End of Life Experience of Symptom Cluster and Their Management in Hong Kong Chinese Patients with Lung Cancer Who Receive Palliative Radiotherapy

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Abstract
Breathlessness, fatigue, and anxiety are distressing symptoms for patients with advanced lung cancer, however, they are not relieved by palliative RT and are often viewed as neglected areas of clinical practice. This paper aims to review definitions of, and explore patients’ experiences of, breathlessness, fatigue, and anxiety. Further, it will outline existing approaches, both pharmacological and non-pharmacological, to treat them. Current treatments and perceptions of these symptoms will be discussed in the context of Hong Kong health care service. The review of literature also shows that breathlessness, fatigue and anxiety appears to have similar emotional origins. A contemporary approach of using a common psychoeducational intervention to treat these symptoms together as a cluster in end of life care will be discussed.

Key words: End of life care; lung neoplasms; Palliative radiotherapy; Fatigue; Anxiety; Breathlessness; Symptom cluster; Psychoeducational intervention

1 Introduction
Lung cancer is one of the leading cancer diagnoses for both genders in Hong Kong [1]. Despite advances in detection and effective treatment, lung cancer remains one of the most dreadful and fatal diseases. The majority of patients either present with advanced disease or develop metastases soon after the initial diagnosis of lung cancer. Anecdotal data shows that 80% of lung cancer cases are diagnosed at stage 3 or 4 in the general hospitals in Hong Kong. The experience of lung cancer often includes profound physical and psychological changes as a result of disease progression and side effects of treatment. Several studies have revealed that patients with lung cancer experience more symptom distress than patients with other types of cancer [23]. Pain, fatigue, insomnia, weight loss, breathlessness, fear, and anxiety appear to be the most common problems in this population [3,4]. Patients also experience more severe symptoms near the end of life [5,6,7].

There is increasing interest in studying symptom clusters in patients with cancer, as patients often experience several symptoms concurrently [12,13,14]. The term ‘symptom cluster’ first appeared in literature in 2001 and is defined as three or more concurrent symptoms that are related to each other [15]. In a study of 220 elderly patients diagnosed with lung cancer [16], results supported that the 7 symptoms of fatigue, nausea, weakness, appetite loss, weight loss, altered taste, and vomiting formed a cluster. Their study implied the importance of systematic appraisal of multiple symptoms, rather than assessment of isolated symptoms. This review paper will focus on 3 selected symptoms, namely breathlessness, fatigue and anxiety, and their consideration as a symptom cluster in patients with end stage lung cancer.

Radiotherapy (RT) plays an important role in the management of advanced lung cancer, and is used in attempt to control the tumor for as long as possible, or to improve symptoms and relieve suffering. RT, however, is a stressful event and can cause severe side effects that compromise quality of life [17-19]. Cooley et al. reported that lung cancer patients receiving radiotherapy had significantly higher symptom distress than those receiving surgery [20].

Although RT is effective in relieving pain, large airway obstruction and atelectasis in patients with advanced lung cancer [21,22], it is not effective in relieving breathlessness due to widespread disease or pleural effusion. Breathlessness, which is a subjective and frightening experience characterized by laboured breathing, has been reported to be experienced by 65% of lung cancer patients [23]. In addition, breathlessness was unrelieved or exacerbated in 72% of patients undergoing radiotherapy [24]. Fatigue is a complex and unpleasant phenomenon encompassing feelings ranging from tiredness to exhaustion [25]. It is identified as the most frequently reported and unrelenting side effect of RT [26,27]. Molassiotis & Chan found fatigue to be prevalent in 80.8% of patients undergoing RT in Hong Kong [28]. Anxiety is the most common psychological symptom in patients with lung cancer, and this is ex-
Breathlessness, fatigue, and anxiety are common and distressing symptoms for patients with advanced lung cancer, however, they are not relieved by palliative RT and are often viewed as neglected areas of clinical practice. A recent review indicated that the experience of symptom cluster worsens during RT\textsuperscript{[32]}, and fatigue, breathlessness, and poor emotion seem to cluster in those patients treated with RT. This paper aims to review definitions of, and explore patients’ experiences of, breathlessness, fatigue, and anxiety. Further, it will outline existing approaches to treat them. The review of literature shows that breathlessness, fatigue and anxiety appears to have similar emotional origins and can be viewed as a symptom cluster. A contemporary approach of using a common psychoeducational intervention to treat these symptoms together as a cluster will be discussed.

