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Early View

Original article

Association of performance at stair-climbing test with complications and survival after lung cancer resection in the VATS era: population-based outcomes

Olli Helminen, Johanna Valo, Heidi Andersen, Johan Söderström, Eero Sihvo

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Title: Association of performance at stair-climbing test with complications and survival after lung cancer resection in the VATS era: population-based outcomes

Authors: Olli Helminen MD, PhD[1,2], Johanna Valo MD[1,3], Heidi Andersen MD[4], Johan Söderström MD[4], Eero Sihvo MD, PhD[1]

[1]Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

[2]Surgery Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

[3]Department of General Thoracic and Esophageal Surgery, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

[4]Department of Pulmonology, Vaasa Central Hospital, Vaasa, Finland

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Contact information of the corresponding author:
Eero Sihvo, MD, PhD
Department of Surgery
Central Finland Central Hospital
Keskussairaalantie 19, 40620 Jyväskylä
FINLAND
tel: +358 142 691 811
e-mail: eero.sihvo@ksshp.fi

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Abstract

Introduction With a population-based cohort in the VATS era, we aimed to evaluate the value of stair-climbing test (SCT) on short- and long-term outcomes of lung cancer surgery.

Methods All patients operated due to primary lung cancer in Central Finland and Ostrobothnia from 2013 to June 2020 were included. For the analysis, clinical variables including the outcome of SCT and cause-specific mortality were available. Short- and long-term outcomes were compared between <11m (n=66) and >12m SCT (n=217) groups.

Results Patients with poor performance (<11 m) had more comorbidities and worse lung function but did not differ in tumor stage or treatment. No differences between groups were observed in major morbidity rate (10.6% vs. 11.1%, p=0.918) or median hospital stay (5 (IQR 4–7) vs. 4 (IQR 3–7), p=0.179). At 1-year, fewer patients were alive and living at home in <11m group (81.3%) compared to >12m group (94.2%), p=0.002. No difference was observed in cancer-specific 5-year survival. Non-cancer-specific survival (62.9% vs. 83.1%, p<0.001) and overall survival (49.9% vs. 70.0%, p<0.001) were worse in <11m group. After adjustment for confounding factors, SCT remained as a significant predictor for non-cancer-specific (4.28; 95%CI 2.10 to 8.73) and overall mortality (2.38; 95%CI 1.43 to 3.98).

Conclusions With SCT-based exercise testing, VATS can be performed safely, with similar major morbidity rate in poor performance group (<11m) compared to >12m group. Poor exercise performance increases non-cancer-specific mortality. Being a major predictor of survival, exercise capacity should be included in prognostic models.

Introduction

The guideline-based recommendation for treatment of early stage lung cancer is surgery. However, surgery is associated with significant morbidity and mortality. The thirty-day mortality reported recently by the European Society of Thoracic Surgeons Database was 2.6%.[1] At 90 days, the 30-day mortality rate of 2.3% in the Finnish population-based series almost doubled to 4.3%.[2] The risk of perioperative mortality and morbidity must therefore be weighed against the long-term benefits of surgery.

In both ERS/ESTS and ACCP guidelines, the preoperative physiologic assessment is recommended to include the evaluation of cardiovascular risk and lung functions.[3,4] With either FEV1 or DLCO below 80%, ERS/ESTS guidelines recommend formal cardiopulmonary exercise testing (CPET) with measurement of VO2 max. For this formal CPET, in both ACCP and ERS/ESTS guidelines, a stair-climbing test (SCT) can be used as a screening test. In both guidelines, the threshold for suboptimal performance was set at 22 m.[4]

In the era of open lung cancer surgery, several studies have evaluated the role of SCT in the assessment of preoperative exercise capacity and complication risk. According to a recent review, SCT is able to predict complication.[5] In this review, the threshold for a poor result and referral to formal cardiopulmonary exercise testing was set at 10 m.[5] The role of SCT in the preoperative physiologic assessment has, however, never been evaluated in the era of minimally invasive lung cancer surgery.

We have shown, at the population level, the benefits of modern guideline-based approach in the preoperative evaluation and treatment of lung cancer patients for the short- and long-term outcomes.[6] The preoperative physiologic assessment included symptom-limited SCT and selective referral to formal cardiopulmonary exercise testing with a result of less than 9 m. Our aim was, in the era of VATS surgery, to evaluate the predictive value of this stair-climbing-based testing of exercise capacity on the short- and long-term outcomes of population-based lung cancer surgery. The primary outcome was major complications. Secondary outcomes were alive and able to live at home at 1-year after surgery, and 5-year estimated overall and disease-specific survival. We hypothesized that SCT could predict these outcomes.

Materials and methods

Design

Since September 2012, a modern guideline-based treatment of lung cancer has been implemented in Central Finland Central Hospital.[6] From Ostrobothnia, lung cancer surgery was centralized to Central Finland Central Hospital in October 2014. Between January 1, 2013, and June 30, 2020, all patients diagnosed and resected with a primary lung cancer in Central Finland and Ostrobothnia were included in this population-based cohort study. Patients who underwent surgical resection were identified from hospital records and the prospective surgical database, and confirmed by data from the Finnish Cancer Registry. The follow-up ended on August 10, 2020. The acquisition of individual patient data from hospital records was approved by the local hospital districts. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1349/5.05.00/2015) and Statistics Finland (TK53-1410-15) approved the study.

Data collection

All Finnish residents are listed by their individually unique and immutable 10-digit national registration numbers in the hospital databases and several national databases. This allows reliable identification of patients from hospital records and the Finnish Cancer Registry, as well as linkage of data. The Finnish Cancer Registry is population-based and covers all parts of Finland. Registration includes the municipality and, therefore, the hospital district where the patient lives. According to Finnish health care policy, all hospital districts are responsible for arranging specialized care for residents in their area. In Central Finland and Ostrobothnia, which had a total population of 456,976 as of December 31, 2017 (8.3% of the Finnish population), the treatment of lung cancer is organized by Central Finland Central Hospital and Vaasa Central Hospital, respectively. Using the histopathological, clinical follow-up, and discharge registries of the two hospitals, all patients diagnosed with primary lung cancer who underwent lung resection with curative intent between January 1, 2013, and June 30, 2020, were identified. Cross-linking of Finnish Cancer Registry data and hospital databases confirmed identification of all surgical cases. From 2015, a prospective surgical database established in Central Finland Central Hospital in 2012 provided the surgical cases. Variables in this database were not designed for this study and the data for all study patients were therefore re-reviewed from hospital records.

Evaluation of physical performance

The protocol of preoperative evaluation in the clinical practice and the formation of study groups is presented in Figure 1. All surgical candidates were sent a preoperative questionnaire including two questions on physical performance: the ability to climb stairs and walking speed. A reported good physical performance included the ability to climb 3 or more flights of stairs and walk at least at a speed of 5 km/h. The physical performance was further confirmed by the operating surgeon at the preoperative clinic. Only those patients (n=58) able to do heavy work, to climb more than 4 floors routinely or participate in strenuous sports such as cross-country skiing were not tested further before surgery. These patients were placed in the study group >12 m. Four patients were excluded from the analysis due to lack of any reported data of physical performance. Of 287 operated patients, 221 underwent a symptom-limited SCT up to a maximum of 4 flights (14.1 m). Only 2 candidates for a pneumonectomy were tested up to 5 flights (17.6 m). Of these 221 patients, 159 climbed more than 12 m. In this group, 9 patients (5.7%), mostly early referrals from Ostrobothnia, underwent a formal CPET with a mean VO2max of 18.1 mL/kg/min. These 159 patients together with the previously mentioned 58 patients formed the study group including 217 patients able to climb >12 m (3.5 flights ie. 12.3m). Since during the test patients finished their climb after a full or half flight, there were no results between 3 and 3.5 flights (or 10.6m to 12.3). In this study, we used 3 flights of 10.6m as a threshold for poor exercise capacity being very close to previously recommended level of 10m.[5] Of 221 patients tested, 66 climbed this10.6m or less and formed the <11 m study group. Of these 66, 42 climbed 3 flights equal to 10.6 m. Although in our practice these patients are considered to be at increased surgical risk, they undergo a formal CPET only very selectively. In this group, the rate was 11.9% (n=5) with a mean VO2max of 14.2 mL/kg/min. Those patients unable to climb more than 2.5 flights (8.8 m) are recommended to undergo a formal CPET and were considered unsuitable for surgery with VO2max under 10 mL/kg/min. The rate of formal CPET in this group of patients (n=22) was 66.7% with a mean VO2max of 12.3 mL/kg/min.

Outcomes and definitions

The 8th edition of the TNM classification was used for staging. This required recoding all necessary surgical patients accordingly. Primary outcomes were major complications. Secondary outcomes were alive and able to live at home at 1-year after surgery, and 5-year estimated overall and disease-specific survival. Complications were graded according to the Clavien-Dindo classification.[7] Major complication was defined as higher than class II. Secondary outcomes were hospital stay, intensive care unit stay, and home discharge rate. The ability to live at home was defined as the proportion of patients, out of all operated patients, who, one year after surgery, were living at home instead of a nursing facility, hospital, terminal care unit, or death.

Statistical analysis

We constructed Kaplan-Meier survival curves according to the life table method to visualize the crude all-cause and recurrence-free survival up to 5 years after surgery. Proportions, means, and median values of other measured variables were compared using the chi-squared test, Mann-Whitney U-test, and T-test as appropriate. The regression models were adjusted for potential confounding factors: age ≥80 years, sex (male, female), Charlson comorbidity index ≥5, ppoFEV1 ≤50%, ppoDLCO ≤50%, tumor histology, tumor stage (I, II, III-IV), neo- or adjuvant treatment (yes/no). For regression analysis, multiple imputation was performed to cover missing values. The following proportion of variables were imputed: smoking in 2.4%, ppoFEV in 1.4% and ppoDLCO in 7.7% For patients who received neoadjuvant treatment, clinical stage was used instead of pathological stage. All statistical analyses were performed using IBM SPSS 26.0 (IBM corp., Armonk, NY, USA).

Results

Preoperative patient evaluation

Overall population-based outcomes in 287 operated patients had major morbidity rate of 10.8%, 30-day mortality rate of 0.3% and 90-day mortality rate of 1.4%. One-year and 5-year overall survival rates were 94.0% and 64.2%. Four patients were excluded due to missing reported data of physical performance. The median age of the 283 included patients was 71. The majority were men (63.6%), had a CCI equal to or more than one (73.9%), and were diagnosed with adenocarcinoma (59.4%) and pathological stage IA disease (50.2%). Overall, 66.7% of all operated patients had either FEV1% or DLCO <80%. Patient baseline characteristics stratified by the result of SCT are presented in Table 1.

Comparison by physical performance and treatment

Surgical procedures and related oncological therapies are summarized in Table 2. Overall VATS rate and the rate during the last 5 years was 78.7% and 88.2%, respectively. This rate or the type of lung resection did not differ between the groups. A trend (p=0.088) in the rate of mediastinal lymphadenectomy was detected between <11 m and >12 m groups (78.8% vs. 85.7%). A similar trend (p=0.088) in lymph node yield was observed with medians of 10 and 12, respectively (Table 2).

