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Title

Patient-reported physical function is associated with survival following lung resection for NSCLC

Running Head:

Physical function and survival in NSCLC

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Abstract:

Background: We investigated the association between preoperative quality of life (QoL) and long-term survival in patients undergoing surgical resection for non-small cell lung cancer (NSCLC).

Methods: Retrospective analysis was conducted on 388 consecutive patients who completed the Quality of Life assessment through the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and lung cancer specific module (LC13), prior to anatomical lung resection for NSCLC (2014-2018).

Survival distribution was estimated by the Kaplan-Meier method. Cox proportional hazard regression and competing risk regression analyses were used to assess the independent association of preoperative patient-reported outcomes with overall and cancer-specific survival.

Results: Higher score in patient-reported Physical Functioning was significantly associated with longer overall survival (Figure 1). Factors significantly associated with poorer overall survival remained older age ($p=0.005$), low BMI ($p=0.007$), male sex ($p<0.001$) and nodal involvement ($p=0.007$).

Competing regression analysis found that worse baseline lung cancer-specific dyspnoea ($p=0.03$), low Body Mass Index ($p=0.01$), worse Performance Status ($p=0.03$) and lymph node involvement ($p=0.01$) were significantly associated with poorer cancer-specific survival.

Conclusions: Higher patient-reported Physical Function score was associated with longer overall survival after resection. Our study highlights the significance of routinely collecting QoL data to aid preoperative decision making in NSCLC.

Table of Abbreviations and Acronyms

Acronym	Full form
QoL	Quality of Life
NSCLC	Non small cell lung cancer
BMI	Body Mass Index
PF	Physical Function
TKI	Tyrosine Kinase Inhibitors
NHS	National Health Service
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire C30
EORTC QLQ-LC13	EORTC Lung Cancer Specific Module
FEV1	Forced Expiratory Volume in 1 second
DLCO	Carbon Monoxide Lung Diffusion Capacity
ECOG	European Cooperative Oncology Group
PS	ECOG Performance Status
COPD	Chronic Obstructive Pulmonary Disorder
CAD	Coronary Artery Disease
CVD	Cerebrovascular Disease
CKD	Chronic Kidney Disease
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

CONSORT	Consolidated Standards of Reporting Trials
PRO	CONSORT Patient Reported Outcomes
IQR	Interquartile Range
OS	Overall Survival
CI	Confidence Interval
EORTC LCCO	EORTC Lung Cancer Specific Module - Coughing
EORTC LCHA	EORTC Lung Cancer Specific Module - Haemoptysis
EORTC LCPC	EORTC Lung Cancer Specific Module – Chest Pain
PROMS	Patient Reported Outcome Measures

1.0 Introduction

As results from recent multimodality trials in lung cancer report improved survival rates, it remains important to ensure adequate quality of life for patients, as life-extending treatment regimens may increase symptom burden. Patient reported outcome measures (PROMs) are becoming important for patient management in the cancer setting, however their collection remains limited in thoracic surgery[1].

Specifically, Quality of Life (QoL) is becoming of critical importance in the context of multimodality cancer care, as patient involvement is paramount in the decision-making process when evaluating different treatment modalities. QoL has provided prognostic information beyond traditional indicators used in oncology, such as performance status[2].

While pre-treatment QoL has been confirmed in oncological settings to provide prognostic information in addition to clinical measures[3-6], QoL research in surgical settings has focused on predicting complications and other postoperative outcomes[7, 8]. However, during the last decade, the few studies which investigated the association between QoL and survival used generic tools or mainly involved thoracotomy procedures [9-11].

Even a minimally invasive approach like video assisted thoracoscopic surgery is associated with worsening of quality of life 12 months after surgery[12], although the VIOLET randomised trial shows that effects are less severe than for open lobectomy[13].

The objective of this study was to assess the association between preoperative QoL and survival in patients undergoing surgical resection for pathological non-small cell lung cancer (NSCLC) using a validated cancer specific questionnaire.

