Lung Cancer 125 (2018) 218–222

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Minute ventilation-to-carbon dioxide slope is associated with postoperative survival after anatomical lung resection

Takuro Miyazaki[a,b,*], Matthew E.J. Callister[c], Kevin Franks[d], Padma Dinesh[a], Takeshi Nagayasu[b], Alessandro Brunelli[a]

[a] Department of Thoracic Surgery, St. James's University Hospital, Leeds, UK
[b] Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[c] Department of Respiratory Medicine, St. James's University Hospital, Leeds, UK
[d] Department of Clinical Oncology, St. James's University Hospital, Leeds, UK

ARTICLE INFO

Keywords:
Lung cancer
Surgery
Cardiopulmonary exercise test

ABSTRACT

Objectives: The aim of the study was to identify whether ventilation-to-carbon dioxide output (V_E/V_{CO2}) slope obtained from cardiopulmonary exercise test (CPET) as part of the preoperative functional workup was an independent prognostic factor for short and long-term survival after major lung resection.

Patients and methods: 974 consecutive patients undergoing lobectomy (n = 887) or segmentectomy (n = 87) between April 2014 to March 2018 were included. 209 (22%) underwent CPET, and pulmonary function tests and several clinical factors including age, sex, performance status and comorbidities were retrospectively investigated to identify the prognostic factors with a multivariable Cox regression analysis.

Results: Among the patients with measured V_E/V_{CO2}, the incidence of cardiopulmonary complications in patients with high V_E/V_{CO2} slope (> 40) was 37% (19 of 51) vs. 27% (33 of 121) in those with lower slope values (p = 0.19). The 90-day mortality in patients with high V_E/V_{CO2} slope (n = 8) was 16% vs. 5% (n = 6) in those with lower slope values (p = 0.03). No overall difference in 2-year mortality was identified between the two groups (VE/VCO2 > 40: 70% (54–80) vs. VE/VCO2 ≤ 40: 72% (63–80), log-rank test, p = 0.39). In a Cox regression analysis V_E/V_{CO2} values were associated with poorer 2-year survival (HR 1.05, 95% CI 1.01–1.10, p = 0.030).

Conclusions: We found that V_E/V_{CO2} slope was an independent prognostic factor for the 90-day mortality and 2-year survival after anatomic pulmonary resection. This finding may assist during the multidisciplinary treatment decision-making process in high-risk patients with lung cancer.

1. Introduction

Assessment of the aerobic capacity using cardiopulmonary exercise test (CPET) is recommended as a second line test dependent on results of initial pulmonary function tests and low technology fitness tests (e.g. stair climbing or shuttle walk test) to stratify the risk of surgery [1].

Low values of maximal oxygen consumption (V_{O2} max) have been associated with high risk of mortality and long-term disability following major lung resection as they reflect the impairment in the oxygen transport system caused by deficits of one or more of its components (i.e. heart, lungs, and skeletal muscles) [1,2]. Recently, however, in a case matched analysis from European Society of Thoracic Surgeons (ESTS) database, low V_{O2} max was not associated with increased morbidity and mortality after video-assisted thoracic surgery (VATS) lobectomy [3].

Although, in clinical practice, V_{O2} max is still the most used and reliable variable for patient selection, the ratio of minute ventilation (V_E) to carbon dioxide output (V_{CO2}), is gaining interest. V_E/V_{CO2} slope is the relationship between VE, plotted on the Y axis, and V_{CO2}, on the X axis, both measured as L/min. It can be determined in submaximal tests and relates to changes in the ventilation-perfusion relationship or hyperventilation [4,5]. The increased V_E/V_{CO2} slope is considered as a prognostic factor in patients with pulmonary hypertension, heart failure [6,7] and respiratory failure [8].

In our specialty, previous reports have shown that patients with V_E/V_{CO2} slope exceeding 35 had a significant higher incidence of

* Corresponding author at: Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan.
E-mail address: miyataku@nagasaki-u.ac.jp (T. Miyazaki).

https://doi.org/10.1016/j.lungcan.2018.10.003
Received 12 June 2018; Received in revised form 30 September 2018; Accepted 1 October 2018

respiratory complications and mortality after major pulmonary resection, while V_{O2} max was not associated with respiratory complications [9]. Moreover, some reports [10–12], which were almost consistent with our previous results [9], demonstrated the efficacy and importance of V_E/V_{CO2} slope for predicting surgical complications in patients with chronic obstructive pulmonary disease (COPD).

However, these reports were limited to COPD patients and acute postoperative complications only. Evidence of the association between this parameter and longer term outcomes (i.e. 90-day mortality and beyond 1-year survival) are missing. Therefore the purpose of this retrospective study was to verify the association between V_E/V_{CO2} slope value and short (90-day) and long term (2-year) survival of NSCLC patients after major pulmonary resection.

2. Patients and methods

This is the retrospective analysis performed on a prospectively maintained institutional database used for quality of care monitoring and clinical service evaluation. All 974 patients who underwent anatomical lung resection including lobectomy and segmentectomy in St. James's Hospital, Leeds, UK, from April 2014 to March 2018 were analysed. For the purpose of this analysis wedge resections were excluded due to minimal invasiveness, and pnemonectomies were also excluded due to excessive invasiveness. The study was reviewed by the Research and Innovation Department of our hospital, which waived NHS Research Ethics Committee review and classified it as a service evaluation.