Short-term outcomes

Of 283 included patients, rates of major morbidity was 10.8%, 30-day mortality 0.4% and 90-day mortality 1.4%. The specific cause of death at 90 days was cardiovascular or respiratory in all cases (Table 3). Of these 4 deaths, 2 occurred at home, both in the <11 m group after normal discharge. Physical performance had no effect on short-term complications (Table 2). The major complication and 90-day mortality rates in the <11 m and >12 m groups were 10.6% and 11.1% (p=0.918) and 3% and 0.9% (p=0.204), respectively. Median hospital stay was 5 (IQR 4–7) and 4 (3–7) days (p=0.179). With a cut-off of 9m in physical performance between groups, major morbidity rates are 20.8% (5/24) in the poor performance group and 10.0% (26/259) in the better performance group (p=0.105).

One-year outcome

At 1 year, a major difference between the <11 m and >12 m group was observed in the number of patients living at home (81.3% vs. 94.2%, p=0.002), Table 2. The leading cause in the <11 m group was other than lung cancer-specific in 14.1%, compared to 3.2% in the >12 m group (p=0.001). Lung cancer-specific death or disease recurrence was the reason for not living at home in 4.7% and 2.6%, respectively. In adjusted analysis, the risk of inability to live at home 1 year after surgery was associated with the result of SCT, age at surgery, comorbidity burden, ppoDLCO% and stage (Table 4).

Long-term outcome

Overall survival was worse in the <11 m group (49.9% vs. 70.0%, p<0.001, Figure 2a). No difference existed between study groups in lung cancer-specific 5-year survival (Figure 2b), but a major difference was seen in non-cancer-specific survival (Figure 2c, Table 2). Of the 31 deaths in the <11 m group, the cause of death was lung cancer in 9 (29.0%) patients, and of the 42 deaths in the >12 m group, the cause of death was lung cancer in 23 (54.8%) patients (p=0.029). Causes of death in the study groups are listed in Table 3.

Age ≥80 years (Figure 3a, p=0.201), ppoFEV1% ≤50% (Figure 3b, p=0.294), ppoDLCO% ≤50% (Figure 3c, p=0.085) had no significant impact on non-cancer-specific survival. Decreased non-cancer-specific survival was detected in patients with increased comorbidity burden (CCI ≥5) Figure 3d, p=0.018). None of these variables had a significant effect on cancer-specific survival (data not shown).

In the multivariable analyses of 5-year outcomes, the result of SCT was an important risk factor for both overall (HR 2.38, 95%CI 1.43–3.98) and non-cancer-specific (HR 4.28, 95%CI 2.10–8.73) mortality (Table 4). The only other similarly important predictor was Charlson comorbidity index ≥5 (Table 4).

Discussion

This study differentiates at the population-level the influence of exercise capacity measured by SCT on outcomes of lung cancer surgery in the VATS era. VATS can be performed safely, with a similar major morbidity rate in the poor performance group (<11 m) compared to the >12 m exercise capacity group. A poor performance in SCT had a major impact on the ability to live at home 1 year after surgery and on long-term non-cancer-specific and overall survival. Being a powerful predictor of survival, exercise capacity should be included in routine prognostic models.

In ERS/ESTS and ACCP guidelines, based on the data from open surgery era, the SCT threshold for safe lung cancer surgery was set at 22 m.[3,4] Contrary to these recommendations, in our practice in the VATS era we set the threshold in SCT for increased risk at 11 m and the threshold for formal exercise testing at 9 m. In our highly selective formal testing policy, a contraindication for any lung cancer surgery, as in both ERS/ESTS and ACCP guidelines, was a peak oxygen consumption of less than 10 mL/kg/min.[3,4] By following these modified guideline-based recommendations in exercise testing in this population-based series, a low 0.3% 30-day and 1.4% 90-day overall mortality was reached. No difference was detected between the SCT groups in the rate of any complications, major morbidity, mortality or hospital stay. With a high VATS rate of 88.2% during the last 5 years together with a segmentectomy rate of 33.9% in our population-based series, SCT can be used as a safe screening tool for a highly selective formal CPET. Therefore, in the VATS era, SCT can be relied on more widely in exercise testing, and the threshold for a poor test result and need for formal exercise testing could be set even below the recently recommended threshold of 10 m.[5] With a 9 m cut-off in this study, a trend of increased major morbidity rate in the poorer performance group (20.8% vs. 10.0%) is evident. With current ERS/ESTS recommendations, the need for formal CPET in this series would have been 66.7%. With our SCT screening and highly selective formal testing, the need for CPET is around 10% at the population-level. This limits the costs of preoperative formal stress testing without compromising the outcome of lung cancer surgery.

In addition to preventing unnecessary morbidity and mortality, the aim of the preoperative physiologic evaluation is to prevent chronic disability.[4,8] Survival and the ability to live at home at one year postoperatively was significantly reduced in the <11 m group, with a rate of 78.8% compared to 94.2% in the >12 m group. Multivariable analysis revealed the following independent predictors for this outcome: performance in SCT, age, Charlson comorbidity index, ppo DLCO and

stage III disease. The cause of death was rarely cancer-related. Therefore, poor performance in SCT is associated with early death related to other causes and chronic disability after surgery. Overall, exercise capacity is a better predictor of survival than cardiovascular risk factors.[9] Of previous predictors of 1-year outcome, only performance in SCT and Charlson comorbidity index were predictors of overall long-term mortality in the multivariable analysis. Contrary to a previous suggestion, worse survival associated with impaired physical performance was solely explained by the increase in death from non-cancer causes.[10] An increased risk of death due to lung cancer has previously been associated with a lower VO2max, a shorter shuttle walk distance, poorer exercise tolerance in SCT, or even poorer self-rated physical fitness.[10–12] This prognostic role has several potential consequences. First, any risk models for long-term survival such as the STS-GTSD-Medicare long-term risk model or Eurolung2 should include some form of exercise testing.[13,14] Second, besides stage, any comparisons of outcomes between treatment modalities such as SBRT and surgery should include exercise capacity, in addition to comorbidity burden and lung functions. Third, physical fitness is a modifiable prognostic factor and could therefore be improved by rehabilitation programs.[15] Last, exercise tolerance could potentially be incorporated in future multifactorial mixed prognostic models to improve the selection of the most appropriate treatment modality for high-risk patients.

In addition to climbed height, desaturation, heart rate change and time are exposures that could be measured during the SCT. Due to a lack of data we could not use desaturation in the analysis. To simplify the testing, we did not include time or heart rate change as exposures, either. Although the average speed of ascent is a good predictor of VO2max, the climbed height correlated well with the measured VO2max in the relatively few CPET patients in this study.[16] Furthermore, a relatively slow ascending speed of 11 m/min, of which most people are capable, predicts VO2max of 15 mL/kg/min.[16] Therefore, patients were instructed to climb at their own speed without stopping until exhaustion or at least 4 floors equaling 14.1 m. In most patients, their maximal height was not reached and none of the patients were tested up to the guideline threshold for safe surgery of 22 m.[3,4,8] With a guideline-guided approach we have been able to almost double our resection rate in these two geographical areas in Finland, mainly due to a higher number of high-risk patients operated.[6] In our district, the mean age of operated patients is three years older than the last published national mean age of 66.6 years.[2] Therefore, this policy of evaluating the physical fitness of every lung cancer surgical candidate and relying on this simplified height-based climbing testing with a maximum test height of 14.1 m seems practical and enables safe operation of truly high-risk patients as well.

The major strength of this study is the population-based design including two geographic areas in Finland. Unlike many population-based studies, we had full access to all medical records. Therefore, we were able to collect accurately all patient demographics including risk factors, details regarding the treatment, and follow-up data. Complete follow-up data were also available from multiple sources. Surgical reports were of importance, since data based only on surgical codes can be misleading and inaccurate in terms of surgical details such as the type of lymphadenectomy. Furthermore, unlike any registry information, complications based on hospital records and a prospective surgical database provide more accurate rates and severity without missing data. The availability of data on routine follow-up and treatment of any possible recurrences in the same hospitals enabled us to collect any cancer recurrences. Medical records of general practitioners treating chronic illnesses and reporting out-of-hospital causes of deaths in these two geographic areas completed the data on cause-specific mortality. Only the cause of death of one patient who died suddenly at home without knowledge of disease recurrence remained unclear. Therefore, we believe that the lung cancer-specific and non-cancer-specific causes of death have been classified reliably. The limited study population and retrospective design, though much of the data were prospectively collected, were weaknesses of this study.

Conclusions

In the VATS era, lung cancer surgery can be performed safely with a similar major morbidity rate in the poor performance group (<11 m) compared to the >12 m exercise capacity group. Routine SCT in lung cancer patients predicts the ability to live at home 1 year after surgery and overall survival. In the VATS era, formal CPET seems not to be necessary in patients climbing more than 9 meters. Based on this study, SCT is a potential parameter to be included in every prognostic model of lung cancer eligible for surgery.

References

1. Salati M, Brunelli A, Decaluwe H, et al. Report from the European society of Thoracic Surgeons Database 2017: Patterns of care and perioperative outcomes of surgery for malignant lung neoplasm. *Eur J Cardio-thoracic Surg*. 2017;52(6):1041-1048. doi:10.1093/EJCTS/EZX272
2. Gunn J, Valo J, Sipilä J, Rautava P, Sihvo E, Kytö V. Trends and results of lung cancer surgery in Finland between 2004 and 2014. *Eur J Cardiothorac Surg*. 2018;54(1):127-133. doi:10.1093/ejcts/ezx486
3. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. 2009;34(1):17-41. doi:10.1183/09031936.00184308
4. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 SUPPL). doi:10.1378/chest.12-2395
5. Boujibar F, Gillibert A, Gravier FE, et al. Performance at stair-climbing test is associated with postoperative complications after lung resection: A systematic review and meta-analysis. *Thorax*. 2020;75(9):791-797. doi:10.1136/thoraxjnl-2019-214019
6. Helminen O, Valo J, Andersen H, Lautamäki A, Vuohelainen V, Sihvo E. Real-world guideline-based treatment of lung cancer improves short- and long-term outcomes and resection rate: A population-based study. *Lung Cancer*. 2020;140:1-7. doi:10.1016/j.lungcan.2019.12.002
7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:00000658-200408000-00003 [pii]
8. Detterbeck FC, Lewis SZ, Diekemper R, Addrizzo-Harris D, Alberts WM. Executive Summary. *Chest*. 2013;143(5):7S-37S. doi:10.1378/chest.12-2377
9. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise Capacity and Mortality among Men Referred for Exercise Testing. *N Engl J Med*. 2002;346(11):793-801. doi:10.1056/nejmoa011858
10. Brunelli A, Pompili C, Berardi R, et al. Performance at preoperative stair-climbing test is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg*. 2012;93(6):1796-1800. doi:10.1016/j.athoracsur.2012.02.068 [doi]
11. Win T, Sharples L, Groves AM, Ritchie AJ, Wells FC, Laroche CM. Predicting survival in

potentially curable lung cancer patients. *Lung*. 2008;186(2):97-102. doi:10.1007/s00408-007-9067-1