We hypothesised that there would be a positive association between preoperative QoL and survival for NSCLC patients undergoing resection.

2.0 Patients and Methods

This study is a retrospective NHS (National Health Service) service evaluation performed on a prospectively maintained database, using clinical and demographic patient data. Self-

reported QoL data in the form of questionnaires were collected from 388 consecutive patients prior to their anatomical lung resection for NSCLC between June 2014 and June 2018 at a single cancer centre in Leeds, United Kingdom.

This study was classified by the local Research and Innovation Committee as a service evaluation so did not require an NHS Research and Ethics Committee review or formal ethical approval.

All operations were performed by qualified thoracic surgeons, and patients were cared for in a dedicated thoracic surgery unit after surgery. Only patients with pathologically staged R0 resections were included in the analysis. A systematic lymph node dissection was performed in all patients. Patients were staged according to the 8th edition of the TNM staging system.

2.1 Quality of life assessment

Health related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), a generic cancer questionnaire validated in patients with cancer, and its Lung Cancer specific module (EORTC QLQ-LC13)[14] EORTC questionnaire responses were rated on a four-point Likert scale and transformed linearly to give scores from 0 to 100. In function scales with multiple items, higher scores indicate a higher level of functioning, while higher scores on symptom scales and single items indicate worse symptoms[15]. Missing items were managed according to the EORTC guidelines[16].

The QLQ-C30 consists of nine multi-item scales (physical, role, emotional, cognitive and social functioning and pain, nausea and vomiting, and fatigue) and six single items (lack of appetite, constipation, diarrhoea, dyspnoea, insomnia and financial difficulties). The QLQ-LC13 consists of one multi-item scale (dyspnoea) and nine single items (cough, haemoptysis, dysphagia, sore mouth, peripheral neuropathy, alopecia, chest pain, arm/ shoulder pain and pain in other body parts). A clinical nurse specialist gave questionnaires to all highly suspected or proven lung cancer patients referred by the multi-disciplinary team meeting to the surgeons

for radical treatment prior to preoperative clinic visit. All questionnaires were self-administered in paper format although assistance was offered.

2.2 Clinical outcomes

For patients included in this study, follow-up was via routine telephone, in-person visits or retrieval of data from the local health care system database. Where applicable, cause of death was recorded based on the official cause of death in the death certificate.

2.3 Statistical Analysis

Numeric variables are presented as means and standard deviations, and categoric variables are presented as count and percentages.

For the purposes of the analysis, survival was defined as the interval between initial surgery until death and/or last contact with the patient. Additionally, data for patients in this study who were not reported as dead at the time of analysis were censored at the date of last contact.

Initially, a univariable Cox regression analysis of the following clinical and demographic variables was performed for overall survival (Table 3): Age, body mass index (BMI), gender, forced expiratory volume in 1 second (FEV1), carbon monoxide lung diffusion capacity (DLCO), European Cooperative Oncology Group (ECOG) performance status (PS), moderate to severe Chronic Obstructive Pulmonary Disorder (COPD) defined as FEV1<80% and FEV1 to FVC ratio<0.7, history of Coronary Artery Disease (CAD), Cerebrovascular Disease (CVD) such as stroke or transient ischemic attack, Chronic Kidney Disease (CKD), Diabetes, type of surgical access (minimally invasive versus open access), extent of resection (pneumonectomy vs lesser resections) and TNM stage. FEV1 and DLCO were expressed as percentage of predicted values. In addition, univariable Cox regression analyses were used to test the association of the individual QLQ-C30 and QLQ-LC13 domains with overall survival. Variables

with p <0.1 resulting from the above univariable analyses were then included in a multivariable Cox proportional hazard regression analysis using a stepwise approach with backward elimination to evaluate their effects on survival.

A competing regression analysis including the same variables selected from univariable analyses was then performed to identify factors associated with lung cancer death where the competing risk events were all deaths occurring due to non-lung cancer causes (other cancers or non-cancer reasons).

