Managing symptoms in patients with advanced lung cancer during radiotherapy: results of a psychoeducational randomized controlled trial

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List of figures and tables

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Abstract (250 words)

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

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

Methods: A pre-test post-test 2-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 3 weeks after the first. Symptom data were collected at 4 time points: prior to the intervention, 3 weeks, 6 weeks, and 12 weeks post intervention.

Results: 140 lung cancer patients receiving palliative RT were recruited from a public funded hospital in Hong Kong. Doubly multivariate MANOVA revealed a significant difference (Time *group interaction effect, $p = .003$) 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 ($p = .002$), fatigue ($p = .011$), anxiety ($p = .001$) and functional ability ($p = .000$) were also found.

Conclusions: PEI was a promising treatment for relieving the symptom cluster and each of the individually assessed symptoms. More effort needs to be directed at studying impact of interventions on common symptom clusters.

Key words: symptom cluster, breathlessness, fatigue, anxiety, psychoeducational intervention, progressive muscle relaxation, advanced lung cancer

Running title: Managing symptoms in patients with advanced lung cancer during radiotherapy: results of a psychoeducational randomized controlled trial

INTRODUCTION

Lung cancer is the leading cancer diagnosis for both genders in Hong Kong.[1] The majority of patients with lung cancer presents with either advanced disease or develop metastases soon after the initial diagnosis. Although radiation treatment (RT) can manage endobronchial or extrinsic lesions of lung cancer and lengthen a patient's life,[2] it can also 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 anxiety[3-5] 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' as well as 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 trials of interventions attempt to treat symptoms together as a cluster. Early in 1995, Lenz et al. published a theory of unpleasant symptoms that focused on explaining the impact of experiencing multiple symptoms.[14] This theory laid a foundation for the trend to now research the treatment of multiple symptoms simultaneously. Given et al.'s[8] study demonstrated the 'value-added' role of a psychoeducational intervention (PEI) in reducing 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. [3, 16-19] Physical stress includes pain, labored breathing while emotional stress may include fear, worry, and anger.

Psycho-educational interventions (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. [6,8,15] In the last few decades, large numbers of studies evaluating PEI 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. While 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 PEI on the intensity and distress generated by these symptoms, when considered as a cluster.

Reduced patient functioning is considered as a common outcome of symptom experience, as advocated by several theories and models. [9, 10] This phenomenon is also supported 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 emphasized the desirability of conducting symptom cluster research on homogenous samples and in a particular culture.[7,20] In this study, the authors developed and tested a psychoeducational intervention (PEI) comprising patient education and PMR for relief of the common cluster of breathlessness, fatigue, and anxiety.

AIMS

The aim of the study was to examine the effectiveness of a PEI combining patient education and progressive muscle relaxation (PMR), compared with a usual care control group on a symptom cluster involving anxiety, breathlessness and fatigue in patients with advanced lung cancer receiving palliative radiotherapy.

Hypothesis:

There will be a significant difference in the pattern of change over time between the PEI and usual care groups in lung cancer patients presenting with the symptom cluster of anxiety, breathlessness, and fatigue.

METHODS

Setting and subjects: A pre-test post-test 2-group randomized controlled trial was conducted in an outpatient RT unit of a public funded hospital in Hong Kong. All patients attending the RT department were approached to consider participating and in order 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 (ES ranging from 0.3-0.8) is the most frequently measured variable for determining the efficacy of PMR and PEI..[21] A medium ES 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 of subjects were as follows:

1. age 16 or above
2. stage 3 or 4 lung cancer and to receive palliative radiotherapy (RT) of an average of 4.3 Grays/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
6. A Karnofsky Performance Status scores of 60% or above, indicating they are capable of some self care and not bedridden.

Exclusion criteria: Patients with known psychiatric morbidity and /or involvement in other clinical trials.

