Journal of Pulmonary & Respiratory Medicine
ISSN: 2161-105X

Coats et al., J Pulm Respir Med 2014, 4:3
DOI: 10.4172/2161-105X.1000183

Research Article Open Access

Exercise-Based Rehabilitation for People with Lung Cancer

Valérie Coats[1,2], **François Maltais**[1,2], **Lise Tremblay**[1,2] **and Didier Saey**[1,2*]

[1]*Faculté de médecine, Université Laval, Québec, QC, Canada*

[2]*Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, Canada*

***Corresponding author:** Didier Saey, Institut Universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Ste-Foy, Québec (Québec), Canada, Tel: + 1-418-656-8711, Ext 2614; E-mail: didier.saey@rea.ulaval.ca

Received date: Mar 01, 2014, **Accepted date:** Apr 29, 2014, **Published date:** May 01, 2014

Abstract

Lung cancer is the leading cause of cancer-related death worldwide. Patients living with lung cancer often experience severe physical and psychological symptoms including dyspnea, fatigue, anxiety, decreased exercise tolerance, muscle weakness and compromised health-related quality of life as a direct consequence of the disease or as an indirect consequence of the cancer therapy itself. As both screening and treatment modalities improve, the number of people living with a diagnosis of lung cancer is increasing. Consequently, management of cancer-related symptoms as well as improvement of overall quality of life and functional status become critical issues in lung cancer patients. Thus, during the last decade, a wide range of exercise prescriptions and training modalities has been proposed and an emerging literature has addressed the effects of exercise-based rehabilitation programs along the continuum of the disease. The aim of this review is to address the latest literature regarding the feasibility and effectiveness of exercise-based rehabilitation for patients with lung cancer receiving treatments (perioperative, during chemotherapy/radiation therapy or following them) or for patients with advanced diseases. We also address how the use of new technologies or training modalities such as home-based telerehabilitation or neuromuscular electrical stimulation appears to be a promising approach to improve accessibility and participation in exercise-based rehabilitation programs. Evidence from our review suggests that pre and post-operative exercise-based rehabilitation appear to be safe and effective approaches to use with patients with lung cancer and for those with advanced disease receiving chemotherapy/radiation therapy. Larger randomized controlled trials are needed to confirm the efficacy of exercise interventions in this population.

Keywords: Lung cancer; Exercise training; Rehabilitation

Introduction

With 1.6 million new cases diagnosed each year and 1.3 million deaths, lung cancer is the leading cause of cancer-related death worldwide and constitutes a pressing health issue which generates significant personal and social costs [1]. By the year 2020, it is estimated that 2.2 million people will be diagnosed with lung cancer [1]. In addition, with a 5-year mortality rate of 85-90%, lung cancer is responsible for more than one quarter of all cancer deaths.

Classification

Two main types of lung cancer can be identified on the basis of histological criteria: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This classification is clinically relevant for the prognosis and treatment plan, as these two types of cancers have different natural histories and therefore need to be treated differently. NSCLC is the most common type of lung cancer, accounting for about 80% of cases. NSCLC progresses and metastasizes less rapidly and is associated with a better prognosis [2,3]. In contrast, SCLC is less common (15-20% of lung cancer cases), but it progresses and metastasizes more rapidly than NSCLC [3]. At the time of diagnosis, the risk that SCLC has already spread to involve other organs is quite high, as about 50% of patients present distant metastasis at the initial staging assessment [4].

Diagnosis and Staging

Lung cancer is staged using the "TNM" classification system which is based on the anatomical extent of the disease. The three letters symbolize the status of the cancerous disease in regard to i) the size of the primary tumor (T), ii) the lymph node involvement (N) and iii) the presence of any distance metastases (M) [2]. Based on this classification, NSCLC can be subdivided in four different stages according to the extent of disease. Stage I: The cancer is confined to the lungs and has not spread to any lymph nodes. Stage II: The cancer has spread to nearby lymph nodesStage III: The cancer has spread considerably in the chest, and generally reached mediastinal lymph nodes. Stage IV: The cancer has spread to both lungs, to pleural space, or outside the chest cavity. As SCLC grows and spreads quickly, its evolution only have two stages: limited, where the cancer cells in patients with tumor are present on one hemithorax, involving just one part of the lung and nearby lymph nodes; and extensive; where the cancer has spread to other regions of the chest or other parts of the body.

Treatment

Lung cancer can be treated by surgical resection, chemotherapy and radiation therapy, either alone or in combination. The choice of treatment is influenced by the therapeutic objectives: to treat the cancer, to prolong life expectancy or to improve the patient's quality of life. Treatment also varies according to the type of lung cancer, the stage of the disease and the patient's physiological and psychological status.

Surgical resection remains the primary and preferred approach to the treatment of stage I and II NSCLC [5]. However, only 20-25% of patients are candidates for lung resection, as surgery is usually only indicated for small cancers confined to one lung and not extending beyond stage IIIA [2].

