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REVIEW

Fatigue in lung cancer patients: symptom burden and management of challenges

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Abstract: Lung cancer (LC) remains the most common cause of cancer death in several countries across the world. Fatigue is the most frequently reported symptom in LC patients throughout the entire course of disease, and all international guidelines recommend early screening for cancer-related fatigue (CRF) and symptoms that can affect patients' quality of life. In patients with LC, fatigue belongs to the symptom cluster of pain, depression, and insomnia, which are commonly observed simultaneously, but are typically treated as separate although they may have common biological mechanisms. The treatment of CRF remains one of the difficult areas in the oncology field: scarce evidence supports pharmacological therapies, while some interesting data arising indicates alternative remedies and physical exercise seem to be one of the most effective approaches for CRF at any stage of LC.

Keywords: fatigue, lung cancer, symptom cluster, quality of life

Introduction

Lung cancer (LC) remains the most common cause of cancer-related death, accounting for approximately 20% of the total cancer death worldwide. Despite important progress occurring in diagnostic and therapeutic areas, only 10.9% of people with LC live 5 years or more.[1] Several trials have shown that the physical symptoms have a great importance in cancer patients, especially in LC.[2,3] A number of cluster symptoms such as anxiety, fatigue, and dyspnea have been associated with poor patient performance, and these often remain a major issue throughout the course of cancer treatment and thereafter.[4] Cancer-related fatigue (CRF) is present during the entire course of the disease, resulting in the impairment of both day-to-day living and overall quality of life (QoL).[5,6] CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment, and it is not strictly linked to recent activity and nor is it relieved by rest.[7] Furthermore, patients with LC indicate relief from tiredness as the most common unmet need, even years after diagnosis.[8] Fatigue is the most represented acute symptom before and after cancer treatment, affecting a large number of patients, ranging between 57% and 100% of the cases,[9] rarely described as an isolated symptom and often associated with depression and sleep disorders.[10] Different causes can justify the onset of fatigue in a patient with cancer, together with cancer itself, such as comorbidities, nutritional status, medications, the reduction of physical activity, and functional status. Different international guidelines have been published regarding the management of CRF, with no specific medication approved to date.[7,11,12] Aware of the

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lack of data in the literature, this paper aims to summarize methods of identification and possible treatments of CRF in LC, with the purpose of suggesting a strategy for a more comprehensive and effective approach.

Material and methods

Articles from 1997 to 2016 were selected using PubMed, which is a very large research database, using as keywords only "fatigue" and "lung cancer". Subsequently, the articles were divided according to the different paragraphs of this review: assessment, fatigue and symptoms cluster, fatigue in several stages of disease, fatigue in active therapies, and, in conclusion, the possible therapeutic approaches. The data collected include more robust evidence and alternate strategy for managing fatigue in patients with LC. The management of this symptom must involve team effort, and for this reason our review paper is addressed to physicians and nurses.

Assessment of CRF

Fatigue has to be screened and scored according to the clinical practice guidelines.[11–13] Any patient must, therefore, be evaluated for severity, duration, and alleviation of factors of CRF from the first visit and during the course of the disease. In addition, the type of fatigue must be identified, considering that CRF can be categorized as either primary or secondary.[13] Primary fatigue is linked to the tumor itself or alterations caused by cytokines produced during cancer treatment[14] as a disturbance of hypothalamic regulatory circuits,[15] changes in the central serotoninergic system, and alteration of circadian melatonin secretion.[16] Factors playing a key role in fatigue development include polymorphisms in genes coding regulatory proteins of oxidative phosphorylation, signal transduction in B-cells, the expression of proinflammatory cytokines, and catecholamine metabolism.[17] Secondary fatigue is caused by one or more disease-related symptom(s) such as sleep disturbance, infection, malnutrition, or anemia. Moreover, CRF can be closely linked to comorbidities, the presence of emotional distress or pain, the physical activity status, alcohol/substance abuse, and use of medications (Table 1). In the CRF evaluation, it is extremely relevant to consider the timing of the disease, in terms of recent diagnosis, disease progression/recurrence, follow-up period, or end of life. As previously mentioned, the correct identification and score of CFR is a fundamental step in treatment decision. Screening can be done through quantitative and semiquantitative scales, even if these assessments are more appropriate for secondary CRF and a validated scale, specific for CRF in LC, is currently not available. Among the most used scales are the following: Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Fatigue, Cancer Fatigue Scale, Multidimensional Fatigue Inventory, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.[18] BFI is the most common questionnaire included in LC clinical trials and is also useful in detecting the severity of fatigue occurring during the previous 24 hours together with the CRF impact on individual's life. Preliminary data reported in the literature suggest a possibility of integration of clinical and molecular assessment in detecting fatigue in LC. In fact, interesting data have been reported about the role of potential predictive biomarkers for primary CRF in non-small-cell lung cancer (NSCLC). A recent Chinese study showed, in 100 LC patients, a correlation of CRF and different factors such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 at the plasma level and 17-hydroxycorticosteroid in the urine, collected before and after chemotherapy. This correlation is statistically significant for TNF-α and IL-1, and fatigue was reported by 88% of patients.[19] The use of validated scales (such as BFI) should always be applied to detect and grade fatigue in LC, not only in the research area but also in clinical practice.

