Cardiopulmonary Rehabilitation After Treatment for Lung Cancer

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Opinion statement

Lung cancer is the leading cause of cancer-related death in women and men in the United States. As of 1987, lung cancer deaths in women exceeded deaths caused by breast cancer. Despite years of research and improvements in surgical, chemotherapeutic, and radiation treatments, this fact remains unchanged. Equally dismal is that the expected 5-year survival rate for all patients with lung cancer is 15%. Although hidden in this number is improved survival for many patients who have early disease, it still translates into significant morbidity and early mortality for many patients. Although prevention is key, optimizing the care of these patients with lung cancer is also paramount. Cardiopulmonary rehabilitation programs have been shown to be effective in treating patients with chronic heart and lung diseases, among other illnesses, regardless of prerehabilitation functioning. Not only do morbidity and mortality from cancer hinge directly on premorbid functioning, health, and status, but functional status as a measure of baseline health is a reliable prognostic indicator for patients with lung cancer. As a result, including a program of exercise in any treatment regimen for cancer is sensible. However, rehabilitation in patients with lung cancer has not been studied well. Data on rehabilitation in patients with other cancers and illnesses (*eg*, chronic obstructive pulmonary disease) are clear in the beneficial effects of supervised exercise on quality of life (QOL). To assess the role of cardiopulmonary rehabilitation in patients with lung cancer undergoing treatment, it is necessary to meld studies regarding patients with noncancerous conditions with studies addressing rehabilitation in patients with cancer. This fusion of information demonstrates that rehabilitation results in significant improvements in QOL in patients who participate, regardless of the disease in question. Although QOL may not always have been an obvious endpoint for treating patients with lung cancer, it is apparent from studies of the patients themselves that an improved QOL is far more important than other goals of therapy.

Introduction

The facts on lung cancer are well known and sobering. In 2002, it was projected that in the United States, approximately 169,000 people would be diagnosed with lung cancer. Of those patients, 154,000 are projected to die within 1 year of diagnosis [1]. In countries outside the United States, the situation is equally grave. Glasgow, Scotland boasts the highest rate of lung cancer in the world and also the highest rate for women with lung cancer in the world [2••]. The costs of lung cancer are extreme, whether discussing sheer healthcare expenditure or the reality of lives cut short and bereaved loved ones.

Patients with lung cancer fall into one of two categories: resectable and nonresectable. Unfortunately, only

50% to 55% of patients diagnosed with lung cancer will be candidates for surgical resection and a significant number of those patients will be excluded from surgery because of prohibitive comorbidities [3]. The patients who are candidates for surgical intervention must meet certain criteria to be surgical candidates, in terms of their staging and medical status. These are patients for whom the role of rehabilitation is clear. It certainly will ameliorate postoperative pain and debilitation and better predict their likelihood of experiencing postoperative complications.

Patients who are not surgical candidates are a more varied and larger group. For these patients, rehabilitation may augment their ability to tolerate chemotherapy or delineate who can receive chemotherapy and who is at higher risk for complications from chemotherapy. Often, rehabilitation simply improves their quality of life (QOL) by relieving their dyspnea and fatigue as part of a palliative plan of care. For any patient, palliation of symptoms is obviously important and a formal rehabilitation program can, if nothing else, contribute significantly toward attaining that objective.

For patients who are candidates for aggressive therapy, surgery or not, rehabilitation will certainly improve their preoperative and pretreatment functional status and should improve outcome. For patients undergoing palliation, the benefits of improving QOL are invaluable. For all patients undergoing care for lung cancer, improving QOL is beneficial regardless of stage of disease or outcome. Literature on treating patients with cancer now recognizes QOL as an important component of assessing the success of therapy. QOL has become a recognized endpoint in cancer therapy regimens, and acceptance of it as a crucial part of treating patients with cancer is growing.

However, a review of the literature shows that although there is a moderate amount devoted specifically to rehabilitation in patients with cancer, there is virtually none specific to patients with lung cancer. There are data regarding peri- and post-therapy rehabilitation in bone marrow transplants and patients with breast cancer and patients with prostate cancer. However, there is very little that addresses the rehabilitation of patients after thoracotomy and video-assisted thoracoscopic surgery. In a recent issue of *Chest*, the American College of Chest Physicians makes no mention of the role of rehabilitation in its evidence-based guidelines for the management of lung cancer [1].

