Published in final edited form as:

Respirology. 2014 January ; 19(1): 105–108. doi:10.1111/resp.12162.

Comparison of performance status with peak oxygen consumption in operable patients with non-small-cell lung cancer

Michael A. ROMAN¹, Graeme J. KOELWYN², Neil D. EVES², Whitney E. HORNSBY³, Dorothy WATSON³, James E. HERNDON II³, Leslie KOHMAN⁴, Gregory LOEWEN⁵, and Lee W. JONES³

¹Division of Respiratory Medicine, Rockyview Hospital, University of Calgary, Calgary, Alberta

²Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia, Kelowna, British Columbia, Canada

³Duke University Medical Center, Durham, North Carolina

⁴Health Science Center at Syracuse, State University of New York, Syracuse

⁵Roswell Park Cancer Institute, Buffalo, New York, USA

Abstract

Background and objective—In this era of increasing options for treatment of ‘surgical’ lung cancer patients, preoperative physiologic assessment of accurate patient selection is becoming more important. The variability in an objective measure of cardiorespiratory fitness (peak oxygen consumption (VO_{2peak})) across performance in operable non-small-cell lung cancer (NSCLC) patients enrolled in the Cancer and Leukemia Group B trial was compared.

Methods—Using a cross-sectional design, 392 NSCLC patients underwent an incremental cardiopulmonary cycling exercise test to symptom limitation with expired gas analysis to determine VO_{2peak} . Performance status (PS) was assessed using the Eastern Cooperative Oncology Group (ECOG) tool.

Results—There was a significant decrease in VO_{2peak} across increasing ECOG categories ($P < 0.0001$). However, there was a large range in VO_{2peak} for any given ECOG category with overlap between categories (ECOG 0: 5.0–31.5 mL/kg/min; ECOG 1: 4.3–24.8 mL/kg/min; ECOG 2: 8.9–21.9 mL/kg/min; ECOG 3: 3.3–11.7 mL/kg/min).

Conclusions—PS scoring systems do not provide a sensitive measure of functional status. Objective measures such as VO_{2peak} may be a useful in the clinical management of oncology patients.

Correspondence: Lee W. Jones, Duke Cancer Institute, Durham, NC 27710, USA. lee.w.jones@duke.edu.

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

Keywords

exercise; exercise test; non-small-cell lung cancer; performance status; physiology

INTRODUCTION

Performance status (PS) scoring systems are part of routine management of patients with thoracic malignancies. Scoring systems such as the Eastern Cooperative Oncology Group (ECOG) performance score provide a subjective evaluation of a patient's global physical functioning and are found to be strong, independent predictors of mortality in patients with thoracic malignancies.¹ Consequently, these tools are also routinely used to determine the optimal therapeutic approach as well as eligibility for clinical trials. Unfortunately, despite extensive clinical use, PS scoring systems have a number of limitations due to their subjectivity, poor reliability between users and inability to predict prognosis in patients with 'good' PS scores (i.e. ECOG 0–1; Karnofsky PS ≥ 70).²

Peak oxygen consumption ($\text{VO}_{2\text{peak}}$) is the gold standard measurement of cardiorespiratory fitness and an objective measure of physical performance. It is a robust predictor of mortality.^{3,4} It is most commonly determined in clinical populations using a cardiopulmonary exercise test (CPET) to symptom limitation. A symptom-limited CPET is a safe method for objectively evaluating functional capacity in a broad range of cancer patients including operable⁵ and inoperable non-small-cell lung cancer (NSCLC).⁶ Presurgical $\text{VO}_{2\text{peak}}$ is a strong, independent predictor of survival in NSCLC with higher $\text{VO}_{2\text{peak}}$ associated with a statistically significant 21–24% reduction in the risk of mortality compared with patients in the lowest $\text{VO}_{2\text{peak}}$ category.⁷

It is not known to what extent $\text{VO}_{2\text{peak}}$ varies across different ECOG PS groups in lung cancer patients. Furthermore, it is unclear if an objective measure of physical performance may be useful in the clinical management. It could be speculated that patients with a poor, physician-determined PS score could have preserved $\text{VO}_{2\text{peak}}$, and if so, these individuals may benefit from treatment reserved for patients with a better PS. Conversely, there also may be a proportion of cancer patients with a good PS but diminished $\text{VO}_{2\text{peak}}$; these patients would presumably be at increased risk of treatment morbidity and worse prognosis. Randomized trials are required to address this question. As an initial step, we sought to investigate the variability in $\text{VO}_{2\text{peak}}$ in a heterogeneous cohort of patients with NSCLC enrolled in the Cancer and Leukemia Group B trial. We hypothesized that mean $\text{VO}_{2\text{peak}}$ would decline across worsening PS scores, but there would be considerable variability and overlap in $\text{VO}_{2\text{peak}}$ between ECOG PS categories.