2 Breathlessness

2.1 Definition and causes of breathlessness The word dyspnea (the formal medical term that describes breathlessness) is derived from Latin where “dys” means difficulty and “pnea” means breathing. Some literature use the terms dyspnea and breathlessness interchangeably. However, West & Popkess-Vawter suggest that dyspnea is laboured breathing observable by others, whereas breathlessness is the subjective feelings of laboured breathing that may or may not be observed by others\textsuperscript{[33]}. Normally, breathing occurs below the level of consciousness and people breathe rhythmically without conscious awareness that it is happening. When stimulating inputs from receptors increase, the central nervous system perceives that the respiratory muscles cannot cope with these inputs nor maintain adequate ventilation, subsequently breathlessness emerges\textsuperscript{[34]}. Patients may experience breathlessness as a result of muscular dysfunction, obstruction within the respiratory system, or due to abnormality of the circulatory system, for example deoxygenation, anemia or poisoning.

The most common cause of breathlessness in cancer patients is the presence of lung or pleural involvement\textsuperscript{[8,35]}. Furthermore, muscular weakness and general fatigue are important conditions causing breathlessness in patients with advanced disease\textsuperscript{[36]}. Some patients report that psychological states, such as anxiety, anger, crying, or laughter, trigger breathlessness\textsuperscript{[37]}. In a qualitative study of Hong Kong Chinese patients with advanced lung cancer, extreme weather (either too hot or too cold) and emotional stress were described as triggers for breathlessness\textsuperscript{[38]}. Patients reported that inadequate nutrition and feelings of hunger associated with the food restrictions required of patients who take Chinese herbal medicine might be a cause of breathlessness. The same study suggests that Chinese people may have their own unique and cultural perception of the causes of breathlessness\textsuperscript{[38]}.  

2.2 The Experience of Breathlessness An episode of breathlessness may last from minutes to an hour. However it will most commonly last for between 5 to 15 minutes\textsuperscript{[37]}. Typically, the episode begins with a trigger (emotional or physical). This precipitates a gradual increase in breathlessness, until a plateau is reached. Thereafter, it subsides either gradually or quickly once patients have ended their activity or rested\textsuperscript{[39]}. During an episode of breathlessness patients experience physical discomfort, such as tightness in the chest, sweating, palpitations, chest pain, weakness, and exhaustion\textsuperscript{[8,37,41]}. Ninety seven percent of subjects used the words ‘tired’ or ‘fatigue’ as a typical descriptor of the sensation of breathlessness\textsuperscript{[39]}. Therefore, fatigue might be constructed to be synonymous with breathlessness by patients with lung cancer. Furthermore, breathlessness imposes restrictions on various social activities such as recreational activities, shopping, driving and sexual activities\textsuperscript{[37]}. Negative emotions are frequently reported by breathless patients. Patients may feel angry, frightened, anxious, and helpless during periods of breathlessness\textsuperscript{[42]}. Breathlessness may be seen as a continuous process of loss, starting from the loss of comfort, bodily control, physical and social activity, overall quality of life and eventually their lives\textsuperscript{[30]}. As breathing is fundamental to life, difficulty in breathing could reinforce feelings that the body is fragile and death is approaching, and such feelings can increase the sense of fear and anxiety\textsuperscript{[40,43]}. Nurses in another study described dying patients with breathlessness as ‘panicky’\textsuperscript{[44]}. Anxiety then contributes to short, shallow, gasping breathing that worsens the severity of breathlessness. This establishes a negative feedback mechanism\textsuperscript{[40]}.  