Table 1 Causes of CRF

Causes of CRF	
Primary CRF	Alterations caused by cytokines, disturbance of hypothalamic regulatory circuits, changes in the central nervous system serotoninergic system, disturbance of circadian melatonin secretion, gene polymorphisms for regulatory proteins of oxidative phosphorylation
Secondary CRF	Sleep disturbance, infection, anemia, malnutrition, emotional distress, pain, reduced physical activity, alcohol/substance abuse, use of medications, comorbidities as COPD

Abbreviations: CRF, cancer-related fatigue; COPD, chronic obstructive pulmonary disease.

Fatigue and cluster symptoms

The majority of patients with LC experience debilitating physical and psychological symptoms. Pain, depression, and fatigue are among the most frequent symptoms reported by LC patients, and their frequency and intensity increase with the approach of death (P=0.001).[20,21] Symptoms are commonly observed to co-occur in a related cluster and can be induced by common biological mechanisms, but are typically treated as separate entities. It has been established that depression is present in about one-third of patients with LC. In a group of 987 patients, depression before treatment was present in 322 (33%) cases and persists in more than 50%

of them through the course of the disease. In this trial, it was shown that small-cell lung cancer (SCLC) patients had a threefold greater prevalence of depression than those with NSCLC (25% versus 9%; $P<0.0001$).[22] It is estimated that 74%–90% of patients with LC experience pain, and several studies report similar rates of incidence for fatigue and insomnia. A recent study reports a simultaneous incidence of fatigue, pain, and insomnia, in the range of 40%–50% of cases.[52] In another trial of 111 patients with solid cancer (the largest group with LC, 20%), it was observed that the prevalence of pain, fatigue, insomnia, and somnolence were 100%, 50%, 80%, and 82%, respectively. All the aforementioned rates suggest a strong correlation between fatigue, pain, and sleep disorders.[23] Genetic polymorphisms in LC, such as mutant alleles in endothelial nitric oxide synthase, seem to be helpful in the identification of high-risk patients for these symptom clusters and also have the potential for development of personalized therapies.[24] A qualitative study of LC patient symptoms indicates that the cluster of respiratory symptoms (such as cough and breathlessness) plays a central role in fatigue onset.[6] Taking into consideration this type of interaction between symptom clusters, a single intervention should be successful to treat them simultaneously, and this approach could improve the perception of each single symptom.[25]

