Preoperative quality of life predicts survival following pulmonary resection in stage I non-small-cell lung cancer†

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Abstract

OBJECTIVES: The objective of this study was to assess the prognostic role of preoperative quality of life (QoL) in patients operated on for early-stage non-small-cell lung cancer (NSCLC).

METHODS: This is an observational analysis of 131 consecutive patients (2003–08) submitted to pulmonary lobectomy and systematic nodal dissection for pathological pT1N0 or pT2N0 stages NSCLC with a complete follow-up (median 40 months). QoL was measured by the Short Form 36v2, a multidimensional survey assessing eight domains and two composite scales (physical component score [PCS] and mental component score [MCS]). Survival was calculated by the Kaplan–Meier method. The log-rank test was used to assess differences between groups. The relationships between survival and QoL composite scales were determined by Cox proportional hazards regression analysis adjusting for the effect of several baseline and clinical variables. PCS and MCS were categorized according to their values greater or lower than 50 percentiles (general population norms).

RESULTS: Fifty-three (40%) patients had PCS <50 and 71 (54%) had MCS <50. Results from physical functioning (P = 0.03) and general health (P = 0.03) scales were directly associated with survival. Multivariable regression showed that significant factors associated with overall survival were age >70 (hazard ratio [HR] 2.4, 95% confidence interval [95% CI] 1.2–4.8, P = 0.01) and PCS <50 (HR 2.3, 95% CI 1.4–4.4, P = 0.01). MCS, pT stage, histology, forced expiratory volume in 1 s, DLCO were not associated with prognosis. Patients with PCS >50 lived longer than those with PCS <50 (5-year overall survival 79 vs 49%, P = 0.01), in both pT1 (5-year overall survival 80 vs 49%) and pT2 stages (5-year overall survival 78 vs 48%). Cancer-specific 5-year survival was better in patients with a preoperative PCS >50 compared with those with PCS <50 (89 vs 73%, P = 0.05). Deaths due to cancer recurrence were similar in patients with PCS <50 and >50 (55 vs 53%, P = 0.9).

CONCLUSIONS: The physical component of QoL was associated with overall and cancer-specific survivals in patients operated on for early-stage NSCLC. Supportive interventions aimed at improving the perception of physical well-being should be tested to verify whether they can improve long-term prognosis after lung cancer surgery.

Keywords: Quality of life • Lung cancer surgery • Survival

INTRODUCTION

Measures of quality of life (QoL) represent a patient-centred outcome evaluating the impact of the disease or its treatment on physical and psychological dimensions.

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PATIENTS AND METHODS

This is a retrospective study performed on prospectively collected data. A total of 294 patients submitted to lobectomy and systematic nodal dissection [9] from June 2003 to June 2008 for pathological stage T1-2N0 NSCLC at a single centre were enrolled in the study. Patients were staged according to the American Joint Committee on Cancer, Sixth Edition guidelines [10].

Patients submitted to induction chemotherapy were excluded. No patients in this series underwent adjuvant chemotherapy or radiotherapy. One hundred and ninety-eight eligible patients had a preoperative assessment of QoL. Of these patients, 67 were lost at follow-up. The remaining 131 patients were used for the analysis.

The study was approved by the local Institutional Review Board of the hospital, and all patients gave their informed consent to participate in it. Operability exclusion criteria included a predicted postoperative forced expiratory volume in one second and predicted postoperative carbon monoxide lung diffusion capacity <30% in addition to a peak oxygen consumption <10 ml/kg/min. All operations were performed through a lateral muscle-sparing, nerve-sparing [11] thoracotomy by board-certified thoracic surgeons.

As a rule, patients were extubated in the operating room and transferred to a dedicated thoracic ward. Postoperative management focussed on early mobilization, antithrombotic and anti-biotic prophylaxis, and physical and respiratory rehabilitation. Thoracotomy chest pain was assessed at least twice daily and controlled through a systemic continuous infusion of nonopioid drugs. Therapy was titrated to achieve a visual analogue score <5 (on a scale ranging from 0 to 10) during the first 48–72 h. No formal preadmission, post-discharge physiotherapy or psychological supportive programmes were administered.

Neurological or psychotropic personal medications, if present, were generally resumed the day following surgery.

