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Peak Oxygen Consumption and Long-Term All-Cause Mortality in Non-Small Cell Lung Cancer

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Abstract

Background—Identifying strong markers of prognosis is critical to optimize treatment and survival outcomes in patients with non-small cell lung cancer (NSCLC). We investigated the prognostic significance of preoperative cardiorespiratory fitness (VO_{2peak}) among operable candidates with NSCLC.

Methods—Using a prospective design, 398 patients with potentially resectable NSCLC enrolled in Cancer and Leukemia Group B (CALGB) 9238 were recruited between 1993 and 1998. Participants performed a cardiopulmonary exercise test to assess VO_{2peak} and were observed for death or until June 2008. Cox proportional models were used to estimate the risk of all-cause mortality according to cardiorespiratory fitness category defined by VO_{2peak} tertiles (<0.96 / 0.96–1.29 / >1.29 $L.min^{-1}$) with adjustment for age, gender, performance status.

Results—Median follow-up was 30.8 months, 294 deaths were reported during this period. Compared with patients achieving a VO_{2peak} <0.96 $L.min^{-1}$, the adjusted hazard ratio (HR) for all-cause mortality was 0.64 (95% CI, 0.46 to 0.88) for a VO_{2peak} of 0.96–1.29 $L.min^{-1}$, and 0.56 (95% CI, 0.39 to 0.80) for a VO_{2peak} of >1.29 $L.min^{-1}$ (p_{trend}= 0.0037). The corresponding HRs

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for resected patients were 0.66 (95% CI, 0.46 to 0.95) and 0.59 (95% CI, 0.40 to 0.89) relative to the lowest VO_{2peak} category (p_{trend}=0.0247), respectively. For non-resected patients, the HRs were 0.78 (95% CI, 0.34 to 1.79) and 0.39 (95% CI, 0.16 to 0.94) relative to the lowest category (p_{trend}=0.0278).

Conclusions—VO_{2peak} is a strong independent predictor of survival in NSCLC that may complement traditional markers of prognosis to improve risk stratification and prognostication.

Keywords

Exercise; lung cancer; all-cause mortality; cardiorespiratory fitness; prognosis

INTRODUCTION

Lung cancer is the second most commonly diagnosed malignancy among American adults accounting for approximately 15% of all cancer diagnoses.[1] An estimated 80% of lung cancer patients will be diagnosed with non-small cell lung cancer (NSCLC) and ~25% will present with early-stage (operable) disease.[1] NSCLC continues to be the leading cause of cancer-related mortality accounting for ~20% of all deaths.[1] Despite significant advancements in surgical procedures and introduction of postoperative chemotherapy, prognosis remains disappointing with five-year relative survival rates ranging from ~70% for patients with stage I disease to only ~25% for stage IIIA disease.[2] Further, there is considerable survival variability within stage due to the heterogeneous features of disease pathophysiology and broad range of clinical comorbid conditions at presentation.[3, 4] Thus, identifying accurate markers of prognosis to optimize treatment and survival outcomes in NSCLC is of major clinical importance.

Among the wide spectrum of predictive and prognostic markers that have been identified, performance status (PS) has consistently been demonstrated to be a strong, independent predictor of survival and a central component of ‘practical’ prognostic models in NSCLC.[3] PS is an assessment of the patient’s physical functioning and capability of self-care as recorded by oncology health professionals but such scoring systems are subjective and have poor inter-rater reliability. Moreover, these instruments fail to characterize the degree or potential causes of physiologic limitation, assess symptom responses to exertion or inform therapeutic intervention.[5]

Cardiorespiratory fitness, as measured by an objective exercise tolerance test, reflects the integrative ability of the cardiopulmonary system to deliver adequate oxygen and substrate to metabolically active skeletal muscles for ATP resynthesis.[6] Peak oxygen consumption (VO_{2peak}) provides the gold standard (direct) assessment of cardiorespiratory fitness. Direct or estimated measurement of VO_{2peak} is a well-established independent predictor of mortality in a broad range of non-cancer populations.[7, 8] Accordingly, formalized exercise tolerance testing can provide powerful prognostic and risk stratification information to clinicians in these populations. In contrast, cardiorespiratory fitness assessment is not used in the oncology setting other than to provide a preoperative functional assessment of pulmonary resection candidates.[5] Nevertheless, these tests may provide prognostic information beyond PS scoring systems currently used in the oncology setting. Here, we

investigate the prognostic significance of preoperative VO_{2peak} on long-term all-cause mortality among operable candidates with NSCLC.

