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REVIEW ARTICLE

Optimizing treatment success in lung cancer: the role of functional testing

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ABSTRACT

Lung cancer, a pervasive and lethal global disease, presents formidable challenges, particularly in advanced stages. The widely used Eastern Cooperative Oncology Group Performance Score (ECOG-PS) faces limitations due to subjectivity and reliance on outdated measures. Recognizing the significance of functional capacity, assessments like the 6-minute walk test (6MWT), stair climb test (SCT), and 30-second sit-to-stand test (STS) have emerged as vital predictors of outcomes for patients with lung cancer. Acknowledging ECOG-PS limitations, there is a demand for dynamic and objective functional capacity measures. Systematized functional testing not only establishes a baseline but facilitates tracking changes during and after treatment. Research indicates that performance in these tests correlates with enhanced outcomes and reduced complications. Integrating systematic functional testing before treatment provides a more objective measure than ECOG-PS, aiding in outcome predictions and serving as a foundation for personalized prehabilitation and rehabilitation interventions, potentially elevating treatment success and patient survival.

Keywords: Functional capacity. Performance status. Prehabilitation. Rehabilitation.

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BACKGROUND

Lung cancer is the most frequently occurring deadly cancer disease worldwide. The survival rate for patients with lung cancer in general is 16-20% after five years but an average of 15-20 months for patients with advanced inoperable lung cancer[1]. The best chance for cure is in the early stage of the disease, where surgery and adjuvant treatment are the preferred option. More than 70% of patients with lung cancer are inoperable at the time of diagnosis.

In general, patients diagnosed with lung cancer are elderly patients (> 70 years) with a low socioeconomic status and who are deconditioned due to an inactive lifestyle. They often experience severe physical and psychological symptoms, such as decreased exercise capacity, muscle weakness, compromised health-related quality of life (HRQOL) and increased anxiety and depression levels, as a direct consequence of the disease[2,3].

When diagnosed, the stage and histology of the tumor decide what treatment (surgery, chemotherapy, immunotherapy, radiotherapy) patients will be offered. For oncological treatment within all cancer types, toxic side-effects, such as nausea, vomiting, mucositis or bone marrow toxicity (leukopenia), are common[4] but patients with advanced-stage lung cancer experience a higher burden of disease symptoms and treatment-related side effects, e.g. pain, fatigue, dyspnea, reduced emotional wellbeing and quality of life, compared to patients with cancer in the head/neck, prostate, breast, gynecological or gastrointestinal regions and in the bladder[5,6].

The expected toxicity must be balanced with the patient's ability to perform daily activities, -self-care and level of tolerance to toxicity to avoid the patient having unreasonable side-effects to the treatment which in the worst case could lead to the patient dying of the treatment and not the disease[7]. Thus, it is of crucial importance to assess and predict the patient's tolerability to treatment as accurately as possible.

PERFORMANCE STATUS

To evaluate the patient's suitability for the appropriate treatment, clinicians worldwide use the Eastern Cooperative Oncology Group Performance Score (ECOG-PS) which is based on the clinicians' estimate of the patient's ability to perform daily activities and their ability of self-care on a 0-5 scale[8]. The concept of performance status in cancer patients can be traced back to the Karnofsky Performance Status (KPS) scale developed by Dr. David A. Karnofsky in the 1940s. It was initially designed to assess the functional status of patients with chronic illness, including cancer. The scale ranged from 0 to 100, with higher scores indicating better functioning[9].

Later, in the 1980s, the Eastern Cooperative Oncology Group introduced a simpler performance status scale ranging from 0 to 5. Grade 0 is equivalent to being fully active. Grade 1 is restricted in strenuous activities but able to carry out housework. Grade 2 is being up and about more than 50% of the day. Grade 3 is being confined to bed or chair more than 50 % of waking hours. Grade 4 is completely disabled and confined to bed, and grade 5 is dead[8].

ECOG-PS is the most commonly used assessment tool in hospital settings and clinical trials for predicting survival and suitability to treatment. However, the scale has several significant limitations.

