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TITLE: POOR PREOPERATIVE PATIENT-REPORTED QUALITY OF LIFE IS ASSOCIATED WITH COMPLICATIONS FOLLOWING PULMONARY LOBECTOMY FOR LUNG CANCER.

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ABSTRACT

Objectives:

To assess whether quality of life (QoL) was associated with cardiopulmonary complications following pulmonary lobectomy for lung cancer.

Methods:

Retrospective analysis of 200 consecutive patients submitted to pulmonary lobectomy for lung cancer (September 2014-October 2015). QoL was assessed by the self-administration of the EORTC-QLQC30 questionnaire within 2 weeks before operation. The individual QoL scales were tested for a possible association with cardiopulmonary complications along with other objective baseline and surgical parameters by univariable and multivariable analyses.

Results

43 patients (21.5%) developed postoperative cardiopulmonary complications, 4 of them died within 30 days (2%). Univariable analysis showed that compared to non-complicated patients, those with complications reported a lower Global Health status (GHS) (59.1(SD 27.2) vs. 69.6(SD 20.6),p=0.02), were older (71.2(SD8.4) vs. 67.7(SD9.4),p=0.03), had lower values of forced expiratory volume in one second (FEV1) (83.9(SD27.2) vs. 91.4(SD20.9),p=0.06) and carbon monoxide lung diffusion capacity (DLCO) (67.9(SD20.9) vs. 74.2(SD17.6),p=0.02), and higher performance score (0.76(SD0.63) vs. 0.53(SD0.64),p=0.02). Stepwise logistic regression analysis showed that factors independently associated with cardiopulmonary complications were age (OR 1.04, 95%CI 1.0-1.09,p=0.02) and patient-reported GHS (OR 0.98, 95%CI

0.96-0.99,p=0.006), whereas other objective parameters (i.e. FEV1, DLCO) were not. The best cutoff value for GHS to discriminate patients with complications after surgery was 50 (c-index 0.65, 95%CI 0.58-0.72).

Conclusions

A poor global health status perceived by the patient was associated with postoperative cardiopulmonary morbidity. Patient perceptions and values should be included in the risk stratification process to tailor cancer treatment.

INTRODUCTION

Patient-reported quality of life (QOL) has been shown to correlate poorly with functional parameters commonly used to assess fitness before lung resection[1-3]. Furthermore, the trajectory of quality of life after lung resection for NSCLC does not always follow the cardiorespiratory impairment expected in high-risk classes[4].

Despite the efforts made to decrease the incidence of adverse events after major resection for lung cancer by improving patient selection, none of the risk models is characterized by 100% of accuracy. Unknown or unmeasured subjective factors may play a role in determining the postoperative course or even the long-term prognosis. For instance, a recent paper has investigated the impact of the visually observed physical status on estimates of surgical risk[6,7] demonstrating that surgeons differentiated relative risk of lobectomy based on clinical vignettes.

Nevertheless, current risk-stratification algorithms do not include patients reported outcomes (PROs) as measures of subjective wellbeing[8].

Investigating the impact of the subjective perception of well being on surgical outcome may help refining the risk stratification by providing a PROs as a global measure of many potential factors.

The objective of this analysis was therefore to assess whether QOL is associated with cardiopulmonary complications following pulmonary lobectomy.

METHODS

This is a retrospective analysis performed on a prospectively maintained database. Two hundred consecutive patients undergoing pulmonary lobectomy for lung cancer (September 2014-October 2015) completed a preoperative quality of life questionnaire and were analyzed. All cancer patients were discussed at multidisciplinary tumor board meetings. Operability exclusion criteria were in accordance with current guidelines[7].

All patients were operated by qualified general thoracic surgeons either by a videoassisted thoracoscopic technique (VATS, n=175) or by muscle sparing thoracotomy (n=25) depending upon the surgical indications (stage, size and location of the tumor). All patients had a systematic mediastinal lymph node dissection along with the lung cancer resection.

Following operation the patients were extubated in the operating room and transferred to a high dependency unit for intense monitoring where they spent the first postoperative night. They were subsequently transferred to a dedicated general thoracic surgical ward unless clinical conditions dictated otherwise.

Postoperative care followed standardized pathways of care and included early as possible mobilization and oral food intake, intense chest physiotherapy and rehabilitation, deep venous thrombosis prophylaxis and chest pain control using a combination of patient controlled analgesia and paravertebral infusion of local anesthetic.