2.3 Management of Breathlessness Traditionally, treatments of breathlessness focus on active medical therapies, such as drainage of pleural fluid\textsuperscript{[45]}. However, performing a thoracentesis might not be beneficial for a bedridden patient with advanced disease for whom drainage might cause discomfort and not reduce breathlessness at all\textsuperscript{[46]}. As the disease becomes further advanced, active treatment should be superseded by supportive measures such as supplemental oxygen, opioids, and non-pharmacological interventions. Some patients may employ cultural specific strategies such as Chinese herbal medicine or gi gong in combating distressing symptoms such as breathlessness\textsuperscript{[46]}. There is no medication specifically available to reduce breathlessness\textsuperscript{[47]}. Usually multiple agents are used to reduce the multiple causes of breathlessness. Oxygen therapy, inhaled bronchodilators, steroids, and oral opioids are the most commonly used items\textsuperscript{[48]}. Unfortunately, the usefulness of these
pharmacological interventions is inconclusive \[^{49,50}\].

To enable a holistic understanding and treatment of breathlessness Bredin et al. examined the effectiveness of an integrative psychoeducational intervention which included a combination of psychological support, breathing retraining, progressive muscle relaxation, and distraction exercise for the reduction of breathlessness in lung cancer patients \[^{23}\]. Their interventions significantly lowered the level of breathlessness, depression and physical symptoms.

3 Fatigue

3.1 Definition and causes of fatigue Fatigue is a complex and common human experience. Acute fatigue happens following periods of physical and mental effort \[^{51}\]. It is usually resolved quickly after rest or relaxation. However, people with cancer may experience a different kind of fatigue, sometimes referred to as chronic fatigue, or cancer-related fatigue, which is disruptive, distressing, and difficult to recover from. This type of fatigue has been variously described in the literature as tiredness, exhaustion, inability to concentrate, malaise, boredom, lack of motivation and decreased mental status \[^{52}\], making the definition of fatigue in cancer patients a challenge.

Ream & Richardson take a broad and holistic view of fatigue \[^{25}\]. Through the process of concept analysis they defined fatigue as a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity\[^{25}\]. This definition was derived from systematic analysis of fatigue literature and further supported by research \[^{53}\], thus providing a pertinent description of fatigue. Such a broad view and definition of fatigue seems to be more valuable and applicable than those who define fatigue as a single variable, such as exercise intolerance \[^{54}\] or low mood \[^{55}\].

Energy deficit is suggested as a major cause of fatigue that results from prolonged stress arising from the disease process \[^{56}\]. Stressors incorporate physical stress such as pain, breathlessness, and infection, as well as emotional stress such as anxiety. For the biochemical cause for fatigue, the accumulation of metabolites such as lactate, hydrogenions and cell destruction end products may cause fatigue \[^{57}\]. But Blesch et al. found none of the biochemical variables were correlated with fatigue \[^{58}\]. Instead they found that physiological and illness related factors such as pain and duration of cancer illness correlated positively with fatigue, whereas activity correlated negatively with fatigue. The various patterns, cycles and duration of chemotherapy and radiotherapy also affect the experience of fatigue \[^{26,59-61}\]. From a psychosocial aspect, anxiety, depression, confusion, and anger have been shown to be associated with fatigue in people with cancer \[^{56,62,63}\].

Because Chinese patients may not complain of a subtle symptom owing to the cultural virtue of tolerance, fatigue is often an underreported and neglected area in clinical practice and research in the Chinese population \[^{64}\]. A qualitative data indicated the universal experience of fatigue by Hong Kong Chinese, but also uncovered some culturally specific descriptors such as ‘down-hearted’ and ‘no soul’ \[^{64}\]. Patients connected fatigue with radiotherapy treatment, over-travelling, and psychological factors, especially worrying about and fearing the illness \[^{64}\]. These studies show that fatigue is complex and suggest that it is unlikely that there is a single cause or mechanism behind it.

3.2 The experience of fatigue Rather than being an isolated physical symptom, fatigue can have a significant impact on an individual’s quality of life \[^{65,66}\]. It can affect one’s physical, psychological, social, and spiritual well-being. Fatigue had detrimental effects on Chinese patients’ health with respects to: physical aspects (e.g. limb weakness, loss of appetite); emotional aspects (e.g. worry, frustration); mental aspects (e.g. short attention span, poor concentration); and functional aspects (e.g. poor work, family, and social functioning) \[^{64}\]. It appears that a subtle change of life style, decreased work productivity and functioning within the family may all be manifestations of fatigue in Chinese cancer patients.