Fatigue in early-stage LC and in survivors

Improvements in curative therapies have led to increased number of cancer survivors: for this reason, recent guidelines have been published to detect, grade, and treat CRF in adult cancer survivors (including LC patients) after completion of primary treatment.[12,26] The symptom in this specific subgroup of LC patients could be due to comorbidities and treatments prescribed to cope with surgical consequences and/or adjuvant chemo/radiotherapy. Nearly 60% of NSCLC survivors are affected by comorbidities, 50% with forced expiratory volume in 1 second (FEV_1) <70%, 22% reported distressed mood, and 21% of them had severe functional restrictions.[27] These deficits can promote the onset and/or worsening of fatigue, as reported in several publications.[28,29] Among LC survivors, the prevalence of fatigue is close to 70% at 4 months after thoracotomy.[30] In 350 patients surgically treated for early-stage NSCLC, the prevalence of fatigue was 57%, with 47% of patients indicating mild fatigue and 17% experiencing moderate-to-severe fatigue.[29] Recent data among 254 completely resected patients with stage IA (57.1% of the population) or IB NSCLC (lobectomy was performed in 77.2% of cases) show an overall incidence of postoperative fatigue equal to 59.8% (37.4% mild and 22.4% moderate-to-severe fatigue). The association between fatigue and functional status and FEV_1/FVC (the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration) was considered before and after surgery, with a mean time from surgery to evaluation equal to 2.9±1.5 years. Before surgery, 59.8% of patients showed a slight decline in lung function (FEV_1/FVC 61%–70%), and 43.3% had chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, or other lung diseases. The prevalence of anxiety and depression after surgery was 18.5% and 10.2%, respectively, indicating that LC itself, together with the specific interventions, may have huge negative effects on the psychological well-being. It has been shown that moderate-to-severe fatigue was negatively associated with preoperative FEV_1/FVC and physical activity and positively related to functional status, concurrent lung diseases, breathing difficulty, depression, and anxiety.[31] Several studies demonstrated that functional status, concurrent lung diseases, depression, and anxiety are independent risk factors for fatigue, whereas physical activity was a protective factor.[24,35] A recent meta-analysis found a strong negative correlation between CRF and continued smoking after surgical treatment.[32] It is, therefore, strongly recommended to increase smoking cessation programs in this setting of patients: continuing smoking can worsen respiratory disorders already present, comorbidity, and also fatigue. Data about the persistence of fatigue in survivors are still controversial; one trial reported a resolution of symptoms[33] at 3–6 months after surgery,[33] while others have observed persistence for years after completion of treatment.[34,35] In addition to the surgical approach, adjuvant treatment can also cause long-term toxicities: sensory neuropathy and hearing loss occured in approximately 45% and 21% of patients who underwent adjuvant platinum-based chemotherapy, together with worsening of CFR and decline of global QoL.[36] In fact, in a phase III study of adjuvant chemotherapy (JBR.10 trial), global QoL of patients decreases both in the observation and chemotherapy arms, mainly because of fatigue and post surgical pain. Patients in the observation arm had a faster physical recovery: at 3 months. The QoL in patients who received chemotherapy was comparable to the observation arm at a median time of 9 months after surgery.[37] In this trial, psychological distress was reported in almost 40% of NSCLC survivors,[38] which is significantly higher than in other cancer survivors. Literature data provide evidence that the surgical and adjuvant therapies may, in some cases, lead to a reduced QoL, in particular with the appearance (or worsening) of the symptom cluster associated with the CFR.

Fatigue and active therapies in LC

Patients receiving chemotherapy or radiotherapy report fatigue during treatment in 90% and from 65% to 100% of cases, respectively.[39,40] Currently, physicians have few tools to cope with this symptom. A wide spectrum of health care needs is widely described by patients with LC and can be grouped into nine distinct domains: physical, daily living, psychological/emotional, spiritual/existential, informational, practical, communication, social and family related, and cognitive. It is well recognized that active treatment for LC causes a high physical impact on patients.[41] In a recent prospective multicenter QoL study in patients treated for NSCLC, fatigue was the most frequently reported physical disorder. Before completing the questionnaires, almost 60% of patients had undergone chemotherapy and about 10% received radio- or chemotherapy. In the multivariate analysis including age, sex, tumor stage, and fatigue, only the latter was found to be an independent prognostic factor affecting survival.[42] In cancer patients (including LC patients) during chemotherapy treatment, diurnal variations of severe fatigue were identified.[43,44] Morning and evening fatigue appear as distinct symptoms, both having a negative impact on prognosis. Interestingly, marital status, annual household income, body mass index, regular exercise, and a state of anxiety are associated only with morning fatigue, while among predictors of evening fatigue, child-care responsibilities, ethnicity (greater correlation with white patients), cancer diagnosis (patients with LC), and prior cancer treatment are reported as factors. Other factors like age, sex, functional status, comorbidity profile, depressive symptoms, sleep disturbance, and annual income of <$30,000 may influence both morning and evening fatigue. In particular, younger age is associated with the highest levels with morning and evening fatigue.[45,46] Data on the relationship between age and fatigue are also described in a trial which explored radiation therapy as a therapeutic approach.[47] Different potential explanations for these results could be the administration of lower doses of chemotherapy for older patients, age-related changes in the hypothalamic–adrenal–pituitary axis, or even a "response shift" in the perception of symptoms in older patients. Another multicenter observational study with a large comprehensive spectrum of active anticancer treatments evaluated, using BFI scale, the incidence of CRF and pain in cancer patients: the largest group (42.6%) comprised LC patients with ongoing anticancer treatment (or within a month), and approximately 60% demonstrated worse than moderate fatigue.[48] In the last 10 years, some targeted therapies (TT) entered the therapeutic armamentarium for advanced NSCLC, and these new drugs are also not devoid of side effects, such as fatigue.[49] An Italian multicenter survey evaluated the tolerance to TT in daily clinical practice, and about 65% of patients reported any grade of fatigue during treatment.[50]