The evidence that does exist is subsumed within the studies involving QOL, which is very appropriate. Studies are missing that specifically examine this highly-specialized patient population and address their rehabilitation needs before, during, and after their therapies. As a result of this dearth of data, many questions remain unanswered. Does rehabilitation change the outcome of a program of chemotherapy and radiation? Can a program of rehabilitation preoperatively improve postsurgical lung function? Would a program of rehabilitation make a patient who otherwise would not be a surgical candidate more appropriate for surgical intervention? If rehabilitation improves QOL, regardless of baseline lung function, would these effects translate into benefits that would allow the patient to undergo more aggressive therapy?

Because of the limited scope of literature regarding rehabilitation in patients undergoing therapy for lung cancer, this paper reviews what does exist regarding rehabilitation in patients with cancer and the literature on pulmonary rehabilitation (PR). Because most patients with lung cancer are smokers or ex-smokers, then what is known regarding PR in patients with chronic obstructive pulmonary disease (COPD) is likely to be applicable to patients with lung cancer.

However, patients with lung cancer bring with them a few specific issues that must be taken into account when considering the data regarding a rehabilitation program and what rehabilitation program to offer patients with lung cancer. These issues are the well-recognized phenomenon of cancer-related fatigue syndrome (CRFS), side effects of chemotherapy and radiation therapy, postoperative surgical pain as it relates to physical mobility and the patient's ability to participate in rehabilitation, and the importance of providing palliative care when appropriate. All of these issues fall within the area of QOL, especially because more than 80% of patients with lung cancer die within 1 year, thus making attention to QOL extremely important [2••]. Therefore, this article devotes a specific section to QOL because it is a well-documented endpoint of a rehabilitation program that can be objectively measured, not to mention its importance to the patients.

PREMORBID CARDIOPULMONARY DISEASE-SPECIFIC TESTING BEFORE UNDERTAKING REHABILITATION

In 1994, the American Heart Association stated that cardiac rehabilitation programs should consist of a multifaceted and multidisciplinary approach to overall cardiovascular risk reduction and that programs that consist of exercise training alone are not considered cardiac rehabilitation [4].

This article has an excellent algorithm to follow and it is available in its entirety at http://www.circulationaha.org. The important points contained within this article include pre-exercise testing to determine clinically significant cardiac disease that would preclude exercising (electrocardiogram and exercise testing are essential). The article also addresses nutrition, diabetes management, and tobacco cessation.

Treatment

Rehabilitation

- Pulmonary rehabilitation has been extensively studied in patients with COPD. Rehabilitation (*ie*, supervised exercise) has also been studied in other groups of specialized patients. These groups include ischemic heart disease, renal insufficiency, and AIDS. There are also studies in patients before bone marrow transplant, a cluster that includes lymphoid and stem cell malignancies and solid tumors [2••,5••]. However, research regarding COPD outweighs, in sheer bulk, these groups. This paper discusses rehabilitation because it has been studied in all of these groups, but with an emphasis on the COPD literature simply because of its magnitude and relevancy when discussing patients with smoking-related lung cancer who assuredly have some component of obstructive lung disease.
- Because of these patients' likely coexisting lung disease, it would be assumed that they would be perfect candidates to participate in PR, but frequently they are excluded from studies devoted to PR because of their comorbidity (*eg*, cancer). Therefore, what is known regarding PR in patients with cancer comes from small studies that are not well controlled or extrapolating data from the COPD database. The recurring theme in reading studies on PR is that patients are excluded for disabling illness. One study notes that frequently the dropouts from these studies are patients with a new diagnosis of lung cancer [6].
- What are the rehabilitative needs of patients with cancer? What are the effects of exercise? Why does it ameliorate fatigue? It appears that exercise normalizes physical efficiency and performance and augments adaptive responses to treatment (*eg*, gains in muscles mass, improved pulmonary perfusion and ventilation, and increased cardiac reserve) [7••]. Resistance exercise has been shown to reduce the loss of muscle mass related to treatment with corticosteroids [7••]. There are improvements in physical and psychologic well being, all of which contribute to better health in patients with cancer.
- Being treated for cancer causes fatigue and a decline in physical performance. It may be that as many as 70% of patients with cancer report both problems, regardless of whether they have had chemotherapy, radiotherapy, or surgery (or some combination of these therapies) [5••]. The loss of energy and debilitation can, in some people, last for years. The number of patients with cancer suffering from these problems may be as high has 30% [5••]. Exercise programs in oncology have largely focused on self-limited problems (*eg*, impairments caused by surgery). However, the problem of energy loss (*ie*, CRFS) can be overwhelming and little attention has been paid to it until recently.
- Patients with cancer fall into a vicious cycle. Exhausted from treatment and having received potentially toxic chemotherapy, these patients are encouraged to rest. They become more sedentary and their exercise endurance declines rapidly [5••]. Patients with COPD and symptom-limited lung disease display a similar phenomenon, often ending up in what one author called the "dyspnea spiral." In avoiding feeling dyspneic, patients become increasingly sedentary, which leads to diminished exercise tolerance, thus aggravating their dyspnea [5••]. The therapies for patients with cancer impair their cardiopulmonary and muscle conditioning, which frequently causes anemia. Therefore, patients require greater effort to perform usual activities [2••]. It has been estimated that 33% or more of the functional decline experienced by patients with cancer occurs because of hypokinetic conditions that arise from prolonged physical inactivity [8••].