Chemotherapy is a systemic treatment designed to destroy malignant cells derived from the primary tumor. Chemotherapy can be administered alone or in combination with radiation therapy before surgery (neoadjuvant chemotherapy) or after surgery (adjuvant chemotherapy). The type of chemotherapy varies according to several factors related to the cancer (histological type, tumor size and tumor site, etc.) or to the patient (functional status, comorbid conditions, etc.). SCLC usually shows a good response to chemotherapy and is therefore primarily treated by this modality, either alone or in combination with radiation therapy [6]. For patients with advanced lung cancer, it has been demonstrated that chemotherapy was also beneficial in palliative care [7]. However, these patients are likely to experience more symptoms and side effects such as nausea, vomiting, infections, loss of appetite and fatigue, associated with decreased exercise capacity and muscle strength, as well as impaired quality of life [8-10].

Radiation therapy is administrated to preventing proliferation of cancer cells. Radiation therapy is often used concomitantly with chemotherapy for curative intent in patients with NSCLC who are ineligible for surgery [11]. Radiation therapy plays an important role in the curative and palliative care of elderly patients with lung cancer because these patients often present several comorbidities or a poor functional status, which exclude surgery and chemotherapy from the available treatment options [11]. The most common systemic adverse effects occurring with radiotherapy include loss of appetite, body hair loss, skin changes in the treated zone and altered sleep patterns. Other effects such as pain on swallowing (radiation esophagitis) and cough are more specifically related to chest radiation therapy.

Clinical Manifestations

Patients with lung cancer often experience severe physical and psychological symptoms such as decreased exercise tolerance, muscle weakness and compromised health-related quality of life (HRQoL) as a direct consequence of the disease or as an indirect consequence of cancer therapy or multiple comorbidities associated with lung cancer (e.g., COPD) [12-15].

Impaired exercise capacity is well documented in patients with lung cancer [14]. Recently, Jones et al. [14] reported in a group of patients with suspected stage I-IIIA NSCLC a mean of peak oxygen uptake and 6 minutes walking distance equivalent to 70% and 68% of predicted, respectively. Reasons for this impairment are complex and multifactorial. Firstly, dyspnea, fatigue, pain, anxiety and depression, which are the most common symptoms for people with lung cancer, play a key role in the reduction of activities of daily living and consequently the reduced physical performance and exercise capacity observed in patients with lung cancer, even at an early stage of the disease [13,16-22]. Also, supporting the role of cancer therapy on exercise intolerance, Spruit et al. [17] reported a 63.6% of predicted 6-min walking distance and a 58.5% of predicted peak cycling load in a group of patients following intensive treatment for lung cancer. Peak oxygen uptake has also been observed to be decreased by 13% and 28% compared to preoperative values 6 months after lobectomy and pneumonectomy, respectively [23]. Adjuvant therapy such as chemotherapy was also found to reduce the capacity to deliver or utilize oxygen and substrates during exercise, thereby contributing to exercise intolerance [15]. Preserved exercise capacity is important in people with lung cancer because in addition being the best predictor of postoperative cardiopulmonary complications exercise capacity is an important element in the decision-making process regarding the feasibility of lung resection surgery, especially in patients with low aerobic capacity. Peak oxygen uptake (VO2peak) has been shown to be decreased by 13% and 28% compared to preoperative values 6 months after lobectomy and pneumonectomy, respectively [23]. Adjuvant therapy such as chemotherapy reduces the capacity to deliver or utilize oxygen and substrates during exercise, thereby contributing to exercise intolerance [15]. Finally, cachexia (severe loss of muscle mass) is another symptom commonly observed in lung cancer patients [24] that significantly contributes to the increased surgical risk and decreased tolerance of anticancer therapy and is associated with poor functional status and exercise capacity [24-27]. Skeletal muscle loss and weakness appears to be the most significant clinical event in cancer cachexia [28] and is associated with decreased overall HRQoL, physical function and fatigue [29].

At the time of diagnosis, patients with lung cancer present impaired HRQoL and considerable psychological distress, such as feelings of anxiety and depression [30]. Patients treated by lung resection demonstrate short-term (4 months) and long-term (4 years) impairment of HRQoL measured by the Quality of Life-Cancer Survivors tool (QOL-CS) and the Medical Outcomes Study 36-item short form (SF-36) [31]. Chemotherapy itself frequently induces further symptoms, including nausea, emesis, polyneuropathy, anemia, and immune deficiency, leading to impairment of quality of life, functional status, mobility, and social functioning [32]. Most of these debilitating symptoms increase as the disease progresses and often persist for many years after treatment [33-35]. In addition, patients with lung cancer have a higher prevalence of psychological distress (present in about 5 to 62% of cases) [36-38] and are reported to have a lower quality of life than patients with other types of cancer [31,35].

Evidence for the Impact of Exercise Rehabilitation

Several studies have demonstrated the impact of exercise rehabilitation at various times during the course of lung cancer. For the purpose of this review we divided the studies according to the stage of the disease and thus we are going to discuss the evidence for the impact of exercise rehabilitation for people with early stage lung cancer (preoperative exercise training and exercise training following lung resection) and in patients with advanced lung cancer.

