Increasing Physical Activity and Exercise in Lung Cancer

Reviewing Safety, Benefits, and Application

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Abstract: Lung cancer continues to be a difficult disease frequently diagnosed in late stages with a high mortality and symptom burden. In part because of frequent lung comorbidity, even lung cancer survivors often remain symptomatic and functionally limited. Though targeted therapy continues to increase treatment options for advanced-stage disease, symptom burden remains high with few therapeutic options. In the last several decades, exercise and physical activity have arisen as therapeutic options for obstructive lung disease and lung cancer. To date, exercise has been shown to reduce symptoms, increase exercise tolerance, improve quality of life, and potentially reduce length of stay and postoperative complications. Multiple small trials have been performed in perioperative non–small-cell lung cancer patients, although fewer studies are available for patients with advanced-stage disease. Despite the increased interest in this subject over the last few years, a validated exercise regimen has not been established for perioperative or advanced-stage disease. Clinicians underutilize exercise and pulmonary rehabilitation as a therapy, in part because of the lack of evidence-based consensus as to how and when to implement increasing physical activity. This review summarizes the existing evidence on exercise in lung cancer patients.

Key Words: Exercise, Physical activity, Non–small-cell lung cancer, Small-cell lung cancer, Quality of life.

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Lung cancer is the second most common cancer type, is the leading cause of cancer death, and is expected to comprise 13% of new cancer diagnoses (224,210 new cases) with 159,260 deaths in 2014.[1] Though improved understanding of cancer biology and targeted therapies is improving outcomes, 1-year and 5-year survival rates remain low at 43% and 17%, respectively.[1] Furthermore, lung cancer patients have high symptom burden including dyspnea, cough, fatigue, anxiety, depression, insomnia, and pain.[2,3] Even lung cancer survivors more than 5 years from diagnosis experience quality of life (QoL) impairment in 35% of cases[4] and report lower physical and health scores compared with healthy patients.[5] Interestingly, the patients who experience QoL improvement after therapy (15%) have no change in symptom burden, suggesting an adaptation to chronic symptoms.[4]

Lung cancer patients are in a uniquely difficult situation in that their disease, their comorbidities, and their treatment may all lead to worsened symptomatology.[6] Chronic obstructive pulmonary disease (COPD) is present concomitantly in 73% of men and 53% of women with newly diagnosed primary lung cancer.[7] The diverse causes of activity limitation are listed by the 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) statement on pulmonary rehabilitation (PR) and include ventilatory or gas exchange limitations, cardiac limitation, lower limb or respiratory muscle dysfunction, anxiety, depression, and poor motivation.[8] Chemotherapy-induced anemia, radiation-induced pneumonitis, and lung resection-related impairment are frequently seen and likely contribute to dyspnea and fatigue.[6,9,10] With significant cancer burden and rising cancer costs (estimated $86.6 billion in 2009),[1] an inexpensive cancer therapy to relieve symptoms and improve QoL is appealing.

Inactivity and low-exercise tolerance are increasingly recognized in chronically ill patients. Multiple studies show lower activity and daily step counts in COPD, peripheral vascular disease, and non–small-cell lung cancer (NSCLC).[11–15] In COPD, for example, physical inactivity is often seen during exacerbation and a predictor of poor outcome.[16,17] The same pattern is seen in pulmonary hypertension, interstitial lung disease, and lung cancer.[3,18]

Adding to their burden, functional capacity significantly declines after lung cancer diagnosis.[19,20] In a recent longitudinal trial, 36% of lung cancer patients (all stages) were noted to reduce or stop walking exercise over the course of 6 months.[21] The term "dyspnea spiral" has been utilized to describe the development of dyspnea, activity avoidance to prevent further dyspnea, and resultant further loss of function. Some estimates suggest up to 1 of 3 of loss in functional capacity in cancer patients is because of prolonged physical inactivity.[19] Historically, providers and caring family members have contributed to physical inactivity by recommending rest to reduce symptom burden, leading to further deconditioning.[22] Lung cancer patients with lower exercise tolerance have worse surgical outcomes, chemotherapy response and tolerance, and survival.[3]

In the last 20 years, increasing physical activity has shown great promise for cancer and chronic lung disease therapy. Because of the significant overlap between lung cancer and chronic lung disease (namely COPD), lung cancer patients may benefit from physical activity more than other cancer patients. Indeed, exercise therapy represents a low-cost way to improve

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symptoms and potentially outcomes in lung cancer. Given the potential benefit of exercise in this population coupled with the lack of clear recommendations for clinicians providing care, we will review the literature to date on exercise, physical activity, and lung cancer.