METHODS

Participants and setting

Full details regarding the study sample, recruitment and procedures have been reported previously.⁸ Participants were enrolled in the Cancer and Leukemia Group B protocol 9238, which was a study to assess the utility of $\text{VO}_{2\text{peak}}$ for prediction of surgical risk including

high-risk patients with low forced expiratory volume in 1 s. Inclusion criteria consisted of: patients with suspected stages I–IIIA NSCLC who were candidates for primary surgery with curative intent, adequate laboratory values (haemoglobin, partial arterial oxygen concentration, hematocrit, potassium) and estimated survival >2 years. Written informed consent was obtained from all participants. Ethics and institutional regulatory board approval was obtained at each medical institution.

Incremental CPET and ECOG performance score

To determine $\text{VO}_{2\text{peak}}$, an incremental, physician-supervised, CPET with 12-lead electrocardiogram monitoring was performed on an electronically braked cycle ergometer with breath-by-breath expired gas analysis according to CPET guidelines for clinical populations.^{9,10} MedGraphics metabolic measurement systems with standardized software were used by all institutions. The highest 30-s average VO_2 was recorded as the $\text{VO}_{2\text{peak}}$. For the primary analysis we chose a $\text{VO}_{2\text{peak}}$ above 14 mL/kg/min as a marker of more favourable functional status because this level of aerobic capacity is associated with decreased mortality in NSCLC.⁷ For exploratory analyses, a $\text{VO}_{2\text{peak}}$ cut-off <10 mL/kg/min was also used, as it has been associated with a very high risk of postoperative death.¹¹ ECOG PS was determined according to established guidelines.¹²

Statistical analysis

All statistical analyses were performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA). The initial analysis provided descriptive information on study outcomes. A one-way analysis of variance was used to determine difference in $\text{VO}_{2\text{peak}}$ between each ECOG group. A Tukey post-hoc test was performed when the analysis of variance determined a significant effect. Linear regression analysis was used to determine the association between $\text{VO}_{2\text{peak}}$ and ECOG score. An alpha-level of 0.05 was used for all analysis.

RESULTS

Peak VO_2 was collected on 392 subjects. The distribution of $\text{VO}_{2\text{peak}}$ scores in each ECOG category is presented in Figure 1. Mean $\text{VO}_{2\text{peak}}$ declined, as ECOG PS increased. Specifically, $\text{VO}_{2\text{peak}}$ was 17.2 ± 4.5 mL/kg/min in the ECOG 0 group, 15 ± 3.7 mL/kg/min for ECOG 1, 13.5 ± 3.1 mL/kg/min for ECOG 2 and 7.5 ± 4.2 mL/kg/min in ECOG 3 subjects. Differences among the four ECOG groups with respect to mean $\text{VO}_{2\text{peak}}$ scores were statistically significant ($P < 0.0001$). Post-hoc pairwise comparisons showed that $\text{VO}_{2\text{peak}}$ levels within the ECOG 0 group were significantly different from all other groups. As depicted in Figure 1, there was substantial overlap in $\text{VO}_{2\text{peak}}$ across different ECOG scores. The range of $\text{VO}_{2\text{peak}}$ was 5.0–31.5 mL/kg/min in the ECOG 0 group, 4.3–24.8 mL/kg/min in the ECOG 1 group, 8.9–21.9 mL/kg/min in the ECOG 2 group and 3.3–11.7 mL/kg/min in the ECOG 3 group.