People with early stage lung cancer

Preoperative exercise rehabilitation: Some studies have explored the impact of exercise-based rehabilitation on exercise tolerance in patients with lung cancer during the pre-operative period and clinical and statistical significant improvements of maximal oxygen uptake (VO2max), exercise tolerance, walking distance and muscle strength have been reported in this setting [12,39-41]. Bobbio et al. [39] reported an average increase in VO2 max of 2.8 ml/kg/min (13.5 ± 1.3 Vs 16.3 ± 1.9 ml/kg/min, $p \leq 0.005$) following a 4-week preoperative exercise rehabilitation program in 12 patients with lung cancer awaiting pulmonary resection surgery [39]. In a recent investigation, Coats et al. 41 reported an improvement of 157 ± 195 seconds ($p \leq 0.005$) in the duration of the cycle endurance test and of 28 ± 29 m ($p \leq 0.005$) in the 6MWT distance after a 4-week preoperative home-based exercise training program administrated in 13 patients with NSCLC awaiting for lung resection surgery. Moreover, the strength of the deltoid, triceps and hamstring muscles was also significantly improved following the intervention [41]. Cesario et al. [12] also reported a clinical and statistical significant increase in exercise tolerance, as reflected by a 79.0 ± 30.4 m ($p \leq 0.005$) improvement in walking distance during the 6-minute walking test following a preoperative rehabilitation program in 12 patients undergoing lung resection surgery. The magnitude of improvement in aerobic capacity after a 4-6 week training program also appeared to be similar to that observed after a longer rehabilitation program (8-12 weeks) [40], suggesting that the benefits of rehabilitation can be generated by the first month of the program.

Exercise rehabilitation following lung resection: Some studies have investigated the role of exercise-based rehabilitation in patients with lung cancer following surgery [16]. The first non-randomized controlled clinical trial to assess the efficacy of a postoperative inpatient training rehabilitation program was conducted by Cesario et al. [42]. This program consisted of a 3-hour supervised session five times a week. While the 6 minute walking distance decreased in the control group, a clinical and statistical significant improvement of 95 m (from 298 ± 71 m to 393 ± 111 m; $p<0.01$) was observed in the rehabilitation group [42]. Similarly, in a nonrandomized clinical pilot study (10 patients), Spruit et al. [17] reported a significant 145-meter (IQR: 65-245; $p \leq 0.05$) improvement in the 6-min walking distance and a 26-Watt (IQR: 16-39; $p \leq 0.05$) improvement of peak cycling power output after participation in an 8-week multidisciplinary inpatient rehabilitation program. In a study by Jones et al. [15] including 20 patients of whom a large proportion (42%) were treated with chemotherapy, significant improvements were observed in exercise performance, quality of life, and fatigue after a 14 week supervised exercise-based pulmonary rehabilitation program. However, patients not receiving chemotherapy appeared to derive a greater benefit from the program. A good training session adherence (rate of 85%) was also observed [15].

Patients with advanced lung cancer

Temel et al. [43] were the first to investigate the feasibility and effectiveness of exercise intervention specifically in patients with newly diagnosed advanced stage NSCLC. Twenty-five patients receiving anticancer therapy were recruited and participated in a 12-week structured outpatient exercise-training program. Only eleven patients (44%) of this sample completed all of the prescribed sessions. However, those patients who were able to complete the program experienced significant improvement in their lung cancer symptoms (cough, shortness of breath and chest discomfort) and no deterioration in the 6-min walk test was observed, which can be considered to be a positive finding in this group of patients in whom deterioration of exercise tolerance would have been observed without intervention [16,43]. On the other hand, in view of the low completion rates, the authors suggested that a less intensive and more accessible program might be more feasible [43].

Similarly, Quist et al. [44] recently conducted a 6-week hospital-based, supervised muscle and cardiovascular training program combined with individual home training in 29 patients with advanced stage lung cancer. They investigated the impact of this program on aerobic capacity, muscle strength and quality of life in patients undergoing chemotherapy. Twenty-five patients with NSCLC (stage III-IV) and four patients with extensive SCLC were recruited. Clinical and statistical significant improvements in VO2peak (Δ 0.09 L/min (95% CI 0.02 to 0.16)) and six-minute walking distance (Δ 39 m (95% CI 13 to 66)) were observed together with increased muscle strength (Δ 17% (95% CI 13 to 21)). A significant improvement in "emotional well-being" (measured by the FACT-L questionnaire) was also observed, but with no other significant changes in quality of life. Adherence to the supervised group training was 73.0% and adherence to the home training program was 8.7% [44]. The authors therefore concluded that exercise training was safe and feasible in patients with advanced lung cancer undergoing chemotherapy and that it generated significant clinical improvements in physical capacity, functional capacity and emotional well-being [44].