Before summarizing the literature, a distinction between "physical activity" and "exercise" should be made. Caspersen et al.[23] defined and distinguished these terms previously. They described physical activity as "a bodily movement by skeletal muscles that results in energy expenditure." Exercise is physical activity that is planned, structured, and repetitive with the goal to obtain or maintain physical fitness.[23] This review's goal is to summarize the effect of increased physical activity on lung cancer outcomes. As such, studies utilizing increased physical activity, exercise regimens, or PR are often compared side-by-side. Although the methods differ in application, lung cancer patients likely benefit through increased overall physical activity rather than the regimen itself. As the reader will see, compliance is an often cited challenge in patients with chronic lung disease, and the regimen that maximizes compliance may be the most effective. Indeed, utilizing an exercise regimen or rehabilitation may have more or less benefit than simply increasing physical activity. However, these two regimens have not yet been directly compared. As such, this review will consider physical activity, exercise regimens, and PR as methods to increase physical fitness that may improve cancer outcomes.

The existing literature lacks a review that includes the progression of exercise's benefit in cancer and lung disease, evaluation of both medically and surgically treated lung cancer patients, and the growing interest of pedometer/accelerometer studies in patients with exercise limitation. To address these issues cohesively, PubMed was searched for the terms "physical activity," "exercise," "lung cancer," "pedometer," and "step counts." Resulting articles were individually reviewed by B.C.B. for their applicability to the topic and included as referenced to create this narrative review. Additional articles outside the searched terms were included to appropriately summarize the existing literature or provide sufficient topical background.

REDUCED CANCER INCIDENCE, MORTALITY, AND SYMPTOM BURDEN

Growing evidence supports activity's benefit in primary and secondary cancer prevention. Much of this work has been done in colon and breast cancer. In 2009–2010, several large trials showed that cardiorespiratory fitness was associated with reduced breast cancer mortality, reduced risk of colon (and overall) cancer development, and reduced mortality with gastrointestinal cancers.[24–26] Reduced lung cancer incidence with higher activity was confirmed in a 2013 review.[27] In fact, physical activity reduces risk of cancer development in multiple cancer types (colon, breast, prostate, pancreatic, endometrial, ovarian, and lung).[28]

In many cancer types, increased physical activity is also associated with reduced cancer-associated mortality. Large trials in Taiwan (n = 416,175 patients followed for ~8 years) and by the National Institutes of Health (NIH) (n = 293,511) showed exercise's association with reduced all-cause mortality,[29] and that self-reported moderately vigorous physical activity led to lower risk of all-cause and cancer-specific mortality (colon, liver, and lung), respectively.[30]

Multiple trials have also shown reduced symptom burden with increased activity. Specifically, exercise can also be used as an adjunctive therapy for cancer-related symptom relief during and after cancer treatment.[28] In a randomized, controlled trial (RCT), Segal et al.[31] showed that breast cancer patients not receiving chemotherapy increased their subjective physical functioning with an exercise regimen. Interestingly, the patients who directed their own regimen appeared to have equal or better improvements. In 2005, Douglas[19] reviewed breast and metastatic tumors, noting that exercise benefited functional capacity, strength, hospital stay, QoL, energy, and fatigue. In hospitalized patients receiving myeloablative chemotherapy, one study found benefit symptom control, cognitive function, and psychosocial function during therapy.[32]

A systematic Cochrane review in 2012 focused on exercise intervention and QoL in cancer patients receiving or planning active treatment. Fifty-six trials were included (4826 patients) and concluded that exercise interventions may have beneficial effects on QoL, physical function, social function, and fatigue.[33] The effects were more noticeable with the moderate and vigorous intensity programs.

Is Physical Activity Appropriate?

Some clinicians have recommended limited activity in cancer patients ostensibly to avoid worsening symptoms. To be sure, lung cancer patients limit activity to avoid the "dyspnea spiral." Similarly, supporting families often limit activity in the cancer patient to prevent acute symptoms. Before advocating more activity, the safety of increasing physical activity in lung cancer patients needs to be established. Research regarding the feasibility and safety of exercise perioperatively (see Table 1),[34,35] in advanced NSCLC (see Tables 2 and 3),[36] and in advanced-stage lung cancer undergoing chemotherapy[37] has been performed and is reviewed here.

Several novel studies utilizing a patient-centered approach were recently performed. By surveying NSCLC survivors (average 3.6 years from surgical treatment), Philip et al.[38] found that most patients desire physical activity advice before cancer treatment, in a face-to-face fashion, from a physician at a cancer center. Another survey-based study in advanced lung cancer patients revealed that patients preferred activity recommendations from their oncologist, though none had received specific advice.[39] These patients also perceived that a lack of recommendation from their physician constituted an acceptance of their exercise regimen. An uncontrolled trial of lung cancer patients (all stages) in 2013 reported ~70% of patients who completed a training program remained physically active.[40] These data highlight that lung cancer patients (regardless of stage) desire exercise guidance and can increase compliance with a dedicated regimen, yet such discussions are often not held.