A two-tailed p-value less than 0.05 indicated statistical significance. All tests were per- formed on Stata 15.0 statistical software (Stata Corp., College Station, TX, USA). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[17]. We followed the Consolidated Standards of Reporting Trials (CONSORT) Patient Reported Outcome (PRO) guidance for the reporting the QoL results[18].

3.0 Results

A total of 388 patients (322 undergoing to lobectomies, 35 segmentectomies and 31 pneumonectomies) completed a baseline QoL assessment prior to their operations and were included in the analysis. The demographic, clinical and surgical characteristics of the patients involved in this study are summarised in Table 1. The sample filling the questionnaire was compared to the entire population of patients with pT1-2N0 NSCLC operated on in the unit in the same period (740 patients), and there was no demographic difference, limiting the selection biases.

Eighty percent of patients had their operation performed through a minimally invasive approach. The baseline QoL scores for each dimension are presented in Table 2. Median follow-up was 55 months (interquartile range [IQR] 42-66). A total of 12 patients died within 30 days from operation (3%). Three-year overall survival (OS) was 72% (95% confidence

interval [CI], 69-75), 42% (95% CI, 32-52), and 81% (95% CI, 70-88) for lobectomies, pneumonectomies, and segmentectomies, respectively. There were 268 patients alive at the time of last follow-up. A total of 239 patients were alive at more than 3 years after surgery.

Table 3 shows the results of the univariable analysis for overall survival. Hazard Ratio (HR) <1 indicates a positive association with survival and HR>1 indicates an inverse association with survival. A negative association ($p<0.1$) was found with overall survival for the following patient variables which were consequently included in the multivariate regression analysis: older age, lower BMI, male sex, lower FEV1%, lower DLCO%, PS>1, pT greater than 1, open access, pneumectomy and positive nodal status.

3.1 Survival & Quality of Life

The results of the Cox univariable analysis in Table 4 showed that of the nine EORTC QLQ C-30 multi-item scales, four were associated with overall survival: Global Health Status, Physical Functioning, Role Functioning and Social Functioning. As expected, better functional scores were associated with longer survival. Out of the 6 single items, fatigue, pain, dyspnoea and appetite loss were negatively associated with survival, i.e., a higher symptomology resulted in a poorer prognosis. For the EORTC LC-13 module, cancer-specific dyspnoea was negatively associated with overall survival as shown in Table 5. Other EORTC LC-13 scales such as coughing (LCCO $p = 0.077$), haemoptysis (LCHA $p = 0.059$) and chest pain (LCPC $p = 0.014$) were associated with overall survival but when tested in the Cox regression analysis, they were not retained in the final model.

A Multivariable Cox proportional hazard regression analysis including variables with $p<0.1$ at univariable analysis was then conducted (Table 6) to test their association with overall survival. After adjusting for other confounders, factors significantly associated with overall survival remained age ($p=0.005$), BMI ($p=0.007$), male sex ($p<0.001$), nodal involvement ($p=0.007$) and preoperative patient-reported Physical Functioning scale ($p<0.001$).

Patients with a higher preoperative EORTC-QLQ-C30 Physical Functioning were shown to live longer than those with a lower self-reported Physical Functioning. This is depicted in Figure 1 which shows the estimated survival functions for different values of physical functioning extracted from the EORTC-C30 questionnaire in representative patients (male or female, positive or negative Nodal stage) and keeping the numeric variables in the model (age, BMI) at their mean values. For instance, a 70 year old male patient with a BMI of 27 and a pT1N0 stage would have an estimated 5-year overall survival of 75%, 65%, 50% and 35% in case of a baseline Physical Functioning of 100, 80, 50 and 30 (corresponding to the 1, 5, 50 and 75 percentiles of baseline PF distribution), respectively. Even more interestingly, the same theoretical patient with positive nodal status would have 50% and 60% 5-year survival in case of a good baseline functional status of PF=80 or PF=100.