MATERIALS AND METHODS

Participants and Setting

Full details regarding the study sample, recruitment and procedures have been reported previously.[9] In brief, study participants were enrolled in the Cancer and Leukemia Group B (CALGB) protocol 9238. CALGB protocol 9238 was a prospective, multi-institutional study to assess the utility of VO_{2peak} for prediction of surgical risk including high risk patients with low FEV_1. Patients with suspected stage I–IIIA lung cancer, with or without preoperative histological confirmation, who were candidates for primary surgery with curative intent were eligible for study participation. Additional eligibility requirements included adequate laboratory values (hemoglobin, PaO_2, hematocrit, potassium) and estimated survival >2 years.[9] Written informed consent was obtained from all participants prior to initiation of any study procedures.

Incremental Cardiopulmonary Exercise Testing

To determine VO_{2peak}, an incremental, physician-supervised, cardiopulmonary exercise test (CPET) with 12-lead ECG monitoring was performed on an electronically-braked cycle ergometer with breath-by-breath expired gas analysis according to CPET guidelines for clinical populations.[5, 10] All institutions used MedGraphics metabolic measurement systems with standardized electronic software. The exercise testing protocol was left to the discretion of the individual investigator. In general, however, preceding exercise, 3 minutes of resting metabolic data was collected before participants began cycling at 20W. Workloads were then increased 5–20W/min until volitional exhaustion or until a symptom-limitation was achieved.[5] Workload increments were determined by the medical history of the participant and at the discretion of the individual investigator. During exercise oxyhemoglobin saturation was monitored continuously using pulse oximetry (BCI, Hand-Held Pulse Oximeter, Waukesha, WN) while blood pressure was measured non-invasively by manual auscultatory sphygmomanometry every two minutes. Patients continued with usual medications on the day of testing. All data was recorded as the highest 30s peak VO_2 elicited during the CPET. Mean percentage of age and sex-predicted VO_{2peak} was calculated from the equations of Fitzgerald et al.[11] and Wilson and Tanaka[12].

Follow-up

Clinical endpoints were collected by the CALGB Statistical Center for at least 6 months post-surgery. Further follow-up survival data was obtained through the social-security death index.

Statistical Considerations

The Cox proportional hazards model was used to examine the impact of preoperative VO_{2peak} on all-cause mortality. The effect of VO_{2peak} ($L.min^{-1}$ and $mL.kg^{-1}\ min^{-1}$) was examined individually in these analyses with and without adjustment for the following covariables: age, gender, and performance status (0 vs. 1, 2). VO_{2peak} was categorized into

three groups for L.min^{-1} (<0.96 L.min^{-1}, 0.96–1.29 L.min^{-1} and >1.29 L.min^{-1}) and mL.kg$^{\cdot -1}$min^{-1} (<13.9 mL.kg$^{\cdot -1}$min^{-1}, 14.0–17.3 mL.kg$^{\cdot -1}$min^{-1}, and >17.4 mL.kg$^{\cdot -1}$min^{-1}). These categories were determined post-hoc via an unbiased tertile split of distributions of all patients. The median value of VO_{2peak} within each category was used as a predictor for linear trend in analyses. Survival time was defined as the time between registration and death; for patients remaining alive, survival was censored at the time of last known follow-up. Two sided p-values at the 0.05 level were used to determine statistical significance. All statistical analyses were performed using SAS Version 9.1.3 for Windows (SAS Institute, Cary, NC) by the CALGB statistical group. Graphics were performed using S-Plus version 8.0 for Windows.

RESULTS

Participant recruitment took place between August 1993 and July 1998. In brief, 422 patients were registered during the study period. Of these, 398 (94%) are included in this ancillary analysis. Major reasons for exclusion are missing adequate medical or exercise testing data (n=24).

Participant Characteristics

The participant demographic and clinical characteristics are shown in Table 1. Mean age was 64 ± 9 years, and 61% were male. For the total sample, 335 (84%) underwent surgical resection while 63 (16%) were deemed inappropriate for surgical resection at the determination of the attending thoracic surgeon. Thirteen patients died within 60 days of pulmonary resection. Overall, mean VO_{2peak} was 1.18 ± 0.42 L.min^{-1} and 15.8 ± 0.43 mL.kg^{-1} min^{-1}; VO_{2peak} (mL.kg^{-1} min^{-1}) was, on average, 36% below that for age and sex-matched normative data for sedentary individuals. FEV_1, FEV_1/FVC ratio, and D_LCO was 1.9 ± 0.8L (70% of predicted), 84 ± 18%, and 15.8 ± 6.0 mL.mm/Hg.min (73% of predicted), respectively.