Quality of life assessment

QoL was assessed before the operation by the administration of the Short Form 36v2 (SF36v2) survey. The questionnaire was administered by one of the staff surgeons during preoperative counselling. Patients were instructed to fill the questionnaire alone, but help was offered to clarify issues or doubts. As a rule, questionnaires were administered within 2 weeks from the operation. The SF36v2 questionnaire [12, 13] is a generic instrument assessing eight health physical and mental concepts (physical functioning [PF], role limitation caused by physical problems [RP], bodily pain [BP], general health perception [GH], vitality [VT], social functioning [SF], role limitation caused by emotional problems [RE], mental health [MH]). Scores standardized to norms and weighted averages are used to create summary PCS and MCS on a standard scale. In the SF36v2, all health dimension scores are standardized to norms by employing a linear transformation of data originally scored on a 0–100 scale. Norm-based scores have a mean of 50 and a standard deviation of 10. As a consequence, for all health dimensions and component scales, any score <50 falls below the general population mean, and each point represents 1/10th of a standard deviation. This allows for a direct comparison of measures among different populations and scales.

Survival

Follow-up was obtained through routine office visits, by telephone contact, or by data retrieved from the Regional Health Care System database. All patients were followed through April 2011. The cause of death was recorded based on the official cause of death reported in the death certificate. Problems with inconsistent physician attribution and misclassification of causes of death should be taken into account when interpreting follow-up analyses on survival.

Statistical analysis

The following baseline and tumour variables were tested for a possible association with survival: age, gender, body mass index (BMI), American Society of Anesthesiologist (ASA) score, Eastern Cooperative Oncology Group (ECOG) score, preoperative haemoglobin concentration, forced expiratory volume in 1 s (FEV1%), carbon monoxide lung diffusion capacity (DLCO%), FEV1/forced vital capacity (FVC) ratio, history of coronary artery disease, preoperative haemoglobin level, pT stage (pT1 vs pT2), histology (adenocarcinoma vs squamous, vs others), SF36v.2 QoL scales. For the purpose of this study, the different QoL scales were categorized according to their values above or below 50 (general population norms). Survival was defined as the interval between surgery to death and 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. The Cox multivariable proportional hazard regression model was used to evaluate the effects of the prognostic factors on survival. Predictors with P-values <0.2 at univariable analysis were used in a multivariable Cox proportional hazards model.

Survival distribution was estimated by the Kaplan–Meier method. Significant differences in the probability of surviving between the strata were evaluated by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from regression coefficients. A significant level of 0.05 was chosen to assess the statistical significance. All tests were performed on Stata 9.0 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

Clinical and surgical characteristics of the patients enrolled in this study are shown in Table 1. The average scores of preoperative QoL domains are reported in Table 2. Most of the SF36 sub-scales with the exception of PF, BP, and vitality were below norms.

A preliminary analysis showed that the patients included in this study were a representative sample of all patients operated on in the same period, but who were excluded because they did not complete the SF36 questionnaire. The baseline characteristics and 5-year survival of the patients without SF36 (not included in the study) were similar to those of the patients with SF36 (63 vs 68%, P = 0.6; see supplementary material).

Table 3 shows the results of the univariable analysis for overall survival. The following variables were found negatively associated (P < 0.2) with overall survival and were used in the multivariable regression analysis: older age, lower FEV1%, PCS <50 and higher...
ECOG score (reflecting poorer performance status). The median follow-up was 40 months.

Survival and clinical prognostic factors

Cox proportional hazards regression model showed that significant factors negatively associated with long-term overall survival were age older than 70 (HR 2.4, 95% CI 1.2–4.8, \( P = 0.01 \)) and PCS <50 (HR 2.3, 95% CI 1.4–4.4, \( P = 0.01 \)).

Survival and quality of life

Patients with a preoperative SF36 PCS >50 lived significantly longer than those with PCS <50 (5-year overall survival 79 vs 49%, \( P = 0.01 \); Fig. 1). This applied for both pT1 (5-year survival, 80 vs 49%) and pT2 stages (5-year survival, 78 vs 48%; Fig. 2).
Of the eight individual SF36 scales, only PF (P = 0.03) and general health (P = 0.03) resulted as being directly associated with survival (Table 4, Fig. 3a and b). Mental composite score was not associated with prognosis.