Therapeutic approaches for fatigue in LC

Specific treatments for CFR have been investigated in a variety of solid tumors, and few data are currently available in LC. In this section, evidences with a greater impact on LC patients have been collected.

Pharmacological treatments

Medications with different mechanisms of action are used to treat CRF, including psychostimulants, phytotherapeutic agents, growth factors, corticosteroids, and antidepressants. However, for the majority of these approaches, there are no strong literature data supporting them as standard treatments. Studies with antidepressants, in particular with paroxetina, did not show a significant improvement of fatigue, unless in case of depressive disorder.[51] Research has shown that 4 mg dexamethasone is effective for CRF.[52] Nevertheless, when dexamethasone is administered in patients undergoing chemotherapy to prevent nausea and/or allergy, at a dosage higher than 4 mg, fatigue is still reported. In a palliative context and for a short period of time, corticosteroids can improve CRF and increase patients' physical activity, but prolonged use should be avoided in view of the risk of steroid-induced myopathy.[13] In the past, progestational steroids were often used for the treatment of fatigue. However, the results of a recent meta-analysis including four trials did not show differences between progestational steroids versus placebo.[51] Different publications describe the effectiveness of psychostimulant agents, such as psychostimulants methylphenidate and modafinil,[53,54] in the treatment of severe CRF, although frequent and continuous use of these drugs is not recommended because of the related side effects. Methylphenidate is contraindicated in patients with poorly controlled arterial hypertension, symptomatic coronary heart disease, arrhythmia, or epilepsy, while modafinil must be avoided in patients with psychosis and severe affective disorders. Furthermore, more recent reports do not confirm the activity of modafinil. Results of a randomized trial comparing modafinil versus placebo in 208 patients with NSCLC did not show any effect on CRF compared to placebo.[55] A meta-analysis of 1,582 participants treated for CRF indicated that methylphenidate was superior to placebo for the treatment of CRF, while no efficacy was shown for modafinil.[56] Preliminary data highlight the role

of thyrotropin-releasing hormone in CRF treatment and improvement in QoL with patients' manifestations of exhaustion, with exhaustion improving within few hours of treatment.[57] However, further studies are needed to confirm these results. There is much evidence on erythropoiesis-stimulating agents (ESA) in ameliorating CRF in anemic patients (also with LC) during chemotherapy.[58] However, anemia is not the only cause of CRF, and these drugs are characterized by a toxicity profile that must be taken into account. Sleeping agents are frequently used to cope with CRF and insomnia in patients with several types of cancer, although there are no results clearly supporting this approach. Interesting data were derived from the use of melatonin agonists in patients with LC receiving chemotherapy.[59,60] However, further studies need to be performed to establish this effect.