BENEFITS IN LUNG CANCER

In 2005, the National Emphysema Treatment Trial (prospective, multicenter trial with 1218 patients) revealed that

TABLE 1. Surgical Studies (n = 22)

Author	Patients	Regimen	N	Result
Sekine et al.[68]	NSCLC with COPD undergoing lobectomy	Preoperative-PR (2 weeks) with postoperative CPT	22	FEV1 preservation, shorter LoS, fewer pulmonary complications
Spruit et al.[50]	NSCLC and SCLC pts after treatment (9 surgeries; 1 chemoradiation)	Posttreatment PR (8 weeks; inpatient)	10	Improved 6MWD and cycle ergometry
Cesario et al.[51]	Lung cancer, preoperative	Preoperative-PR (4 weeks)	8	Improved operability
Jones et al.[54]	Suspected stages I–IIIA NSCLC	Preoperative cycle ergometry for 5 sessions	20	Improved 6MWD and VO2
Bobbio et al.[66]	NSCLC (stage I or II), COPD, and VO2 <15	Preoperative-PR (4 weeks)	12	Improved VO2 to >15 ml/kg/min
Pehlivan et al.[56]	NSCLC (stages I–IIIB)	Preoperative physical therapy	60	Improved LOS, SaO2, exercise capacity, V/Q distribution
Arbane et al.[57]	NSCLC referred for VATS	Postoperative exercise regimen (12 weeks, inpatient and outpatient)	53	No change in QoL or 6MWD. Reduction in quadriceps strength loss
Benzo et al.[69]	Lung cancer and moderate/severe COPD	Preoperative-PR (10 sessions)	19	4 weeks of preoperative-PR difficult to implement; shorter chest tube times and nonsignificant reduced LOS
Granger et al.[34]	Adults undergoing lung resection for suspected lung cancer	Postoperative, twice daily sessions as inpatient and twice weekly sessions as outpatient (8 weeks)	15 (LC 10)	Exercise was safe and feasible. 57% of patients participated outpatient therapy
Divisi et al.[52]	NSCLC (stage I) and COPD	Preoperative-PR (4 weeks)	27	Improved PaO2, VO2, and FEV1. Reduced inoperability
Stigt et al.[60]	NSCLC, resectable	Postoperative-PR (twice/week for 12 weeks)	49	No change in QoL. Exercise tolerance improved. More reported pain and limitations
Coats et al.[87]	NSCLC before resection	Preoperative, home-based exercise regimen (exercise 3×/week for 4 weeks)	16	Improved exercise tolerance and muscle strength
Sterzi et al.[59]	NSCLC undergoing resection	Postoperative PR, inpatient for 3weeks	110	Improved exercise tolerance (through 6MWT)
Stefanelli et al.[67]	NSCLC (stages I and II) and COPD	Preoperative-PR (3 weeks)	40	Improved VO2 and maintained after surgery
Hoffman et al.[86]	NSCLC undergoing thoracotomy (stages I–IIIA)	Light intensity walking and balance (Wii; Nintendo, Redmond, WA) for 6 weeks	7	Feasible. Improved cancer-related fatigue, walking, balance, and # steps/day)
Bradley et al.[35]	Presumed lung cancer undergoing curative surgery	Preoperative and postoperative rehabilitation program, multidisciplinary	58	Feasible. Improvement in 6MWD and FEV1 (Preoperative portion). 54% quit smoking
Morano et al.[55]	NSCLC undergoing resection and abnormal spirometry	Preoperative-PR (4 weeks)	24	Preoperative-PR reduced fibrinogen and improved functionality and QoL
Brocki et al.[89]	Lung cancer patients after chest surgery	Outpatient weekly sessions for 10weeks	78	No QoL or symptom benefit after 1 year (pain benefit at 4 months)
Arbane et al.[58]	NSCLC undergoing resection	Postoperative inpatient exercise (for 4 weeks) and recommended outpatient regimen	131	No change in physical activity, strength, or QoL. If airflow obstruction, QoL improvement
Chang et al.[80]	NSCLC undergoing lobectomy	Postoperative walking (12 weeks)	66	Improved FEV1, FVC, and 6MWT
Hoffman et al.[79]	NSCLC undergoing thoracotomy and chemotherapy	Walking and balance exercises (Wii) for 16 weeks	5	Trends toward symptom, functionality, and QoL improvement
Mujovic et al.[70]	NSCLC undergoing resection and COPD	Preoperative-PR (2–4 weeks)	83	Improved exercise tolerance, FEV1, FVC, and dyspnea

NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; COPD, chronic obstructive pulmonary disease; PR, pulmonary rehabilitation, CPT, chest physiotherapy; FEV1, forced expiratory volume in 1 second; LoS, length of stay; QoL, quality of life; 6MWD, 6-minute walk distance; FVC, forced vital capacity; pts, patients; V/Q, ventilation-perfusion.