- To a great extent, what is known regarding the effect of being sedentary (*eg*, bed rest and chair rest) comes from aeronautics research regarding astronauts and the long- and short-term effects of weightlessness. The astronauts exhibited rapid loss of physical conditions and emotional decline, especially in increased fatigability and depression [7••]. Studies by the National Aeronautics and Space Administration have demonstrated that therapeutic exercise counters these effects [7••].
- Several studies examine the effects of aerobic exercise in patients with cancer, all of which found an improvement in performance [2••]. Since the study by Winningham [7••] in 1983 involving patients with breast cancer showed improved functional capacity, studies have shown the benefits of exercise therapy in patients with cancer. These studies have reinforced the idea that exercise in patients with cancer positively affects the symptoms of CRFS (*eg*, improved energy, less depression and fatigue, less nausea, and less weight loss) [7••]. In 1986, Winningham [7••] published guidelines for exercise in patients with cancer. Dimeo *et al.* [5••] showed lower lactate levels and heart rates in patients undergoing treadmill exercise training after bone marrow transplants. Dimeo *et al.* [5••] also showed that exercise in patients receiving bone marrow transplant reduced chemotherapy-related complications, length of hospitalizations, and duration of bone marrow regeneration. Dimeo *et al.* [2••] undertook a study on the effects of exercise in patients undergoing high-dose chemotherapy and autologous peripheral stem cell transplantation. The results of that study confirmed that aerobic exercise reduced treatment-related fatigue and improved the psychologic state of patients receiving high-dose chemotherapy [2••].
- The study by Winningham [7••] provided a prescription for exercise for patients with cancer, which consists of six variables: initial status of the patient (S), type (T) of activity, intensity (I) of activity (best measured by heart rate), frequency (F) of activity, duration (D) of activity, and progression (P) of the activity.
- These variables provide a structure for any exercise program so that the outcomes will be more predictable and more valuable because additions to the data are based on exercise in patients with cancer [7••]. Any patient who is considered for enrollment in this program must be screened for risk factors, especially cardiopulmonary disease, that would make exercise dangerous [7••].
- Some patients with lung cancer will undergo surgical therapy for their disease. Surgical patients present a few specific issues that should be mentioned. Patients who undergo surgical therapy for their lung cancer should not expect severe debilitation postoperatively. With appropriate preoperative evaluation and peri- and postoperative care, only patients who have undergone pneumonectomies can expect impaired exercise performance [9]. In a group of 77 patients who had surgical intervention for lung cancer, patients who had pneumonectomies had a decline in exercise capacity of 28% (maximal oxygen uptake declined 28%) [9]. Pneumonectomy has been associated with higher postoperative complication. Predictive factors include age, low forced expiratory volume in 1 second (FEV_1), heart disease, and poor preoperative pulmonary toilet [10]. Data suggest that simply calculating postoperative FEV_1 underestimates the actual FEV_1 and that the combination of incentive spirometry (ICS) and inspiratory muscle training (IMT) postoperatively significantly increases postoperative lung function [11]. In patients who received no ICS and IMT, actual postoperative FEV_1 was underestimated by 70 mL (lobectomy subgroup) and 100 mL (pneumonectomy subgroup) [11]. In patients receiving ICS and IMT, their actual postoperative FEV_1 levels were higher by 570 mL and 680 mL in lobectomy and pneumonectomy groups, respectively [11].