Quality of Life assessment

QOL was assessed by the administration of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30), Version 3, within 2 weeks before operation. The EORTC QLQ-C30 is an internationally validated cancer specific quality of life questionnaire[8]. It is composed of multi-item and single-item scales measuring global health status (akin to overall quality of life), five functional scales analysing physical, role, emotional, cognitive and social functioning and nine symptom scales analysing fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties.

The score range is from 0 to 100 after linear transformation of their raw scores. A high score for a functional scale represents a high level of functioning (healthier), while a high score for a symptom scale represents a high level of symptomatology/problems.

This instrument has been extensively tested for reliability and validity[9-10].

Statistical analysis:

The principle endpoint of the analysis was the incidence of postoperative cardiopulmonary complications occurring within 30 days from the operation or over a longer period if the patient was still in the hospital. Cardiopulmonary complications were defined according to the joint STS-ESTS standard definitions[11] and included the followings: respiratory failure requiring mechanical ventilation longer than 24 hours or re-intubation, Acute Respiratory Distress Syndrome (ARDS), pulmonary embolism, pulmonary edema, pneumonia, atelectasis requiring bronchosopy, atrial fibrillation needing medical treatment or cardioversion, acute myocardial ischemia, acute cardiac

failure, stroke, acute kidney failure. Several baseline and surgical variables, including the EORTC QLQC30 scales were tested for a possible association with cardiopulmonary complications using univariable analysis. Normal distribution of the variables was tested by using the Shapiro Wilk normality test. Numeric variables with normal distribution were compared by using the unpaired Student's t test, while those without normal distribution were compared by the Mann Whitney test. Categorical variables were compared using the Chi square test. The exact Fisher's test was used when the frequency in one or more cells was less than 10.

In addition to the EORTC quality of life scales, the following variable were tested: age, sex, body mass index (BMI), forced expiratory volume in one second expressed as percentage of normal for age sex and height (FEV1%), carbon monoxide lung diffusion capacity expressed as percentage of normal for age sex and height, history of coronary artery disease (CAD), cerebrovascular disease (CVD), diabetes or chronic kidney disease (CKD), Eastern Cooperative Oncology Group performance score (ECOG), surgical approach (VATS vs. open surgery), pathologic tumour stage (pT1 vs. pT>1). Those variables resulting significant ($p<0.05$) at univariable analysis were then used as independent predictors in a stepwise logistic regression with backward elimination. Variables with $p<0.05$ were retained in the final model and their reliability tested by bootstrap analysis with 1000 samples. In the bootstrap analysis, repeated samples with the same number of subjects as the original database were generated with replacement and the logistic regression repeated in each of these simulated samples. The variables occurring in more

than 50% of the samples were judged stable and retained in the final model[12-14].

ROC analysis was used to determine the best cut off value of significant QoL scales associated with complications. The best cut off was determined by identifying the point closest to the top-left part of the ROC curve plot.

The analysis was performed by using the STATA 12.0 (Stata Corp., College Station, TX) statistical software.

RESULTS

The baseline objective characteristics of the patients included in this study are shown in table 1. Their preoperative QoL scales are reported in table 2. 43 patients (21.5%) developed cardiopulmonary complications within 30 days from operation, 4 of them died in-hospital or within 30 days (2%).

Cardiopulmonary complications in order of frequency were the followings: 23 pneumonia, 18 atrial fibrillation, 11 atelectasis requiring bronchoscopy, 9 respiratory failures, 5 ARDS, 3 pulmonary edema, 3 myocardial infarct. Twenty five patients had more than one complication.

Objective variables significantly associated with complications after univariable analysis were: age (p=0.03), FEV1 (p=0.06), DLCO (p=0.02), performance score (p=0.02) and previous history of cerebrovascular disease (p=0.08) (table 3).

Univariable analysis showed that patients with any complications had poorer Global Health status (GHS) (p=0.02), lower Physical Functioning (p=0.09) and Role Functioning (p=0.09) values. They also had greater appetite loss

(p=0.047) and dypnoea (p=0.07) compared to non complicated ones. No other QOL scales were associated with outcome (table 4).

Stepwise logistic regression analysis showed that the only factors that remained independently associated with cardiopulmonary complications were age (p=0.02) and GHS scale (p=0.006), whereas other objective parameters (i.e. FEV1, DLCO) were not (table 5).