There is considerable variation in $\text{VO}_{2\text{peak}}$ within each ECOG category. In the ECOG 0 and 1 categories, the $\text{VO}_{2\text{peak}}$ was >14 mL/kg/min in 78% and 62%, respectively, while in the ECOG 2 category, only 32% ($n = 9$) had a $\text{VO}_{2\text{peak}}$ >14 mL/kg/min. Only 2% of the ECOG

0 subjects and 8% of the ECOG 1 subjects had a $VO_{2peak} < 10$ mL/kg/min. This is compared with 7% (two subjects) in the ECOG 2 group. Twenty-one per cent of ECOG 2 patients ($n = 6$) had a $VO_{2peak} > 16$ mL/kg/min compared with 57% in the ECOG 0 group and 40% in the ECOG 1 group. All patients with ECOG 3 ($n = 3$) had a VO_{2peak} of < 12 mL/kg/min.

DISCUSSION

In this era of increasing options for treatment of ‘surgical’ lung cancer patients, preoperative physiological assessment of accurate patient selection is becoming increasingly important. As expected, patients with a better ECOG PS (i.e. 0 and 1) had a higher mean VO_{2peak} than those with the poor PS (i.e. ECOG 2–3). However, considerable variability exists in VO_{2peak} in operable NSCLC patients independent of ECOG PS score. Importantly, these differences indicate considerable discrepancy in assessment of physical PS between the widely accepted tool used in routine clinical practice (i.e. ECOG) and the gold assessment of cardiorespiratory fitness (VO_{2peak}). Given the importance of physical performance measurement in the oncology setting, objective measures such as VO_{2peak} may further assist prognostication and mortality risk prediction in patients with both operable and advanced malignancies.

Findings of this exploratory study indicate that approximately a third of patients classified with ‘good’ PS (i.e. ECOG 0–1) have significantly diminished VO_{2peak} (< 14 mL/kg/min). This finding may explain, in part, why PS systems may not accurately predict prognosis in patients with ‘good’ PS.² As a consequence, reliance on subjective PS scoring systems may result in misclassification of a significant proportion of NSCLC patients that, in turn, may have important implications for treatment selection, clinical trial eligibility, mortality risk prediction and therapeutic intervention. This finding corroborates our prior study showing considerable variability in functional capacity, as measured by a 6-min walk test, across Karnofsky PS categories in 171 patients with recurrent malignant glioma,² although this is the first study to exploit the gold standard assessment of cardiorespiratory fitness (i.e. VO_{2peak}). In other clinical settings, cardiorespiratory fitness significantly reclassifies patients for cardiovascular mortality risk beyond the widely clinically established Framingham risk score.¹³

It was also noteworthy that four ECOG 0 subjects (2%) and 14 ECOG 1 subjects (8%) had a VO_{2peak} below 10 mL/kg/min. These patients would potentially qualify for aggressive NSCLC treatment based on PS alone but would not be considered candidates for lung cancer resection surgery if pulmonary function testing was marginal.¹¹ Moreover, such patients have low cardiovascular reserve and, we speculate, are more likely to experience severe treatment-associated toxicity, therapy discontinuation and shorter survival. Taking this finding, with the significant variability in VO_{2peak} across ECOG groups, the use of VO_{2peak} could help optimize therapeutic management by identifying patients with a poor ECOG score who actually still have a high aerobic capacity. These individuals might benefit from aggressive combination therapy, which normally would be withheld due to a low PS. Alternatively, those with a low VO_{2peak} score but with an ECOG of 0–1 or Karnofsky PS 70 would likely not benefit from aggressive therapy. Guided therapy utilizing VO_{2peak} has

the potential to maximize both quality of life and survival gains for all patients, which may not be the case with current PS measures.

While CPET is the gold standard for assessment of cardiorespiratory fitness, it is not currently used as part of the decision-making process to guide lung cancer therapy. Our data, which shows a significant lack of congruency between PS and VO_{2peak} , may be an important first step to change this current paradigm. Future research is now needed to develop a parsimonious index to help further guide clinical decision-making in the optimization of treatment prescription to improve patient outcomes. Our data suggest that VO_{2peak} may be a useful tool to include in such an index and, in combination with other quantifiable measures, could strengthen the predictive capacity of how patients respond to treatment independent of PS.

There are several limitations in our study. This was a cross-sectional study intended to provide pilot data to illustrate the need for a more objective measure of functional capacity in NSCLC than PS. This study also included a limited number of patients with poor PS as patients with a prognosis of less than 2 years were excluded. Further study with a larger ECOG 2 population is required.

In conclusion, we provide preliminary evidence illustrating considerable variability in an objective measure of physical PS in comparison with a clinically established subjective measure (ECOG PS). Studies examining whether objective performance measures can more accurately reclassify NSCLC patients into prognosis risk categories than current measures are warranted.