There is also growing interest in exercise-based rehabilitation in the palliative care setting. The available literature supports the positive impact of exercise-based rehabilitation on physical function, symptoms and quality of life [45,46]. Based on a pilot survey of fifty patients with advanced cancer, 92% of patients would be interested in and able to participate in a physical activity program 46. Furthermore, 84% of participants would prefer a home-based individual physical activity program [46]. Jensen et al. [45] are currently conducting a study designed to investigate various physical training programs adapted to patients with advanced lung cancer undergoing palliative chemotherapy or radiation therapy and to evaluate their effects on physical performance, quality of life, symptom burden, and efficacy of cancer therapy [45].

Intervention modalities

A wide range of exercise prescriptions and training modalities have been proposed. The most common types of aerobic exercise used are bike [12,15,17,39,40,42,43,47-52] and treadmill [12,17,42,43,49-51] and only a few studies have also prescribed over-ground walking [40,47,48,53] or stepping [50,51,53].

In addition to the prescribed aerobic exercise, most studies also included resistance training [17,39,42-44,48-51,53] stretching exercises [17,39,43,44,50], relaxation [44,54] or education sessions [12,42,51]. Resistance exercises comprised the use of free weights [12,39,42,43,48,53] or machines [17,44,50,54] with an intensity of about 60-80% of one maximal repetition.

The prescription of aerobic exercise training can be based on maximal heart rate, maximal work load or using the Borg perceived exertion scale. Moderate to high training intensity (between 60 and 80% of maximal work load or 4-6/10 on Borg scale) is the most commonly targeted intensity [17,39,40,42,47-49,51]. Continuous training sessions are generally used [12,17,39,42,43,48,50,53,55]. However, interval training (alone or in combination with continuous training) can also be used in symptomatic individuals to achieve the target intensity [15,40,51,52]. Higher work intensity can also be achieved by interval training with prescribed intensities of up to 100% of baseline VO2peak [40]. The frequency of exercise sessions typically prescribed is at least two or three sessions per week [12,15,17,39,40,42,43,47-53,55], each lasting about [10–45] min with a 30-minute exercise time as the standard for most studies [39,40,42,43,47,49,52,55].

Safety and feasibility

The recent literature shows that patients with lung cancer are able to safely participate in a training rehabilitation program before or during cancer treatment [16]. No adverse events were reported in any of the studies that tested physical training [12,15,17,39,40,42-44]. Patients also appear to be able to complete the prescribed exercise program, as the overall adherence rate was between 72% and 85% [15,40], comparable to the rates reported in COPD [56]. However, patients with advanced cancer appear to experience greater difficulties maintaining a high level of adherence to physical rehabilitation programs provided in the hospital setting [43]. In the study by Temel et al. [43] conducted on a population of patients with advanced lung cancer, only 44% of patients completed all sixteen proposed exercises sessions 43. Nevertheless, a recent study by Quist et al. [44] reported a completion rate of 79.3%, confirming the feasibility of exercise training for patients with advanced lung cancer. These findings are particularly relevant, as some authors have reported correlations between adhesion and certain cancer-related symptoms such as dyspnea and fatigue [57].

Future Perspective

Studies addressing the question of the feasibility and efficacy of exercise-based rehabilitation in patients with lung cancer mainly concerned in-hospital supervised exercise programs [16,40,43]. However, this modality of rehabilitation could be considered to be constraining for some patients and was associated with poor compliance to the program. Accessibility to this type of program may also be relatively limited in routine clinical settings [58]. There is therefore an emerging need to develop new modalities of exercise rehabilitation for patients with lung cancer. Home-based programs or the use of new technologies to provide rehabilitation at the home may therefore constitute interesting approaches for the future.

Home-based rehabilitation

After noting the low completion rates in patients with advanced stages of the disease, home-based rehabilitation has been proposed as an interesting alternative for patients with lung cancer [43].

Coats et al. [41] recently assessed the feasibility and potential benefit of a short (4 weeks) home-based exercise training program in 13 patients under investigation for NSCLC and awaiting lung resection surgery. The main finding of this study was that a short, moderate intensity, home-based exercise training program was feasible, safe and well tolerated in this context. Participation in the program generated physiological effects, including improved cycling endurance, walking distance and muscle strength. In addition, all patients engaged in the home-based program completed 75% of the prescribed exercise sessions. However, the small sample size and the absence of control group in this study are potential limitations concerning interpretation of the results.

These results were confirmed in a larger trial of a home-based exercise intervention in a mixed cancer population (colon and lung cancer) recently conducted by Cheville et al. [59]. Sixty-six patients were randomized to usual care or incremental walking and home-based strength training. Following this 8-week program, the intervention group reported improved mobility, fatigue and sleep quality compared with the usual care group [59]. A good adherence rate was also observed among the intervention group participants with 76.9% of patients meeting the requirements for participation. In contrast, with a low adherence rate of only 8.7%, Quist et al. [44] concluded that a home-based exercise intervention used as a supplement to supervised training for patients with inoperable lung cancer undergoing chemotherapy was not a realistic option. In addition, Lowe et al. [44] recently published a case series demonstrating the challenges of implementing a home-based functional walking program for advanced cancer patients receiving palliative care [60]. Further feasibility studies on home-based rehabilitation are therefore required, particularly in patients with advanced cancer.