Outcome measures:

Primary outcome measures

Breathlessness

Patients' subjective experience of the intensity of breathlessness was assessed through a 100 mm visual analogue scale. VAS has been used in previous studies and 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 Scale (PFS)[22] 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 Inventory (STAI)[24] was used to assess state anxiety. The A-state scale consists of 20 items for measuring immediate feelings of apprehension, nervousness and worry. A-state 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 Survey[26] was used. The subscale includes a multi-item scale measuring 4 dimensions: 1) physical functioning; 2) role limitation due to physical problem; 3) role limitation due to emotional problem; and 4) social functioning. 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 on PEI or complementary therapies were also assessed.

Intervention

Breathlessness, fatigue, and anxiety are multifaceted symptoms that comprise cognitive, psychological and behavioral components, suggesting a combination of education and relaxation may produce a more holistic effect.[4,6,15,28] Development of the PEI in this study was informed by previous research on breathlessness, fatigue and anxiety in cancer patients[4,6,29] and the literature on PEIs. PEI alters patients' perception and sensation of symptoms through stress reduction; clarification of misconception; and the adoption of adaptive behaviors.[30] 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.[3,4,18,20] Patients were enabled to adopt adaptive behaviors to delay the intensification of symptoms through the following components: preparatory information; discussion of symptoms' experience; exploration of meanings of, and goals associated with, symptoms; advice on self-care strategies; and training and practice in progressive muscle relaxation (PMR) (see Figure 1).

Insert Figure 1 here.

A 40-minutes 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 (see Appendix 1). The intervention

was delivered by registered nurses with 2 years clinical experience. A 2-day training session was given to the intervention nurses focusing on the educational package and the practice of PMR.

A Chinese audiotape 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 2nd 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 5-7 minutes discussion of side effects focusing on skin care by a therapy radiographer. Patients were also invited to attend an optional group talk given by a registered nurse and a medical social worker about general care before or after the commencement of RT. Patients in both intervention and control group were offered this usual care.

Patients' 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

Patient adherence to the relaxation exercise was recorded in a simple health diary (calendar) by patients for 12 consecutive weeks. Health diary is commonly used in

clinical research and shown to be a practical and sensitive tool to record health actions over time.[27]

Data collection procedure

Data were collected by a research assistant who was blind 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), 3 months (T3). For maximum effect of PMR regular daily practice for 3-6 weeks is necessary.[31,32] In order to detect the full effect of the intervention as well as changes in the intensity of symptoms expected to become gradually worse as RT progressed with a peak at around week 3-6,[33] and the longer term effects of the intervention some months after RT had finished, a repeated measures design was adopted to detect the pattern of changes over time.

Data analysis

Doubly multivariate MANOVA were 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 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 Statistics Package for Social Sciences SPSS version 13.0 for windows.

The analyses of changes in outcome variables between T0 – T2 were the main focus, data relating to changes between T0-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 due to poor scores on the Karnofsky scale and Abbreviated Mental Tests. 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 (9.43/10) and Karnofsky scores (84/100) were high. Less than half of patients had distant metastasis (46%), co-morbidity (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, complementary therapies, or other supportive service. Less than half (33%) attended the usual care group talk which 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 significantly more advanced stage of cancer ($\chi^2 = 4.13$, $P < .05$) as compared to the intervention group. Table 1 shows mean symptom scores and functional ability for each study group from baseline to week 12.

Insert Table 1 here.

Correlations between outcome variables

Significant and moderate positive intercorrelations between breathlessness, fatigue, and anxiety at T0, T1, T2, and T3 were found ($p<.01$) and all pairs of variables' associations had correlations of <.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 – T2

Due to the baseline difference of stage of cancer 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 non-significant effects of the interaction terms time*stage ($p>.05$) and time*group*stage ($p>.05$) 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, $p = .003$). According to Cohen[34], the strength of Eta Squared values (.14) can be interpreted as a large intervention effect.

Insert Table 2 here.