A competing regression analysis was then performed to identify factors associated with cancer specific survival where the competing risk events were all deaths which occurred either as a result of non-cancer causes or other cancers. These factors included: low BMI, a Performance Status greater than 1, lymph node involvement and a higher baseline dyspnoea level and are displayed in Table 7. Only factors resulting associated with lung cancer death after backward elimination are shown.

The competing multivariable regression analysis identified that baseline dyspnoea was negatively associated with cancer specific survival (HR=1.01, CI=1.00-1.02, p=0.03). Figure 2 demonstrates this finding and the cumulative incidence of lung cancer death at higher scores for dyspnoea.

4.0 Comment

4.1 Main Finding

In this prospective study, after adjusting for several clinical and pathological factors, we showed that better patient reported Physical Functioning was significantly associated with

greater overall survival. Worse patient reported dyspnoea score was significantly associated with decreased cancer specific survival.

4.2 Context

Our results confirmed previously published results of the prognostic role of patients' self-reported health status using a validated self-reporting tool such as the EORTC QLQ-C30 and QLQ-LC13 in in surgical lung cancer patients[11]. The EORTC QLQ-C30 and the QLQ-LC13 questionnaire were already used to demonstrate the prognostic role of patient-reported QoL parameters in advanced NSCLC and to be a reliable tool to collect such data, which should become routine in clinical practice [2, 19, 20].

4.3 Clinical Inferences

The findings from this real-world analysis indicate that preoperative QoL provides valuable information which, alongside other oncological parameters, may improve prediction of NSCLC prognosis and survival after resection. Although further investigation is necessary to denote the mechanisms by which QoL is associated with survival, it can be inferred that patient reported QoL represents a subjective impact of NSCLC on the physical, emotional and social aspects of health.

We found that dyspnoea and Physical Functioning were superior to standard clinical factors in predicting survival. Dyspnoea may be influenced by other factors such as deconditioning and cardiac disease in addition to pulmonary function. Dyspnoea may also reflect the subjective experience of symptoms which may not be adequately captured by objective parameters or pulmonary function tests. Similarly, the entirely self-reported nature of Physical Functioning may make it more sensitive to functional limitation than PS, a more objective parameter which is assigned by the physician based on what the patient reports, explaining the greater predictive power of Physical Functioning.

Collection of QoL data can help identify high-risk cancer groups that may benefit from multi-modality treatments such as immunotherapy, and access to data on change of QoL

predicting higher risk of NSCLC recurrence can help guide adjuvant treatment. There may also be genetic factors predisposing some NSCLC patients to better QoL, thus improving survival[21]. Patients in good physical shape prior to surgery have better outcomes and fewer complications following major operation [22, 23]. This is consistent with the association between Physical Functioning scores and survival amongst our patient population. QoL data provided valuable information for clinicians to make more informed decisions on treatment for NSCLC patients, so it can be inferred that patient-reported QoL measures could be integrated within pre-operative guidelines for all NSCLC patients. However, the quality of PROMS (patient reported outcome measures) reporting must improve to maximise its clinical impact on NSCLC survival [5, 24].

Nevertheless, PROMs collection will help in detecting physical and emotional high-risk groups which will benefit from preoperative exercise training or psychological support, allowing faster recovery[26, 27].

4.4 Limitations

This study has potential limitations. We did not use the updated version of the EORTC Lung Cancer module[25] which includes surgery-specific items which may have affected our results. Due to the retrospective nature of this study, lower QoL scores may reflect other occult predictors of poor prognosis which are outside the scope of our investigation and the questionnaire. Nevertheless, our findings remained unchanged after adjusting for such potential prognostic factors.

As we were unable to collect all postoperative QoL data due to staff limitations, we did not analyse change in QoL over time despite evidence indicating its significance as a prognostic factor for survival [3, 19].