Cancer-specific survival

Cancer-specific 5-year survival was also longer in patients with a preoperative PCS >50 compared with those with PCS <50 (89 vs 73%; P = 0.05; Fig. 4). A similar proportion of patients died of cancer recurrence among the groups with PCS <50 and PCS >50 (55% of total deaths in the group with PCS <50 vs 53% in the one with PCS >50%, P = 0.9).

DISCUSSION

Main finding

We found that, after adjusting for other clinical and pathological factors, the physical component of QoL was associated with overall and cancer-specific survivals in patients operated on for pathological stage T1-2N0 NSCLC. Patients with higher physical component of QoL (PCS >50) lived significantly longer than patients with lower score (PCS <50) independent of other confounding factors.

Context

Our results confirmed the prognostic role of patients’ self-reported health status. This information has already been the object of a few investigations.

Möller and Sartipy [8] have analysed the prognostic role of perioperative changes of QoL among a heterogeneous series of patients submitted to lung cancer surgery. Using the SF-36 survey, they found that postoperative declines of at least 10% in the PCS and MCS were associated with 18 and 13% higher risks of death, respectively. They also found that a higher baseline PCS score was associated with a longer survival, supporting our findings.

Efficace et al. [5] have used the EORTC quality of life questionnaire (QLQ)-30 and lung cancer-13 modules to demonstrate the

<table>
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<th>Variables</th>
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<tr>
<td>Physical component score &gt;50</td>
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</tr>
<tr>
<td>Mental component score &gt;50</td>
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<td>Role limitation caused by physical problems &gt;50</td>
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<td>Bodily pain &gt;50</td>
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<td>General health perception &gt;50</td>
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<tr>
<td>Vitality &gt;50</td>
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<tr>
<td>Social functioning &gt;50</td>
<td>0.8</td>
</tr>
<tr>
<td>Role limitation caused by emotional problems &gt;50</td>
<td>0.9</td>
</tr>
<tr>
<td>Mental health &gt;50</td>
<td>0.8</td>
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Figure 3: Kaplan-Meier overall survival estimates according to the preoperative SF36 PF domain (log-rank test, P = 0.04) (A) and preoperative SF36 general health domain (log-rank test, P = 0.03) (B).

Figure 4: Kaplan-Meier cancer-specific survival estimates according to the preoperative SF36 physical component score (log-rank test, P = 0.05).

Maione et al. [6] found that the global score of EORTC QLQ-C30 measured before treatment was associated with survival in a series of elderly patients with advanced NSCLC receiving chemotherapy.
Finally, Herndon et al. [7] found that only the pain domain remained predictive of survival in a series of patients with advanced NSCLC.

In contrast with a recent paper [14], we also found that an age older than 70 years was another independent predictor of post-surgical survival. As a matter of fact, major anatomic surgery is still reported to be performed less frequently in elderly patients, as demonstrated in studies confirming that the benefit of lobectomy for survival is not as evident for patients >71 years of age [15].

Limitations

- We included only patients submitted to lobectomy for pathological stage I NSCLC (T1-2N0). Generalization of our findings to other stages of disease or other types of operation needs further investigations.
- Owing to the retrospective nature of the study, we cannot completely rule out the possibility that lower QoL scores may reflect other occult predictors of poor prognosis. Nevertheless, our findings remained unchanged even after adjusting for other potential prognostic factors. Future prospective investigations are needed to better clarify the exact correlation between QoL and prolonged survival.
- We decided to adopt the SF-36v2 questionnaire, a generic QoL tool. Although the EORTC QLQ-30 survey has been shown to behave similarly to the SF-36 in assessing the perioperative changes in generic QoL scales, it has been shown to be superior in evaluating specific symptoms [16–18]. The use of this latter instrument in future investigations may contribute to finding additional information.
- Approximately one-third of the patients initially eligible for the study were lost at follow-up. This may be in part explained by the absence of a centralized institutional follow-up system and the broad catchment area.
- This analysis has been limited to patients who were able to complete the preoperative QoL questionnaire. However, we are confident that they were a representative sample of our patients, as demonstrated by their similar survival compared with those who were not able to complete the QoL survey (see Appendix).