3.3 Management of fatigue Primary therapies used to treat fatigue focus on modification of the causes of fatigue, for example correction of metabolic abnormalities or treatment for anemia with agents such as erythropoietin \[^{67}\]. Other pharmacological interventions, including psychostimulants and corticosteroids, are not yet supported by research \[^{67}\].

Because of the lack of pharmacological interventions to treat fatigue, patients frequently use a variety of self-help methods to cope with it, including energy conservation, talking to friends or doing something different \[^{46,54,68}\]. Cancer patients with fatigue are usually advised to get more rest or simply take it easy. However, patients frequently report having more fatigue after a long sleep or period of rest \[^{68}\]. Some authors suggest that short and frequent rests are beneficial \[^{70,71}\]. Energy conservation activities, such as sitting rather than standing are also recommended \[^{70,71}\].

Exercise has been reported to be effective in reducing fatigue in cancer patients \[^{72}\]. In women with breast cancer receiving chemotherapy, exercise was found to be effective in reducing levels of fatigue \[^{73}\]. However, the effect appeared to be immediate and did not carry over to subsequent days. To ensure safety, Winningham suggested that cancer patients be screened for cardiopulmonary deficit, musculoskeletal problems, and sensory/cognitive limitations that compromise exercise tolerance before they engage in any exercise program, indicating that exercise may not be a suitable option for all cancer patients \[^{74}\].

Many psychosocial interventions such as preparatory inform-
mation and relaxation techniques are suggested for relief of fatigue based on Aistars’ theory that stress is a major cause of it. These interventions are reported to result in higher energy levels and reduced feelings of fatigue [75-78]. Given the multidimensional nature of fatigue, intervention programs usually incorporate a variety of strategies such as exercise, energy conservation, and psychosocial support. These appear to have the potential to achieve more effective relief of fatigue than single strategies used in isolation [79].

4 Anxiety

4.1 Definition and causes of anxiety Anxiety is the most common psychological symptom experienced by patients with lung cancer. This is due primarily to the fact that they are facing a rapidly progressive fatal disease with a myriad of associated stressors [80]. The concept of anxiety is generally coupled with fear. Kierkegaard, an existential philosopher, in his earliest discussions of anxiety described anxiety as “a vague diffuse uneasiness” in that no apparent danger exists [81]. Lazarus & Anerill suggested that anxiety reflected tension created by reduced cognitive ability to assign full meaning to a stressful event [82]. Utilizing these definitions and criteria, it is easy to understand that the threatening and damaging experience of lung cancer and its treatment can stimulate the occurrence of anxiety.

General origins of anxiety in cancer patients include the diagnosis of the cancer itself, changes in biopsychological conditions, life-style alternations, and dependence on health professionals [83]. Many of the medications that are taken by cancer patients may cause anxiety, for example central nervous system (CNS) stimulants, CNS depressants, antipsychotics, and cardiopulmonary medications such as digitalis and aminophylline. In patients with lung cancer, anxiety is commonly associated with the disease, poor symptom management, or an exacerbation of a pre-existing anxiety disorder [84]. Lung cancer patients who experience breathlessness and who lack understanding about possible symptoms report high level of anxiety and a fear of suffocation [10,31].

Radiation treatment itself causes stress and anxiety in many patients [17]. Prior to starting radiotherapy, it is common for patients to be preoccupied with the spread of disease, side effects, doubts about the relief of symptoms, and survival [85]. Towards the end of treatment, anxiety may again escalate because of concern about the cessation of treatment, worry over new tumor growth and diminished contact with health care professionals [85].

4.2 The experience of anxiety Anxiety is a highly personal experience and it can lead to reactions that range from mild anxiety to panic [45]. Mild anxiety reactions manifest in a heightened sensitivity to environmental stimuli. Moderate anxiety reactions can lead to decreased attentiveness and physical signs such as sweating, restlessness, insomnia and loss of appetite. Severe anxiety can distort thought processes, and reduce one’s ability to reason and make decisions. In the case of panic, an individual may exhibit a wide range of anxiety reactions such as dizziness, palpitations, and feelings of unreality.