PR before and after lung volume reduction surgery improved exercise tolerance, dyspnea, and QoL.[41] With the frequent coexistence of lung cancer and COPD, studies evaluating PR and increased activity in lung cancer have become more frequent. Despite multiple small trials evaluating physical activity in lung cancer patients, the evidence is difficult to generalize secondary to differences in the populations studied. That is, exercise is applied to patients in limited-stage, advanced-stage, perioperative, home-based, and inpatient settings. As such, disease presentations need to be reviewed individually to provide appropriate context.

Perioperative Exercise

Holden et al.[42] recognized the potential importance of activity in lung cancer in 1992. The group noted that lower exercise tolerance (through cycle ergometer, 6-minute walk

TABLE 2. Medical Studies (n = 11)

Author	Patients	Regimen	N	Result
Temel et al.[88]	NSCLC (stage IIIb or IV), ECOG 0–1	8 weeks of twice weekly inpatient exercise sessions during cancer therapy	25	Program completers (11) had improved symptoms, though <50% could complete the program
Andersen et al.[91]	Lung cancer, any stage (able to walk >50 m)	7 weeks of twice weekly, outpatient sessions	45	<50% completed regimen. Improved incremental and endurance shuttle walk tests
Quist et al.[37]	NSCLC (stages III and IV) or SCLC (extensive stage)	Inpatient and home-based training sessions	29	Exercise interventions feasible, though low home adherence. Improved VO2, 6MWD, and emotional well being
Cheville et al.[74]	Stage IV cancer (lung and colon)	Home-based, incremental walking and strength training; 8 weeks.	66 (34 with LC)	Improved mobility, fatigue, and sleep quality with low dropout rate
Andersen et al.[40]	Lung cancer (all stages)	Outpatient, twice weekly exercise sessions and unsupervised sessions alternating (9 weeks total)	51	51% completed training. Of completers, 69% continued daily physical activity. No change in VO2
Lin et al.[21]	Lung cancer (all stages)	Walking exercise for 6 months	107	Walking stopped in 36% of patients. Improved QoL
Henke et al.[73]	Advanced NSCLC and SCLC	Inpatient exercise sessions 5 days/ week during chemotherapy	46	29 completed. Improved physical function, hemoptysis, pain, and cognitive functioning scores; 6MWT strength, and dyspnea
Jensen et al.[93]	Metastatic cancer (23% lung)	Therapist evaluation of appropriate exercise or therapy	528 (125 LC)	Exercise/therapy feasible in >90% of patients
Kuehr et al.[92]	NSCLC (stages I–IIV) receiving chemotherapy or combined chemoradiation	Inpatient (5×/week) and outpatient (3×/week) sessions for 8 weeks	40	Exercise in feasible during cancer therapy and improved exercise tolerance, endurance, and strength
Granger et al.[15]	NSCLC (stages I–IIIB) before treatment	Step-counting for 6 months	50	GPS is feasible. NSCLC patients walk less than healthy patients
Granger et al.[85]	NSCLC (stages I–IIIB) during treatment	Step-counting for 6 months	50	NSCLC patients have less activity, are weaker, are more depressed, and less self-reported activity at 6 months

ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; COPD, chronic obstructive pulmonary disease; SCLC, small-cell lung cancer; 6MWD, 6-minute walk distance; QoL, quality of life; LC, lung cancer; GPS, global positioning system; MD, medical doctor.

distance [6MWD], and stair climbing) was associated with poorer postoperative outcome.[42] Conversely, higher maximum and peak oxygen consumption (VO_2) are associated with improved postoperative survival and improved all-cause mortality in early-stage NSCLC, respectively.[43,44] The suggestion that more active patients had better outcomes has given rise to significant interest in evaluation of lung cancer patients before surgery.

The treatment for early-stage lung cancer (stages I and II) is surgery,[45] and patients have increased surgical risk related to obstructive lung disease.[42,46] Unfortunately, pulmonary resection is associated with activity reduction at 1 month (larger resections being more debilitating)[47] and reduced functional health status and worse pain scores at 6 months.[48] As such, many activity studies have focused on preoperative and postoperative exercise regimens to try and minimize activity and functional loss.

The study approaches have been diverse. In 1997, Weiner et al.[49] showed that incentive spirometry and inspiratory muscle training before and after surgery increased muscle strength and forced expiratory volume in 1 second in COPD patients undergoing resection. A pilot study in 2006 showed that an 8-week inpatient PR program after surgery led to improvements in exercise capacity through 6MWD and cycle ergometry.[50] The following year, Cesario et al.[51] reported an observational study where inpatient PR and smoking cessation were achieved in patients previously refused for surgery. In eight patients, surgery was subsequently able to be performed because of improved exercise tolerance with no mortality. A similar oxygen uptake improvement was noted by Divisi et al.[52] with an outpatient PR program. These data suggest that perioperative exercise in lung cancer patients might improve both operability and operative risk, though the studies are small.