Natural remedies

Ginseng is one of the most valuable herbs and has been used for more than 5,000 years in oriental medicine. In the United States, it is currently one of the most widely used food supplements. Two types of ginseng are commercially available: American ginseng (*Panax quinquefolius*) and Asian ginseng (*Panax ginseng*), and several studies have shown that both help cope with fatigue.[61–63] A recent trial investigated the therapeutic effects of fermented red ginseng (FRG) extract in 60 patients with NSCLC treated with chemotherapy. FRG was administered for 60 days and significantly improved the Fatigue Symptom Inventory score, psychological status, physical conditions, and QoL; it was also shown to have a positive impact on treatment toxicity profile.[64] Preliminary data show the ability of purified dry extract of *Paullinia cupana* (guaraná, PC-18) to help with CRF in patients with solid tumors, including LC.[65,66] Guaraná is an Amazonian plant; its main active ingredient is caffeine, but with slower release compared to that of pure coffee. Yiqi Jianpi Huaji Decoction is a traditional Chinese medicinal formula consisting of 12 natural ingredients and has recently been associated with efficacy in treating CRF in LC patients receiving chemotherapy. Among 124 patients, 63 were assigned to "the treatment group" and 61 cases to the control group; all received chemotherapy regimens according to their conditions. Patients in the treatment group took Yiqi Jianpi Recipe (YJR) decoction from the first day of chemotherapy, one dose per day, for two consecutive weeks, while those in the control group took no Chinese medical decoction. The trial suggests that YJD decoction could significantly relieve CRF in LC patients, with a significant impact on QoL.[67]

Nonpharmacological treatments and complementary therapies

Several tools have been proven to be useful in alleviating CRF without medications. Two recent meta-analyses recommend certain specific psychosocial interventions and physical exercise in several cancers, including LC. Physical exercise, negatively perceived in the past, is currently considered the key element in the nonpharmacological management for CRF.[68,69] Data are more robust in preoperative regimen and in survivors.[70,71] Physical activity has been associated with improvements of QoL, fatigue, and functional capacity in various groups of cancer survivors.[72] After surgery, a significantly reduced peak oxygen consumption per unit time (VO_2) with a decrease of patient's ability to tolerate exercise has been reported.[73,74] Therefore, pulmonary rehabilitation programs for postoperative patients with LC have shown an improvement in functional ability and a greater adherence to exercise capacity. In early-stage LC, emerging evidences suggest that routine exercise is associated with improvements in QoL and fatigue.[74,75] However, a validated exercise regimen has not been clearly defined for perioperative or advanced-stage LC. Several studies confirmed that increased physical activity may improve cluster symptoms and fatigue in patients with LC in the perioperative setting, although the location, duration, and intensity of exercise are not yet defined.[76–78] Currently, the official guidelines of the American Cancer Society, the National Comprehensive Cancer Network, and American College of Sports Medicine recommend routine physical activity in NSCLC patients, when feasible.[79–81] In addition, in a translational context, physical exercise could be studied in relation to the histological subtype and the genetic/molecular profile to identify patient groups more responsive to treatment.[82] The main recommended psychosocial interventions for CFR include cognitive behavioral therapeutic approaches, psychoeducation, topical counseling, energy conservation and activity management, and methods for the promotion and reinforcement of regeneration.[83,84] However, these data were derived from studies of mixed tumors (mainly women with breast cancer). Mindfulness-based stress reduction (MBSR) is an interesting psychosocial intervention, and this technique was applied in a small group of patients with advanced-stage LC. The qualitative analysis showed that the training could instigate a process of change in participants. Significant differences were not found in pulmonary symptoms, fatigue, and pain. Although mean scores of anxiety and depressive symptoms in both patients and partners decreased after MBSR, these changes were not statistically significant.[85] Data

from a randomized controlled trial are expected (MILON study):[86] this trial compares MBRS with a standard approach in reducing psychological distress and improving QoL in patients with LC and their partners. The assessment of QoL will provide us clear details on the effect of MBRS on CRF in LC patients. Some studies showed that acupuncture could relieve pain, fatigue, and dyspnea in LC patients during all phases of the disease.[87–89] Acupressure has been evaluated in two studies for its effect on CRF reaching interesting results. A pilot trial evaluated the effects of acupressure on fatigue in 57 LC patients receiving six cycles of chemotherapy: they were randomized into three groups, one with acupressure with essential oils, a second with only acupressure, and a third group with sham acupressure. All subjects received acupressure once every morning for 5 months. Subjects who received acupressure with essential oils and acupressure had significantly less fatigue in daily living activities and a better quality of sleep at day 1, cycle three, than subjects who received sham acupressure.[90] Several other complementary therapy modalities can be helpful in improving fatigue and QoL of patients with LC, such as hypnosis, yoga, massage therapy, and Tai Chi.[91–93]

