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Physical Activity and Lung Cancer Survivorship

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Lung Cancer Survivorship

Approximately 26,000 individuals per year, in the U.S, will survive more than 5 years after initial diagnosis of lung cancer.[1] Given improving prognosis, long-term treatment-related morbidity and overall quality of life are becoming increasingly recognized as outcomes of major clinical importance in the management of lung cancer.[5-10] Indeed, a lung cancer diagnosis and associated therapeutic management is associated with unique and varying degrees of adverse physical/functional impairments that dramatically reduce patient's ability to exercise. Limited capability to exercise may predispose to increased susceptibility to other common age-related diseases, poor quality of life (QOL), and even an increased risk of dying from lung cancer or other related causes. The purpose of this article is to review the importance of exercise capacity and utility of exercise therapy as a complementary therapy following a lung cancer diagnosis.

Lung Cancer Survivors Have Poor Exercise Capacity

All forms of regional (i.e., pulmonary resection or radiotherapy) and systemic therapies (i.e., chemotherapy and small molecule inhibitors) used in lung cancer are associated with unique and varying degrees of adverse physical/functional impairments that dramatically reduce a patients' ability to tolerate exercise.[13] Exercise tolerance, also known as cardiorespiratory fitness reflects the integrative capacity of components in the oxygen (O_2) cascade to supply adequate O_2 for adenosine triphosphate (ATP) resynthesis.

Lung cancer patients have significant and marked reductions in VO_{2peak}. For example, in a prospective cohort study of 346 operable lung cancer patients, Loewen et al.[18] reported that the exercise tolerance, before pulmonary resection, was 25% to 44% below age-sex-matched individuals without a history of lung cancer.[18] Following pulmonary resection, Jones et al. recently reported that mean VO_{2peak} was 38% below age-sex matched sedentary individuals without cancer.[19] Finally, further work by Jones et al. found VO_{2peak} to be 38% below age-sex matched values among patients with inoperable (advanced disease) undergoing cytotoxic therapy (e.g., systemic chemotherapy and/or regional radiotherapy).[20] These findings demonstrate the following: (1) VO_{2peak} is markedly reduced among lung cancer patients across the entire lung cancer survivorship continuum (i.e., presurgery to postsurgery to advanced disease), and (2) lung cancer surgery is associated with dramatic reductions in exercise tolerance however, use of conventional cancer therapy may lead to additional detrimental effects on exercise tolerance.

Central Importance of Exercise Tolerance Following a Lung Cancer Diagnosis

Prior to lung cancer surgery, exercise tolerance has been shown to be a strong predictor of surgical complication rate.[18, 21-26] Specifically, patients with a preoperative exercise tolerance <20 $mL.kg.^{-1}min^{-1}$ are not at increased risk of complications; patients with a exercise tolerance <15 $mL.kg.^{-1}min^{-1}$ are at an increased risk of perioperative complications; and patients with a exercise tolerance <10 $mL.kg.^{-1}min^{-1}$ are at a very high risk of perioperative complications. [26-28] 18, 21-26

Following lung cancer surgery, Jones et al. reported that exercise tolerance is a strong predictor of overall quality of life (QOL), fatigue, and other QOL domains.[19] In a prospective study among 173 postsurgical lung cancer patients, Kenney et al.[6] reported significant decrements in QOL and higher lung cancer-related symptoms (i.e., fatigue, pain, sleep quality, etc.) following pulmonary resection. Importantly, physical functioning (a surrogate of exercise tolerance) was the strongest predictor of overall QOL. Finally, Coups et al.[30] reported that postsurgical lung cancer patients meeting national physical activity recommendations (i.e., at least moderate-intensity exercise,≥30 minutes/session, on ≥5 days/week) reported significantly higher QOL relative to patients not meeting the recommendations.