Anxiety can be accompanied by many other psychiatric symptoms, especially depression [86]. There is a great deal of overlap in the manifestations of depression and anxiety. For example, sleep disturbance and loss of appetite are common in both. Despite some similarity in manifestation, the prevalence and severity of depression appears to be quite stable [86,87] whereas anxiety usually fluctuates after the diagnosis and/or treatment of lung cancer [87].

4.3 Management of Anxiety Anxiety-reducing interventions may be used individually or in combination. These interventions include pharmacologic approaches, educational support, and cognitive-behavioral techniques.

The most commonly used medications to treat anxiety are the benzodiazepines, and most of them are marketed as anxiolytic agents. Sedation, confusion, and reduced motor coordination are common side effects. Tolerance, addiction, and withdrawal effects may occur in patients taking benzodiazepines. Patient education plays an important role in reducing anxiety in patients with cancer, as anxiety is often related to misunderstandings about the illness and/or its treatments [88]. An educational program called “I can cope” produced a demonstrable reduction in the level of anxiety in cancer patients [89]. This group educational program not only addressed the need for information, but also focused on the sensory experience of cancer illness and treatment. Other educational approaches have been found to be effective in reducing anxiety in cancer patients [18,89].

Specific relaxation techniques include meditation, progressive muscle relaxation (PMR), hypnosis, biofeedback, and guided imagery [79]. Gruber et al. randomly assigned 13 patients with breast cancer to either a PMR group, or to a delayed treatment control group [90]. Both groups showed a significant reduction in anxiety shortly after they began treatment. Hypnosis aided by imagery was found to be effective in reducing pain and anxiety in cancer patients [91]. However, the diversity of relaxation techniques in scattered studies makes it difficult to draw a conclusion about their effects.

5 Similarities and inter-relationships among breathlessness, fatigue and anxiety

Lenz et al. advocated that symptoms can occur alone, but acknowledged that more often multiple symptoms are experienced simultaneously [92]. The nature of associations among symptoms’ intensities was further developed by Dodd et al. in their discussion of the concept of a symptom cluster [15]. Kirkova and Walsh asserted that cancer symptom clusters seem to be dynamic constructs, and the relationship among the
Within a cluster, the symptom experience is more intense and frequent. A preliminary study of 27 subjects was conducted in Hong Kong Chinese to show that breathlessness, fatigue, and anxiety occurred simultaneously. The moderately strong correlation of their intensity scores warranted these symptoms being considered as a cluster in patients with advanced lung cancer. Whilst the specific cluster of breathlessness, fatigue, and anxiety has not yet been fully established, there are several studies that demonstrate similarities and correlations between groups of symptoms that have involved these 3 symptoms. For example, the physiological aspects of breathlessness have been found to be similar to anxiety. Both result in increased heart and respiration rate. Furthermore, stress is identified as a common trigger for all these symptoms. In a study of 171 patients with lung cancer, they found that the three symptoms of pain, fatigue, and breathlessness, interfered with patients’ daily activities but their impacts were different. Breathlessness and fatigue interfered predominantly with physical activities, whereas pain interfered with all activities almost equally. In recent studies and review of symptom clusters in patients with advanced cancer, fatigue and breathlessness were often found to be included in the same cluster.

Other studies have confirmed that anxiety can exacerbate the experience of fatigue and breathlessness. Studies of patients with lung cancer found significant positive correlations among fatigue, breathlessness, and anxiety. Anxiety accounted for 34.1% of the total variance in predicting the degree of physical symptom distress. In comparison, physical symptom distress accounted for 48.8% of the total variance when predicting psychological symptom distress. Physical symptom distress is worsened by psychological symptom distress and vice versa.

6 Discussion

Despite their high prevalence and distressful nature, the management of breathlessness, fatigue, and anxiety was seldom addressed in most health care settings in Hong Kong. No formal assessment or nursing intervention was provided for patients who were experiencing these symptoms. Oncology nurses and patients often expressed a lack of knowledge regarding effective management of these symptoms. Patients believed that such symptoms were a part of the cancer experience, that nothing could be done, and that symptoms must be tolerated. Usual care in this care setting comprised an individual patient briefing and a group talk focused on the causes of cancer, the procedure of RT, the importance of skin care, maintaining a well-balanced diet, pain management strategies, and the availability of social services. There was little information about, nor any formal intervention for, fatigue, breathlessness or anxiety.