Our analysis was limited to patients who were able to complete the preoperative QoL questionnaire. An accurate consent rate cannot be reported due to the service evaluation nature of the study and reliance on voluntary staff assistance to collect data. Despite this, a

sensitivity analysis indicated that the clinical characteristics of included patients were representative of the entire cohort of patients treated in that period (data not reported).

4.5 Conclusion

Our study, along with others, highlights the importance of collecting QoL data in clinical practice alongside other information to aid pre-surgical decision making for NSCLC patients. This data provides tangible information to the surgeon and patient regarding the rationale for an operation and enables accurate prediction of survival and associated complications for individuals with NSCLC. The study demonstrates that self-reporting QoL questionnaires such as the EORTC-QLQ-C30 and QLQ-LC13 contain modalities, such as the Physical Functioning component, which forms a good prognostic factor for predicting survival in NSCLC patients following resection.

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Tables

Table 1: Patient characteristics (N:388)

Patient characteristics	Mean (SD) or Count (%)
Age	68.9 (9.6)
BMI	27.1 (5.1)
Sex (Male), *n(%)*	*188 (49%)*
FEV1%	87.9 (22.3)
DLCO%	73.3 (19.0)
Performance Status >1, *n(%)*	*48 (12%)*
Chronic Obstructive Pulmonary Disease, *n(%)*	*83 (21%)*
Coronary Artery Disease, *n(%)*	*29 (7.5%)*
Cerebrovascular Disease, *n(%)*	*21 (5.4%)*
Chronic Kidney Disease, *n(%)*	*12 (3.1%)*
Diabetes, *n(%)*	*41 (11%)*
Open access, *n(%)*	*77 (20%)*
Pneumonectomy, *n(%)*	*31 (8.3%)*
pT>1, *n(%)*	*215 (55%)*
Nodal Involvement, *n(%)*	*79 (20%)*

Abbreviations: DLCO: carbon monoxide lung diffusion capacity; FEV1: forced expiratory volume in one second.

383 **Table 2:** Baseline QLQ-C30 scores

Variables	Median (25-75 IQR)
Global Health Status	66.7 (58.3-83.3)
Physical Functioning	86.7 (73.3-100)
Role Functioning	100 (66.7-100)
Emotional Functioning	75 (58.3-91.7)
Cognitive Functioning	83.3 (83.3-100)
Social Functioning	100 (77.7-100)
Fatigue	22.2 (0-33.3)
Nausea and vomiting	0 (0-0)
Pain	0 (0-16.6)
Dyspnoea	33.3 (0-33.3)
Insomnia	33.3 (0-66.6)
Appetite loss	0 (0-33.3)
Constipation	0 (0-0)
Diarrhoea	0 (0-0)
Financial difficulties	0 (0-0)
Lung cancer Dyspnoea	11.1 (0-22.2)

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387 **Table 3:** Results of the univariable Cox regression analysis testing the association of patient-
388 related and tumour-related variables with overall survival

Patient characteristics	**HR** (95% CI)	**P-value**
Age	1.02 (1.00-1.04)	0.02
BMI	0.94 (0.90-0.98)	0.001
Sex (Male)	2.32 (1.61-3.42)	<0.001
FEV1%	0.99 (0.98-0.99)	0.02
DLCO%	0.98 (0.97-0.99)	0.002
PS>1	1.53 (0.93-2.48)	0.09
COPD	1.41 (0.92-2.07)	0.11
CAD	1.35 (0.71-2.47)	0.34
CVD	1.77 (0.91-3.33)	0.09
CKD	1.37 (0.67-3.48)	0.31
Diabetes	1.13 (0.66-1.95)	0.63
Open access	2.00 (1.35-2.93)	<0.001
Pneumonectomy	1.63 (0.92-2.90)	0.09
pT>1	1.72 (1.19-2.49)	0.004
pN positive	2.22 (1.52-3.24)	<0.001

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390 **Abbreviations:** BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney
391 disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease;

392 DLCO: carbon monoxide lung diffusion capacity; FEv1: forced expiratory volume in 1

393 second; pN: pathologic nodal stage; PS: performance score; pT: pathologic T stage.