- Rehabilitation is not limited to physical exercise. Other areas that have been studied in the rehabilitation of patients with cancer are sleep, nutrition, and pharmacologic therapies. Drugs obviously have therapeutic and counterproductive effects, and each patient's regimen must be evaluated and re-evaluated carefully and regularly. For example, treating anemia may be beneficial and there are data on using methylphenidate as therapy for patients experiencing cognitive problems [7••]. With the use of any medication, the patient accepts a risk of side effects. This is an area of active research.
- Studies have found that patients with cancer report fatigue as a far more distressing symptom and part of their cancer therapy, even more than pain [7••]. Fatigue (*ie*, CRFS) for patients with cancer is multifaceted [7••]. CRFS is not simply fatigue. It comprises of weakness, poor sleep, depression, and cognitive impairments, in addition to anhedonia and social isolation, linked by a constant unremitting exhaustion [7••]. Management of CRFS requires attention to many details and likely requires a multidisciplinary approach. Part of a rehabilitation program for patients with cancer must include an approach that would facilitate addressing CRFS.
- Sleep disorders are a well-recognized problem in many patient populations, and patients with cancer are certainly no exception. An extensive discussion of sleep disorders is beyond the scope of this article and deserves its own forum. However, within cancer literature, there is an important triad to remember when exploring rehabilitation in patients with cancer: sleep patterns, depression, and fatigue. These three problems overlap and also lead healthcare workers to rule out other important disorders (*eg*, thyroid disease and sedation from medication). Multidisciplinary evaluation of a patient with fatigue and decline in functional status is important and can include a formal sleep study and evaluation by a psychiatrist. Olders and Winningham [12] found that excessive rapid eye movement sleep contributes to fatigue and depression. This group developed sleep evaluation protocols and sleep modification techniques [7••].
- Nutrition is an important factor in determining how well or how poorly patients with cancer feel. Cancer is a disease of accelerated metabolism by abnormal cells (catabolism overtakes and vanquishes normal anabolic processes) [7••]. The toll this takes on the availability of oxygen in cellular mitochondria to convert food into fuel is significant, and addressing the nutritional needs of patients is paramount [7••]. The effects of a poor nutritional status are multiple (*eg*, failing immune systems, dehydration, altered digestion, and neurologic derangements) [7••]. Complicating this is the abundance of unregulated nutritional supplements that may be helpful but also carry significant toxicity.
- Multiple studies have proven that PR has short-term benefits and results in improved QOL, which has been reported by the patients themselves, and lessens sensation of dyspnea for patients. It has also been shown to improve functional status and health status [13,14]. A PR program that includes education, breathing retraining, and chest physiotherapy followed by exercise training results in improved dyspnea, functional exercise capacity, and health-related QOL [15]. Other authors have shown similar marked benefits with lower-intensity exercise programs [15]. One study even showed fewer COPD exacerbations, hospitalizations, and need for supplemental oxygen in its PR participants when compared to controls [15]. The study also demonstrated an improved forced vital capacity, which appears to be attributable to improved strength in inspiratory muscles [15]. PR lowers hyperventilation and improves maximal oxygen uptake and 6-minute walk distance [13]. Data also show that the benefits occur regard-

less of stage of COPD and baseline lung function [15–17]. Exercise training will improve exercise capacity and QOL. Irrespective of severity of lung disease, exercise training will result in quantitative improvements in maximal oxygen uptake and work capacity [16,18].