Peak VO_2 and All-Cause Mortality

Median follow-up was 30.8 months. During this period, 294 deaths were recorded (74% of the total sample). The median time from the cardiopulmonary exercise test to death was 3.7 years (95% CI: 3.0 to 4.5) and 1.4 years (95% CI: 1.0 to 1.7) among surgical patients and non-surgical patients, respectively. For the entire sample, mortality rates declined across increasing absolute (L.min^{-1}) and relative (mL.kg.$^{-1}$min^{-1}) VO_{2peak} categories (adjusted P_{trend}= 0.0037 and adjusted P_{trend}= 0.08, respectively). Compared with patients achieving a VO_{2peak} <0.96 L.min^{-1}, the adjusted hazard ratio (HR) for all-cause mortality was 0.64 (95% CI, 0.46 to 0.88) for a VO_{2peak} of 0.96–1.29 L.min^{-1} and 0.56 (95% CI, 0.39 to 0.80) for a VO_{2peak} of >1.29 L.min^{-1} (Table 2; Figure 1). The 5-year relative survival rate from the time of exercise testing was 28% for patients achieving a VO_{2peak} <0.96 L.min^{-1} relative to 32% and 39% for patients achieving a VO_{2peak} 0.96–1.29 L.min^{-1} and >1.29 L.min^{-1}, respectively. Compared with a peak VO_2 <13.9 mL.kg.$^{-1}$min^{-1}, (<3.9 METs) values of 14.0–17.3 mL.kg.$^{-1}$min^{-1} (4 METs to 4.9 METs) and >17.4 mL.kg.$^{-1}$min^{-1} (>5.0 METs) were associated with a 21% and 24% reduction in the risk of all-cause mortality (Table 3; Figure 2).

The corresponding HRs for resected patients are also shown in Tables 2 and 3. Compared with a peak VO_2 <0.96 L.min^{-1}, values of 0.96–1.29 L.min^{-1} and >1.29 L.min^{-1} were associated with a 34% and 41% reduction in the risk of all-cause mortality. The adjusted *P* for trend was 0.0247. The adjusted *P* for trend was non-significant (p_{trend}=0.39) for relative VO_{2peak} (mL.kg.$^{-1}$min^{-1}) (Table 3). For non-resected patients, the HRs were 0.78 (95% CI, 0.34 to 1.79) and 0.43 (95% CI, 0.16 to 0.94) relative to the lowest VO_{2peak} (L.min^{-1}) category (p_{trend}=0.02) (Table 2). The median length of survival from the time of exercise testing was 13.3 months for patients achieving a VO_{2peak} <0.96 L.min^{-1} relative to 16.1 months and 28.0 months for patients achieving a VO_{2peak} 0.96–1.29 L.min^{-1} and >1.29 L.min^{-1}, respectively. The corresponding HRs for relative VO_{2peak} (mL.kg.$^{-1}$min^{-1}) were 0.34 (95% CI, 0.17 to 0.67) and 0.32 (95% CI, 0.14 to 0.71) relative to the lowest VO_{2peak} category (p_{trend}=0.0015) (Table 3; Figure 3). Results of all analyses were unchanged after excluding the 13 patients who died of surgical complications within 60 days of exercise testing.

DISCUSSION

Our data demonstrate a strong and graded inverse association between VO_{2peak} and all-cause mortality in patients with NSCLC. Compared with patients in the lowest VO_{2peak} categories, higher VO_{2peak} was associated with a statistically significant 21% to 24% reduction in the risk of mortality. These findings were consistent for age, gender, and performance status. The magnitude of risk reduction was even stronger for non-resected patients; in these patients, a VO_{2peak} > 0.96 L.min^{-1} or 13.9 mL.kg.$^{-1}$min^{-1} was associated with a 24% to 61% reduction in the risk of mortality relative to the lowest VO_{2peak} categories. Each 1.0 mL.kg.$^{-1}$min^{-1} increase in VO_{2peak} was associated with a 4% reduction in all-cause mortality.

The magnitude of risk reduction in the current study is similar to the prognostic value of VO_{2peak} in patients with ischemic heart disease and chronic heart failure. For example, Kavanagh et al.[13] reported that compared with a VO_{2peak} <13 mL.kg.$^{-1}$min^{-1} values of ≥13 mL.kg.$^{-1}$min^{-1} were associated with a 50% and 29% reduction in the risk of cardiac mortality and all-cause mortality among >2,380 women referred for cardiac rehabilitation. Each 1.0 mL.kg.$^{-1}$min^{-1} increase in VO_{2peak} was associated with a 10% reduction in cardiac mortality. Similarly, Gitt et al.[14] reported that a VO_{2peak} <14 mL.kg.$^{-1}$min^{-1} was associated with a 3-fold risk of death among 223 consecutive patients with heart failure. The strong prognostic value of VO_{2peak} has been confirmed by several research groups.[7, 8]