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Table 4: Results of the univariable Cox regression for overall survival with EORTC QLQ-C30 domains

Variables	**HR** (95% CI)	**P-value**
Global Health Status	0.99 (0.98-1.00)	0.10
Physical Functioning	0.98 (0.97-0.99)	<0.001
Role Functioning	0.99 (0.98-0.99)	0.001
Emotional Functioning	1.00 (0.99-1.01)	0.71
Cognitive Functioning	1.00 (0.99-1.01)	0.45
Social Functioning	0.99 (0.98-0.99)	0.005
Fatigue	1.01 (1.00-1.01)	0.001
Nausea and vomiting	1.00 (0.99-1.02)	0.18
Pain	1.01 (1.00-1.01)	0.002
Dyspnoea	1.01 (1.00-1.01)	0.003
Insomnia	1.00 (0.99-1.00)	0.29
Appetite loss	1.01 (1.00-1.01)	0.03
Constipation	1.00 (0.99-1.01)	0.14
Diarrhoea	1.00 (0.99-1.01)	0.91
Financial difficulties	1.00 (1.00-1.01)	0.12

419 **Table 5:** Results of the univariable Cox regression for overall survival with EORTC QLQ-LC13

420 domains

Variables	**HR** (95% CI)	**P-value**
Dyspnoea	1.01 (1.00-1.02)	0.001
Coughing	1.01 (0.99-1.01)	0.08
Haemoptysis	1.01 (0.99-1.03)	0.06
Sore Mouth	1.00 (0.99-1.01)	0.40
Dysphagia	1.00 (0.99-1.02)	0.38
Peripheral Neuropathy	1.00 (0.99-1.01)	0.23
Alopecia	0.99 (0.98-1.01)	0.79
Pain in chest	1.01 (1.00-1.02)	0.01
Pain in arm or shoulder	1.00 (0.99-1.01)	0.35
Pain in other parts	1.00 (0.99-1.01)	0.58

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Table 6: Results of the multivariable Cox regression for overall survival

Variable	HR	SE	P value	95% CI
Age	1.03	0.01	0.005	1.01-1.05
BMI	0.95	0.02	0.007	0.91-0.98
Sex (Male)	2.16	0.43	<0.001	1.46-3.17
DLCO	0.99	0.01	0.07	0.98-1.01
pT>1	0.72	0.14	0.09	0.49-1.05
pN positive	1.75	0.36	0.007	1.17-2.61
Physical Functioning scale	0.98	0.01	<0.001	0.97-0.99

Abbreviations: BMI: Body mass index; CI: confidence interval; DLCO: carbon monoxide lung diffusion capacity; HR: hazard ratio; pN: pathological nodal stage; pT: pathological T stage;. SE: Standard Error;

Table 7: Results of the competing regression analysis

Variable	SHR	SE	P value	95% CI
BMI	0.94	0.022	0.009	0.90-0.99
PS>1	2.11	0.70	0.03	1.10-4.05
pN positive	2.07	0.58	0.010	1.19-3.60
EORTC LC13 Dyspnea scale	1.01	0.01	0.03	1.01-1.02

Abbreviations: BMI: Body mass index; CI: confidence interval; pN: pathological nodal stage; PS: performance status; SE: Standard Error; SHR: sub-distribution hazard ratio

Figures and Legends

Figure 1: Overall survival function by different values of Physical Functioning (higher values of Physical Functioning represent better functional status) in different representative patients (numeric variables in the model kept at their mean values-age 70, BMI 27 kg/m^2, DLCO 73%: a) male with pT1N0 stage, b) male with pT1Npositive stage; c) female with pT1N0 stage; d) female with pT1Npositive stage.

Abbreviations: PF = Physical Functioning

Figure 2: Cumulative incidence of lung cancer death by different representative values of pre-operative Dyspnoea (higher value of Dyspnoea represents worse symptoms)

Abbreviations: DY = dyspnoea