A 2013 Cochrane review with three RCTs and 178 patients evaluated exercise therapy in NSCLC patients within 12 months of undergoing lung resection. Perioperative exercise increased exercise capacity, although no change in QoL or strength was identified.[53] The review noted that more studies were needed as they identified potential benefit but recognized small sample size and concerns about bias in the existing studies.

Both preoperative and postoperative regimens have subsequently been examined separately, with mixed results. Small trials in 2007 and 2014 showed that preoperative exercise training increased 6MWD, increased VO_2, and improved QoL before surgery.[54,55] A RCT with 60 NSCLC patients confirmed improved oxygenation, exercise capacity, and length

TABLE 3. Reviews (n = 9)

Author	Patients	Regimen, Review Type	N	Result
Thompson et al.[2]	Lung cancer	Noninvasive interventions, systematic review	9 studies, 833 patients	Nursing program reduced breathlessness, nursing follow-up provided equal satisfaction and symptom control (vs. MD follow-up), and counseling improved QoL, exercise improved power perception
Shannon[71]	Lung cancer	PR, systematic review	N/A	PR may improve performance status , VO2, QoL, and exercise tolerance in lung cancer
Granger et al.[61]	NSCLC	Exercise intervention, systematic review	16 studies, 675 patients	Exercise interventions are safe. Preoperative and posttherapy interventions improved exercise capacity and symptoms. QoL changes were inconsistent
Payne et al.[36]	NSCLC (stages IIIB and IV)	N/A, systematic review	5 studies (203 patients)	Exercise is not harmful and may be beneficial (weight loss, strength, functional performance) though inconsistent
Singh et al.[62]	Cancer patients (predominantly lung cancer)	Physical exercise before surgery, systematic review	18 studies (966 patients)	Preoperative exercise may increase exercise capacity, improve QoL, and reduce LOS
Cavalheri et al.[53]	NSCLC undergoing resection	Exercise training within 12 months of lung resection (Postoperative), Cochrane Review	3 RCTs (178 patients)	Perioperative exercise may increase exercise capacity (through 6MWD). No change in QoL of strength
Rochester et al.[3]	Lung cancer patients	PR (4–7 weeks), systematic review	N/A	PR increases exercise endurance, VO2, strength and may reduce LOS, chest tube time, and postoperative complications. In patients with chemotherapy, increases strength, endurance, and QoL
Crandall et al.[63]	NSCLC patients treated surgically (stages I–IV)	Exercise regimen preoperative, postoperative, or both, systematic review	28 studies	Improved exercise capacity and strength; reduced fatigue, LOS, and postoperative complications
Rodriguez-Larrad et al.[64]	Lung cancer patients undergoing resection	Preoperative or postoperative PR, systematic review	8 studies (599 patients)	Preoperative-PR improves functional capacity and postoperative morbidity. Not seen with Postoperative PR

PR, pulmonary rehabilitation; LoS, length of stay; QoL, quality of life; 6MWD, 6-minute walk distance.

of stay (LoS) with a preoperative exercise regimen.[56] By contrast, a RCT on patients undergoing exercise intervention after thoracotomy showed no change in QoL or exercise tolerance (though perhaps a reduction in strength loss).[57] More recent trials in NSCLC patients utilizing postoperative exercise regimens have been mixed, finding potential change in walking distance but no change in strength or QoL.[58,59] Stigt et al.[60] even noted increased pain and limitations with an early postoperative PR regimen. These data suggest potential benefit in preoperative activity regimens but unclear benefit (and potentially higher morbidity) in postoperative regimens.

In addition, at least four reviews of perioperative exercise in lung cancer have been performed recently.[61–64] All reviews found that exercise interventions were safe. In Granger et al.'s[61] review, preoperative and postoperative activities were noted to increase exercise capacity and inconsistently effect QoL or symptom burden. Focusing on presurgical exercise interventions (n = 966 patients) with cancer (especially lung cancer), Singh et al.[62] found that exercise may improve physical function, improve QoL, and reduce LoS. Both 2014 reviews found benefit in exercise treatment perioperatively for NSCLC patients undergoing resection (exercise capacity, muscle strength, fatigue, postoperative complications, and LoS).[63] However, Rodriguez-Larrad et al.[64] only noted benefit in the preoperative regimen. In summary, the evidence appears to show that exercise is safe perioperatively, functional status is improved with variable effects, and preoperative interventions may be more beneficial (Tables 1 and 3).