12. Solomon A, Borodulin K, Ngandu T, Kivipelto M, Laatikainen T, Kulmala J. Self-rated physical fitness and estimated maximal oxygen uptake in relation to all-cause and cause-specific mortality. *Scand J Med Sci Sport*. 2018;28(2):532-540. doi:10.1111/sms.12924
13. Onaitis MW, Furnary AP, Kosinski AS, et al. Prediction of Long-Term Survival After Lung Cancer Surgery for Elderly Patients in The Society of Thoracic Surgeons General Thoracic Surgery Database. *Ann Thorac Surg*. 2018;105(1):309-316. doi:10.1016/j.athoracsur.2017.06.071
14. Brunelli A, Chaudhuri N, Kefaloyannis M, et al. Eurolung risk score is associated with long-term survival after curative resection for lung cancer. In: *Journal of Thoracic and Cardiovascular Surgery*. Mosby Inc.; 2020. doi:10.1016/j.jtcvs.2020.06.151
15. Crandall K, Maguire R, Campbell A, Kearney N. Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): A systematic review. *Surg Oncol*. 2014;23(1):17-30. doi:10.1016/j.suronc.2014.01.001
16. Koegelenberg CFN, Diacon AH, Irani S, Bolliger CT. Stair climbing in the functional assessment of lung resection candidates. *Respiration*. 2008;75(4):374-379. doi:10.1159/000116873

Table 1 Baseline and tumor characteristics in stair-climbing test groups

	All patients (n=283)	<11m stairs (n=66)	>12m stairs (n=217)	p value
Age yrs (median, IQR)	71 (64-76)	71 (66-76)	71 (64-76)	0.404
BMI kg/m^2 (mean, SD)	26.1 (4.4)	27.4 (6.1)	25.7 (3.7)	0.033
Male, n (%)	180 (63.6)	39 (59.1)	141 (65)	0.384
Charlson comorbidity index				0.012
0	74 (26.1)	6 (9.1)	68 (31.3)	
1	79 (27.9)	22 (33.3)	57 (26.3)	
2	59 (20.8)	16 (24.2)	43 (19.8)	
3-4	51 (18.0)	13 (19.7)	38 (17.5)	
5 or higher	20 (7.1)	9 (13.6)	11 (5.1)	
Smoking history				0.017
Never	54 (19.1)	10 (15.2)	44 (20.3)	
Former	117 (41.3)	20 (30.3)	92 (42.4)	
Current	112 (39.6)	36 (54.5)	74 (34.1)	
Stair-climbing height m, mean (SD)	12.9 (2.7)	8.8 (3.0)	14.1 (0.4)	<0.001
VO2max, mean (SD) (n=36)	15.2 (19.4)	12.8 (1.6)	19.1 (3.7)	<0.001
FEV1%, mean (SD)	80.8 (19.4)	71.6 (17.7)	81.9 (18.7)	<0.001
ppoFEV1%, mean (SD)	67.7 (17.3)	60.6 (14.7)	69.7 (17.6)	<0.001
DLCO, mean (SD)	79.7 (19.3)	72.7 (19.7)	81.9 (18.7)	0.001
ppoDLCO%, mean (SD)	67.3 (17.1)	62.3 (16.2)	67.6 (17.4)	0.006
Histology, n (%)				0.001
Adenocarcinoma	168 (59.4)	27 (40.9)	141 (65)	
Squamous cell cancer	81 (28.6)	30 (45.5)	51 (23.5)	
Other	33 (11.7)	9 (13.6)	25 (11.5)	
Tumor size cm, median (IQR)	2.3 (1.5-4.0)	2.6 (1.8-4.1)	2.2 (1.5-4.0)	0.135
PET-CT, n (%)	218 (77.0)	53 (80.3)	165 (76)	0.471
Invasive staging, n (%)	67 (23.7)	17 (25.8)	50 (23)	0.649
Pathological UICC Stage, n (%)[1]				0.865
I	174 (61.5)	42 (63.6)	132 (60.8)	
II	67 (23.7)	14 (21.2)	53 (24.4)	
III-IV	42 (14.8)	10 (15.2)	32 (14.7)	

[1]Patiens who received neoadjuvant treatment were classified according to clinical stage

Table 2. Treatment and outcomes stratified with stair-climbing test result

	All patients (n=283)	<11m stairs (n=66)	>12m stairs (n=217)	p value
Operative approach				
VATS	226 (79.9)	56 (84.8)	170 (78.3)	0.248
Type of surgery				0.394
Pneumonectomy	3 (1.1)		3 (1.4)	
Bilobectomy	4 (1.4)		4 (1.8)	
Lobectomy	165 (58.3)	35 (53.0)	130 (59.9)	
Segmentectomy	96 (33.9)	25 (37.9)	71 (32.7)	
Wedge	9 (3.2)	4 (6.1)	5 (2.3)	
Combination	5 (1.8)	2 (3.0)	3 (1.4)	
Bronchus	1 (0.4)		1 (0.5)	
Lymph node dissection				0.088
No N2	24 (8.5)	5 (7.6)	19 (8.8)	
N2 sampling[1]	21 (7.4)	9 (13.6)	12 (5.5)	
Systematic N2 dissection	238 (84.1)	52 (78.8)	186 (85.7)	
Lymph nodes examined, median (IQR)	12 (7-16)	10 (5-15)	12 (8-16)	0.114
Oncological therapy				
Neoadjuvant	33 (11.7)	5 (7.6)	28 (12.9)	0.238
Adjuvant	61 (21.6)	12 (18.2)	49 (22.6)	0.447
Complications, n (%)				
Any type	94 (33.2)	23 (34.8)	71 (32.7)	0.748
Minor (CDC Grade I–II)	63 (22.3)	16 (24.2)	47 (21.7)	0.659
Major (CDC Grade IIIa–V)	31 (11.0)	7 (10.6)	24 (11.1)	0.918
Mortality, n (%)				
30-day	1 (0.4)	0	1 (0.5)	0.581
90-day	4 (1.4)	2 (3.0)	2 (0.9)	0.204
Hospital stay, median (IQR)	5 (3-7)	5 (4-7)	4 (3-7)	0.179
Discharged to				
Home, n (%)	233 (82.3)	50 (75.8)	183 (84.3)	0.110
1-year alive and at home[2]	230 (90.9)	52 (81.3)	178 (94.2)	0.002
Survival				
5-year overall	64.7%	49.9%	70.0%	<0.001
5-year cancer-specific	83.0%	79.3%	84.3%	0.458

5-year non-cancer specific	77.9%	62.9%	83.1%	<0.001

[1]One or two N2 stations.

[2]Alive and at home included patients operated at least 1 year before the end of follow-up

Table 3. Cause of death by group.

Group	**<11m (n=66)**	**>12m (n=217)**
Any cause	31 (46.9)	42 (19.4)
Lung cancer	9 (13.6)	23 (10.6)
Other	22 (33.3)	19 (8.8)
Respiratory	8 (12.1)	4 (1.8)
Cardiac	3 (4.5)	4 (1.8)
Nervous system	2 (3.0)	3 (1.4)
GI	3 (4.5)	1 (0.4)
Another cancer	3 (4.5)	3 (1.4)
Septicemia	1 (1.5)	0 (0.0)
Pelvic fracture	0 (0.0)	1 (0.5)
Alcoholism	0 (0.0)	2 (0.9)
Suicide	0 (0.0)	1 (0.5)
Sudden death without disease recurrence	2 (3.0)	0 (0.0)

Table 4. Odds ratios with 95% confidence intervals (CI) of alive or at home 1-year after surgery, and hazard ratios (HRs) with 95% CI of recurrence risk and mortality of common risk factors and stair-climbing test for lung cancer adjusted for confounding factors.

Variable	Not alive or not at home 1-year after surgery OR (95% CI)	Lung-cancer specific mortality HR (95% CI)	Non-cancer specific mortality HR (95% CI)	Overall mortality HR (95% CI)
Stair climbing <11 (v >12m)				
Adjusted[1]	***3.82 (1.28-11.4)***	1.25 (0.55-2.85)	***4.28 (2.10-8.73)***	***2.38 (1.43-3.98)***
Age at surgery >80 (v <80)				
Adjusted[1]	***9.82 (2.31-41.8)***	1.08 (0.28-4.11)	***3.38 (1.20-9.48)***	1.97 (0.89-4.35)
Male sex (v female)				
Adjusted[1]	0.54 (0.18-1.66)	1.11 (0.51-2.43)	***2.86 (1.27-6.45)***	***1.76 (1.01-3.07)***
Former smoker (v never)				
Adjusted[1]	NA	1.99 (0.53-7.50)	1.73 (0.61-4.87)	1.82 (0.82-4.06)
Current smoker (v never)				
Adjusted[1]	NA	2.21 (0.56-8.78)	1.43 (0.50-4.12)	1.65 (0.72-3.81)
Charlson comorbidity index ≥5 (v <5 points)				
Adjusted[1]	***5.57 (1.38-22.6)***	2.90 (0.90-9.35)	***3.40 (1.21-9.54)***	***2.79 (1.32-5.90)***
ppo FEV1 ≤50% (v >50%)				
Adjusted[1]	1.81 (0.55-5.98)	0.86 (0.34-2.16)	1.65 (0.70-3.87)	1.14 (0.62-2.10)
ppo DLCO ≤50% (v >50%)				
Adjusted[1]	***4.33 (1.27-14.8)***	0.96 (0.37-2.48)	1.81 (0.79-4.14)	1.43 (0.78-2.63)
Adenocarcinoma (vs. squamous cell cancer)				
Adjusted[1]	1.35 (0.41-4.47)	1.54 (0.63-3.74)	1.69 (0.78-3.67)	1.50 (0.85-2.63)
pStage II (v Stage I)				
Adjusted[1]	2.50 (0.62-9.98)	***3.27 (1.23-8.68)***	1.27 (0.57-2.81)	1.66 (0.92-3.02)
pStage III (v Stage I)				
Adjusted[1]	***8.18 (1.53-43.7)***	***5.75 (1.75-18.9)***	0.44 (0.08-2.31)	2.04 (0.89-4.70)