The objective measurement of cardiorespiratory fitness using maximal (with direct or estimated assessment of VO_{2peak}) or submaximal exercise testing for mortality prediction has not been exploited in the oncology setting. Several recent observational studies have provided the first evidence that self-reported physical activity (i.e., 9–18 MET-hrs.wk or ≥3–6hrs.wk of moderate paced walking) is associated with a ~30% to ~50% reduction in cancer-specific and all-cause mortality among early-stage breast and colorectal cancer patients.[15, 16] However, given the stark limitations of self-report assessment of physical activity exposure, there are several methods available to clinicians and investigators that enable the objective determination of cardiorespiratory fitness in the oncology setting. The method should be

determined by careful consideration of several factors including the purpose of the assessment (e.g., to determine exercise tolerance, prescribe exercise training, for cardiovascular diagnostics), the setting (e.g., hospital vs. community setting), and the cancer patient population (e.g., adjuvant vs. palliative care setting). These considerations have been reviewed in detail by our group elsewhere.[5] In this study, we selected CPET because it provides the most accurate assessment of cardiorespiratory fitness and has been found to be a stronger predictor of prognosis than estimated methods of VO_{2peak}.[17] Despite the stark advantages of CPET, studies investigating the prognostic importance of submaximal testing (without gas exchange measurement) as well as functional capacity testing (e.g., six minute walk test) in lung and other solid malignancies are required. Such tests may be more appropriate in frail or elderly palliative patients, or when conducting a large number of tests in a non clinic-based setting. To this end, Kasymjanova et al.[18] reported that six minute walk distance predicted prognosis in 45 patients with inoperable NSCLC.

The physiologic or molecular mechanisms underlying the association between VO_{2peak} and mortality in NSCLC remain to be elucidated.[19] In healthy populations, as well as those with CVD, the strong inverse relationship between cardiorespiratory fitness and CVD mortality is mediated by the association between high aerobic capacity (or exercise training-induced changes), established CVD risk factors, and possibly mitochondrial function.[20] These pathways likely contribute, in part, to the graded mortality reduction observed in this study among resected patients as CVD is responsible for ~20%–30% of deaths in this group.[3] In addition, high aerobic capacity and/or exercise-induced improvements in VO_{2peak} may also impact cancer-specific mortality via direct and/or indirect mechanisms.[3] For direct mechanisms, several postulated biologic pathways have been proposed to underlie the relationship between exercise and cancer progression including modulation of circulating metabolic and sex-steroid hormone concentrations, immune surveillance, and systemic inflammation / oxidative damage.[21] These pathways are centrally intertwined with the cardinal features of solid tumor progression. In contrast, higher VO_{2peak} and/or chronic aerobic training is postulated to be associated with lower circulating concentrations of metabolic and sex steroid hormones, enhanced immunity, and lower inflammation / oxidative injury.[21] These effects are thought to act in concert to inhibit tumor progression although scant direct or correlative evidence currently exists to support this notion.[22]

‘Indirect’ factors such as muscle wasting (atrophy) may also play a role. In this study, low absolute VO_{2peak} was strongly associated with a higher risk of mortality among resected patients whereas a weak association was observed for relative VO_{2peak} (adjusted for body mass) suggesting that other factors associated with body composition and/or muscle structure / function may be important in determining prognosis in NSCLC. Measures of skeletal muscle function, cross-sectional area, and whole-body composition (lean vs. body mass) are powerful predictors of mortality in non-cancer chronic diseases[23] (e.g., heart failure, pulmonary disease, and renal failure), as well as other cancer populations[24–26] that, similar to NSCLC, experience a wasting syndrome. It is postulated that muscle and adipose tissue provide important energy reserves when exposed to a metabolic catabolic disease.[27] The prognostic value of body composition / skeletal muscle function, in addition to cardiorespiratory fitness, in NSCLC is warranted.

Our findings may have implications for lung cancer mortality risk prediction and treatment. First, preoperative VO_{2peak} is a well-established risk stratification tool to determine surgical complication risk[28–31] and, on the basis on our findings, may have utility for long-term mortality prediction. VO_{2peak} may provide an unbiased assessment of physical performance not permitted by current subjective PS scoring systems which may, in turn, provide more accurate prognostication and personalized care. To this end, our findings suggest that a VO_{2peak} of <14 mL.kg.$^{-1}$min^{-1} (determined from unbiased tertile data segregation) may identify patients with poor prognosis although confirmation is required. Other physiological objective measures, other than cardiorespiratory fitness testing, such as FEV_1 may also be prognostic. In ancillary analyses, we found that mortality rates declined significantly across increasing absolute FEV_1 (P_{trend}= 0.0109) although FEV_1 became non-significant with the addition of VO_{2peak} in the multivariate model (analysis not presented). These preliminary results suggest that it is critically important to consider the integrative capacity of all organ components involved in O_2 transport (as measured by VO_{2peak}), as opposed to one component (such as lung function), when performing mortality risk prediction.

