectiveness is another important outcome to address in future trials. The present study suggests an add-on value of this PEI. Costs in the present study mainly concerned additional personnel used to deliver the intervention. Theoretically, this cost could be offset by the cost of poor symptom management (such as frequency of hospitalization, length of hospital stay, and pharmacological treatments). Future studies may need to explicitly address the issue of resource utilization and cost effectiveness in their design.

Study Limitations

The high attrition rate encountered at Week 12 was mainly because of death. Missing data
were not at random but were related to outcomes that can lead to attrition bias. Findings should be viewed with caution because of the missing data. Future studies may consider using the Palliative Performance Scale, which may be a more reliable predictor than the Karnofsky Performance Status scale in estimating how long a patient can be enrolled in a study. Second, more patients in the control group had a more advanced stage of cancer and distant metastasis. Although stage of cancer did not significantly affect the outcome differences between study groups, this revealed a failure in the randomization process. In relation to study design, a placebo group was not used. An attention placebo group would have served to achieve blinding of subjects and to detect the effects of attention, whereas the usual care group compares the intervention effect with the existing service. There also is little information on patients’ perceptions and feelings toward the process and outcome of the intervention. Qualitative interviews may be useful in future studies to solicit this information.

Conclusion

The results of this study suggest that the PEI is a promising treatment for relieving this symptom cluster and each of the individually assessed symptoms at Week 6 after palliative RT, as well as improving patients’ functional ability. The long-term effect of PEI on the symptom cluster at Week 12 was inconclusive. The study provides evidence for the assessment and management of breathlessness, fatigue, and anxiety as a symptom cluster. Findings are encouraging and add to the theoretical body of knowledge on cancer symptom management. Researchers are encouraged to advance the theory, measurement, and management of symptom clusters, especially in relation to clarifying the mechanisms of interrelationship among symptoms within a cluster, and to investigate treatment interventions. Clinically, it is prudent for clinicians to view some symptoms as a cluster where they influence, and will be influenced by, each other. Managing a cluster, rather than individual symptoms, should be regarded as a contemporary approach in the provision of effective and efficient cancer and palliative care.

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References


Appendix

Protocol for Educational Intervention

An interactive educational session is delivered by a nurse RA. This package of interventions aims at reassuring the patients that something can be done to help them cope with their side effects. Contents of the package include:

1. Preparatory information on the possible and prominent symptoms, focusing on breathlessness, fatigue, and anxiety;
2. Discussion of symptoms and factors that ameliorate or exacerbate them;
3. Exploration of the meaning of breathlessness, fatigue, and anxiety and their feelings about them;
4. Advice and support for patients on self-care strategies for managing those symptoms.

Patients are allowed time to ask questions and have the opportunity to have the information repeated for them in an unhurried manner.

The package is supplemented by four Chinese leaflets focusing on understanding the symptoms and patients’ self-care in managing those symptoms.

Leaflet 1: Coping with Breathlessness

*Cause of breathlessness:* Destruction of lung tissue by tumor, pleural effusion, increased mucus secretion, weakness of abdominal and chest muscles, anxiety, fear.

*Self-care:* Smoking cessation, new breathing technique (slow deep breaths through pursed lips), positioning, relaxation exercise, cool air, means of dealing with frightening thoughts during respiratory distress.

Leaflet 2: Coping with Fatigue

*Cause of fatigue:* Demands of cancer and the treatment, feeling sick and other symptoms, loss of appetite, infection or fever, anxiety, depression, stress.

*Self-care:* Rescheduling of day-to-day activities, nutritious diet, mild exercise, sleep enhancement, relaxation exercise.

Leaflet 3: Coping with Anxiety

*Cause of anxiety:* Physical changes or side effects of the treatment, disability, breathlessness, and fear of suffocation.

*Self-care:* Relaxation exercise, ventilation of feelings, meditation, support group.

Leaflet 4: Guide for PMR

An audiotape of all information corresponding to that in the leaflet is provided to all the participants. Information in the leaflet/audiotape is derived from the literature and the publications produced by the Hong Kong Cancer Fund and CancerBACUP (permission to use the material was obtained from both organizations). All the educational materials have been reviewed by an expert panel composed of radiologists and nurse specialists. The readability of the leaflets is at the primary six educational level. This has been tested in 10 persons with primary six level of education to ensure its readability.