To control for the effect of surgical factors such as intraoperative complications needing conversion, we performed an additional analysis including this variable as independent predictor along with age and GHS. This test showed that age (p=0.015) and GHS (p=0.008) retained their independent significant association with cardiopulmonary complication even after controlling for the effect of conversion.

A threshold effect was sought using ROC analysis. The best cutoff value for GHS to discriminate patients with complications was 50 (c-index 0.65, 95%CI 0.58-0.72) (figure 1). 23 patients had a preoperative GHS<50 and 11 (48%) of them developed complications. Among the 178 patients with GHS>50, 33 (18%) developed complications (p=0.001) (table 6).

DISCUSSION

Main Findings

We were able to show that the subjective perception of a poor global health status is associated with postoperative cardiopulmonary morbidity after pulmonary lobectomy.

Our finding suggests that the level of preoperative QoL represents important information that can be used along with other preoperative parameters to refine the evaluation of patients to be submitted to lung resection for NSCLC. Most notably, this is the first time to our knowledge, that a patient reported parameter supersedes the traditional objective risk factors of postoperative outcomes in a context using modern functional guidelines to select patients for operation.

Findings in the context of existing literature

The objective functional parameters measured before operation (pulmonary function tests and exercise test) have traditionally been considered surrogates of the patients' health status, in particular when discussing with them the possible lung cancer treatment options. The increasing number of publications on patient reported outcomes (PROMs) during the last decade have led to reconsider the importance and the different weight of objective and subjective outcomes in thoracic surgery.

Few trials have attempted to identify some objective factors associated with perioperative changes in QoL. In particular, Handy and coll demonstrated that patients with poor DLCO had worse preoperative physical functioning and quality of life in addition to worse postoperative quality of life, health and functioning, and psychological/spiritual status. However, in that study a generic questionnaire was administered precluding the evaluation of more specific cancer-related symptoms[15]. In a previous paper, we were able to identify that some important quality of life domains were correlated with the postoperative perceived health status by using the SF-36 in 172 patients submitted to pulmonary resections[16].

Preoperative objective parameters should not be considered as a surrogate of quality of life inasmuch as the latter is a multidimensional concept encompassing social, emotional, cognitive, physical, and functional well-being[17]. Other studies confirmed the presence of unaccounted factors in the standardized definition of high-risk surgical candidates, showing no significant changes in terms of QoL evolutions when compared to their low-risk counterparts (i.e. older/younger, COPD/no COPD, low/High VO2Max)[4,18-20].

The overall failure to predict how the patient will feel months after surgery questions the entire process of surgical patient selection. The most update guidelines in fact do not include quality of life or other Patients Reported Outcomes scores in their algorithms[7,21]. In 2010 the British Thoracic Society[22] for the first time introduced in the risk assessment for surgery flow-chart the acceptance of risk by the patient which can be considered a complex process involving still unknown body-mind interactions.

Clinical Inference

One explanation to our results can be found in the presence of unknown patient's characteristics associated with the early postoperative outcome and that are better reflected into self rated-parameters rather than in objective measures. This may refer to the concept of interoception, the individual's superior ability to sense and incorporate even non-conceptualized sensations of bodily status into self-ratings of health[23-24].

The same interpretation can also apply to the recent published papers where physical and mental components of QoL were associated with overall and cancer-specific survival in early stages non-small cell lung cancer patients[25-26].

Other authors have tried to explain different and unexpected results after introducing patient reported outcomes in clinical health-applied research, with the Wilson-Cleary Model linking clinical variables with QoL[27]. To improve patient's outcomes is in fact pivotal to identify causal pathways that link different types of outcomes to each other, especially when patient-reported ones are included. The model implies that symptom status, functional health, general health perceptions, and overall quality of life are casually connected dimensions of QoL. According with this model, the General Health Summary Score as the most reliable predictors of post-operative complications can be interpreted as expression of a multi-level continuum, with a domain of physiologic variables as the starting point and unaccounted personal and environments factors playing an important role.

The emerging evidence of a genetic substrate influencing the subjective perception of physical and emotional well-being[28] may help in the future to explain the association between components of health related quality of life and occurrence of postoperative complications independent of other objective risk factors.

We found that almost half of the patients with GHS<50 developed complications compared to 18% of those with a higher preoperative GHS. This information has important clinical implications.