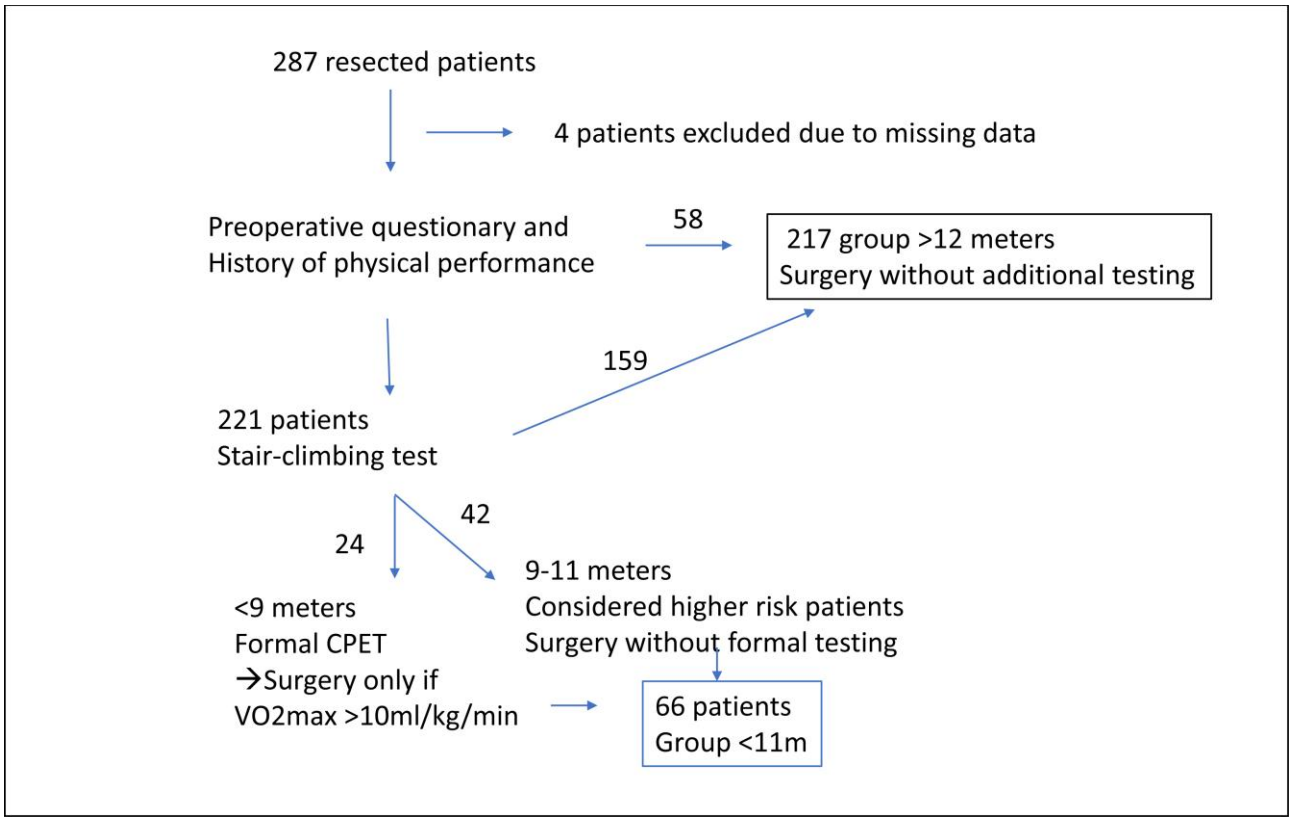
[1] Adjustment for age, sex, tobacco use, Charlson comorbidity index, ppoFEV1, ppoDLCO, histological type, stage, neo- or adjuvant treatment, stair climbing group (<11m, >12m).

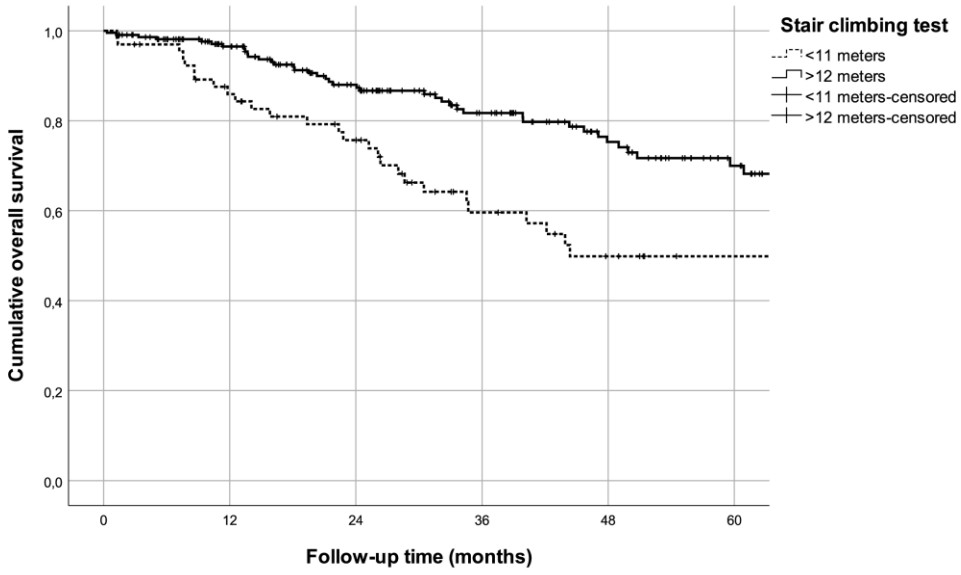
Figure legends

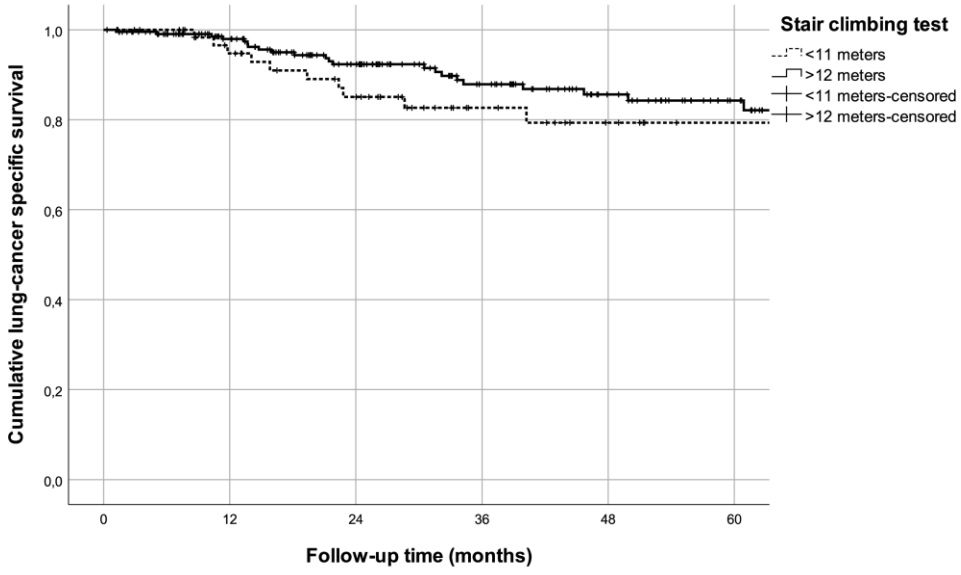
Figure 1: Flowchart showing preoperative determination of physical performance and formation of study groups

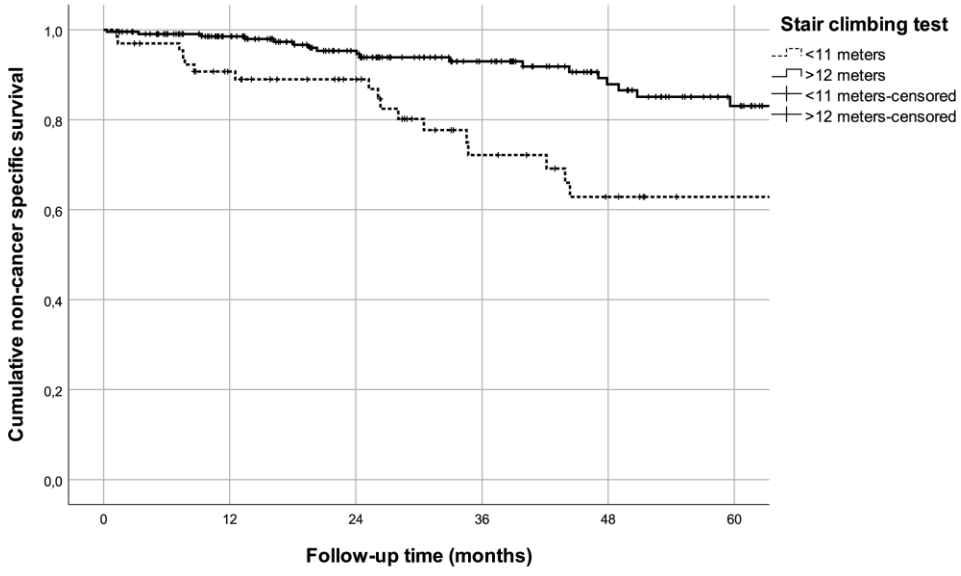
Figure 2 a-c: Overall survival (a), lung-cancer-specific survival (b) and non-cancer-specific survival (c) stratified by study group (<11 m and >12 m in stair-climbing test)

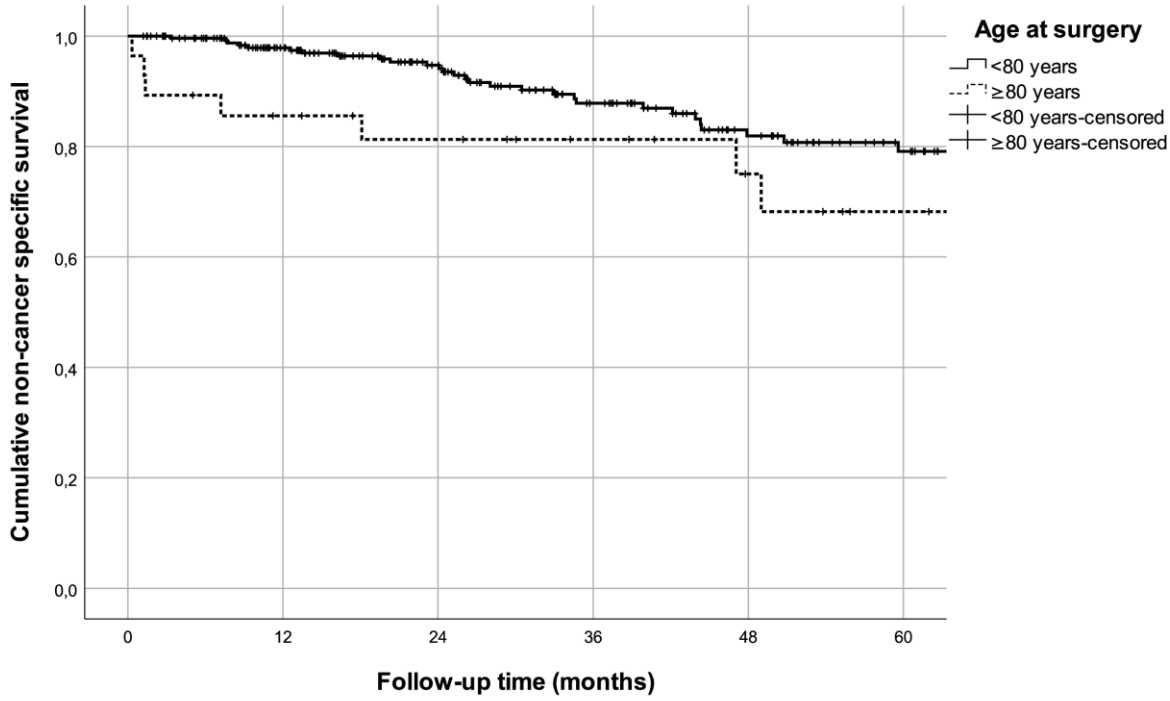
Figure 3 a-d: Non-cancer-specific survival stratified by other patient-related risk factors including age (a), ppoFEV1% (b), ppoDLCO% (c) and Charlson comorbidity index (d)