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. In order to reduce the possibility of a Type I error the original alpha level of .05 was divided by 3, giving a new alpha level of .017.[35]

Univariate tests on breathlessness showed a significant difference ($p =. 002$) in the pattern of change in breathlessness between the two study groups across T0-T2 (time * group effect) with small effect (Partial Eta Squared = .04). There was a significant

difference (p =. 011) in the pattern of change in fatigue with a small effect size (Partial Eta Squared = .033). In terms of anxiety, again there was a significant difference (p =. 001) in the pattern of change with small effect (Partial Eta Squared = .051) (see Table 3).

Insert Table 3 here.

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 = .000), suggesting there was a significant difference in the pattern of change in scores of functional ability from T0-T2 for the two groups with moderate effect size (.11).

Insert Table 4 here

Long-term effect of PEI

Due to 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 = .004).

Univariate tests showed that there was a significant difference in the pattern of change (time*group effect) in breathlessness (p =.001) and anxiety (p = .005) between the two study groups across T0-T3 with a small effect (Partial Eta Squared = .043 and .035). No

significant difference was found in the pattern of change in fatigue across T0-T3 (p = .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= .002).

Patients' adherence to and participation in 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 4-5 times 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 current study provides support for the management of breathlessness, fatigue, and anxiety together as a symptom cluster; results suggests that PEI interventions provide a promising approach for the treatment of multiple symptoms within a cluster simultaneously in this group.

Meta-analysis of previous cancer trials of PEI report effect sizes ranging from small to moderate, depending on the symptom under investigation and the type of intervention.[28,36] Comparisons among effect sizes are difficult to make because of the diversity of interventions and study designs. Nevertheless, a major strength of the current 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 group might go undetected if each dependent variable were to be examined separately. Weinfurt[37] 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.

A further strength is that the study used three independent instruments to measure the intensity of the three selected symptoms. This allows the performance of multivariate tests as well as univariate tests (in order 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.[8,15]

The current 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 orientated interventions and conclusions drawn from previous reviews;[32,38,39] 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.[40]

In view of the generally poor health status of subjects, it was important that outcome measures were concise so as not to overburden patients. Therefore, the current 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, measuring the distress from dyspnea and other symptoms using a VAS 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 current study suggests an add-on value of this PEI. Costs in the current 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 due to death. Missing data were not at random but were related to outcomes that can lead to attrition bias. Finding should be viewed with caution due to the missing data. Future study may consider using the Palliative Performance Scale (PPS) [41] which may be a more reliable predictor than

the Karnofsky 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 employed. An attention placebo group would have served to achieve blinding of subjects and detect the effects of attention, whilst the usual care group compares the intervention effect with existing service. There is also little information on patients' perceptions and feelings towards the process and outcome of the intervention. Qualitative interviews may be useful in future studies to solicit this information

