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Pompili, C, Omar, S, Ilyas, MH et al. (5 more authors) (2023) Patient-reported physical function is associated with survival following lung resection for NSCLC. *The Annals of Thoracic Surgery*, 116 (3). pp. 563-569. ISSN 0003-4975

<https://doi.org/10.1016/j.athoracsur.2022.09.047>

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1 **Title**

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

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5 **Running Head:**

6 Physical function and survival in NSCLC

7

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24 **Conflict of Interest Statement**

25 All authors declare no known competing financial interests or personal relationships that
26 could have appeared to influence the work reported in this paper.

27

28 **Funding Statement**

29 No funding was received for this study.

30

31 **Classifications:**

32 Lung cancer surgery, Quality of Life, Lung

33

34 **Word Count:** 4491

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46 **Abstract:**

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

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

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

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

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

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

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71 **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

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79 **1.0 Introduction**

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

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

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

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

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

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

102 **2.0 Patients and Methods**

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

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

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

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

115 **2.1 Quality of life assessment**

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

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

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

133

134 **2.2 Clinical outcomes**

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

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139 **2.3 Statistical Analysis**

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

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

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

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

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

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

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170 **3.0 Results**

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

178 Eighty percent of patients had their operation performed through a minimally invasive
179 approach. The baseline QoL scores for each dimension are presented in Table 2. Median
180 follow-up was 55 months (interquartile range [IQR] 42-66). A total of 12 patients died within
181 30 days from operation (3%). Three-year overall survival (OS) was 72% (95% confidence

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

185 Table 3 shows the results of the univariable analysis for overall survival. Hazard Ratio (HR)
186 <1 indicates a positive association with survival and $HR > 1$ indicates an inverse association
187 with survival. A negative association ($p < 0.1$) was found with overall survival for the following
188 patient variables which were consequently included in the multivariate regression analysis:
189 older age, lower BMI, male sex, lower FEV1%, lower DLCO%, $PS > 1$, pT greater than 1, open
190 access, pneumectomy and positive nodal status.

191 **3.1 Survival & Quality of Life**

192 The results of the Cox univariable analysis in Table 4 showed that of the nine EORTC QLQ
193 C-30 multi-item scales, four were associated with overall survival: Global Health Status,
194 Physical Functioning, Role Functioning and Social Functioning. As expected, better functional
195 scores were associated with longer survival. Out of the 6 single items, fatigue, pain, dyspnoea
196 and appetite loss were negatively associated with survival, i.e., a higher symptomology
197 resulted in a poorer prognosis. For the EORTC LC-13 module, cancer-specific dyspnoea was
198 negatively associated with overall survival as shown in Table 5. Other EORTC LC-13 scales
199 such as coughing (LCCO $p = 0.077$), haemoptysis (LCHA $p = 0.059$) and chest pain (LCPC p
200 $= 0.014$) were associated with overall survival but when tested in the Cox regression analysis,
201 they were not retained in the final model.

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

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

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

224 The competing multivariable regression analysis identified that baseline dyspnoea was
225 negatively associated with cancer specific survival (HR=1.01, CI=1.00-1.02, p=0.03). Figure
226 2 demonstrates this finding and the cumulative incidence of lung cancer death at higher
227 scores for dyspnoea.

228 **4.0 Comment**

229 **4.1 Main Finding**

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

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

234 **4.2 Context**

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

241 **4.3 Clinical Inferences**

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

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

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

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

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

271 **4.4 Limitations**

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

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

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

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

286 **4.5 Conclusion**

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

295

296 **Acknowledgements**

297 None.

299 **References**

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378 **Tables**379 **Table 1:** Patient characteristics (N:388)

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

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

382

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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386

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

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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

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419 **Table 5:** Results of the univariable Cox regression for overall survival with EORTC QLQ-LC13
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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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429 **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

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

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441 **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

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

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456 **Figures and Legends**

457 **Figure 1:** Overall survival function by different values of Physical Functioning (higher values
458 of Physical Functioning represent better functional status) in different representative patients
459 (numeric variables in the model kept at their mean values-age 70, BMI 27 kg/m², DLCO 73%:
460 a) male with pT1N0 stage, b) male with pT1Npositive stage; c) female with pT1N0 stage; d)
461 female with pT1Npositive stage.

462 **Abbreviations:** PF = Physical Functioning

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

466 **Abbreviations:** DY = dyspnoea

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