First of all, patient reported Global Health Status may be included in future flowcharts used to select patients for operation. This QoL domain is calculated from only two questions of the EORTC C30 questionnaire (1.How would you rate your overall health during the past week? and 2.How would you rate your

overall quality of life during the past week?). Both these questions are scored using a 1 to 7 scale where 1 represents very poor global health/quality of life and 7 an excellent global health/quality of life). The two scores are averaged (raw score) and then a linear transformation is performed using the following equation to yield a score ranging from 0 to 100: GHS=((raw score-1)/6))X100. The inclusion of a shorter version of these questionnaires in the preoperative algorithms can be warranted especially after the publication of the new version of the EORTC Lung Cancer Module containing for the first time surgical items[29].

Moreover, the information that a low GHS score is associated with poor early outcome may warrant the institution of rehabilitation and physical supporting programs to be proposed and studied for efficacy. These programs can improve the patient well being and potentially reduce postoperative morbidity.

To date there is no composite measure that includes both objective measures and patient-derived utilities. However major initiatives are arising highlighting the crucial role of PROMs in the standard set of outcomes, like the ICHOM Standard Set for Lung Cancer or the US Patient Centered Outcomes Research Institute. Our group developed a survival aggregate score (SAS), including objective and subjective patient-based parameters, to refine the prognostic stratification of patients with early stage NSCLC after surgical treatment[20].

The inclusion of the PROMs in large databases would be challenging to realize in clinical practice, but more efforts need to be done in the surgical field to increase the representativeness of these outcomes in the everyday clinical practice where they are largely missing[30]. To facilitate and support these measurements researchers in UK have developed a technical system for

regularly collecting PROMs online, at repeated post-diagnostic time-points, for linking and storing these with patients' clinical data in cancer registries, and for electronically managing the related patient monitoring and communications[31].

Limitations

This study may have potential limitations.

This is a single centre investigation and generalization of results to other settings or Countries needs to be verified by independent studies. Differences in case-mix, economic, social and cultural characteristics of patients may have an impact on results.

The analysis has been performed on patients with lung cancer considered suitable for lobectomy. Generalization to benign diseases or sublobar resections needs to be verified.

We excluded patients undergoing to pneumonectomy as this operation has been consistently found associated per se with an increased risk of complications and mortality. The association between QoL measures and outcome after pneumonectomy warrant a separate analysis.

Most of the operations (88%) have been performed through a VATS approach. It would be interesting to verify whether similar results would be found analyzing a population with a larger proportion of thoracotomies.

Admittedly, the discrimination ability of GHS is only moderate as indicated by the c-index value. This may be due to other factors associated with complications, which may be unknown or unaccounted for, or imprecision of the quality of life measurement instrument in this setting.

In fact, the results may be influenced by the instrument used to measure QoL. In this study we used the EORTC QLQC30, which is a generic questionnaire specifically validated for cancer patients. The utilization of other QoL tools (i.e.SF36) may lead to different findings and warrant specific analyses allowing for comparison with general population.

Conclusion

The subjective perception of a poor global health status is associated with postoperative cardiopulmonary morbidity after pulmonary lobectomy. This finding warrants the adoption of a holistic approach during the surgical shared-decision-making process. Patient perceptions and values should be included in the risk stratification process to tailor cancer treatment.

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Table 1: Characteristics of the patients included in the analysis

Variables	
Age (years)	68.5 (9.2)
Sex male (n,%)	84 (42%)
BMI (kg/m^2)	27.2 (5.1)
FEV1%	89.8 (22.5)
DLCO%	72.8 (18.4)
Diabetes (n,%)	20 (10%)
CAD (n,%)	14 (7%)
CVD (n,%)	14 (7%)
CKD (n,%)	10 (5%)
ECOG score	0.58 (0.60)
VATS (n,%)	175 (87.5%)

Results are expressed as mean and standard deviation for numeric variables and as numbers and percentages for categorical variables. BMI: body mass index, FEV1: forced expiratory volume in one second; DLCO: carbon monoxide lung diffusion capacity; CAD: coronary artery disease; CVD: cerebrovascular disease; CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group score; VATS: videoassisted thoracoscopic surgery.

Table 2: Preoperative quality of life EORTC-QLQC30 scales.

Scales	
GHS	67.4 (22.5)
PF2	83.5 (18.6)
RF2	84.2 (24.7)
EF	73.9 (26.4)
CF	85.7 (19.4)
SF	86.8 (24.2)
FA	23.8 (23.5)
NV	3.85 (13.3)
PA	16.8 (25.8)
DY	25.6 (28.0)
SL	32.3 (33.3)
AP	14.5 (26.4)
CO	9.74 (22.5)
DI	6.67 (17.8)
FI	9.40 (23.1)

Results are expressed as means and standard deviations. GHS: global health status; PF2: physical functioning; RF2: role functioning; EF: emotional functioning; CF: cognitive functioning; SF: social functioning; FA: fatigue; NV:

468 nausea and vomiting; PA: pain; DY: dyspnoea; SL: insomnia; AL: appetite loss;
469 CO: constipation; DI: diarrhoea; FI: financial difficulties.