Early palliative care in LC

The goal of palliative care is to relieve suffering and promote QoL for patients and families. In the past, palliative care usually began at the end of active treatment. Practice guidelines from the World Health Organization and leadership from the oncology and palliative care communities advocate a different model of palliative care, that could be introduced from the point of diagnosis of life-threatening illness.[94] Some authors evaluated early palliative care (EPC) in LC as having a positive benefit in QoL and physical symptoms such as pain and depression, already defined as symptoms associated with CRF.[95–97] In addition, EPC may promote QoL by improving management of symptoms due to medical comorbidities such as congestive heart failure and COPD, which are often present in these patients. More data are clearly needed to identify the valid integration methods of EPC and active care.

Summary and conclusion

CRF is the most common and debilitating symptom in patients with cancers, including LC.[5,6] In the entire history of LC, from diagnosis until the end of life, fatigue is present in 57%–100% of patients, which has a huge influence on QoL.[9,12,26,39,40] The incidence of fatigue can change depending on the time of the disease in which it is evaluated and on coexistence of comorbidity, cluster symptoms, and treatments, which can improve or worsen the situation. Fatigue can be primary, when related to the tumor, while it is defined as secondary if it is due to treatment, nutritional status, laboratory abnormalities, use/abuse of substance, and/or comorbidities.[13–17] A careful screening by using validated scales (quantitative and semiquantitative) is recommended from the time of diagnosis.[18] No dedicated scale is standardized for LC, and the BFI is the most widely used scale. There are interesting data on predictive biomarkers of primary CRF in NSCLC: plasma levels of TNF-α and IL-1 seem to be correlated with CRF.[19] Several studies have identified the concomitance of some symptoms in patients with LC, such as anxiety, depression, fatigue, and sleep disturbances, that are commonly treated as separate entities, even though there are evidences suggesting their close connection, also through the same biological pathways.[20,22,23,52] A close link exists between pain and fatigue and among breathing symptoms and fatigue.[6] The vast majority of patients with LC present with comorbidities, such as COPD and heart diseases, that can worsen the CRF. Fatigue is not exclusively reported during the treatment of LC and at the end of life, and also for this reason, practice guidelines from the World Health Organization and leadership from the oncology and palliative care communities proposed the introduction of EPC in all cancer patients, including those with LC.[94] Several studies have evaluated fatigue in LC survivors after radical resection.[12,26–35,37] The prevalence of fatigue ranges from 60% to 70% at 4 months after thoracotomy.[30] Fatigue, small impact in lung function, anxiety, depression, and decreased physical activity have been observed after surgical and adjuvant treatments.[36–38] Some authors have reported a resolution of symptoms at 3–6 months after surgery, while other papers observed persistence of these symptoms for years.[33–35] The management of fatigue and its cluster symptoms becomes essential for the QoL care of patients with LC at any stage of the disease. Up to now, no standard treatment is recommended to cope with fatigue, and 4 mg of dexamethasone is the only drug approved for CRF.[7] The use of psychostimulant agents is burdened by significant side effects, and modafinil use in LC patients has not achieved the expected results for the treatment of CRF.[53–56] Sleeping and antidepressant agents are often prescribed without any evidence supporting their use in this context.[59,60] The administration of ESA can relieve CRF, but only in anemic patients undergoing chemotherapy.[58] Natural remedies such as ginseng,[61–64] cognitive behavioral therapeutic approaches, psychoeducation, topical counseling,[83,84] energy conservation as MBSR,[85,86] acupuncture,[87–89] acupressure,[90] hypnosis, yoga, massage therapy, and Tai Chi exercise,[91–93] have been described as valuable aids in the treatment of CRF in LC patients. Physical exercise is a nonpharmacological

treatment for fatigue, with more evidence in LC at any stage. Several studies have confirmed that increased physical activity may improve cluster symptoms and fatigue in patients with early- and advanced-stage LC, even without a precise schema for the application of this technique.[68–82] A proposal for CRF management in patients with LC is described in Table 2. Data present in literature are often reported in a mixed group of tumors, not taking into account the pecu-