Second, our findings indicate that VO_{2peak} may be an attractive therapeutic target to improve clinical outcome in NSCLC. Numerous reports have provided unequivocal evidence that aerobic training is associated with a 15% to 20% improvement in VO_{2peak}[32] in 12–15 weeks while changes in cardiorespiratory fitness are associated with substantial reductions in cardiovascular mortality irrespective of baseline fitness.[33] Few studies have investigated the role of exercise training in NSCLC.[34] Our group recently completed two pilot studies investigating the feasibility, safety, and preliminary efficacy of high-intensity supervised aerobic training on peak VO_{2peak} among NSCLC patients in the preoperative (4–6 weeks of training)[35] and postoperative (14 weeks of training)[36] setting. VO_{2peak} increased 2.4 mL.kg.$^{-1}$min^{-1} (14.6%) and 1.7 mL.kg.$^{-1}$min^{-1} (11%) and preoperative and postoperative setting, respectively.[35, 36] Based on the findings of this study, these improvements would potentially translate into a ~10% and ~7% improvement in overall survival. In comparison, adjuvant chemotherapy is associated with an absolute 5.3% improvement in survival over 5 years.[37] This preliminary data provide ‘proof of principle’ that a supervised aerobic training is safe and well-tolerated among operable NSCLC patients. On the basis of this data, our group is conducting an ongoing trial investigating the optimal type of exercise training to improve VO_{2peak} in post-surgical NSCLC patients as well as change in the physiological mechanisms (i.e., organ components involved in O_2 transport) that govern VO_{2peak}.[38]

This study had several limitations. We only had information on death from any cause; the specific cause of death is not known. We also do not have information on disease recurrence and progression, disease stage or type and dose of any anticancer therapy (e.g., locoregional radiotherapy, chemotherapy, etc.), and the reasons for surgical ineligibility. Thus, analyses were not adjusted for these important covariates. Also patient selection bias may exist because of exclusion of patients deemed physically unable to perform exercise testing.

VO_{2peak} is a strong independent predictor of survival in NSCLC that may complement traditional markers of prognosis to improve risk stratification and prognostication. Our findings further indicate that exercise training and/or other therapeutic strategies that

augment VO_{2peak} may hold considerable promise for improving prognosis in patients with NSCLC.

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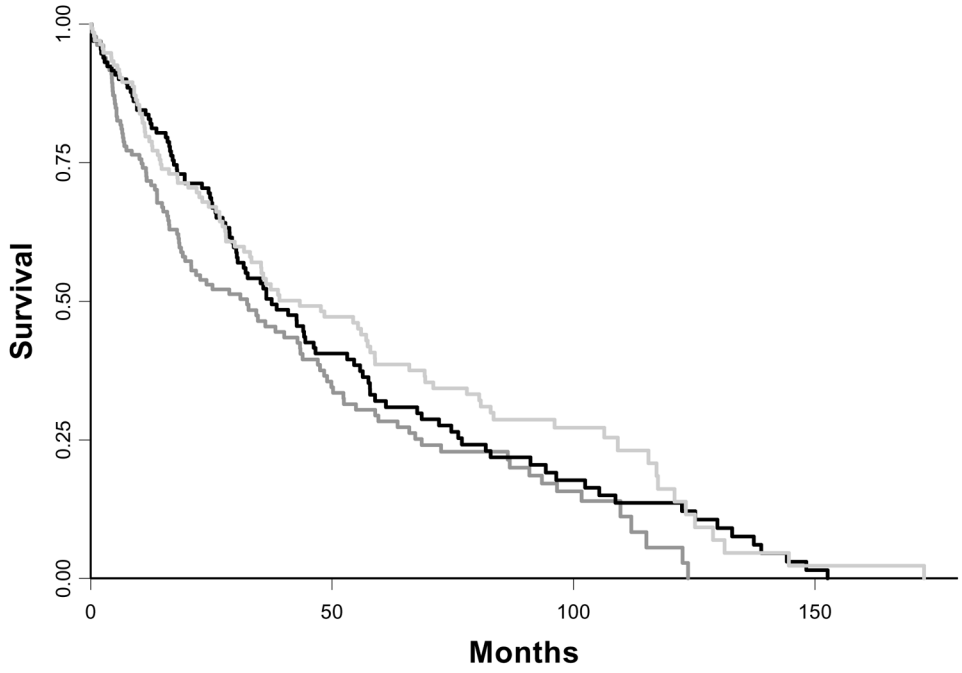

Figure 1.