New rehabilitation technologies

The use of new technologies or training modalities such as home-based telerehabilitation or neuromuscular electrical stimulation appears to be a promising approach in order to improve accessibility and participation in rehabilitation programs.

Neuromuscular electrical stimulation (NMES)

Although conventional training interventions are most commonly used for exercise-based rehabilitation, there is a growing interest in alternatives such as neuromuscular electrical stimulation (NMES) as a new exercise training strategy for patients with advanced disease, including patients with severe COPD and lung cancer [61-63]. NMES is a technology that induces skeletal muscle contractions by applying electrical stimulation to the motor neuron or muscle. It can be self-administered and can induce muscle contraction equivalent to 20-40% of the patient's maximum voluntary contraction [64]. Because NMES is a passive treatment modality, it potentially requires less motivation and changes in lifestyle than traditional resistance exercises [65,66]. However, despite its potential benefits, only a few studies have investigated NMES in patients with lung cancer. NMES has been shown to induce encouraging improvement of quality of life, walking distance and quadriceps strength in a case study [67] and a pilot study [66]. However, in a recent randomized study, Maddock et al. [68] failed to demonstrate any improvement of quadriceps muscle strength, thigh lean mass, and physical activity level after NMES in patients with NSCLC receiving palliative chemotherapy [68]. Adherence was also low, as only 50% patients achieved the minimum level of adherence (performing NMES 3 times weekly) [68]. Feasibility and efficacy of NMES in patients with lung cancer therefore still need to be determined.

Telerehabilitation

Telerehabilitation, which consists of using communication and information technologies to provide clinical rehabilitation services from a distance [69], is a method that allows interactive follow-up between the physiotherapist and the patient and represents an interesting way to provide efficient pulmonary rehabilitation services in both urban and rural areas [70]. Real-time interaction allows the healthcare professional to modify and adjust the intervention from a distance and to interact with the patient to provide adequate and personalized supervision [71,72]. The feasibility of a home-based exercise telerehabilitation program has been demonstrated in many adult and elderly population [73-77]. The clinical efficacy and participant's adherence to telerehabilitation were recently demonstrated in a large-scale clinical trial [78,79]. Telehealth interventions in respiratory medicine are mainly used for monitoring [80] or teaching [70] to improve self-management of health conditions [70,80-83]. In lung cancer, telerehabilitation could therefore represent a response to the difficulties of accessibility and adherence to rehabilitation interventions for these patients, who experience declining daily functional capacity and quality of life.

Game consoles

An emerging literature proposes an approach based on the use of a Nintendo Wii console as a therapeutic tool. The use of Nintendo Wii for therapeutic purposes is emerging approach to rehabilitation (Wii-rehabilitation) due to its low cost, its ease of use and its ability to increase patient motivation and the time devoted to therapeutic activities [84,85]. Its potential to improve adherence to the rehabilitation program has also been recently highlighted [86]. This technique has now been used in various populations and has been shown to effectively improve mobility and muscle function of the upper limb in stroke survivors; balance and functional mobility in individuals with Parkinson's disease [87] and endurance time in patients with chronic obstructive pulmonary disease [88]. More specifically in the cancer setting, in addition to increasing relaxation, distraction created by the use of computer games has been shown to be effective to reduce chemotherapy-related side effects [89]. It has also been recently observed that, in addition to the positive impact on functional performance, a home-based rehabilitation program using a Wii console was a feasible, safe and well tolerated modality in patients with lung cancer treated by lung resection surgery [90]. Although it has not been extensively studied to date, use of Wii for rehabilitation appears to be a promising approach in the lung cancer setting.