In addition to the strong relationship between exercise tolerance and perioperative and postoperative surgical complication rate, exercise tolerance may also be an independent predictor of risk of dying following a lung cancer diagnosis. To date, only two studies have evaluated the prognostic importance of exercise tolerance following a cancer diagnosis and both studies have been conducted in lung cancer. The first study, conducted by Kasymjanova and colleagues[44], examined the prognostic value of the six minute walk test in 45 patients diagnosed with inoperable non-small cell lung cancer. Median survival was 6.7 months (95% confidence interval 2.6-10.8) in patients walking <400m compared with 13.9 months (95% confidence interval 10.0-17.8) in patients walking ≥400 m. A walk distance of ≥400 m was the only variable with a significant effect on survival in multivariate analyses. In the second study, Jones et al.[45] investigated the prognostic significance of exercise tolerance prior to lung cancer surgery in 398 patients with potentially surgical lung cancer. Compared with patients in the lowest exercise tolerance category, there were significant reductions in the risk of dying for higher levels of exercise tolerance.

Overall, these data provide strong evidence that interventions that can improve exercise tolerance may improve surgical risk and/or recovery, symptom control, and possibly, risk of dying following a lung cancer diagnosis. Exercise training is acknowledged as one of the most effective interventions to improve exercise tolerance. Here, we provide an overview of studies examining the effects of exercise training following a lung cancer diagnosis. Specifically, the role of exercise in three lung cancer settings will be reviewed: (1) operable disease - pre-surgery, (2) operable disease - post-surgery, and (3) inoperable disease. An overview of these studies is provided in Table 1.

Exercise Therapy Following a Lung Cancer Diagnosis

Exercise Therapy for Operable Lung Cancer – Prior to Surgical Resection

Two small pilot studies have investigated the efficacy of presurgical exercise training on measures of exercise tolerance and other outcomes in patients undergoing pulmonary resection for suspected lung cancer. The first study, conducted by Jones et al.[20], investigated the safety and feasibility of supervised aerobic training on exercise tolerance and QOL among 25 patients with suspected lung cancer scheduled for pulmonary resection. Aerobic training consisted of stationary cycling, five times a week at 60-100% of baseline exercise tolerance until surgical resection. The overall attendance rate for the exercise sessions was 72% (range: 0%-100%). Exercise tolerance increased significantly from baseline to presurgery. Exploratory analyses indicated that presurgical VO_{2peak} decreased postsurgery, but did not decrease beyond baseline values.[20] In the second study, Bobbio et al.[22] investigated the impact of a short-term preoperative pulmonary rehabilitation program on VO_{2peak} in 12 patients with chronic obstructive pulmonary disease (COPD) undergoing lobectomy for non-small cell lung cancer. The pulmonary rehabilitation program consisted of physical therapy (breathing and coughing techniques) and a combined aerobic and resistance training program. Aerobic training was conducted at 50% to 80% of maximal work rate for 30 minutes, 5 days a week for 4 weeks. Resistance training included upper and trunk muscle exercises performed with free weights under the supervision of physical therapist. Results indicated a significant improvement in exercise tolerance in the short-term exercise intervention.

The results of these studies provide initial evidence that relatively short-term exercise training is associated with significant improvements in exercise tolerance among patients undergoing thoracic surgery for malignant lung lesions, although more studies are required.

Exercise Therapy for Operable Lung Cancer - Post Surgical Resection

To date however, only three published studies have investigated the utility of exercise training following lung cancer surgery. First, Spruit and colleagues[60] investigated the effects of a 8-week multidisciplinary inpatient rehabilitation program among 10 patients with severely impaired pulmonary function following treatment for operable lung cancer. The multidisciplinary rehabilitation program consisted of a multicomponent exercise training program including aerobic training (daily cycle ergometry, treadmill walking at 60% and 80% of baseline peak cycling load and baseline treadmill load, respectively), resistance training (upper and lower extremity exercises at 60% of one-repetition maximum), and general flexibility and mobilization exercises. Results indicated that the rehabilitation program was associated with significant improvements in measures of exercise tolerance. [60] In the second study, Cesario et al.[61] investigated the effects of a 28-day inpatient rehabilitation program among 25 patients following pulmonary resection. The rehabilitation program consisted of five weekly, three-hour sessions including incremental cycle ergometry (30 mins/day at ~70% of maximal workload), resistance exercises and treadmill walking, and education. All patients underwent spriometry and 6MW testing at baseline and postintervention. In comparison with patients who refused entry into the study (n=186), inpatient rehabilitation was associated with significant improvements in six minute walk distance with no changes in any pulmonary function outcomes.[61]