Kaplan-Meier survival curves for all-cause mortality by VO_{2peak} ($L.min^{-1}$) category for all patients (n=398)

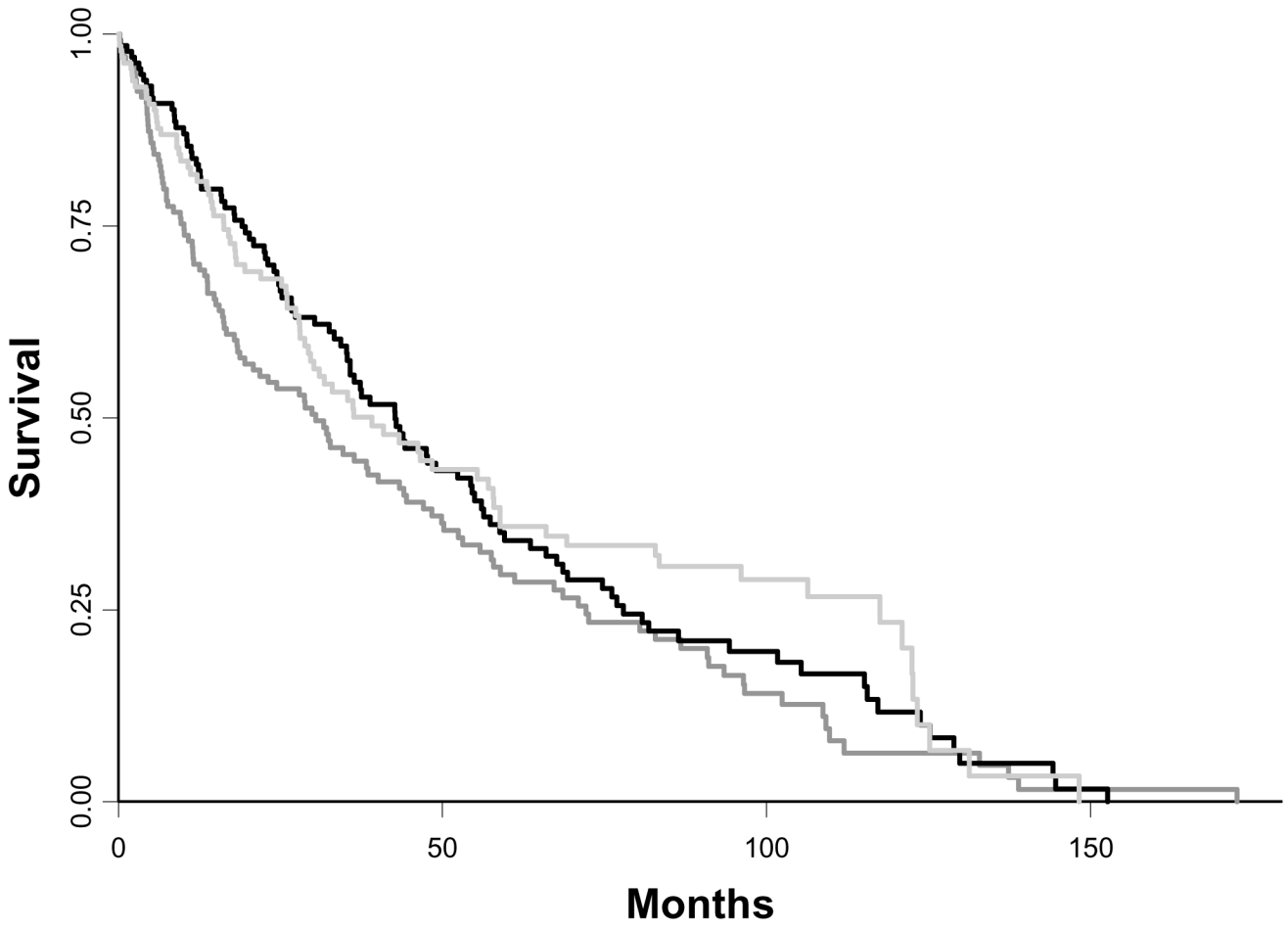

Figure 2.
Kaplan-Meier survival curves for all-cause mortality by VO_{2peak} (mL.kg.$^{-1}$min^{-1}) category for all patients (n=398)