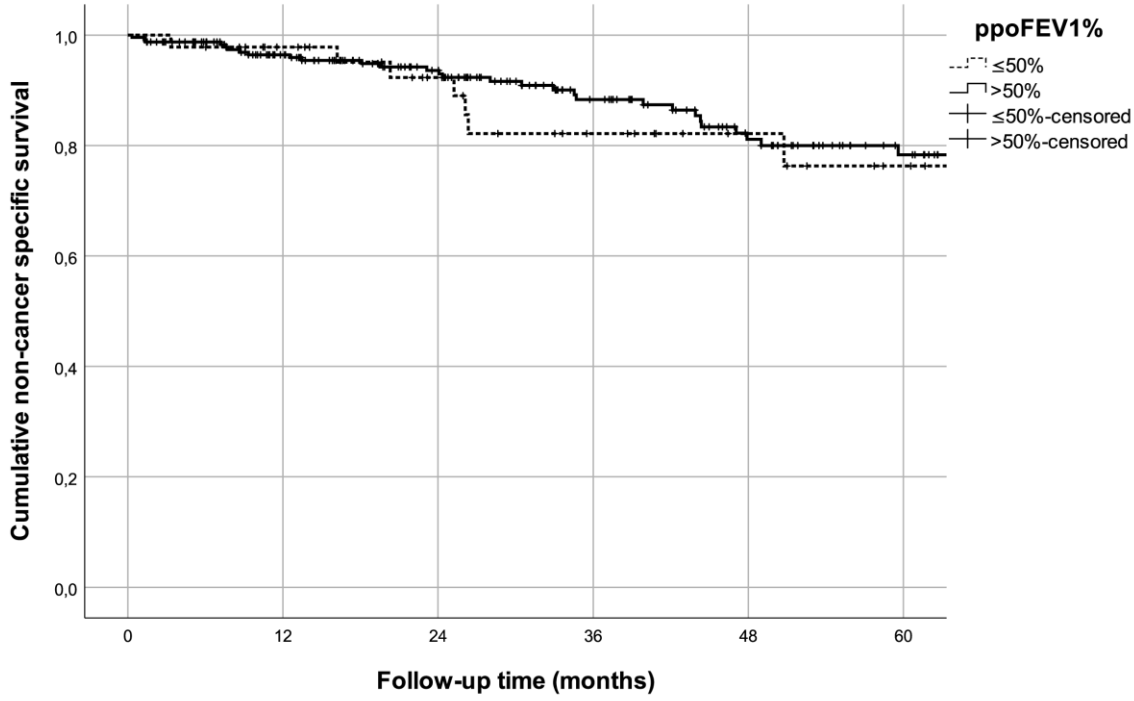

287 resected patients
4 patients excluded due to missing data
Preoperative questionary and
History of physical performance
58
217 group >12 meters
Surgery without additional testing
159
221 patients
Stair-climbing test
42
24
9-11 meters
Considered higher risk patients
Surgery without formal testing
<9 meters
Formal CPET
→Surgery only if
VO2max >10ml/kg/min
66 patients
Group <11m

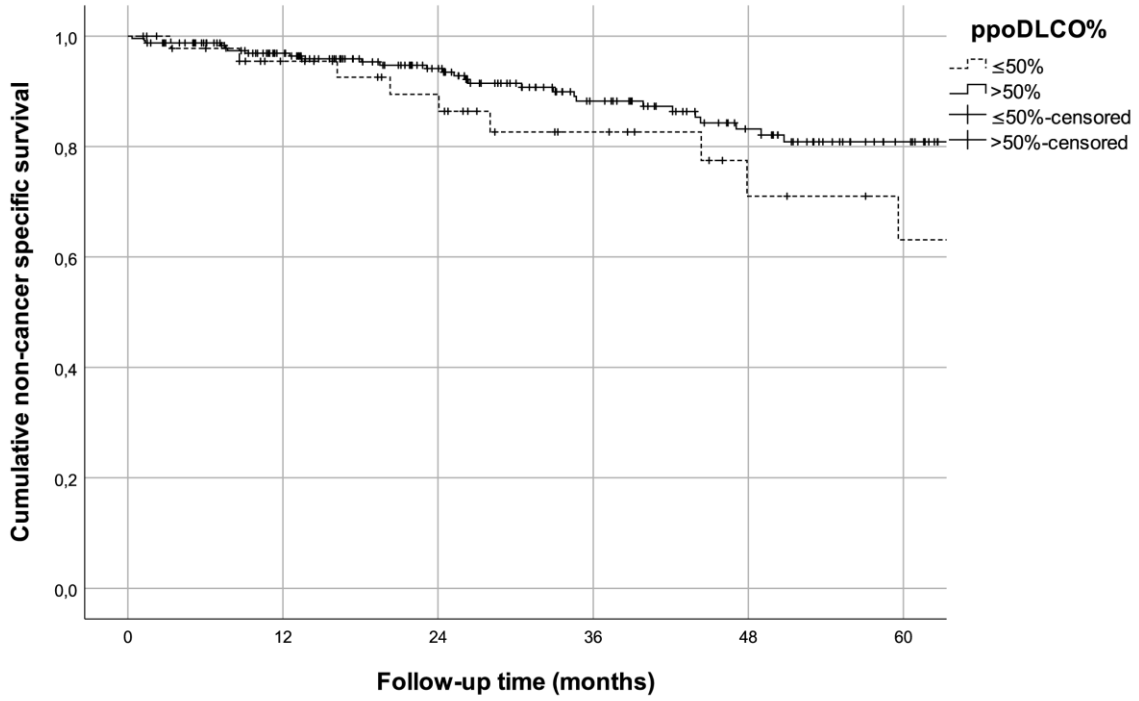

Stair climbing test
<11 meters
>12 meters
<11 meters-censored
>12 meters-censored
Cumulative overall survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)

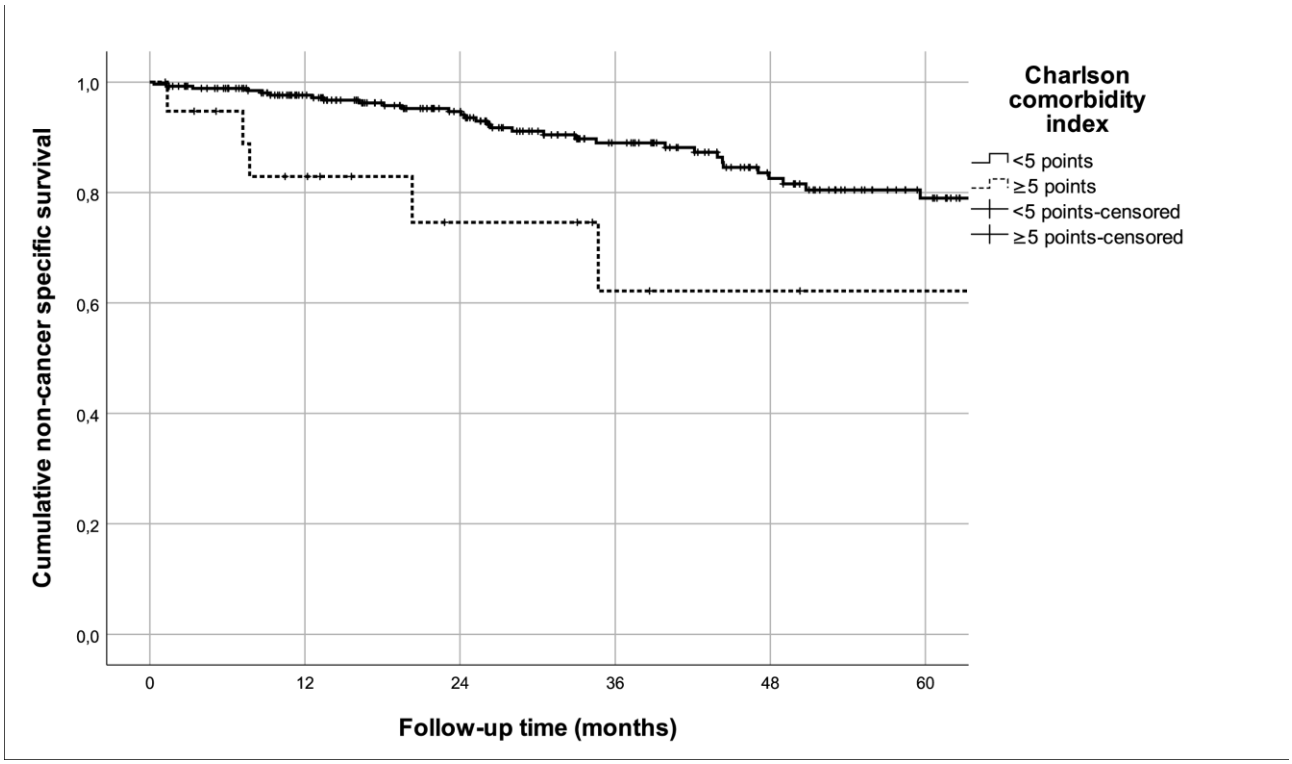

Stair climbing test
<11 meters
>12 meters
<11 meters-censored
>12 meters-censored
Cumulative lung-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)


Stair climbing test
<11 meters
>12 meters
<11 meters-censored
>12 meters-censored
Cumulative non-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)


Cumulative non-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)
Age at surgery
<80 years
≥80 years
<80 years-censored
≥80 years-censored


Cumulative non-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)
ppoFEV1%
≤50%
>50%
≤50%-censored
>50%-censored


ppoDLCO%
≤50%
>50%
≤50%-censored
>50%-censored
Cumulative non-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)


Charlson comorbidity index
<5 points
≥5 points
<5 points-censored
≥5 points-censored
Cumulative non-cancer specific survival
1,0
0,8
0,6
0,4
0,2
0,0
0
12
24
36
48
60
Follow-up time (months)

Title: Association of performance at stair-climbing test with complications and survival after lung cancer resection in the VATS era: population-based outcomes

Authors: Olli Helminen MD, PhD[1,2], Johanna Valo MD[1,3], Heidi Andersen MD[4], Johan Söderström MD[4], Eero Sihvo MD, PhD[1]

[1]Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

[2]Surgery Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

[3]Department of General Thoracic and Esophageal Surgery, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

[4]Department of Pulmonology, Vaasa Central Hospital, Vaasa, Finland

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Ethical statement: The study was approved by the hospital districts. Because of the retrospective nature of the study, patient informed consent or ethical statement was not required. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contact information of the corresponding author:
Eero Sihvo, MD, PhD
Department of Surgery
Central Finland Central Hospital
Keskussairaalantie 19, 40620 Jyväskylä
FINLAND
tel: +358 142 691 811
e-mail: eero.sihvo@ksshp.fi

Abstract 245 words, main text 3090 words, 4 tables, 3 figures

Abstract

Introduction With a population-based cohort in the VATS era, we aimed to evaluate the value of stair-climbing test (SCT) on short- and long-term outcomes of lung cancer surgery.