The final study, conducted by Jones et al.[62], examined the effects of supervised aerobic training on changes in VO_{2peak} and QOL among 20 newly diagnosed postsurgical non-small cell lung cancer patients (stage I-IIIB) 4-6 weeks post-resection.[19] Aerobic training consisted of three endurance cycle ergometry sessions per week at 60% to 100% of baseline exercise tolerance for 14 weeks. Results indicated significant improvements in exercise tolerance as well as patient-reported outcomes such as QOL and fatigue. Results of these pilot studies provide 'proof of principle' that exercise training is a safe and feasible intervention in lung cancer patients following surgery. Larger studies are warranted.

Exercise Therapy for Advanced Lung Cancer

The majority of patients (~75%) diagnosed with lung cancer present with inoperable (advanced) disease. Examining the effects of exercise training in this setting represents a unique challenge. Specifically, patients with advanced lung cancer are often older and commonly present with a diverse range of cardiovascular and/or musculo-skeletal complications that may limit their ability to tolerate exercise. In addition, these patients present with diffuse tumor burden in the lungs as well as systemic metastatic disease commonly located in bone, kidney, liver, and brain. Furthermore, these patients receive aggressive combination therapy that simultaneously adversely impact the ability to tolerate exercise and elevate the risk of an exercise-associated adverse event.[67]

Only one study to date has examined the role of exercise training in patients with advanced lung cancer. Temel et al.[68] examined the efficacy of an 8-week structured combined aerobic and resistance training hospital-based program among 20 patients with newly diagnosed inoperable lung cancer. Eleven patients (44%) completed the study. Significant reductions in lung cancer symptoms with maintenance of cardiorespiratory fitness, as measured by a 6-minute walk test. Further research is needed to examine the safety and efficacy of appropriate exercise interventions in *select* patients with advanced lung cancer..

Clinical Recommendations

The current literature base is insufficient to provide evidence-based, lung cancer-specific exercise prescription guidelines. Nevertheless, as reviewed in this chapter, emerging evidence corroborates work in other cancer populations that chronic (repeated) exercise therapy performed at least 3 days/week at a moderate intensity (e.g., 50% to 70% of heart rate reserve) is associated with improvements in exercise tolerance, QOL, and fatigue following a diagnosis of early-stage lung cancer. Exercise prescriptions guidelines are also informed by the results of recent landmark epidemiological, observational studies reporting that regular exercise (i.e., 3-5 d.wk, ≥30mins/session, 50%-70% of heart rate reserve) is associated with substantial reductions in cancer-specific mortality and all-cause mortality following a diagnosis of early-stage breast and colorectal cancer relative to those who were physically inactive.[69-74] Taken together, standard exercise prescription guidelines for healthy adults (i.e., 3-5 d.wk, ≥30mins/session, 50%-70% of heart rate reserve) appear prudent for early-stage lung cancer patients both during and following adjuvant therapy until further evidence becomes available.

Summary

Research examining the role and efficacy of exercise in persons diagnosed with lung cancer is in its infancy relative to exercise research in the other major cancer diagnoses (e.g., breast, prostate). Nevertheless, for patients with early-stage lung cancer, both before and after pulmonary resection, the preliminary evidence suggests that supervised aerobic training is safe and feasible in these patients and potentially associated with improvements in several clinically relevant endpoints. Among patients with advanced lung cancer, further preliminary research assessing the safety and feasibility of exercise in this setting is warranted. Although much more work is required, exercise therapy may represent an important component of multidisciplinary management of patients diagnosed with lung cancer.

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