Firstly, the scale is based on the discretion of the doctor and can be influenced by the professional experience of the doctor and the interactions between the patient and the doctor[10]. It is a subjective measure and several studies have found poor reliability and validity in the evaluations[11,12]. Secondly, the ECOG-PS is an outdated measure. It is based on work from the 1940s and has remained unchanged since then despite major advances in cancer treatment modalities and changed safety profiles of the drugs[13]. ECOG-PS still has a prognostic value for survival but is no longer a good predictor of complications with the contemporary therapeutics[13]. For these reasons, the ECOG-PS provides a considerable risk of misclassification of tolerability to treatment with some patients classified/evaluated as either having sufficient ECOG-PS to tolerate treatment but in reality, having a too poor functional capacity to tolerate treatment or on the contrary having insufficient ECOG-PS to tolerate treatment but in reality, having a remaining reserve functional capacity.

The ECOG-PS scale does not provide a quantifiable measure for functional capacity and does not provide an aim for an intervention to counteract the decline, whereas a continuous and objective measure will monitor the patient's functional capacity closely and provide quantifiable measures functioning as targeted aims for prehabilitation or rehabilitation interventions when a decline is detected. When objective data is obtained for functional capacity, it will be possible to estimate the level of functional decline expected for future patients with lung cancer after surgery, during and after anti-neoplastic treatment with the possibility of intervening if the patient is at risk of a complicated course of treatment. Maintaining a high level of functional capacity and independence is in the top three rated issues affecting the quality of life of patients with lung cancer[14].

FUNCTIONAL CAPACITY

Functional capacity in patients in general refers to the ability to perform physical activities and daily tasks despite the impact of the disease and its treatments. Cancer and its treatments can often lead to various physical and functional impairments, affecting a patient's overall ability to function[15]. There are various tests designed to measure functional capacity, assessing an individual's ability to perform everyday activities including counting repetitions or timing activities[13]. Tests like the 6-minute walk test (6MWT), stair climb test (SCT), 30-second chair stand test (STS) and many more have been used in noncancer clinical populations to measure functional capacity and predict outcomes before and after treatment[16-18]. Along with the introduction and evolution of exercise to patients with cancer throughout the last two decades, functional capacity has been introduced to various cancer populations[19].

6-MINUTE WALK TEST

The 6MWT is a widely used clinical tool to assess functional capacity and exercise tolerance, particularly in individuals with respiratory and cardiovascular conditions[20]. The 6MWT is performed along a straight corridor of 20 meters. The patients are instructed to cover the longest distance possible by walking back and forth at their own pace in six minutes between two cones marking the lane[20]. The 6MWT was first introduced by Balke in 1963 and was initially developed to assess exercise tolerance in patients with cardiovascular disease, specifically those with heart failure[21]. The first study to evaluate the 6MWT in patients with lung cancer was Holden et al. in 1992[22]. This study evaluated two types of functional capacity test (6MWT, SCT) in prediction of death or prolonged mechanical ventilation after lung resection in high-risk patients. In total 16 patients underwent evaluation prior to resection. Eleven patients (group I) had minor or no complications (arrhythmia, atelectasis, pneumonia) and five patients (group 2) died within 90 days of surgery. Exercise testing showed that group I had a longer six-minute walk distance and a higher stair climb than group 2. The study also concluded that a six-minute walk distance of greater than 1,000 feet (305 m) and a stair climb of greater than 44 steps were predictive of successful surgical outcome. This was also confirmed in a recent review that found short distance of 6MWT and low number of steps were associated with higher mortality and complication after treatment for lung cancer[23]. The 6MWT is a validated and commonly used field walking test in patients with lung cancer[16,24,25], and the minimal important difference of the six-minute walk distance is estimated to be between 22 m and 42 m or a change of 9.5%[26].

There are a few studies that have examined the impact functional capacity has on the prognosis in patients with advanced lung cancer[27,28]. In a cross-sectional study, Kasymjanova et al.[28] used the 6MWT as an objective measure for functional capacity and found that a low functional level (< 400 meters) before the first cycle of chemotherapy was associated with earlier disease progression and death in patients with advanced lung cancer. They found that if the participants walked less than 400 m in a six-minute walking distance (6MWD), they had a 56 % increased risk of death. This study also showed that treatment with two cycles of chemotherapy reduced the functional level significantly. This was confirmed by Jones et al.[27] who found a reduced risk of death of 13% for every 50 m improvement in baseline 6MWT.