All patients were selected for pulmonary resection according to current functional guidelines and after discussion during a multidisciplinary tumour board meeting [13]. A preoperative symptom-limited CPET on an electronically braked cycle ergometer was performed to detect the deficit in their oxygen transport system when the postoperative predicted (ppo) FEV1 or ppoDL_{CO} (or both) are < 30%, or if the distance walked during shuttle walk test was shorter than 400 m, according to the locally accepted guidelines [1,14].

Patients were operated by specialist thoracic surgeons through a muscle-sparing, nerve-sparing thoracotomy or VATS. Following the operation, the patients were extubated in the operating room and transferred to an intensive care unit for constant monitoring where they spent the first postoperative night. They were subsequently transferred to a dedicated general thoracic surgical ward. Postoperative treatment focused on early as possible mobilization, chest physiotherapy, and physical rehabilitation administered by a specialized physiotherapist. Surgical pain was managed with a combination of intravenous patient controlled and local paravertebral analgesia. The details of this enhanced recovery pathway was previously describedelsewhere [13].

The exercise test involved the patient undertaking a symptom limited CPET test with heart (ECG) monitoring. After measurement of resting data, patients commenced unloaded cycling on a Lode Corival ergometer (Netherlands) until oxygen uptake stabilised. They then cycled at a constant rate of 60 rpm on a ramping protocol, which increased by 1 W every 6 s until either they reached their maximally tolerated level or the test was stopped due to significant ECG or blood pressure changes.

Peak power output (measured in watts), oxygen uptake (VO2), the ratio of dead space to tidal volume (Vd/Vt) and the ventilation (VE) to carbon dioxide output (VCO2) slope (VE/VCO2 slope) were measured during the CPET test using an Ultima CPET metabolic cart (Medical Graphics, UK).

The VE/VCO2 slope was calculated using the slope calculation option of the software package both to anaerobic threshold (if obtained) and to peak VO2. For the purpose of this study the value at anaerobic threshold was considered. If AT was not reached, the value at peak VO2 was considered.

2.1. Statistical analysis

Risk factors and outcomes were defined and standardized at database outset and in keeping with the joint Society of Thoracic Surgeons and European Society of Thoracic Surgeons statement [15]. The following complications occurring in hospital or within 30 days from the operation were included in the major cardiopulmonary morbidity outcome: adult respiratory distress syndrome, pneumonia, pulmonary embolism, pulmonary oedema, atelectasis requiring bronchoscopy, respiratory failure (needing longer than 24 h mechanical ventilation or needing re-intubation after surgery), arrhythmia requiring electrical or medical cardioversion, myocardial ischemia, cardiac failure, stroke and acute renal failure.

The normal distribution of numeric variables was first assessed by the Shapiro-Wilk normality test. Numeric variables with normal distribution were tested by the unpaired Student t test, and those without normal distribution were compared by means of Mann-Whitney test. Categorical variables were tested by the chi-square test or Fisher's exact test (in case of less than 10 observations in at least one cell). No adjustment for multiple testing was performed.

The following variables were tested along with V_E/V_{CO2} for a possible association with 90-day mortality: age, gender, performance status (Eastern Cooperative Oncology Group: PS), forced expiratory volume in one second (FEV1%), carbon monoxide lung diffusion capacity (DL_{CO}%), body mass index (BMI), coronary artery disease (CAD), cerebrovascular disease (CVD), and surgical access (thoracotomy or VATS). Variables were initially screened by univariate analysis. Those with a $p < 0.1$ were entered as predictors in a stepwise logistic regression analysis with backward elimination (p for retention < 0.1).

Survival was defined as the interval between surgery to death or last contact. Patients who were not reported as dead at the time of the analysis were censored at the date they were last known to be alive. Survival distribution was estimated by the Kaplan-Meier method. Significant differences in probability of surviving between the groups were evaluated by log-rank test. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on 2-year overall survival. Follow-up was obtained by data retrieved from the centralized electronic Patient Pathway Manager clinical information system of the hospital. All patients were followed up through March 2018. Median follow up was 738 days (IQR 418-1119).

The following variables were tested along with V_E/V_{CO2} for a possible association with 2-year overall survival: age, gender, PS, FEV1%, DL_{CO}%, body mass index BMI, CAD, CVD, and surgical access (thoracotomy or VATS). In addition, pathological T and N descriptors were also examined to adjust the survival analysis. All statistical tests were performed on the statistical software Stata 15.0 (StataCorp, LP, College Station, Tex).

3. Results

974 patients underwent lobectomy (n = 887) or segmentectomy (n = 87) during the study period. 801 (82%) operations were performed through VATS. 209 patients had CPET as part of the preoperative functional workup. Table 1 showed the comparison between patients with (n = 209, 21%) and without CPET (n = 765, 79%). Patients who performed CPET were older ($p < 0.0001$), had lower FEV1 ($p < 0.0001$), lower DL_{CO} ($p < 0.0001$), and higher incidence of CAD ($p = 0.002$) and had a worse performance status ($p = 0.01$). The incidence of cardiopulmonary complications in patients with CPET was 30% versus 21% in those without ($p = 0.003$). Similarly, the 90-day mortality was more than double in those with CPET (7.7% vs. 2.9%, $p = 0.002$).