CONCLUSION

The results of the study suggest that the PEI was 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 mechanism of inter-relationship 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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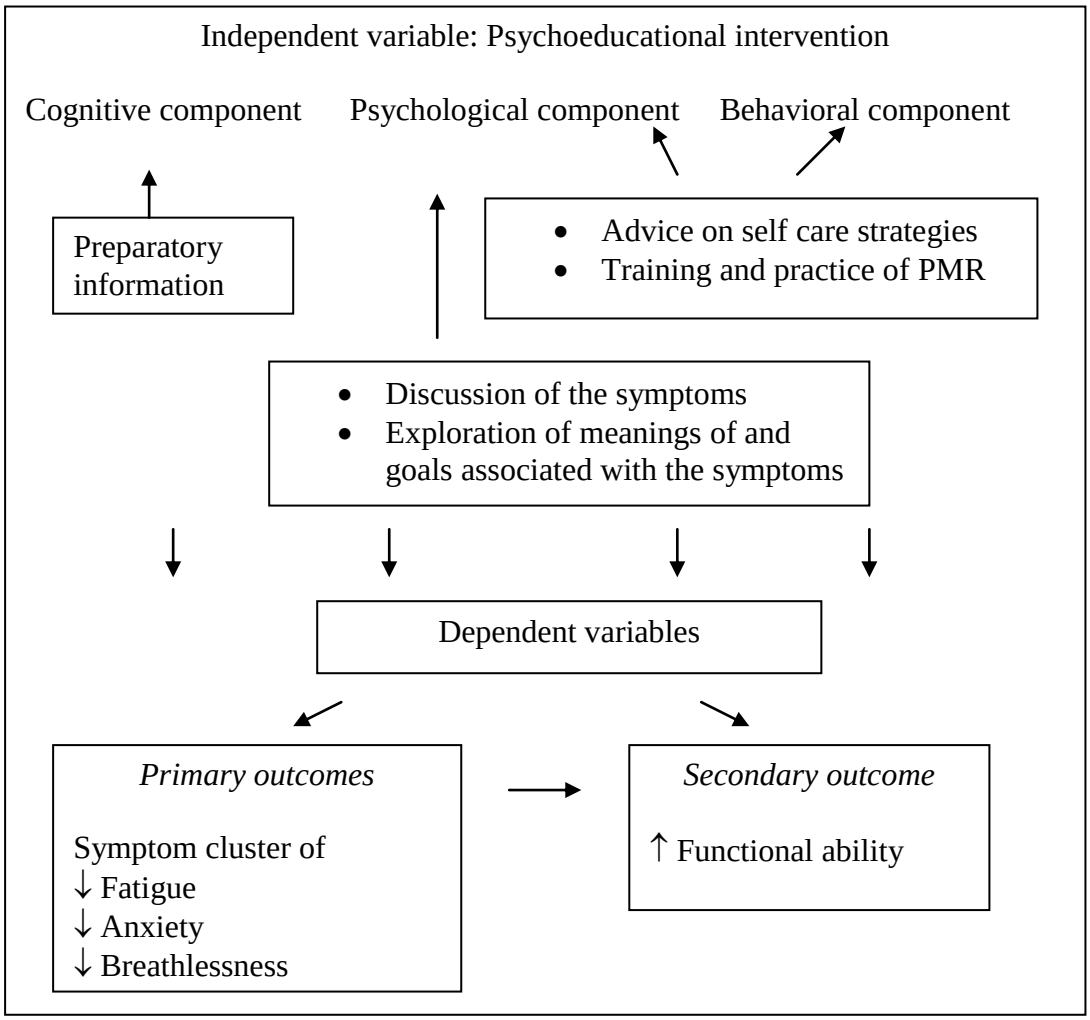
Figure 1 Analytical model depicting the relationship between the intervention and outcomes



Protocol for educational intervention

An interactive educational session is delivered by nurse research assistant. This package of intervention aims at reassuring the patients that something can be done to help them cope with their side effects. Content 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 feeling about them;
(4) advice and support for patients on self care strategies of managing those symptoms.

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

The package is supplemented by 4 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 progressive muscle relaxation

An audiotape of all information corresponding to that in the leaflet is provided to all participants. Information of the leaflet/audiotape is derived from literature and the publications produced by 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 educational level of primary six. This has been tested on 10 persons with primary six level of education to ensure its readability.

Table 1: Mean scores and standard deviations of breathlessness, fatigue, anxiety and functional ability in each study group from baseline to week 12