Conclusion

As both screening and treatment modalities improve, the number of people living with a diagnosis of lung cancer is increasing. Management of cancer-related symptoms and improvement of overall quality of life and functional status have therefore become critical issues in lung cancer patients. Consequently, there is an emerging literature about pulmonary rehabilitation for people with lung cancer. Based on the findings of our review, pre and post-operative exercise-based rehabilitation appear to be a safe and effective approach to patients with lung cancer and in patients with advanced disease receiving chemotherapy/radiation therapy. However, because of the poor accessibility to rehabilitation programs in lung cancer patients, new strategies adapted to this challenging population need to be developed. Larger randomized controlled trials are needed to confirm the efficacy of exercise interventions in this population.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.
2. Detterbeck FC, Boffa DJ, Tanoue LT (2009) The new lung cancer staging system. Chest 136: 260-271.
3. DeVita V, Lawrence T, Rosenberg S (2008) DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. Philadelphia.
4. Travis WD, Travis LB, Devesa SS (1995) Lung cancer. Cancer 75: 191-202.
5. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC (2013) Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest143(5 Suppl):e278S-313S.
6. Livingston RB, Moore TN, Heilbrun L, Bottomley R, Lehane D, et al. (1978) Small-cell carcinoma of the lung: combined chemotherapy and radiation: a Southwest Oncology Group study. Ann Intern Med 88: 194-199.
7. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, et al. (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346: 92-98.
8. Ferreira KA, Kimura M, Teixeira MJ, Mendoza TR, da Nóbrega JC, et al. (2008) Impact of cancer-related symptom synergisms on health-related quality of life and performance status. J Pain Symptom Manage 35: 604-616.
9. Adamsen L, Midtgaard J, Rorth M, Borregaard N, Andersen C, et al. (2003) Feasibility, physical capacity, and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. Support Care Cancer11:707-716.
10. Franceschini J, Santos AA, El Mouallem I, Jamnik S, Uehara C, et al. (2008) [Assessment of the quality of life of patients with lung cancer using the Medical Outcomes Study 36-item Short-Form Health Survey]. J Bras Pneumol 34: 387-393.
11. Bayman N, Alam N, Faivre-Finn C (2010) Radiotherapy for lung cancer in the elderly. Lung Cancer 68: 129-136.
12. Cesario A, Ferri L, Galetta D, Cardaci V, Biscione G, et al. (2007) Pre-operative pulmonary rehabilitation and surgery for lung cancer. Lung Cancer 57: 118-119.
13. Jones LW, Eves ND, Kraus WE, Potti A, Crawford J, et al. (2010) The lung cancer exercise training study: a randomized trial of aerobic training, resistance training, or both in postsurgical lung cancer patients: rationale and design. BMC cancer10:155.
14. Jones LW, Eves ND, Mackey JR, Peddle CJ, Haykowsky M, et al. (2007) Safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer. Lung Cancer 55: 225-232.
15. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, et al. (2008) Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 113: 3430-3439.
16. Granger CL, McDonald CF, Berney S, Chao C, Denehy L (2011) Exercise intervention to improve exercise capacity and health related quality of life for patients with Non-small cell lung cancer: a systematic review. Lung Cancer 72: 139-153.
17. Spruit MA, Janssen PP, Willemsen SC, Hochstenbag MM, Wouters EF (2006) Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. Lung Cancer52:257-260.
18. Hopwood P, Stephens RJ (2000) Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 18: 893-903.
19. Brown DJ, McMillan DC, Milroy R (2005) The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. Cancer 103: 377-382.
20. Maddocks M, Byrne A, Johnson CD, Wilson RH, Fearon KC, Wilcock A (2010) Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer18:1539-1544.
21. Bolliger CT, Jordan P, Solèr M, Stulz P, Tamm M, et al. (1996) Pulmonary function and exercise capacity after lung resection. Eur Respir J 9: 415-421.
22. Lutz S, Norrell R, Bertucio C, Kachnic L, Johnson C, et al. (2001) Symptom frequency and severity in patients with metastatic or locally recurrent lung cancer: a prospective study using the Lung Cancer Symptom Scale in a community hospital. J Palliat Med 4: 157-165.
23. Nezu K, Kushibe K, Tojo T, Takahama M, Kitamura S (1998) Recovery and limitation of exercise capacity after lung resection for lung cancer. Chest 113: 1511-1516.
24. Tisdale MJ (2002) Cachexia in cancer patients. Nat Rev Cancer 2: 862-871.
25. Inui A (2002) Cancer anorexia-cachexia syndrome: current issues in research and management. CA Cancer J Clin 52: 72-91.
26. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, et al. (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12: 489-495.