STAIR CLIMB TEST

The history of SCT, as a form of functional capacity assessment, dates back several decades. Stair climbing was first reported as a preoperative test and while the specific protocols can vary, the first protocol to our knowledge used in patients with lung cancer was from the study of Van Nostrand et al. in 1968[29]. Here patients were told to climb as many steps (11 steps per flight of stairs) as possible prepneumonectomy. The patients were asked to climb at a pace of their own choice the maximum number of steps and to stop only for exhaustion, limiting dyspnea, leg fatigue, or chest pain. The study found a higher mortality rate following in those patients unable to climb two flights of stairs[29]. As mentioned above Holden et al.[22] found a stair climb of greater than 44 steps were predictive of successful surgical outcome for patient with lung cancer who underwent resection. In 2004 Brunelli et al.[30]

found patients who were unable to perform a preoperative SCT had an increased risk of mortality after major lung resection. Reasons for not taking the test were the following: severe symptomatic musculoskeletal disease (one muscular dystrophy, 15 osteoarthrosis, two recent hip fractures, two recent femoral fractures); symptomatic neurological disease; severe peripheral vascular disease; cardiac ischemic disease; blindness; psychiatric disease; morbid obesity; cachexia. Therefore, nine of these 45 patients had clinical contraindications to perform the test (recent stroke, intracranial aneurysm, cardiac ischemic disease, blindness and psychiatric disease), whereas the other 36 patients were impeded to perform a proper exercise test by severe comorbidities. Half of these patients did not survive postoperative complications. In 2008 Brunelli et al.[31] once again confirmed that performance at an STC was reliably associated with postoperative morbidity and mortality and the group recommended the use of this simple and economic test in all lung resection candidates. Patients who perform poorly at the stair-climbing test should undergo a formal cardiopulmonary exercise test with measurement of oxygen consumption to optimize their perioperative management[29]. Finally, in 2012, Brunelli et al.[32] found in an observational analysis of a prospective database that included 296 patients who underwent pulmonary lobectomy for pathologic stage T1 N0 or T2 N0 non-small cell lung cancer (NSCLC) (2000 to 2008). Patients who received chemotherapy were excluded. The analysis showed preoperative symptom-limited stair-climbing test as preoperative cardiopulmonary fitness was a significant prognostic factor in patients after resection for early-stage NSCLC[32].

30-SECOND SIT-TO-STAND TEST

The STS is a functional performance test commonly used in clinical settings to assess lower limb strength and endurance, particularly in older adults. This test measures the time it takes for an individual to stand up from a seated position and sit back down as many times as possible within a 30-second period. The individual is asked to sit in a standard chair with arms folded across their chest. Upon a signal, the person stands up and sits back down repeatedly for 30 seconds. The total number of completed stands within the time frame is recorded.

The STS was first introduced by Jones et al. in 1999[33] as a simple and quick functional test to assess lower limb strength and balance in healthy older adults. The test was designed to be easily administered in clinical settings without the need for specialized equipment.

The STS has been validated and found to be a reliable measure of lower limb strength in frail, older adults with chronic obstructive pulmonary disease[34]. In 2012, Peddle-McIntyre C et al.[35] was the first group to introduce STS to a population of patients with lung cancer ($n = 15$). Patients were offered a progressive resistance exercise intervention three times a week for approximately 12 weeks. The STS was part of four tests measuring objective physical functioning and after the intervention, patients with lung cancer significantly improved the amount of stands in 30 seconds in the STS (baseline 11.2 ± 3.1, final 15.4 ± 3.8, diff. 4.2 [2.3 to 6.1]; $p < 0.001$). Although an improved STS is significantly associated with better HRQOL in older adults[36] and patients with prostate cancer[37], no studies (to our knowledge) have yet shown this in a population with lung cancer.

FUTURE IMPLICATIONS

The ECOG-PS is commonly used to evaluate a patient's suitability for treatment. However, it has limitations, including subjectivity and outdated measures. Assessing and predicting a patient's tolerability to treatment is crucial, considering the balance between expected toxicity and the patient's ability to perform daily activities. In a newly published report by Scott et al.[13], the accentuated need for an objective and dynamic measure of functional capacity is highlighted to accurately discriminate between patients across the continuum of cancer care in all settings.

Functional capacity, measured through various tests such as the 6MWT, SCT and STS, plays a significant role.

Studies suggest that better performance in these functional tests is associated with improved outcomes, reduced complications, showing prognostic value and enhanced quality of life in patients with lung cancer. The rationale and value for prehabilitation (physical exercise training before surgery) and rehabilitation (physical exercise training after surgery) in patients with lung cancer are emerging disciplines.