- However, PR has questionable long-term benefits, with initial marked improvement appearing to precede a decline in QOL later [6]. However, most studies of PR do not have long follow-up periods, thus assessing long-term effects is difficult. One exception was a study by Wijkstra *et al.* [19] who followed patients with COPD after PR for 18 months and showed a sustained QOL [6,16].
- Research has shown that many varieties of exercise have positive impacts on QOL and other symptoms. A dose-dependent relationship exists between intensity of exercise and response in these patients (higher-intensity exercise results in greater improvements in performance) [13]. A standard PR program exercises patients on a treadmill or stationary bicycle to 70% or more of maximum for 20 to 30 minutes two to three times weekly [13]. Another regimen uses isolated peripheral muscle training only. This regimen has similar results in improved muscle endurance and treadmill stamina [13].
- The information that has not been shown is what exercise program provides the best results, whether one program is better or whether the factor that matters is simply the exercise and not what form it takes. What level of exercise works? What intensity? How frequent? Upper extremity or lower? Aerobic exercise or calisthenics? Aerobic exercise or strengthening? Or combined? Inpatient, outpatient, or at home? Or all three? How long should the program last? These are questions that, for the most part, remain to be answered definitively.

Quality of life

- A review of the literature on rehabilitation after cancer treatment, including lung cancer, reveals a myriad of articles regarding QOL indices. Rehabilitation programs aim to make the patients feel better, thus a discussion of QOL, its components, and how to optimize them is appropriate. In lung cancer, in which long-term survival is dismal, QOL is recognized as an important factor in deciding therapy for patients. The assessments by patients of their QOL differ from the assessments by their physicians, underscoring the subjective nature of QOL [20]. QOL has been studied extensively in patients with lung cancer. Many tools for assessing QOL in objective ways have been used, studied, and accepted or rejected. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30) has been validated as a useful and accurate tool in assessing patients with lung cancer when coupled with the EORTC QLQ LC-13, which measures specific lung cancer-related symptoms and treatment side effects [21•].
- There is little literature devoted to objective data regarding rehabilitation, specifically of patients after cancer therapy, although there is obviously a large body of research devoted to pretreatment assessment and rehabilitation. Rehabilitation has benefits in improving and alleviating dyspnea and improving the QOL reported by patients.
- In lung cancer literature, the use of performance status as a measure of QOL is reasonable because performance status is a crucial prognostic factor and predictor of survival [21•]. Retrospective data show that chemotherapy in patients with lung cancer that resulted in an improvement in performance status had a positive effect on QOL [21•]. Prospective data have supported the importance of performance status in prognosis by showing that

patients receiving chemotherapy for advanced non–small cell lung cancer who report better baseline health respond better to treatment and have a lower risk of death [22].

- In patients who underwent surgery for lung cancer, QOL measured by the Functional Living Index-Cancer was predictive of survival, even when corrected for stage of disease [23]. Preoperative carbon monoxide diffusing capacity (DLCO) and not forced expiratory volume in 1 second predicts postoperative QOL [24]. Patients with a DLCO less than 45% had significant postoperative impairment of physical functioning, psychologic stability, and pain [24]. DLCO was the only predictor of postoperative QOL, whereas preoperative chemoradiation, extent of resection, postoperative complications, and adjuvant therapy had no adverse affect on functional health status or QOL 6 months after surgery [24]. This finding has been replicated in other studies and appears to correlate regardless of whether patients undergo lobectomy or pneumonectomy [24].
- Quality of life is clearly linked to baseline health and performance status, which includes baseline psychologic status. One study showed that long-term survivors of non–small cell lung cancer are more likely to report good QOL if they did not begin therapy for lung cancer with distressed mood and comorbid illnesses [25].
- This discussion of QOL as an endpoint is a summation at best, although its value in assessing patients undergoing therapy for lung cancer cannot be underestimated and QOL as a topic deserves a more extensive review. However, as a treatment goal, it is a crucial component of any rehabilitation program.

Conclusions

- This discussion of rehabilitation in patients undergoing therapy for lung cancer has reviewed literature specific to patients with cancer and patients with chronic diseases that respond to rehabilitation. Although these patient populations are varied and their needs are even more diverse, the recurring theme is that rehabilitation results in improved QOL, measured by alleviation of troublesome symptoms (*eg*, dyspnea and fatigue) and improvement in performance status. It remains to be seen what role rehabilitation will assume in the lung cancer protocols of the future. However, it does seem to make sense that the benefits reaped by patients with COPD are referential to patients with lung cancer who likely suffer from COPD. Data devoted to patients with cancer show the benefits of including an organized exercise program in therapies for malignancies. The task for the future is to design these programs to suit the needs of patients and to address how rehabilitation can affect the outcomes of therapies for lung cancer and other malignancies.

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