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485 **Table 3**: Results of the univariable comparison of baseline objective variables
486 between complicated and non-complicated patients

Variables	Complicated (43 patients)	Non complicated (157 patients)	p-value
Age (years)	71.2 (8.4)	67.7 (9.4)	0.028
Sex male (n,%)	18 (42%)	66 (42%)	0.98
BMI (kg/m^2)	26.4 (4.8)	27.4 (5.1)	0.55
FEV1%	83.9 (27.2)	91.4 (20.9)	0.055
DLCO%	67.9 (20.9)	74.2 (17.6)	0.019
ECOG score	0.76 (0.61)	0.53 (0.59)	0.021
CAD (n,%)	4 (9.3%)	10 (6.4%)	0.50
CVD (n,%)	6 (14.0%)	8 (5.1%)	0.083
CKD (n,%)	2 (4.7%)	8 (5.1%)	1
Diabetes (n,%)	6 (14.0%)	14 (8.9%)	0.39
VATS (n,%)	36 (83.7%)	139 (88.5%)	0.43
pT1 stage (n,%)	21 (49%)	72 (46%)	0.73

Results are expressed as mean and standard deviation for numeric variables and as numbers and percentages for categorical variables. BMI: body mass index, FEV1: forced expiratory volume in one second; DLCO: carbon monoxide lung diffusion capacity; CAD: coronary artery disease; CVD: cerebrovascular disease; CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group score; VATS: Video Assisted Thoracoscopic Surgery approach.

Table 4: Results of the univariable comparison of patient reported quality of life scales between complicated and non-complicated patients

Scales	Complicated (43 patients)	Non complicated (157 patients)	p-value
GHS	59.1 (27.2)	69.6 (20.6)	0.021
PF	79.7 (20.0)	84.5 (18.2)	0.089
RF	80.5 (23.8)	85.2 (24.9)	0.092
EF	73.6 (28.1)	74.0 (26.1)	0.86
CF	80.1 (25.1)	87.2 (17.4)	0.15
SF	83.7 (25.7)	87.6 (23.8)	0.23
FA	29.3 (27.6)	22.4 (22.1)	0.20
NV	6.91 (17.9)	3.03 (11.8)	0.31
PA	18.7 (26.1)	16.3 (25.7)	0.38
DY	30.9 (25.1)	24.2 (28.6)	0.071
SL	38.2 (36.9)	30.7 (32.2)	0.23
AP	22.0 (32.1)	12.6 (24.4)	0.047
CO	15.5 (28.0)	8.23 (20.6)	0.13
DI	9.75 (18.6)	5.84 (17.5)	0.10
FI	6.50 (23.8)	10.2 (22.9)	0.19

511 Results are expressed as means and standard deviations. GHS: global health
512 status; PF2: physical functioning; RF2: role functioning; EF: emotional
513 functioning; CF: cognitive functioning; SF: social functioning; FA: fatigue; NV:
514 nausea and vomiting; PA: pain; DY: dyspnoea; SL: insomnia; AL: appetite loss;
515 CO: constipation; DI: diarrhoea; FI: financial difficulties.

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Table 5: Results of the stepwise logistic regression analysis (dependent variable: cardiopulmonary complications).

Predictors	OR	95% CI	p-value	Bootstrap%
Age	1.05	1.01-1.09	0.022	65%
GHS	0.98	0.96-0.99	0.006	75%

GHS: QoL General Health Status. Bootstrap: percentage of significancy in 1000 bootstrap samples.

538 **Table 6**: Incidence of cardiopulmonary complications by GHS score

GHS score	n. patients	Cardiopulmonary complications (n,%)
<30	11	6 (55%)
30-50	38	11 (29%)
50-80	76	15 (20%)
>80	75	11 (15%)

539 GHS: EORTC Global Health Status

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551 **Figure Legend:**

552 **Figure 1:** Receiver Operating Characteristic curve showing the accuracy of the
553 Quality of Life scale General Health Status lower than 50 in predicting
554 postoperative cardiopulmonary complications.

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