PULMONARY REHABILITATION

After the National Emphysema Treatment Trial showed clinical benefit in COPD and subsequent trials showed reduced hospitalizations,[65] many tried applying PR to lung cancer patients. The 2013 ATS/ERS's statement on PR redefined the program's goals. Whereas the 2006 definition focused on a multidisciplinary approach to improve symptom burden and functionality in chronic respiratory disease patients, the 2013 definition further prioritizes "patient-tailored therapies" including exercise training, education, and behavior change to promote long-term adherence.[8]

Two groups have shown increased VO_{2MAX} with preoperative-PR after a 4-week regimen in patients with lung cancer and COPD.[52,66] A subsequent RCT showed that the oxygen consumption improvement was maintained postoperatively.[67] In addition to potentially offering surgery to patients previously considered "inoperable," PR may improve postoperative outcomes. In 2005, a small cohort of patients undergoing lobectomy received preoperative PR and postoperative chest physiotherapy. This regimen was associated with shorter stay, improved postoperative lung volumes, and reduced pulmonary complications.[68] Benzo et al.[69] showed preoperative PR in lung cancer patients with COPD resulted in shorter chest tube times and a nonsignificant reduction in LoS. A more recent prospective, single group trial by Mujovic et al.[70] showed improvements in forced expiratory volume in 1 second, vital capacity, 6MWD, and dyspnea after preoperative PR. Gains were the most significant in patients with the worst preoperative functional capacity. That is, the most benefit might be gained in the patients least likely to otherwise participate in exercise. PR has been shown to improve performance status, chemotherapy-induced fatigue, and exercise tolerance[71] with a 2014 review confirming improved exercise endurance, oxygen uptake, strength, endurance, and QoL.[3] Multidisciplinary implementation has also noted up to 54% smoking cessation.[35] To summarize, PR improves lung volumes, oxygen uptake, and exercise tolerance in patients with lung cancer and may improve "operability" while reducing postoperative complications (Tables 1 and 3).

Exercise in Advanced Disease

With encouraging results perioperatively, some groups have postulated benefit in advanced-stage lung cancer. Similar to COPD, functional capacity in advanced NSCLC is an independent predictor of survival with ~13% reduced risk of death per 50 m increase in 6MWD.[18] As one might expect, patients with advanced-stage disease have lower lung function, strength, walking distance, and QoL compared with patients with early-stage disease (stages I and II).[72]

Similar to perioperative studies, regimens have been diverse. Quist et al.[37] developed a regimen of group training (with a physiotherapist) and home training for patients with advanced NSCLC and extensive stage small-cell lung cancer . Although home adherence was low (<10%), benefits in oxygen uptake, exercise tolerance, and emotional well being were recognized from the group sessions.[37] Henke et al.[73] performed a RCT in advanced-stage lung cancer patients receiving inpatient chemotherapy; implementing daily endurance training and every-other-day strength training, the group noted improvements in physical function scores, self-reported symptoms (pain, neuropathy, cognitive functioning, and dyspnea), and exercise tolerance. A RCT in stage IV cancer (lung and colorectal) patients in 2013 showed that home-based exercise (walking and strength training) improved mobility, fatigue, and sleep quality.[74] These data suggest that increased physical activity may improve exercise tolerance and symptom burden in patients with advanced-stage lung cancer, although the location, duration, and intensity to be recommended are not clear. Though incompletely answered, these topics have been approached (Tables 2 and 3).

How Much Exercise?

Despite clear benefit to increased physical activity in cancer, a frequent question is "how much is enough?" The ATS/ERS 2013 PR statement recognizes this limitation: "In addition, it is not known how much improvement in physical activity is clinically relevant or meaningful (E32)."[8] For comparison, the American Heart Association has recommended 150 minutes per week of moderate intensity exercise for healthy patients.[75] By contrast, a small trial showed the average time to breathlessness in patients with stages III and IV thoracic cancer (NSCLC, small-cell lung cancer, and mesothelioma) was 4 minutes.[76]

The popularity of step counting with pedometers or accelerometers has been rising, providing direct comparison between the activity of healthy and chronically ill patients. Ten thousand steps per day is an often-cited goal in healthy patients,[77] although likely difficult to achieve in chronically ill patients. Estimates of normal step count in a healthy, active person have been 8000 to 10,000 steps per day.[77,78] Given that monitored step counts in patients with chronic illness (e.g., peripheral vascular disease and COPD) are much lower (3400–5680),[11,12,14] 10,000 steps per day seems difficult to reach in lung cancer. However, a recent study showed improved QoL associated with patients who walk for exercise,[21] suggesting less intense activity goals also have benefit. Furthermore, light intensity regimens in NSCLC after thoracotomy and stage IV cancer (lung and colon) showed potential to improve mobility, fatigue, functional status, QoL, and sleep quality using a step count[74] or walking and balance regimen.[79]