	Grouping	N	Range of scale	Mean	Std. Deviation
Baseline breathing	Control	70	0-100	20.386	22.4501
	Intervention	70		17.114	17.8614
Week 3 breathing	Control	66		34.000	26.7634
	Intervention	69		18.855	19.8689
Week 6 breathing	Control	59		31.356	25.3539
	Intervention	68		19.103	23.1163
Week12 breathing	Control	40		30.778	30.2399
	Intervention	62		19.855	26.9540
Baseline fatigue	Control	70	0-10	4.4262	2.84993
	Intervention	70		3.8024	2.64077
Week 3 fatigue	Control	66		4.8939	2.96700
	Intervention	69		3.5145	2.91221
Week 6 fatigue	Control	59		4.9831	2.99995
	Intervention	68		3.1887	2.62181
Week 12 fatigue	Control	40		3.9708	2.81249
	Intervention	62		3.2581	2.79387
Baseline anxiety	Control	70	20-80	43.2429	10.58771
	Intervention	70		42.8286	10.39505
Week 3 anxiety	Control	66		43.6212	11.76274
	Intervention	69		42.1304	11.51459
Week 6 anxiety	Control	59		44.5424	11.95007
	Intervention	68		39.2500	10.24094
Week 12 anxiety	Control	40		40.6500	11.29908
	Intervention	62		39.8065	10.36362
Baseline functional ability	Control	70	0-100	53.0149	27.07606
	Intervention	70		50.3393	27.14660
Week 3 functional ability	Control	66		46.9255	30.55070
	Intervention	69		51.6697	30.20989
Week 6 functional ability	Control	59		44.1702	30.44309
	Intervention	68		57.5123	27.69611
Week 12 functional ability	Control	40		53.4948	33.05262
	Intervention	62		56.3508	31.44884

Table 2: Multivariate test results with study group and stage of cancer as independent variables across T0-T2

	Pillai's Trace Value	F	Sig.	Partial Eta Squared	Observed Power
GROUP	.083	4.064	.008	.083	.835
STAGE	.045	2.092	.104	.045	.525
TIME	.084	2.005	.069	.084	.715
TIME * GROUP	.138	3.485	***.003***	.138	.939
TIME * STAGE	.019	.426	.861	.019	.172
TIME* GROUP* STAGE	.032	.725	.630	.032	.279

Table 3: Univariate test on transformed breathlessness, fatigue and anxiety from T0 – T2 with study group and stage of cancer as independent variables

Breathlessness							
	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
GROUP	3.553	1	3.553	7.368	.007	.051	.769
STAGE	.009	1	.009	.018	.893	.000	.052
TIME	1.691	2	.866	5.845	.004	.041	.865
TIME* GROUP	1.814	2	.928	6.269	***.002***	.044	.888
TIME * STAGE	.336	2	.172	1.160	.314	.008	.251
TIME* GROUP* STAGE	.193	2	.099	.667	.511	.005	.160
Fatigue							
	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
GROUP	14.315	1	14.315	11.116	.001	.076	.912
STAGE	2.403	1	2.403	1.866	.174	.014	.274
TIME	.028	2	.015	.051	.944	.000	.058
TIME* GROUP	2.605	2	1.368	4.681	***.011***	.033	.768
TIME * STAGE	.059	2	.031	.106	.891	.001	.066
TIME* GROUP* STAGE	.587	2	.308	1.055	.347	.008	.229
Anxiety							
	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Power
GROUP	.072	1	.072	2.582	.110	.019	.358
STAGE	.142	1	.142	5.120	.025	.036	.613
TIME	.001	2	.000	.076	.906	.001	.061
TIME* GROUP	.065	2	.037	7.246	***.001***	.051	.909
TIME * STAGE	.000	2	.000	.029	.959	.000	.054
TIME* GROUP* STAGE	.004	2	.002	.457	.609	.003	.120

Table 4: Mixed between-within subjects ANOVA of functional ability from T0-T2 with both study group and stage of cancer as independent variables

Effect	Sum of Squares	Pillai's Trace Value	F	Sig.	Partial Eta Squared	Observed Power
GROUP	3253.278		1.728	.191	.013	.257
STAGE	2607.701		1.385	.241	.010	.215
TIME		.017	1.175	.312	.017	.254
TIME * GROUP		.108	8.144	***.000***	.108	.956
TIME*STAGE		.003	.221	.802	.003	.084
TIME * GROUP* STAGE		.000	.009	.991	.000	.051