PREHABILITATION

Prehabilitation in patients with lung cancer refers to a proactive and multidisciplinary approach aimed at optimizing functional capacity and health of individuals before they undergo cancer treatment, such as surgery, chemotherapy, or radiation therapy. The goal of prehabilitation is to enhance the physical and psychological well-being of patients, improve their overall fitness, and prepare them for the potential challenges associated with cancer treatments[38] and the studies conducted so far have promising results. In a meta-analysis from 2023, Voorn et al. found after pooling sixteen studies (RCTs and observational studies) that prehabilitation reduces postoperative pulmonary complications (OR 0.45), postoperative severe complications (OR 0.51), and length of stay (mean difference -2.46 days), but not postoperative mortality (OR 1.11) after interventions of prehabilitation[38]. However, Voorn et al. also concluded that the risk of ineffectiveness was high for half of the prehabilitation programs and certainty of evidence was very low to moderate[39]. Tailoring prehabilitation interventions to the specific needs and abilities of each patient and the collaboration among healthcare professionals, including physical therapists, nutritionists, psychologists, and oncologists, to design a comprehensive care plan are imperative to reach the overall aim of prehabilitation of improving the patient's physical and mental resilience, reduce the risk of complications during and after cancer treatment, and enhance the potential for a faster and more successful recovery. By addressing the patient's functional capacity and overall health before treatment, prehabilitation aims to optimize outcomes and improve the patient's quality of life throughout their cancer journey[40,41].

REHABILITATION

Rehabilitation for patients with lung cancer involves a comprehensive and individualized program aimed at restoring and enhancing their physical, emotional, and functional capacity during and after undergoing cancer treatment[42]. The goal of rehabilitation is to help patients regain their functional capacity and independence, improve their quality of life, and cope with any lingering effects of the disease and its treatment. Our own research has demonstrated the effect of exercise interventions for both patients in an early stage of lung cancer and in an advanced stage of lung cancer. In 2018 and 2020, we found that early rehabilitation (14 days after surgery) compared to late rehabilitation (14 weeks after surgery) was feasible and although we saw no difference in the commencement (early versus late) of a postoperative exercise program for patients with lung cancer on exercise capacity, we found an improvement in quality of life (QOL) and a reduction in fatigue in the early rehabilitation group after 12 weeks of exercise[43,44]. In 2020, we published the to date largest study (n = 218) within advanced stage lung cancer during chemotherapy and/or radiation (the EXHALE study). We found a reduction in the level of anxiety and depression and an increase in all muscle strength outcomes and in social well-being in the intervention group compared to patients randomized to usual care[45] and based on our results we recommended future patients with advanced inoperable lung cancer should be considered for supervised exercise during their disease. The EXHALE program is implemented for patients with advanced stage lung cancer in the region of Copenhagen today. We also conducted a feasibility study in patients with locally advanced stage lung cancer undergoing concomitant chemoradiotherapy and demonstrated that daily moderate-to-high intensity cycle ergometer exercise was feasible, safe and well tolerated among newly diagnosed with locally advanced lung cancer[46].

Rehabilitation is typically an ongoing process that may continue for an extended period, depending on the individual's progress and needs. It plays a crucial role in helping patients' transition from active cancer treatment to survivorship, supporting their recovery and improving their overall quality of life[47].

PERSPECTIVE

Systematized functional testing for lung cancer patients before treatment presents considerable potential, offering a more objective assessment than the Performance Scale. Certain functional tests have demonstrated their ability to predict survival rates and post-treatment complications. This predictive capability can ensure patients receive the most appropriate treatment, thereby increasing the likelihood of survival/treatment success.

It also allows clinicians to establish a baseline measurement of patients' functional levels and track any changes during or after treatment. It sheds light on the effectiveness of rehabilitation and its correlation with factors like QOL. Furthermore, functional testing can assist in identifying patients who may be borderline candidates for treatment. Referring these individuals to prehabilitation can potentially prepare them for a specific treatment, thereby improving their chances of survival. Introducing functional capacity and subsequently intervening with prehabilitation or rehabilitation to new treatment modalities such as neoadjuvant chemotherapy have huge potential to improve functional capacity and health for patients with lung cancer.

Analysis of the Danish Lung Cancer Registers reveals a subset of early-stage patients who do not undergo surgery, with reasons unclear from the register data. Assessing their functional level could uncover candidates who could benefit from prehabilitation, thereby making them suitable candidates for surgery.

DISCLOSURES

The authors have nothing to disclose.

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