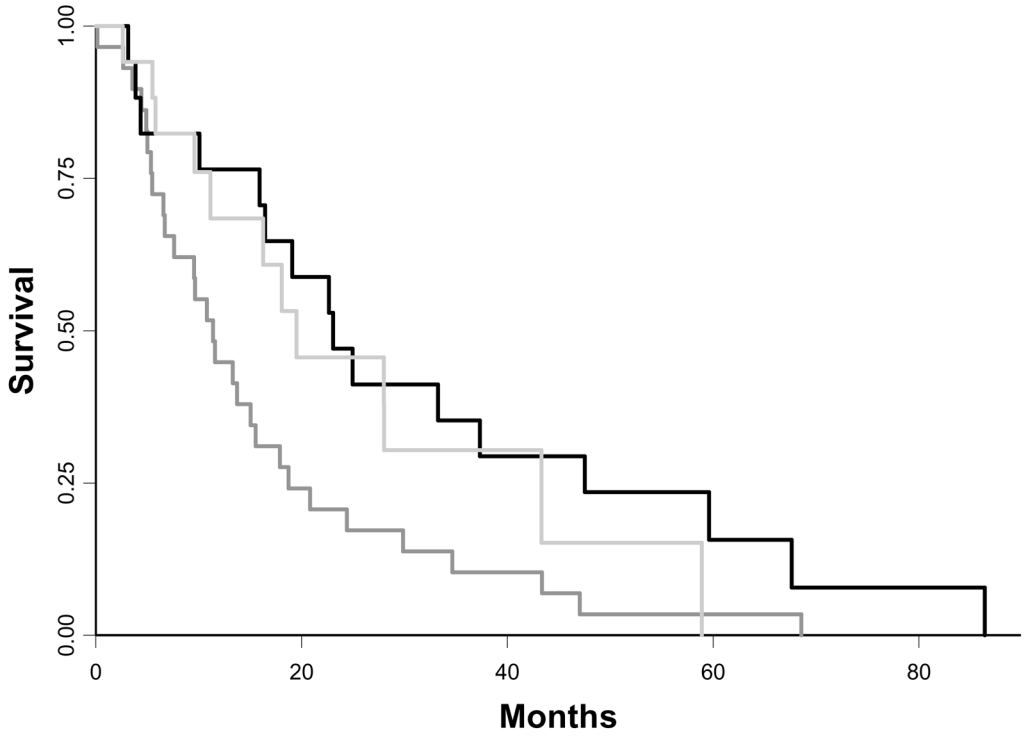

Figure 3.

Kaplan-Meier survival curves for all-cause mortality by VO_{2peak} (mL.kg.$^{-1}$min^{-1}) category for non-resected patients (n=63)

Table 1

Characteristics of the Participants

		VO_{2peak} (L.min^{-1})		
Variable	**All Subjects**	**<0.96 L.min^{-1}**	**0.96–1.29 L.min^{-1}**	**>1.29 L.min^{-1}**
Number (%)	398 (100)	132 (33)	131 (33)	135 (33)
Demographics				
Age, years	64 ± 9	67 ± 10	66 ± 9	62 ± 9
Male – no. (%)	242 (61)	37 (28)	87 (66)	118 (87%)
White Race – no. (%)	364 (91)	119 (90)	123 (94)	122 (90%)
Performance status – no (%)				
0	187 (47)	43 (33)	63 (48)	81 (60%)
1	174 (44)	69 (52)	61 (46)	44 (32%)
2	28 (7)	14 (11)	7 (6)	7 (5%)
missing	9 (2)	6 (5)	0 (0)	3 (2%)
Pulmonary Function Data				
FEV_1, liters,	1.9 ± 0.8	1.4 ± 0.6	1.9 ± 0.6	2.5 ± 0.7
FEV_1/FVC, %	84 ± 18	80 ± 20	82 ± 19	91 ± 15
D_{LCO}, mL.mm/Hg.min	15.8 ± 6.0	10.9 ± 3.6	15.0 ± 4.2	20.4 ± 5.5
Cardiorespiratory Fitness Data				
Resting Data				
Heart rate, beats/min	86 ± 16	89 ± 16	84 ± 15	86 ± 16
Systolic blood pressure, mmHg	131 ± 20	133 ± 22	131 ±18	129 ± 19
Diastolic blood pressure, mmHg	77 ± 11	76 ± 11	76 ± 11	77 ± 13
Peak Data				
Heart rate, beats/min	130 ± 21	126 ± 23	127 ± 21	139 ± 19
Systolic blood pressure, mm Hg	168 ± 26	163 ± 24	168 ± 28	173 ± 25
Diastolic blood pressure, mm Hg	88 ± 16	87 ± 16	87 ± 15	88 ± 18
VO_{2peak}, L.min^{-1}	1.18 ± 0.42	0.76 ± 0.14	1.13 ± 0.09	1.6 ± 0.33
VO_{2peak}, mL.kg^{-1}·min^{-1}, predicted (%)	15.8 ± 4.3	12.8 ± 3.3	15.5 ± 3.0	19.1 ± 4.1
Percent below age-sex normative VO_{2peak} (mL.kg^{-1}·min^{-1})	36	40	37	32