Acknowledgments

The following institutions participated in this study: Alliance Statistical Center, Duke University Medical Center, Durham, NC (Daniel J. Sargent supported by CA33601); Dana-Farber Cancer Institute, Boston, MA (Harold J. Burstein supported by CA32291); Memorial Sloan-Kettering Cancer Center, New York, NY (Clifford A. Hudis supported by CA77651); Mount Sinai School of Medicine, New York, NY (Lewis R. Silverman supported by CA04457); Roswell Park Cancer Institute, Buffalo, NY (Ellis Levine supported by CA59518); State University of New York Upstate Medical University, Syracuse, NY (Stephen L. Graziano supported by CA21060); University of California at San Francisco, San Francisco, CA (Charles J. Ryan supported by CA60138); University of Chicago, Chicago, IL (Hedy L. Kindler supported by CA41287) and The University of Iowa, Iowa City, IA (Daniel A. Vaena supported by CA47642); University of Maryland Greenebaum Cancer Center, Baltimore, MD (Martin Edelman supported by CA31983). The research for Cancer and Leukemia Group B 9238 (Alliance) was supported, in part, by grants from the National Cancer Institute (CA31946) to the Alliance for Clinical Trials in Oncology (Monica M. Bertagnolli, Chair) and to the Alliance Statistical Center (Daniel J. Sargent, CA33601).

Abbreviations

CPET	cardiopulmonary exercise test
ECOG	Eastern Cooperative Oncology Group
NSCLC	non-small-cell lung cancer
PS	performance status
VO_{2peak}	peak oxygen consumption

References

1. Blanchon F, Grivaux M, Asselain B, et al. 4-Year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index. *Lancet Oncol.* 2006; 10:829–36. [PubMed: 17012045]
2. Jones LW, Cohen RR, Mabe SK, et al. Assessment of physical functioning in recurrent glioma: preliminary comparison of performance status to functional capacity testing. *J Neurooncol.* 2009; 94:79–85. [PubMed: 19212703]
3. Blair SN, Kannel WB, Kohl HW, et al. Surrogate measures of physical activity and physical fitness. Evidence for sedentary traits of resting tachycardia, obesity, and low vital capacity. *Am J Epidemiol.* 1989; 129:1145–56. [PubMed: 2729253]
4. Blair SN, Kohl HW, Paffenbarger RS, et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA.* 1989; 262:2395–401. [PubMed: 2795824]
5. Jones LW, Eves ND, Peterson BL, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical non-small cell lung cancer patients: a pilot study. *Cancer.* 2008; 113:3430–9. [PubMed: 18988290]
6. Jones LW, Eves ND, Mackey JR, et al. Safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer. *Lung Cancer.* 2007; 55:225–32. [PubMed: 17113185]
7. Jones LW, Watson D, Herndon JE, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer.* 2010; 116:4825–32. [PubMed: 20597134]
8. Loewen GM, Watson D, Kohman L, et al. Pre-operative exercise VO2 measurement for lung resection candidates: results of cancer and leukemia group B protocol 9238. *J Thorac Oncol.* 2007; 2:619–25. [PubMed: 17607117]
9. Jones LW, Eves ND, Haykowsky M, et al. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol.* 2008; 9:757–65. [PubMed: 18672211]
10. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2003; 167:211–77. [PubMed: 12524257]
11. Colice GL, Shafazand S, Griffin JP, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest.* 2007; 132:161S–77S. [PubMed: 17873167]
12. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5:649–55. [PubMed: 7165009]
13. Balady GJ, Larson MG, Vasan RS, et al. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. *Circulation.* 2004; 110:1920–5. [PubMed: 15451778]

SUMMARY AT A GLANCE

We provide preliminary evidence illustrating considerable variability in an objective measure of physical performance status ($\text{VO}_{2\text{peak}}$) in comparison with a clinically established subjective measure (ECOG performance status).

Figure 1.

Comparison of peak oxygen consumption (VO_{2peak}) to Eastern Cooperative Oncology Group (ECOG) performance status (PS) in a population of non-small-cell lung cancer patients. Dot represents mean, box represents standard deviation and whiskers the data range. *Differences between mean VO_{2peak} scores were statistically significant ($P < 0.0001$).