27. Op den Kamp CM, Langen RC, Minnaard R, Kelders MC, Snepvangers FJ, et al. (2012) Pre-cachexia in patients with stages I–III non-small cell lung cancer: Systemic inflammation and functional impairment without activation of skeletal muscle ubiquitin proteasome system. Lung Cancer76:112-117.
28. Johns N, Stephens NA, Fearon KC (2013) Muscle wasting in cancer. Int J Biochem Cell Biol 45: 2215-2229.
29. Wilcock A, Maddocks M, Lewis M, Howard P, Frisby J, et al. (2008) Use of a Cybex NORM dynamometer to assess muscle function in patients with thoracic cancer. BMC Palliat Care 7: 3.
30. Dagnelie PC, Pijls-Johannesma MC, Lambin P, Beijer S, De Ruysscher D, et al. (2007) Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy. Ann oncol 18:940-944.
31. Sugimura H, Yang P (2006) Long-term survivorship in lung cancer: a review. Chest 129: 1088-1097.
32. Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, et al. (2010) Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 28: 1835-1842.
33. Kenny PM, King MT, Viney RC, Boyer MJ, Pollicino CA, et al. (2008) Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. J Clin Oncol 26: 233-241.
34. Sarna L, McCorkle R (1996) Burden of care and lung cancer. Cancer Pract 4: 245-251.
35. Sanders SL, Bantum EO, Owen JE, Thornton AA, Stanton AL (2010) Supportive care needs in patients with lung cancer. Psychooncology 19: 480-489.
36. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S (2001) The prevalence of psychological distress by cancer site. Psychooncology 10: 19-28.
37. Graves KD, Arnold SM, Love CL, Kirsh KL, Moore PG, et al. (2007) Distress screening in a multidisciplinary lung cancer clinic: prevalence and predictors of clinically significant distress. Lung Cancer 55: 215-224.
38. Walker MS, Zona DM, Fisher EB (2006) Depressive symptoms after lung cancer surgery: Their relation to coping style and social support. Psychooncology 15: 684-693.
39. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, et al. (2008) Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 33: 95-98.
40. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, et al. (2007) Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 110: 590-598.
41. Coats V, Maltais F, Simard S, Fréchette E, Tremblay L, et al. (2013) Feasibility and effectiveness of a home-based exercise training program before lung resection surgery. Canadian respiratory journale10-16.
42. Cesario A, Ferri L, Galetta D, Pasqua F, Bonassi S, et al. (2007) Post-operative respiratory rehabilitation after lung resection for non-small cell lung cancer. Lung Cancer 57: 175-180.
43. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, et al. (2009) A structured exercise program for patients with advanced non-small cell lung cancer. J Thorac Oncol 4: 595-601.
44. Quist M, Rørth M, Langer S, Jones LW, Laursen JH, et al. (2012) Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: a pilot study. Lung Cancer 75: 203-208.
45. Jensen W, Oechsle K, Baumann HJ, Mehnert A, Klose H. et al. (2014) Effects of exercise training programs on physical performance and quality of life in patients with metastatic lung cancer undergoing palliative chemotherapy-A study protocol. Contemporary clinical trials37: 120-128.
46. Lowe SS, Watanabe SM, Baracos VE, Courneya KS (2009) Associations between physical activity and quality of life in cancer patients receiving palliative care: a pilot survey. J Pain Symptom Manage 38: 785-796.
47. Jones LW, Eves ND, Peddle CJ, Courneya KS, Haykowsky M, et al. (2009) Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab 34: 197-202.
48. Arbane G, Tropman D, Jackson D, Garrod R (2011) Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: Randomised controlled trial. Lung Cancer71:229-234.
49. Cesario A, Dall'Armi V, Cusumano G, Ferri L, Margaritora S, et al. (2009) Post-operative pulmonary rehabilitation after lung resection for NSCLC: a follow up study. Lung Cancer 66: 268-269.
50. Litterini AJ FV (2008) The change in fatigue, strength, and quality of life following a physical therapist prescribed exercise program for cancer survivors. Rehabil Oncol11-17.
51. Morris GS, Gallagher GH, Baxter MF, Brueilly KE, Scheetz JS, et al. (2009) Pulmonary rehabilitation improves functional status in oncology patients. Arch Phys Med Rehabil 90: 837-841.
52. Riesenberg H, Lübbe AS (2010) In-patient rehabilitation of lung cancer patients--a prospective study. Support Care Cancer 18: 877-882.
53. Wall LM (2000) Changes in hope and power in lung cancer patients who exercise. Nurs Sci Q 13: 234-242.
54. Adamsen L, Stage M, Laursen J, Rorth M, Quist M (2012) Exercise and relaxation intervention for patients with advanced lung cancer: a qualitative feasibility study. Scand J Med Sci Sports 22:804-815.
55. Sekine Y, Chiyo M, Iwata T, Yasufuku K, Furukawa S, et al. (2005) Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg 53: 237-243.
56. Fischer MJ, Scharloo M, Abbink JJ, van 't Hul AJ, van Ranst D, et al. (2009) Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. Respir Med 103: 1564-1571.
57. Peddle CJ, Jones LW, Eves ND, Reiman T, Sellar CM, et al. (2009) Correlates of adherence to supervised exercise in patients awaiting surgical removal of malignant lung lesions: results of a pilot study. Oncol Nurs Forum 36: 287-295.
58. Brooks D, Sottana R, Bell B, Hanna M, Laframboise L, et al. (2007) Characterization of pulmonary rehabilitation programs in Canada in 2005. Can Respir J 14: 87-92.
59. Cheville AL, Kollasch J, Vandenberg J, Shen T, Grothey A, et al. (2013) A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. J Pain Symptom Manage 45: 811-821.
60. Lowe SS, Watanabe SM, Baracos VE, Courneya KS (2013) Home-based functional walking program for advanced cancer patients receiving palliative care: a case series. BMC Palliat Care 12: 22.
61. Maddocks M, Gao W, Higginson IJ, Wilcock A (2013) Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database Syst Rev 1: CD009419.
62. Vivodtzev I, Debigaré R, Gagnon P, Mainguy V, Saey D, et al. (2012) Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. Chest 141: 716-725.
63. Vivodtzev I, Pépin JL, Vottero G, Mayer V, Porsin B, et al. (2006) Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. Chest 129: 1540-1548.
64. Maffiuletti NA (2010) Physiological and methodological considerations for the use of neuromuscular electrical stimulation. Eur J Appl Physiol 110: 223-234.
65. Ambrosino N1, Strambi S (2004) New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. Eur Respir J 24: 313-322.
66. Maddocks M, Lewis M, Chauhan A, Manderson C, Hocknell J, et al. (2009) Randomized Controlled Pilot Study of Neuromuscular Electrical

Stimulation of the Quadriceps in Patients with Non-Small Cell Lung Cancer. J Pain Symptom Manage 38:950-956.