Step counting has also been advocated for chronically ill patients as a way to increase physical activity whereas not overburdening the patient. Regimens as simple as postoperative walking have shown improved lung volumes and physical function.[80] The promise of walking therapy is emphasized by the utility of the 6MWD as an outcome predictor in congestive heart failure,[6] COPD,[81] preoperative NSCLC,[42] and NSCLC patients undergoing chemotherapy.[82] In several studies, the 6MWD was a superior predictor to cardiopulmonary exercise testing.[42,81]

Again, studied regimens vary significantly. A 2006 review of physical activity in chronic disease reported benefit after moderate activity for 30 to 60 minutes per day or walking >1 hour per week.[83] One large trial (nonmetastatic breast cancer) suggested the greatest benefit occurred after walking 3 to 5 hours per week at an average pace.[84] Two recent observational, multicenter, prospective studies were published, confirming feasibility of tracking physical activity in NSCLC patients and providing useful data for future studies. A pretreatment study with 50 NSCLC patients (stages I–IIIB) noted less activity (6200 vs. 8563 steps/d in healthy controls), higher depression, and lower motivation in cancer patients at diagnosis.[15] In a similar study the same year (n = 50 patients with stages I–IIIB NSCLC), cancer patients were found to be weaker, have poorer nutrition, and self-reported activity that declined over 6 months after diagnosis compared with healthy controls.[85]

In summary, the research to date recognizes that chronically ill cancer patients have different exercise limitations than their healthy counterparts. Low intensity regimens such as daily walking or step-counting may provide a safe mechanism

to increase physical activity while identifying an individual patient's activity limits.

What Location?

One should also give thought to the ideal location of exercise. On one hand, an inpatient or physical therapist-guided session will optimize technique and safety. On the other hand, outpatient, self-directed regimens would certainly be cheaper and more convenient for the patient. Recent trials have shown feasibility, increased exercise tolerance, and symptom relief.[86,87] Many existing trials have utilized inpatient regimens.[34,37,50,57,58,73,88] However, there is some evidence that outpatient, self-directed regimens work as well or better. Brocki et al.[89] studied 78 patients in 2014 with a RCT, showing no QoL or self-reported functionality advantage to supervised exercise 12 months postoperatively. In fact, the trend was in favor of unsupervised exercise, though no significance was recognized. Though feasible, Jacobsen et al.[90] found no benefit in QoL or LoS utilizing a self-directed exercise regimen before stem cell transplant. These conflicting results may suggest that self-directed regimens have potential benefit, though patient selection, exercise regimen, and how to implement the program are not yet clear.

Barriers

Several barriers exist in how best to study and implement physical activity programs in lung cancer patients. Comorbid disease (especially COPD) and high symptom burden make completion of an aggressive exercise regimen challenging. In an NIH study in 2009, less than 50% of participants with lung cancer were able to complete an exercise study, despite improvements in dyspnea after completion.[88] Similarly, Andersen et al.[91] noted a more than 50% dropout rate, with patients completing the intervention found to have improved exercise tolerance, though no change in QoL or pulmonary function. In 40 NSCLC patients (stages II–IV), Kuehr et al.[92] showed 55% adherence of all patients (higher in patients immediately after the intervention) utilizing a combined inpatient and outpatient exercise intervention. Patients completing the exercise intervention had improvements in 6MWD and muscle strength. These studies highlight the evidence to date; i.e., exercise has benefit in lung cancer patients, though it is difficult to implement.

With the potential benefit of increasing activity coupled with concomitant activity-limiting lung disease, low intensity interventions are being applied. Even noninvasive regimens (i.e., breathing techniques or counseling) have shown some benefit in symptom burden.[2] Despite limited exercise tolerance, a large retrospective study of cancer patients receiving inpatient palliative care (n = 528, 24% lung cancer) showed that physical exercise or physical therapy were feasible in more than 90% of terminally ill cancer patients to achieve symptom relief, and physical exercise could be performed in 54%.[93] Pedometer studies present an attractive alternative. Recent studies in NSCLC patients report step count data collection 36–56% of the time, worsening with time from enrollment.[15,85] Feasibility studies of pedometer/accelerometer compliance have been performed in healthy,[94] COPD,[11,95,96] and NSCLC[15,85] patients. However, with frequent pulmonary comorbidity, cancer therapy, and symptom burden, maintaining step count compliance is difficult.

LUNG CANCER SURVIVORS

Another interesting group is lung cancer survivors (defined as patients surviving 5 years after diagnosis). Despite definitive treatment, lung cancer survivors have persistent symptom burden, especially fatigue.[97] Fatigue is more likely in patients with a history of pulmonary disease, depression, and anxiety[97] and less likely in those meeting physical activity guidelines.[97] With reduced symptoms in more active patients, the same benefits suggested in lung cancer patients (especially improved symptoms and QoL) might apply.