Any pharmacological treatments that were used were mainly introduced to treat the pathophysiological aspects of these symptoms. It is generally acknowledged that multiple physiological, pathological and psychological factors and mechanisms can influence symptom manifestation and experience. Using opiates and steroids to treat breathlessness will typically only partially relieve the sensation of breathlessness. Such pharmacological approaches do not address emotional components. Patients received no non-pharmacological interventions for their breathlessness, except some general advice such as resting and prop-up positioning. Similarly, when patients express their concern about fatigue the common response from health care professionals is that fatigue is normal and patients should take it easy. However, cancer patients report experiencing more fatigue after resting, sleeping, or reducing their physical activity. Pharmacological treatments for fatigue, such as erythropoietin, that focus on the correction of metabolic abnormalities or anemia are not common practice in Hong Kong. Anxiety is commonly treated through anxiolytic agents such as the benzodiazepines. However, anxiolytics have side effects including sedation and confusion, and they impact on motor coordination. In Hong Kong psychological interventions for anxiety are mainly provided by clinical psychologists and are only prescribed for those with a medical diagnosis of clinical anxiety. In short, the inadequacy of existing treatments in practice and the rapid worsening of symptoms in patients with lung cancer prompt health care professionals to consider the potential of non-pharmacological interventions as a complementary method for the relief of symptoms. There was a need to identify interventions that were low risk and able to address the complex nature of these symptoms.

In general, the majority of patients with lung cancer receive palliative care on an outpatient basis. To a certain extent, they are expected to be responsible for their own self-care, including coping with symptoms that occur at home, although they are approaching the end stage of their life. Effective self-care can take place only when a patient has the knowledge and skill to perform necessary self-care practice, and the confidence and motivation to initiate and sustain self-care efforts. End of life care designed for outpatients undergoing RT need to address the educational element of self-care in symptom control. Psycho-educational interventions (PEI) appear to play an important role in reducing symptoms in patients with cancer. Williams specifically highlighted that PEIs showed promise to improve patients’ ability to cope with symptom cluster. The three selected symptoms, breathlessness, fatigue, and anxiety have a common emotional origin of stress, and that the emotional state of patients affects their perception and reporting of symptoms. PEI 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 \cite{19,78,79,100}. They enable patients to cope with the cancer experience through instructive material and cognitive behavioral techniques \cite{101}. In the last few decades, large numbers of studies evaluating PEI in patients with cancer have been conducted \cite{98}. 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 psycho-educational interventions in patients with lung cancer, in contrast to other cancers \cite{80}. The majority of studies focused on assessing interventions that aimed to reduce psychological distress and treat with early stage cancer \cite{94,102}. Patients with other distressing symptoms or a cluster of symptoms and in the advanced stage of illness have so far been neglected. Therefore studies that identify and test the effect of PEI on relieving fatigue, breathlessness, and anxiety in patients undergoing lung cancer radiotherapy are necessary.

In view of the demands faced by health care professionals in clinical practice and poor prognosis faced by patients with advanced lung cancer, a brief and effective intervention is important to achieve the maximum use of health care resources. Treating multiple symptoms together as a cluster that may be responsive to a common intervention appeared to be a promising approach in cancer symptom management \cite{32,103}. The concept of symptom clusters is now acknowledged to be at the cutting edge of science in symptom management \cite{105}. There is a need to establish a scientific basis to support the simultaneous management of breathlessness, fatigue, and anxiety when arising as a cluster. This may serve to achieve the most effective use of workers’ as well as patients’ time, and to maximize the overall effect of an intervention.

7 Conclusion

Breathlessness, fatigue, and anxiety are distressing symptoms for patients with advanced lung cancer, however, they are not relieved by palliative RT and are often neglected areas of clinical practice. Existing research does not provide conclusive evidence as to the most effective interventions for the aforementioned symptoms. The high prevalence of the selected symptoms clearly demonstrates a need to identify and test a PEI targeting these symptoms. The contemporary approach of treating a cluster of symptoms together offers promising solution in the arena of end of life cancer care.

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