67. Crevenna R, Marosi C, Schmidinger M, Fialka-Moser V (2006) Neuromuscular electrical stimulation for a patient with metastatic lung cancer--a case report. Support Care Cancer 14: 970-973.

68. Maddocks M, Halliday V2, Chauhan A3, Taylor V4, Nelson A5, et al. (2013) Neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer receiving palliative chemotherapy: a randomized phase II study. PLoS One 8: e86059.

69. Kairy D, Lehoux P, Vincent C, Visintin M (2009) A systematic review of clinical outcomes, clinical process, healthcare utilization and costs associated with telerehabilitation. Disabil Rehabil 31:427-447.

70. Stickland M, Jourdain T, Wong EY, Rodgers WM, Jendzjowsky NG, et al. (2011) Using Telehealth technology to deliver pulmonary rehabilitation in chronic obstructive pulmonary disease patients. Can Respir J 18:216-220.

71. Winters JM (2002) Telerehabilitation research: emerging opportunities. Annu Rev Biomed Eng 4: 287-320.

72. Bashshur R, Shannon G, Krupinski E, Grigsby J (2011) The taxonomy of telemedicine. Telemed J E Health 17: 484-494.

73. Hoenig H, Nusbaum N, Brummel-Smith K (1997) Geriatric rehabilitation: state of the art. J Am Geriatr Soc 45: 1371-1381.

74. Poon P, Hui E, Dai D, Kwok T, Woo J (2005) Cognitive intervention for community-dwelling older persons with memory problems: telemedicine versus face-to-face treatment. Int J Geriatr Psychiatry 20:285-286.

75. Russell TG, Buttrum P, Wootton R, Jull GA (2004) Rehabilitation after total knee replacement via low-bandwidth telemedicine: the patient and therapist experience. J Telemed Telecare 10 Suppl 1: 85-87.

76. Cabana F, Boissy P, Tousignant M, Moffet H, Corriveau H, et al. (2010) Interrater agreement between telerehabilitation and face-to-face clinical outcome measurements for total knee arthroplasty. Telemed J E Health 16:293-298.

77. Tousignant M, Moffet H, Boissy P, Corriveau H, Cabana F, et al. (2011) A randomized controlled trial of home telerehabilitation for post-knee arthroplasty. J Telemed Telecare 17: 195-198.

78. Moffet H TC, Nadeau S (2013) Evidence of the Non-Inferiority of In-Home Telerehabilitation after Total Knee Arthroplasty. American Telemedicine Association.

79. Moffet H TM, Nadeau S (2013) In-Home Telerehabilitation after Total Knee Arthroplasty: results of a non-inferiority clinical Trial. CPA National Congress.

80. Pinnock H, Hanley J, Lewis S, MacNee W, Pagliari C, et al. (2009) The impact of a telemetric chronic obstructive pulmonary disease monitoring service: randomised controlled trial with economic evaluation and nested qualitative study Prim Care Respir J 18:233-235.

81. Vitacca M, Bianchi L, Guerra A, Fracchia C, Spanevello A, et al. (2009) Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. Eur Respir J 33: 411-418.

82. Sicotte C, Pare G, Morin S, Potvin J, Moreault MP (2011) Effects of home telemonitoring to support improved care for chronic obstructive pulmonary diseases. Telemedicine journal and e-health17:95-103.

83. Vontetsianos T, Giovas P, Katsaras T, Rigopoulou A, Mpirmpa G, et al. (2005) Telemedicine-assisted home support for patients with advanced chronic obstructive pulmonary disease: preliminary results after nine-month follow-up. J Telemed Telecare Suppl 1:86-88.

84. Laver K, Ratcliffe J, George S, Burgess L, Crotty M (2011) Is the Nintendo Wii Fit really acceptable to older people? A discrete choice experiment. BMC Geriatr 11: 64.

85. Green CS, Bavelier D (2008) Exercising your brain: a review of human brain plasticity and training-induced learning. Psychol Aging 23: 692-701.

86. Taylor MJ, McCormick D, Shawis T, Impson R, Griffin M (2011) Activity-promoting gaming systems in exercise and rehabilitation. J Rehabil Res Dev 48: 1171-1186.

87. Esculier JF, Vaudrin J, Beriault P, Gagnon K, Tremblay LE (2012) Home-based balance training programme using Wii Fit with balance board for Parkinsons's disease: a pilot study. J Rehabil Med 44:144-150.

88. Albores J, Marolda C, Haggerty M, Gerstenhaber B, Zuwallack R (2013) The use of a home exercise program based on a computer system in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev 33:47-52.

89. Vasterling J, Jenkins RA, Tope DM, Burish TG (1993) Cognitive distraction and relaxation training for the control of side effects due to cancer chemotherapy. J Behav Med 16: 65-80.

90. Hoffman AJ, Brintnall RA, Brown JK, Eye Av, Jones LW, et al. (2013) Too sick not to exercise: using a 6-week, home-based exercise intervention for cancer-related fatigue self-management for postsurgical non-small cell lung cancer patients. Cancer Nurs 36: 175-188.