Similar to active lung cancer patients, recommendations for activity in lung cancer survivors are unclear. In a roundtable consensus statement for cancer survivors, the American College of Sports Medicine recommended avoiding inactivity, staying as active as conditions allow, and setting goals similar to healthy counterparts.[98]

How Does Activity Help?

The mechanisms of exercise as a therapy for cancer are incompletely understood. Suspected mechanisms include alteration in hormone metabolism, systemic inflammation, immune response, oxidative stress, cell cycle changes, increased p53, or increased apoptosis mediators with increased activity.[55,99–102] Several bench studies suggest an alteration in the body's immune response with exercise. In 1994, a mouse model with breast adenocarcinoma showed that moderate exercise can increase the phagocytic activity of intratumoral white blood cells, though no change in tumor size.[103] A 2013 study showed that Tai Chi in lung cancer patients (after resection) altered the ratio of interferon-producing CD_3 to IL-4-producing CD_3.[104] Karvinen et al.[105] showed that exercise training may attenuate leukopenia associated with chemotherapy in NSCLC therapy.

Because Virchow's triad (hypercoagulability, venous stasis, and endothelial injury) is likely present in many cancer patients, the association between lung cancer and venous thromboembolic (VTE) disease may also play a role in activity. Lung cancer patients have higher risk of VTE disease (including deep vein thrombosis and pulmonary embolism) compared with the general population,[106,107] worsened in those with advanced disease and undergoing chemotherapy.[108] VTE disease in lung cancer patients is associated with higher healthcare utilization,[109] though the effect on survival is unclear.[110,111] Combining higher morbidity without clearly worsened mortality suggests that VTE disease could impair QoL and activity tolerance in lung cancer patients. Activity, then, may improve venous stasis and reduce VTE disease burden in patients with lung cancer. This topic deserves further study.

Several animal studies have evaluated the effect of exercise on lung tumors. Higgins et al.[100] showed that daily exercise in mice with lung cancer slowed the growth of lung tumors. Paceli et al.[112] showed anaerobic activity reduced the incidence of lung tumors in mice exposed to Urethane. Subsequent investigators suggested that aerobic activity did

not show benefit because of reactive oxygen species burden in untrained mice, suggesting that exercise before the lung stressor might be more beneficial.[113]

FUTURE DIRECTIONS

There are still large gaps in the published literature to be addressed. No definitive, large, prospective trials have been performed to evaluate the benefit of exercise in lung cancer patients. Second, the ideal mode, intensity, location, and duration of exercise have yet to be established. The lack of consensus makes clinical recommendations challenging. Third, clinicians' goal should be to personalize an activity or exercise regimen for the individual patient. To optimize compliance, unachievable goals must be identified. However, there may also be harm associated with excessive anaerobic activity. Filaire et al.[102] note that intense exercise increases oxidative stress whereas moderate physical activity reduces oxidative stress, suggesting an ideal exercise intensity for maximal benefit. Although we might suspect more aggressive exercise regimens for younger, ostensibly more "functional" patients, a 2013 prospective trial in advanced lung cancer noted that the younger group of patients (<50 years) had worse pulmonary function and exercise correlates (perhaps because of more advanced disease at diagnosis).[114] Although poorer function in younger patients is probably not generalizable across different cancer groups, the finding does suggest that a single exercise protocol will not likely fit all patient groups.

CONCLUSION

In closing, applying exercise regimens or increasing physical activity in lung cancer patients has yet to show a mortality benefit. Though mortality is often the "standard procedure" in therapy implementation, QoL should not be overlooked as a treatment goal in itself, especially in patients with frequently incurable disease. Decreased quality at end of life can lead to premature death, and many cancer patients view QoL as important as the duration of their survival.[115] A landmark study in 2010 even showed that palliative care in patients with metastatic NSCLC could lead to increased survival.[116]

The evidence to-date suggests benefit of exercise in all stages of lung cancer and lung cancer survivors. The ideal mechanism of implementation, however, is not yet known. Exercise barriers are significant, yet survey studies showing patient desire for pretreatment counseling coupled with insufficient provider recommendations on the topic are concerning. Home-based, low-intensity exercise and recent success with pedometer studies in COPD and lung cancer populations show promise in monitoring and implementing activity prescriptions.

With multiple small studies and varied approaches, application to clinical practice remains difficult. This review shows uniform recognition that exercise and physical activity are safe in lung cancer, patients are requesting increased activity counseling, and multiple studies and reviews show potential clinical benefit in QoL, exercise tolerance, and postoperative complications. Furthermore, we know that inactivity in cancer patients is associated with worse outcomes.[3] Therefore, clinicians should (at minimum) consider PR early, counsel against inactivity, and encourage physical activity in lung cancer patients of all stages and lung cancer survivors.

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