Methods All patients operated due to primary lung cancer in Central Finland and Ostrobothnia from 2013 to June 2020 were included. For the analysis, clinical variables including the outcome of SCT and cause-specific mortality were available. Short- and long-term outcomes were compared between <11m (n=66) and >12m SCT (n=217) groups.

Results Patients with poor performance (<11 m) had more comorbidities and worse lung function but did not differ in tumor stage or treatment. No differences between groups were observed in major morbidity rate (10.6% vs. 11.1%, p=0.918) or median hospital stay (5 (IQR 4–7) vs. 4 (IQR 3–7), p=0.179). At 1-year, fewer patients were alive and living at home in <11m group (81.3%) compared to >12m group (94.2%), p=0.002. No difference was observed in cancer-specific 5-year survival. Non-cancer-specific survival (62.9% vs. 83.1%, p<0.001) and overall survival (49.9% vs. 70.0%, p<0.001) were worse in <11m group. After adjustment for confounding factors, SCT remained as a significant predictor for non-cancer-specific (4.28; 95%CI 2.10 to 8.73) and overall mortality (2.38; 95%CI 1.43 to 3.98).

Conclusions With SCT-based exercise testing, VATS can be performed safely, with similar major morbidity rate in poor performance group (<11m) compared to >12m group. Poor exercise performance increases non-cancer-specific mortality. Being a major predictor of survival, exercise capacity should be included in prognostic models.

Introduction

The guideline-based recommendation for treatment of early stage lung cancer is surgery. However, surgery is associated with significant morbidity and mortality. The thirty-day mortality reported recently by the European Society of Thoracic Surgeons Database was 2.6%.[1] At 90 days, the 30-day mortality rate of 2.3% in the Finnish population-based series almost doubled to 4.3%.[2] The risk of perioperative mortality and morbidity must therefore be weighed against the long-term benefits of surgery.

In both ERS/ESTS and ACCP guidelines, the preoperative physiologic assessment is recommended to include the evaluation of cardiovascular risk and lung functions.[3,4] With either FEV1 or DLCO below 80%, ERS/ESTS guidelines recommend formal cardiopulmonary exercise testing (CPET) with measurement of VO2 max. For this formal CPET, in both ACCP and ERS/ESTS guidelines, a stair-climbing test (SCT) can be used as a screening test. In both guidelines, the threshold for suboptimal performance was set at 22 m.[4]

In the era of open lung cancer surgery, several studies have evaluated the role of SCT in the assessment of preoperative exercise capacity and complication risk. According to a recent review, SCT is able to predict complication.[5] In this review, the threshold for a poor result and referral to formal cardiopulmonary exercise testing was set at 10 m.[5] The role of SCT in the preoperative physiologic assessment has, however, never been evaluated in the era of minimally invasive lung cancer surgery.

We have shown, at the population level, the benefits of modern guideline-based approach in the preoperative evaluation and treatment of lung cancer patients for the short- and long-term outcomes.[6] The preoperative physiologic assessment included symptom-limited SCT and selective referral to formal cardiopulmonary exercise testing with a result of less than 9 m. Our aim was, in the era of VATS surgery, to evaluate the predictive value of this stair-climbing-based testing of exercise capacity on the short- and long-term outcomes of population-based lung cancer surgery. The primary outcome was major complications. Secondary outcomes were alive and able to live at home at 1-year after surgery, and 5-year estimated overall and disease-specific survival. We hypothesized that SCT could predict these outcomes.

Materials and methods

Design

Since September 2012, a modern guideline-based treatment of lung cancer has been implemented in Central Finland Central Hospital.[6] From Ostrobothnia, lung cancer surgery was centralized to Central Finland Central Hospital in October 2014. Between January 1, 2013, and June 30, 2020, all patients diagnosed and resected with a primary lung cancer in Central Finland and Ostrobothnia were included in this population-based cohort study. Patients who underwent surgical resection were identified from hospital records and the prospective surgical database, and confirmed by data from the Finnish Cancer Registry. The follow-up ended on August 10, 2020. The acquisition of individual patient data from hospital records was approved by the local hospital districts. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1349/5.05.00/2015) and Statistics Finland (TK53-1410-15) approved the study.

Data collection

All Finnish residents are listed by their individually unique and immutable 10-digit national registration numbers in the hospital databases and several national databases. This allows reliable identification of patients from hospital records and the Finnish Cancer Registry, as well as linkage of data. The Finnish Cancer Registry is population-based and covers all parts of Finland. Registration includes the municipality and, therefore, the hospital district where the patient lives. According to Finnish health care policy, all hospital districts are responsible for arranging specialized care for residents in their area. In Central Finland and Ostrobothnia, which had a total population of 456,976 as of December 31, 2017 (8.3% of the Finnish population), the treatment of lung cancer is organized by Central Finland Central Hospital and Vaasa Central Hospital, respectively. Using the histopathological, clinical follow-up, and discharge registries of the two hospitals, all patients diagnosed with primary lung cancer who underwent lung resection with curative intent between January 1, 2013, and June 30, 2020, were identified. Cross-linking of Finnish Cancer Registry data and hospital databases confirmed identification of all surgical cases. From 2015, a prospective surgical database established in Central Finland Central Hospital in 2012 provided the surgical cases. Variables in this database were not designed for this study and the data for all study patients were therefore re-reviewed from hospital records.

Evaluation of physical performance

The protocol of preoperative evaluation in the clinical practice and the formation of study groups is presented in Figure 1. All surgical candidates were sent a preoperative questionnaire including two questions on physical performance: the ability to climb stairs and walking speed. A reported good physical performance included the ability to climb 3 or more flights of stairs and walk at least at a speed of 5 km/h. The physical performance was further confirmed by the operating surgeon at the preoperative clinic. Only those patients (n=58) able to do heavy work, to climb more than 4 floors routinely or participate in strenuous sports such as cross-country skiing were not tested further before surgery. These patients were placed in the study group >12 m. Four patients were excluded from the analysis due to lack of any reported data of physical performance. Of 287 operated patients, 221 underwent a symptom-limited SCT up to a maximum of 4 flights (14.1 m). Only 2 candidates for a pneumonectomy were tested up to 5 flights (17.6 m). Of these 221 patients, 159 climbed more than 12 m. In this group, 9 patients (5.7%), mostly early referrals from Ostrobothnia, underwent a formal CPET with a mean VO2max of 18.1 mL/kg/min. These 159 patients together with the previously mentioned 58 patients formed the study group including 217 patients able to climb >12 m (3.5 flights ie. 12.3m). Since during the test patients finished their climb after a full or half flight, there were no results between 3 and 3.5 flights (or 10.6m to 12.3). In this study, we used 3 flights of 10.6m as a threshold for poor exercise capacity being very close to previously recommended level of 10m.[5] Of 221 patients tested, 66 climbed this10.6m or less and formed the <11 m study group. Of these 66, 42 climbed 3 flights equal to 10.6 m. Although in our practice these patients are considered to be at increased surgical risk, they undergo a formal CPET only very selectively. In this group, the rate was 11.9% (n=5) with a mean VO2max of 14.2 mL/kg/min. Those patients unable to climb more than 2.5 flights (8.8 m) are recommended to undergo a formal CPET and were considered unsuitable for surgery with VO2max under 10 mL/kg/min. The rate of formal CPET in this group of patients (n=22) was 66.7% with a mean VO2max of 12.3 mL/kg/min.

Outcomes and definitions

The 8th edition of the TNM classification was used for staging. This required recoding all necessary surgical patients accordingly. Primary outcomes were major complications. Secondary outcomes were alive and able to live at home at 1-year after surgery, and 5-year estimated overall and disease-specific survival. Complications were graded according to the Clavien-Dindo classification.[7] Major complication was defined as higher than class II. Secondary outcomes were hospital stay, intensive care unit stay, and home discharge rate. The ability to live at home was defined as the proportion of patients, out of all operated patients, who, one year after surgery, were living at home instead of a nursing facility, hospital, terminal care unit, or death.

Statistical analysis

We constructed Kaplan-Meier survival curves according to the life table method to visualize the crude all-cause and recurrence-free survival up to 5 years after surgery. Proportions, means, and median values of other measured variables were compared using the chi-squared test, Mann-Whitney U-test, and T-test as appropriate. The regression models were adjusted for potential confounding factors: age ≥80 years, sex (male, female), Charlson comorbidity index ≥5, ppoFEV1 ≤50%, ppoDLCO ≤50%, tumor histology, tumor stage (I, II, III-IV), neo- or adjuvant treatment (yes/no). For regression analysis, multiple imputation was performed to cover missing values. The following proportion of variables were imputed: smoking in 2.4%, ppoFEV in 1.4% and ppoDLCO in 7.7% For patients who received neoadjuvant treatment, clinical stage was used instead of pathological stage. All statistical analyses were performed using IBM SPSS 26.0 (IBM corp., Armonk, NY, USA).

Results

Preoperative patient evaluation

Overall population-based outcomes in 287 operated patients had major morbidity rate of 10.8%, 30-day mortality rate of 0.3% and 90-day mortality rate of 1.4%. One-year and 5-year overall survival rates were 94.0% and 64.2%. Four patients were excluded due to missing reported data of physical performance. The median age of the 283 included patients was 71. The majority were men (63.6%), had a CCI equal to or more than one (73.9%), and were diagnosed with adenocarcinoma (59.4%) and pathological stage IA disease (50.2%). Overall, 66.7% of all operated patients had either FEV1% or DLCO <80%. Patient baseline characteristics stratified by the result of SCT are presented in Table 1.

Comparison by physical performance and treatment

Surgical procedures and related oncological therapies are summarized in Table 2. Overall VATS rate and the rate during the last 5 years was 78.7% and 88.2%, respectively. This rate or the type of lung resection did not differ between the groups. A trend (p=0.088) in the rate of mediastinal lymphadenectomy was detected between <11 m and >12 m groups (78.8% vs. 85.7%). A similar trend (p=0.088) in lymph node yield was observed with medians of 10 and 12, respectively (Table 2).