		VO_{2peak} (L.min^{-1})		
Variable	**All Subjects**	**<0.96 L.min^{-1}**	**0.96–1.29 L.min^{-1}**	**>1.29 L.min^{-1}**
V_E, L/min	48 ± 18	33 ± 9	47 ± 10	64 ± 17

Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. Abbreviations: VO_{2peak}, peak oxygen consumption; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; D_{LCO}, carbon monoxide diffusing capacity; V_E, ventilation

Table 2

Association Between VO_{2peak} ($L.min^{-1}$) and All-Cause Mortality

	VO_{2peak} ($L.min^{-1}$)						
Analysis	**<0.96**		**0.96–1.29**		**>1.29**		**P_{trend}**
All Patients							
No. of events	101		101		92		
No. at risk	132		131		135		
Median, Months	32.4	19.1 to 43.4	37.5	30.2 to 46.6	43.3	33.0 to 58.8	
5-year survival, %	28	20 to 37	32	23 to 41	39	29 to 48	
Unadjusted, HR	Referent		0.78	0.59 to 1.03	0.69	0.52 to 0.92	0.0146
Adjusted*, HR	Referent		0.64	0.46 to 0.88	0.56	0.39 to 0.80	0.0037
Resected Patients							
No. of events	72		86		79		
No. at risk	103		115		117		
Median, Months	42.8	28.7 to 52.4	44.0	35.2 to 57.5	55.4	35.3 to 69.3	
5-year survival, %	35	25 to 46	35	26 to 45	43	33 to 53	
Unadjusted, HR	Referent		0.84	0.61 to 1.16	0.77	0.56 to 1.06	0.1222
Adjusted*, HR	Referent		0.66	0.46 to 0.95	0.59	0.40 to 0.89	0.0247
Non-resected patients							
No. of events	29		15		13		
No. at risk	29		16		18		
Median, Months	13.3	5.5 to 19.1	16.1	9.6 to 23.1	28.0	11.1 to 37.3	
Unadjusted, HR	Referent		1.02	0.54 to 1.92	0.65	0.33 to 1.28	0.2354
Adjusted*, HR	Referent		0.78	0.34 to 1.79	0.43	0.16 to 0.94	0.0278

Abbreviations: HR, hazard ratio; VO_{2peak}, peak oxygen consumption

*Adjusted for age, gender, and performance status

Table 3

Association Between VO_{2peak} (mL.kg.$^{-1}$min^{-1}) and All-Cause Mortality

	VO_{2peak} (mL.kg.$^{-1}$min^{-1})						
Analysis	**<13.9**		**14.0–17.3**		**>17.3**		**P_{trend}**
All Patients							
No. of events	111		101		82		
No. at risk	134		133		131		
Median, Months	30.5	18.7 to 43.4	42.7	35.2 to 54.6	39.1	29.3 to 57.9	
5-year survival, %	30	22 to 38	34	25 to 43	36	26 to 45	
Unadjusted, HR	Referent		0.80	0.61 to 1.05	0.74	0.56 to 0.99	0.0403
Adjusted*, HR	Referent		0.79	0.59 to 1.04	0.76	0.56 to 1.04	0.0837
Resected Patients							
No. of events	82		85		70		
No. at risk	105		116		114		
Median, Months	44.0	31.7 to 57.5	43.9	35.8 to 56.3	46.2	31.0 to 66.0	
5-year survival, %	37	27 to 47	37	27 to 47	40	29 to 50	
Unadjusted, HR	Referent		0.91	0.67 to 1.24	0.84	0.61 to 1.16	0.2888
Adjusted*, HR	Referent		0.88	0.64 to 1.21	0.86	0.61 to 1.21	0.3937
Non-resected patients							
No. of events	29		16		12		
No. at risk	29		17		17		
Median, Months	11.4	6.7 to 15.5	23.1	15.9 to 47.5	19.5	11.1 to 43.3	
Unadjusted, HR	Referent		0.45	0.24 to 0.86	0.57	0.29 to 1.13	0.0385
Adjusted*, HR	Referent		0.34	0.17 to 0.67	0.32	0.14 to 0.71	0.0015

Abbreviations: HR. hazard ratio; VO_{2peak}, peak oxygen consumption

*Adjusted for age, gender, and performance status