Table 2 Management of CRF in patients with lung cancer

Screening		**Revaluations**	
When	From the diagnosis	Lung cancer treated with surgery and/or neoadjuvant/adjuvant therapy[a] or with chemoradiotherapy alone	Metastatic LC
How	Use of validated scales for fatigue:[18] BFI (widely used in trials in LC), FACT-F, CFS, MFI Performance status evaluation: KPS Use of validated scales for QoL:[5] EORTC SF-36 QLQ-C30, SF-36 questionnaire, ESAS, others Use of validated scales for pain:[20,21,23] VAS pain, NRS pain Sleep quality:[23] sleep duration, trouble falling asleep, wake up feeling exhausted, sleepy during the day Assessment of comorbidities:[22,28,29,31] COPD, CVD, endocrine disorders (thyroid disease), anxiety-depressive syndrome, others Daily use of drugs:[13–17] Opioids, benzodiazepines, neuroleptic, others Abuse of substances:[13–17] Drugs, alcohol Laboratory tests:[13–17] Blood count; thyroid, liver, and kidney function Presence of cluster symptoms:[20,21,23,52] Anxiety, depression (use HADS), insomnia, somnolence Presence of respiratory cluster symptoms:[6] Cough, breathlessness Measuring lung function with PFTs:[27] Spirometry to evaluate FEV_1/FVC Assessment of physical activity:[68–73,74–82] Type of activity before and after the diagnosis. Current limitations Other factors:[45,46] ethnicity, socioeconomic and social situation, family relationships	Assessment for fatigue, pain, anxiety, depression, insomnia, somnolence and respiratory cluster symptoms at regular intervals in time (for each symptom it is recommended to always use the same scale) Performance Status (KPS) at regular intervals in time Measuring lung function with PFTs at regular intervals in time Assessment of physical activity Evaluation of symptoms related to adjuvant chemotherapy (sensory neuropathy to the legs)	Assessment for fatigue, pain, anxiety, depression, insomnia, somnolence, and respiratory cluster symptoms at regular intervals in time during treatment (for each symptom, it is recommended to always use the same scale) Performance status (KPS) at each clinic visit Measuring lung function with PFTs at regular intervals in time if stable disease and no obvious clinic progression Assessment of physical activity Evaluation of symptoms related to chemotherapy, target therapy and/or radiotherapy (if in use active therapies)
Proposed treatment		**Proposed treatment**	
Promote pulmonary rehabilitation programs if there is a presence of deficits Promote physical activity based on the KPS and comorbidity Pain control (if present) Psychotherapy (if present distress)[b] Multidisciplinary approach[c] Natural remedies, complementary therapies[d] EPC		Promote pulmonary rehabilitation programs if there is a presence of deficits (patients with COPD) Promote physical activity based on the KPS and comorbidity Pain control (if present) Psychotherapy (if present distress)[b] Multidisciplinary approach[c] Natural remedies, complementary therapies[d] Palliative care	

Notes: [a]Chemotherapy and/or radiotherapy; [b]cognitive behavioral therapeutic approaches, psychoeducation, topical counseling, energy conservation and activity management, and methods for the promotion and reinforcement of regeneration; [c]if fatigue associated and/or worsened by other comorbidities (such as heart failure, thyroid disease); [d]hypnosis, yoga, and massage therapy.

Abbreviations: LC, lung cancer; BFI, Brief Fatigue Inventory; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; CFS, Cancer Fatigue Scale; MFI, Multidimensional Fatigue Inventory; KPS, Karnofsky Performance Status; QoL, quality of life; EORTC SF-36 QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ESAS, Edmonton Symptom Assessment System; VAS, Visual Analog Scale; NRS, Numeric Rating Scale; HADS, Hospital Anxiety and Depression Scale; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; PFTs, pulmonary function tests; FEV_1/FVC, forced vital capacity ratio; EPC, early palliative care.

liarity of LC, which is frequently diagnosed in patients with several comorbidities; this can have a significant impact on fatigue. These data, together with the unpredictability of this tumor, should stimulate clinicians and researchers to develop a customized screening and treatment for CRF in patients with LC.

Disclosure

The authors report no conflicts of interest in this work.

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