Short-term outcomes

Of 283 included patients, rates of major morbidity was 10.8%, 30-day mortality 0.4% and 90-day mortality 1.4%. The specific cause of death at 90 days was cardiovascular or respiratory in all cases (Table 3). Of these 4 deaths, 2 occurred at home, both in the <11 m group after normal discharge. Physical performance had no effect on short-term complications (Table 2). The major complication and 90-day mortality rates in the <11 m and >12 m groups were 10.6% and 11.1% (p=0.918) and 3% and 0.9% (p=0.204), respectively. Median hospital stay was 5 (IQR 4–7) and 4 (3–7) days (p=0.179). With a cut-off of 9m in physical performance between groups, major morbidity rates are 20.8% (5/24) in the poor performance group and 10.0% (26/259) in the better performance group (p=0.105).

One-year outcome

At 1 year, a major difference between the <11 m and >12 m group was observed in the number of patients living at home (81.3% vs. 94.2%, p=0.002), Table 2. The leading cause in the <11 m group was other than lung cancer-specific in 14.1%, compared to 3.2% in the >12 m group (p=0.001). Lung cancer-specific death or disease recurrence was the reason for not living at home in 4.7% and 2.6%, respectively. In adjusted analysis, the risk of inability to live at home 1 year after surgery was associated with the result of SCT, age at surgery, comorbidity burden, ppoDLCO% and stage (Table 4).

Long-term outcome

Overall survival was worse in the <11 m group (49.9% vs. 70.0%, p<0.001, Figure 2a). No difference existed between study groups in lung cancer-specific 5-year survival (Figure 2b), but a major difference was seen in non-cancer-specific survival (Figure 2c, Table 2). Of the 31 deaths in the <11 m group, the cause of death was lung cancer in 9 (29.0%) patients, and of the 42 deaths in the >12 m group, the cause of death was lung cancer in 23 (54.8%) patients (p=0.029). Causes of death in the study groups are listed in Table 3.

Age ≥80 years (Figure 3a, p=0.201), ppoFEV1% ≤50% (Figure 3b, p=0.294), ppoDLCO% ≤50% (Figure 3c, p=0.085) had no significant impact on non-cancer-specific survival. Decreased non-cancer-specific survival was detected in patients with increased comorbidity burden (CCI ≥5) Figure 3d, p=0.018). None of these variables had a significant effect on cancer-specific survival (data not shown).

In the multivariable analyses of 5-year outcomes, the result of SCT was an important risk factor for both overall (HR 2.38, 95%CI 1.43–3.98) and non-cancer-specific (HR 4.28, 95%CI 2.10–8.73) mortality (Table 4). The only other similarly important predictor was Charlson comorbidity index ≥5 (Table 4).

Discussion

This study differentiates at the population-level the influence of exercise capacity measured by SCT on outcomes of lung cancer surgery in the VATS era. VATS can be performed safely, with a similar major morbidity rate in the poor performance group (<11 m) compared to the >12 m exercise capacity group. A poor performance in SCT had a major impact on the ability to live at home 1 year after surgery and on long-term non-cancer-specific and overall survival. Being a powerful predictor of survival, exercise capacity should be included in routine prognostic models.

In ERS/ESTS and ACCP guidelines, based on the data from open surgery era, the SCT threshold for safe lung cancer surgery was set at 22 m.[3,4] Contrary to these recommendations, in our practice in the VATS era we set the threshold in SCT for increased risk at 11 m and the threshold for formal exercise testing at 9 m. In our highly selective formal testing policy, a contraindication for any lung cancer surgery, as in both ERS/ESTS and ACCP guidelines, was a peak oxygen consumption of less than 10 mL/kg/min.[3,4] By following these modified guideline-based recommendations in exercise testing in this population-based series, a low 0.3% 30-day and 1.4% 90-day overall mortality was reached. No difference was detected between the SCT groups in the rate of any complications, major morbidity, mortality or hospital stay. With a high VATS rate of 88.2% during the last 5 years together with a segmentectomy rate of 33.9% in our population-based series, SCT can be used as a safe screening tool for a highly selective formal CPET. Therefore, in the VATS era, SCT can be relied on more widely in exercise testing, and the threshold for a poor test result and need for formal exercise testing could be set even below the recently recommended threshold of 10 m.[5] With a 9 m cut-off in this study, a trend of increased major morbidity rate in the poorer performance group (20.8% vs. 10.0%) is evident. With current ERS/ESTS recommendations, the need for formal CPET in this series would have been 66.7%. With our SCT screening and highly selective formal testing, the need for CPET is around 10% at the population-level. This limits the costs of preoperative formal stress testing without compromising the outcome of lung cancer surgery.

In addition to preventing unnecessary morbidity and mortality, the aim of the preoperative physiologic evaluation is to prevent chronic disability.[4,8] Survival and the ability to live at home at one year postoperatively was significantly reduced in the <11 m group, with a rate of 78.8% compared to 94.2% in the >12 m group. Multivariable analysis revealed the following independent predictors for this outcome: performance in SCT, age, Charlson comorbidity index, ppo DLCO and

stage III disease. The cause of death was rarely cancer-related. Therefore, poor performance in SCT is associated with early death related to other causes and chronic disability after surgery. Overall, exercise capacity is a better predictor of survival than cardiovascular risk factors.[9] Of previous predictors of 1-year outcome, only performance in SCT and Charlson comorbidity index were predictors of overall long-term mortality in the multivariable analysis. Contrary to a previous suggestion, worse survival associated with impaired physical performance was solely explained by the increase in death from non-cancer causes.[10] An increased risk of death due to lung cancer has previously been associated with a lower VO2max, a shorter shuttle walk distance, poorer exercise tolerance in SCT, or even poorer self-rated physical fitness.[10–12] This prognostic role has several potential consequences. First, any risk models for long-term survival such as the STS-GTSD-Medicare long-term risk model or Eurolung2 should include some form of exercise testing.[13,14] Second, besides stage, any comparisons of outcomes between treatment modalities such as SBRT and surgery should include exercise capacity, in addition to comorbidity burden and lung functions. Third, physical fitness is a modifiable prognostic factor and could therefore be improved by rehabilitation programs.[15] Last, exercise tolerance could potentially be incorporated in future multifactorial mixed prognostic models to improve the selection of the most appropriate treatment modality for high-risk patients.

In addition to climbed height, desaturation, heart rate change and time are exposures that could be measured during the SCT. Due to a lack of data we could not use desaturation in the analysis. To simplify the testing, we did not include time or heart rate change as exposures, either. Although the average speed of ascent is a good predictor of VO2max, the climbed height correlated well with the measured VO2max in the relatively few CPET patients in this study.[16] Furthermore, a relatively slow ascending speed of 11 m/min, of which most people are capable, predicts VO2max of 15 mL/kg/min.[16] Therefore, patients were instructed to climb at their own speed without stopping until exhaustion or at least 4 floors equaling 14.1 m. In most patients, their maximal height was not reached and none of the patients were tested up to the guideline threshold for safe surgery of 22 m.[3,4,8] With a guideline-guided approach we have been able to almost double our resection rate in these two geographical areas in Finland, mainly due to a higher number of high-risk patients operated.[6] In our district, the mean age of operated patients is three years older than the last published national mean age of 66.6 years.[2] Therefore, this policy of evaluating the physical fitness of every lung cancer surgical candidate and relying on this simplified height-based climbing testing with a maximum test height of 14.1 m seems practical and enables safe operation of truly high-risk patients as well.

The major strength of this study is the population-based design including two geographic areas in Finland. Unlike many population-based studies, we had full access to all medical records. Therefore, we were able to collect accurately all patient demographics including risk factors, details regarding the treatment, and follow-up data. Complete follow-up data were also available from multiple sources. Surgical reports were of importance, since data based only on surgical codes can be misleading and inaccurate in terms of surgical details such as the type of lymphadenectomy. Furthermore, unlike any registry information, complications based on hospital records and a prospective surgical database provide more accurate rates and severity without missing data. The availability of data on routine follow-up and treatment of any possible recurrences in the same hospitals enabled us to collect any cancer recurrences. Medical records of general practitioners treating chronic illnesses and reporting out-of-hospital causes of deaths in these two geographic areas completed the data on cause-specific mortality. Only the cause of death of one patient who died suddenly at home without knowledge of disease recurrence remained unclear. Therefore, we believe that the lung cancer-specific and non-cancer-specific causes of death have been classified reliably. The limited study population and retrospective design, though much of the data were prospectively collected, were weaknesses of this study.

Conclusions

In the VATS era, lung cancer surgery can be performed safely with a similar major morbidity rate in the poor performance group (<11 m) compared to the >12 m exercise capacity group. Routine SCT in lung cancer patients predicts the ability to live at home 1 year after surgery and overall survival. In the VATS era, formal CPET seems not to be necessary in patients climbing more than 9 meters. Based on this study, SCT is a potential parameter to be included in every prognostic model of lung cancer eligible for surgery.

References

1. Salati M, Brunelli A, Decaluwe H, et al. Report from the European society of Thoracic Surgeons Database 2017: Patterns of care and perioperative outcomes of surgery for malignant lung neoplasm. *Eur J Cardio-thoracic Surg*. 2017;52(6):1041-1048. doi:10.1093/EJCTS/EZX272
2. Gunn J, Valo J, Sipilä J, Rautava P, Sihvo E, Kytö V. Trends and results of lung cancer surgery in Finland between 2004 and 2014. *Eur J Cardiothorac Surg*. 2018;54(1):127-133. doi:10.1093/ejcts/ezx486
3. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. 2009;34(1):17-41. doi:10.1183/09031936.00184308
4. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 SUPPL). doi:10.1378/chest.12-2395
5. Boujibar F, Gillibert A, Gravier FE, et al. Performance at stair-climbing test is associated with postoperative complications after lung resection: A systematic review and meta-analysis. *Thorax*. 2020;75(9):791-797. doi:10.1136/thoraxjnl-2019-214019
6. Helminen O, Valo J, Andersen H, Lautamäki A, Vuohelainen V, Sihvo E. Real-world guideline-based treatment of lung cancer improves short- and long-term outcomes and resection rate: A population-based study. *Lung Cancer*. 2020;140:1-7. doi:10.1016/j.lungcan.2019.12.002
7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:00000658-200408000-00003 [pii]
8. Detterbeck FC, Lewis SZ, Diekemper R, Addrizzo-Harris D, Alberts WM. Executive Summary. *Chest*. 2013;143(5):7S-37S. doi:10.1378/chest.12-2377
9. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise Capacity and Mortality among Men Referred for Exercise Testing. *N Engl J Med*. 2002;346(11):793-801. doi:10.1056/nejmoa011858
10. Brunelli A, Pompili C, Berardi R, et al. Performance at preoperative stair-climbing test is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg*. 2012;93(6):1796-1800. doi:10.1016/j.athoracsur.2012.02.068 [doi]
11. Win T, Sharples L, Groves AM, Ritchie AJ, Wells FC, Laroche CM. Predicting survival in

potentially curable lung cancer patients. *Lung*. 2008;186(2):97-102. doi:10.1007/s00408-007-9067-1