Clinical inferences

Our findings suggest that the level of preoperative QoL represents important information that can be used along with other oncological parameters to refine the evaluation of prognosis.

Further research is needed to clarify the mechanism of the relationship between QoL and survival. A possible explanation could be that the QoL status represents a subjective measure of the impact of lung cancer or its treatment on physical and emotional aspects not otherwise captured by more traditional objective data. To find an association between QoL and other hidden factors, Sloan et al. [19] found several specific gene patterns that were related to QoL among lung cancer patients. This may lead to future investigations linking onco-psychogenomics and survival. Patients feeling in better shape before surgery can have a lower risk of early and late cardiopulmonary complications following an operation. This would explain the reduction of mortality for causes other than cancer recurrence. However, we found that a better PCS was also associated with a longer cancer-specific survival and with a reduction in cancer-related mortality. The beneficial effects of physical function on cancer recurrence have been the focus of recent investigations and may be related to a reduction in body weight and composition, beneficial changes in metabolic and sex hormones, growth factors, adipokines, immune function or inflammation [20–22]. This is in line with recent findings showing that preoperative exercise tests [23] and DLCO [24] were also associated with long-term survival.

Recommendation

Our study underscores the importance of routinely collecting QoL data in clinical practice as they could complement other prognostic factors in the presurgical decision-making process. Information about QoL can be used not only to discuss with the patient the physiological and functional risks of the operation, but also to refine the assessment of long-term prognosis.

In conclusion, we found that the physical component of QoL was associated with overall and cancer-specific survivals in patients operated on for early-stage NSCLC. Studies analysing the effect of supportive interventions aimed at improving the perception of physical well-being are warranted to verify whether these measures can possibly improve long-term prognosis after lung cancer surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at EJCTS online.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr. A. Martin-Ucar (Nottingham, UK): Congratulations for your work. It is very well delivered and well designed, a great idea. I really enjoyed it. I am just going to ask you a question, which I am sure you have got an answer for. Two years ago you told us that the EORTC questionnaire was better for lung cancer patients than the SF 36. Why have you changed your idea?

Dr. Pompili: Thank you. This is a good point. Why we decided to adopt the SF 36? Although it is a generic survey, version 2 allows for the comparison between populations and with the general population, and it provides a normalized score, which made it possible to use a cut off of 50, representing the norm of the general population of quality of life scores. This was made with the purpose of categorizing the quality of life scores and use them in the multivariable analysis.

Dr. B. Baldusck (Antwerp, Belgium): Thank you for your nice presentation. The team of Ancona is really known for its quality of research life and you are really pioneers in this field. I have two questions.

In the prospective study that you will do probably, are you going to give all patients who scored less than the 50 percentile some rehabilitation before surgery? Are you going to postpone surgery for these patients? And a second question is, are you using any new digital devices that can calculate the quality of life much faster if a patient is in front of you in the clinic before surgery?

Dr. Pompili: Regarding your first question, being the preoperative Physical Composite Score a potentially modifiable prognostic factor, supportive physical interventions may be planned in the future for those patients with reduced physical perception of their quality of life. Although, the preoperative quality of life appears in this regard to have an important prognostic role, the role of perioperative changes in the quality of life after lung cancer surgery will certainly need to be investigated further to see better if surgery itself should change the prognosis of lung cancer and if so whether the type of surgery could have an impact.

For the second question, I do not have the digital measurement of quality of life. It should be better and maybe help to solve the current problems with the traditional surveys. In fact, we still had a consistent number of patients who refused to fill their questionnaire before and after surgery.

Dr. T. Lerut (Leuven, Belgium): In your retrospective study you certainly have all the data of the pathologic staging, and all T1s are not the same. The tumor characteristics and the grading and also the tumor size and other factors may influence. Did you have a chance to look at that and incorporate it in your analysis?

Dr. Pompili: Thank you. Unfortunately, it was not possible to retrieve the tumor grading or other tumor characteristics. This would be interesting and in line with future oncogenomics research about quality of life. With this type of research the genetic signature of the tumor may be correlated with quality of life and perhaps with other types of still unidentified factors associated with both prognosis and psychological profile of the patient.