12. Solomon A, Borodulin K, Ngandu T, Kivipelto M, Laatikainen T, Kulmala J. Self-rated physical fitness and estimated maximal oxygen uptake in relation to all-cause and cause-specific mortality. *Scand J Med Sci Sport*. 2018;28(2):532-540. doi:10.1111/sms.12924
13. Onaitis MW, Furnary AP, Kosinski AS, et al. Prediction of Long-Term Survival After Lung Cancer Surgery for Elderly Patients in The Society of Thoracic Surgeons General Thoracic Surgery Database. *Ann Thorac Surg*. 2018;105(1):309-316. doi:10.1016/j.athoracsur.2017.06.071
14. Brunelli A, Chaudhuri N, Kefaloyannis M, et al. Eurolung risk score is associated with long-term survival after curative resection for lung cancer. In: *Journal of Thoracic and Cardiovascular Surgery*. Mosby Inc.; 2020. doi:10.1016/j.jtcvs.2020.06.151
15. Crandall K, Maguire R, Campbell A, Kearney N. Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): A systematic review. *Surg Oncol*. 2014;23(1):17-30. doi:10.1016/j.suronc.2014.01.001
16. Koegelenberg CFN, Diacon AH, Irani S, Bolliger CT. Stair climbing in the functional assessment of lung resection candidates. *Respiration*. 2008;75(4):374-379. doi:10.1159/000116873

Table 1 Baseline and tumor characteristics in stair-climbing test groups

	All patients (n=283)	<11m stairs (n=66)	>12m stairs (n=217)	p value
Age yrs (median, IQR)	71 (64-76)	71 (66-76)	71 (64-76)	0.404
BMI kg/m^2 (mean, SD)	26.1 (4.4)	27.4 (6.1)	25.7 (3.7)	0.033
Male, n (%)	180 (63.6)	39 (59.1)	141 (65)	0.384
Charlson comorbidity index				0.012
0	74 (26.1)	6 (9.1)	68 (31.3)	
1	79 (27.9)	22 (33.3)	57 (26.3)	
2	59 (20.8)	16 (24.2)	43 (19.8)	
3-4	51 (18.0)	13 (19.7)	38 (17.5)	
5 or higher	20 (7.1)	9 (13.6)	11 (5.1)	
Smoking history				0.017
Never	54 (19.1)	10 (15.2)	44 (20.3)	
Former	117 (41.3)	20 (30.3)	92 (42.4)	
Current	112 (39.6)	36 (54.5)	74 (34.1)	
Stair-climbing height m, mean (SD)	12.9 (2.7)	8.8 (3.0)	14.1 (0.4)	<0.001
VO2max, mean (SD) (n=36)	15.2 (19.4)	12.8 (1.6)	19.1 (3.7)	<0.001
FEV1%, mean (SD)	80.8 (19.4)	71.6 (17.7)	81.9 (18.7)	<0.001
ppoFEV1%, mean (SD)	67.7 (17.3)	60.6 (14.7)	69.7 (17.6)	<0.001
DLCO, mean (SD)	79.7 (19.3)	72.7 (19.7)	81.9 (18.7)	0.001
ppoDLCO%, mean (SD)	67.3 (17.1)	62.3 (16.2)	67.6 (17.4)	0.006
Histology, n (%)				0.001
Adenocarcinoma	168 (59.4)	27 (40.9)	141 (65)	
Squamous cell cancer	81 (28.6)	30 (45.5)	51 (23.5)	
Other	33 (11.7)	9 (13.6)	25 (11.5)	
Tumor size cm, median (IQR)	2.3 (1.5-4.0)	2.6 (1.8-4.1)	2.2 (1.5-4.0)	0.135
PET-CT, n (%)	218 (77.0)	53 (80.3)	165 (76)	0.471
Invasive staging, n (%)	67 (23.7)	17 (25.8)	50 (23)	0.649
Pathological UICC Stage, n (%)[1]				0.865
I	174 (61.5)	42 (63.6)	132 (60.8)	
II	67 (23.7)	14 (21.2)	53 (24.4)	
III-IV	42 (14.8)	10 (15.2)	32 (14.7)	

[1]Patiens who received neoadjuvant treatment were classified according to clinical stage

Table 2. Treatment and outcomes stratified with stair-climbing test result

	All patients (n=283)	<11m stairs (n=66)	>12m stairs (n=217)	p value
Operative approach				
VATS	226 (79.9)	56 (84.8)	170 (78.3)	0.248
Type of surgery				0.394
Pneumonectomy	3 (1.1)		3 (1.4)	
Bilobectomy	4 (1.4)		4 (1.8)	
Lobectomy	165 (58.3)	35 (53.0)	130 (59.9)	
Segmentectomy	96 (33.9)	25 (37.9)	71 (32.7)	
Wedge	9 (3.2)	4 (6.1)	5 (2.3)	
Combination	5 (1.8)	2 (3.0)	3 (1.4)	
Bronchus	1 (0.4)		1 (0.5)	
Lymph node dissection				0.088
No N2	24 (8.5)	5 (7.6)	19 (8.8)	
N2 sampling[1]	21 (7.4)	9 (13.6)	12 (5.5)	
Systematic N2 dissection	238 (84.1)	52 (78.8)	186 (85.7)	
Lymph nodes examined, median (IQR)	12 (7-16)	10 (5-15)	12 (8-16)	0.114
Oncological therapy				
Neoadjuvant	33 (11.7)	5 (7.6)	28 (12.9)	0.238
Adjuvant	61 (21.6)	12 (18.2)	49 (22.6)	0.447
Complications, n (%)				
Any type	94 (33.2)	23 (34.8)	71 (32.7)	0.748
Minor (CDC Grade I–II)	63 (22.3)	16 (24.2)	47 (21.7)	0.659
Major (CDC Grade IIIa–V)	31 (11.0)	7 (10.6)	24 (11.1)	0.918
Mortality, n (%)				
30-day	1 (0.4)	0	1 (0.5)	0.581
90-day	4 (1.4)	2 (3.0)	2 (0.9)	0.204
Hospital stay, median (IQR)	5 (3-7)	5 (4-7)	4 (3-7)	0.179
Discharged to				
Home, n (%)	233 (82.3)	50 (75.8)	183 (84.3)	0.110
1-year alive and at home[2]	230 (90.9)	52 (81.3)	178 (94.2)	0.002
Survival				
5-year overall	64.7%	49.9%	70.0%	<0.001
5-year cancer-specific	83.0%	79.3%	84.3%	0.458

5-year non-cancer specific	77.9%	62.9%	83.1%	<0.001

[1]One or two N2 stations.

[2]Alive and at home included patients operated at least 1 year before the end of follow-up

Table 3. Cause of death by group.

Group	**<11m (n=66)**	**>12m (n=217)**
Any cause	31 (46.9)	42 (19.4)
Lung cancer	9 (13.6)	23 (10.6)
Other	22 (33.3)	19 (8.8)
Respiratory	8 (12.1)	4 (1.8)
Cardiac	3 (4.5)	4 (1.8)
Nervous system	2 (3.0)	3 (1.4)
GI	3 (4.5)	1 (0.4)
Another cancer	3 (4.5)	3 (1.4)
Septicemia	1 (1.5)	0 (0.0)
Pelvic fracture	0 (0.0)	1 (0.5)
Alcoholism	0 (0.0)	2 (0.9)
Suicide	0 (0.0)	1 (0.5)
Sudden death without disease recurrence	2 (3.0)	0 (0.0)

Table 4. Odds ratios with 95% confidence intervals (CI) of alive or at home 1-year after surgery, and hazard ratios (HRs) with 95% CI of recurrence risk and mortality of common risk factors and stair-climbing test for lung cancer adjusted for confounding factors.

Variable	Not alive or not at home 1-year after surgery OR (95% CI)	Lung-cancer specific mortality HR (95% CI)	Non-cancer specific mortality HR (95% CI)	Overall mortality HR (95% CI)
Stair climbing <11 (v >12m)				
Adjusted[1]	***3.82 (1.28-11.4)***	1.25 (0.55-2.85)	***4.28 (2.10-8.73)***	***2.38 (1.43-3.98)***
Age at surgery >80 (v <80)				
Adjusted[1]	***9.82 (2.31-41.8)***	1.08 (0.28-4.11)	***3.38 (1.20-9.48)***	1.97 (0.89-4.35)
Male sex (v female)				
Adjusted[1]	0.54 (0.18-1.66)	1.11 (0.51-2.43)	***2.86 (1.27-6.45)***	***1.76 (1.01-3.07)***
Former smoker (v never)				
Adjusted[1]	NA	1.99 (0.53-7.50)	1.73 (0.61-4.87)	1.82 (0.82-4.06)
Current smoker (v never)				
Adjusted[1]	NA	2.21 (0.56-8.78)	1.43 (0.50-4.12)	1.65 (0.72-3.81)
Charlson comorbidity index ≥5 (v <5 points)				
Adjusted[1]	***5.57 (1.38-22.6)***	2.90 (0.90-9.35)	***3.40 (1.21-9.54)***	***2.79 (1.32-5.90)***
ppo FEV1 ≤50% (v >50%)				
Adjusted[1]	1.81 (0.55-5.98)	0.86 (0.34-2.16)	1.65 (0.70-3.87)	1.14 (0.62-2.10)
ppo DLCO ≤50% (v >50%)				
Adjusted[1]	***4.33 (1.27-14.8)***	0.96 (0.37-2.48)	1.81 (0.79-4.14)	1.43 (0.78-2.63)
Adenocarcinoma (vs. squamous cell cancer)				
Adjusted[1]	1.35 (0.41-4.47)	1.54 (0.63-3.74)	1.69 (0.78-3.67)	1.50 (0.85-2.63)
pStage II (v Stage I)				
Adjusted[1]	2.50 (0.62-9.98)	***3.27 (1.23-8.68)***	1.27 (0.57-2.81)	1.66 (0.92-3.02)
pStage III (v Stage I)				
Adjusted[1]	***8.18 (1.53-43.7)***	***5.75 (1.75-18.9)***	0.44 (0.08-2.31)	2.04 (0.89-4.70)

[1] Adjustment for age, sex, tobacco use, Charlson comorbidity index, ppoFEV1, ppoDLCO, histological type, stage, neo- or adjuvant treatment, stair climbing group (<11m, >12m).

Figure legends

Figure 1: Flowchart showing preoperative determination of physical performance and formation of study groups

Figure 2 a-c: Overall survival (a), lung-cancer-specific survival (b) and non-cancer-specific survival (c) stratified by study group (<11 m and >12 m in stair-climbing test)

Figure 3 a-d: Non-cancer-specific survival stratified by other patient-related risk factors including age (a), ppoFEV1% (b), ppoDLCO% (c) and Charlson comorbidity index (d)