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ORIGINAL ARTICLE

Quality of life six months after lung cancer surgery is associated with long-term survival

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Abstract

Background. The aim of this study was to analyze the association between quality of life six months following lung cancer surgery and survival. *Methods.* In a prospective population-based cohort study, quality of life was estimated by the Medical Outcomes Study 36-Item Short Form (SF-36) questionnaire before and six months after surgery for lung cancer. Cox regression models adjusting for potential confounding factors were used to analyze the association between SF-36 scores six months after surgery and survival. We also estimated the risk of death in patients scoring below the normal population mean at six months after surgery. *Results.* We included 249 patients, and 79 patients were excluded because of histopathology other than primary lung cancer. After six months, 11 patients had died, and 18 patients did not respond to the second SF-36 questionnaire, leaving a study population of 141 patients with SF-36 data from both baseline and follow-up. During a median follow-up of 4.0 years, 35 deaths occurred. The SF-36 physical and mental component summary scores assessed at six months after lung cancer surgery were significantly associated with survival. Mental component summary scores below the mean of the age- and gender-matched normal population were associated with a three-fold increase in the risk of death. *Conclusions.* Quality of life scores six months after surgery contained prognostic information regarding long-term survival that was independent of baseline scores. If these findings can be validated, cross-sectional post-treatment measurements of quality of life can prove valuable, especially when baseline information is unavailable.

Patient reported outcomes are gaining increasing interest as valuable prognostic markers of survival in different fields, particularly oncology [1]. Baseline or pretreatment patient reported outcomes are associated with survival following coronary artery bypass graft surgery [2,3], cystic fibrosis [4], coronary artery disease [5], advanced lung cancer [6–10], prostate cancer [11], and various other cancers [12,13]. Moreover, post-treatment quality of life has been shown to be associated with survival in patients with prostate cancer [11], with breast cancer [14], after cardiac surgery [15], and after esophageal cancer surgery [16]. However, there is a paucity of studies exploring the potential association between aspects of health-related quality of life after lung cancer surgery and long-term survival. In a prior study, we found a strong relationship between baseline quality of life parameters and survival [17]. The primary objective of the present study was to investigate if a post-treatment quality of life assessment was prognostic for survival. Furthermore, we analyzed if patients with worse quality of life scores than the normal reference population had lower survival compared to patients who scored higher than the matched reference population. We performed a prospective population-based cohort study to investigate health-related quality of life at baseline and six months after lung surgery. The aim was to analyze the association between quality of life six months after lung cancer surgery and survival.

Patients and methods

From April 2006 to April 2008, 249 patients scheduled for lung surgery at Karolinska University Hospital were included in a prospective population-based

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cohort study. Because of histopathology other than primary lung cancer, 79 patients were excluded. Karolinska University Hospital is the only referral center for thoracic surgery in Stockholm County, serving approximately 20% of the total population of Sweden. Health-related quality of life was assessed with the Medical Outcomes Study 36-Item Short Form (SF-36) questionnaire [18,19]. The SF-36 evaluates eight dimensions of health: physical functioning, role limitations due to physical problems, bodily pain, vitality, general health perception, social function, role limitations due to emotional problems, and mental health. Scores for each domain range from 0 to 100, with higher scores indicating better health status. The SF-36 also provides summary scales for overall physical and mental health-related quality of life, with the use of norm-based methods [20]; higher scores indicate better health status. The subscales and summary scores can be compared with the general population [21]. All patients completed the baseline SF-36 questionnaire before surgery. Six months after the operation, the SF-36 questionnaire was mailed to the patients, and they were asked to complete and return the questionnaire by mail. A reminder was sent after one month to those patients who had not returned the second questionnaire, and a final reminder was sent one month later. Clinical patient details were prospectively collected in a study database. The study was approved by the regional Human Research Ethics Committee, Stockholm, Sweden (Dnr: 2006/359-31/3). Informed consent was obtained from all patients.

Survival

Survival status was determined in June 2011 by using the Swedish personal identity number [22] and the continuously updated Total Population Register at Statistics Sweden.

Statistical analyses

Continuous variables are reported as the means and the standard deviation. Cumulative survival was estimated using the Kaplan-Meier method. Survival time was calculated from the date of the surgery to the date of death, or to June 15, 2011. Statistical analyses were performed using IBM SPSS Statistics 19 (IBM, Armonk, NY, USA) and STATA 11.2 (Stata, College Station, TX, USA).

We performed two separate analyses to investigate the relationship between quality of life estimates at six months after surgery and survival. First, the association between SF-36 scores and survival was analyzed using Cox proportional hazard models (Models 1 and 2). Second, patients were categorized into two groups, "Better" or "Worse", depending on whether they had higher or lower SF-36 scores at six months after surgery compared to the age- and gender-matched reference groups from the general Swedish population. Again, Cox proportional hazard models were used to analyze the association between category (Better/Worse) and survival (Model 3).

In Model 1 we adjusted for age (continuous variable, years), gender, comorbidities, extent of resection, tumor stage, smoking status, and postoperative complications. In Model 2, we also included the corresponding baseline SF-36 summary or subscale score as a continuous variable to control for confounding by the baseline value. We reported the hazard ratios for a 10-point difference in the SF-36 summary and subscale scores on the 0–100 scale. In Model 3, we adjusted for the same potential confounding factors as in Model 1 and reported hazard ratios and 95% confidence intervals with the group category "Better" as the reference category. Furthermore, we included the corresponding baseline SF-36 scores in Model 3 to control for confounding by the baseline value. However, because this analysis gave identical results as did Model 3, the data are not shown. If the patients had any comorbidities, they were classified as "Comorbidity: Yes"; otherwise, they were classified as "Comorbidity: No". Comorbidity was defined as the presence of any of the following: ischemic heart disease, hypertension, congestive heart disease, diabetes mellitus, peripheral vascular disease, and/or cerebrovascular disease. Ischemic heart disease was defined as a history of angina pectoris, myocardial infarction, or revascularization procedure (i.e. coronary artery bypass surgery or percutaneous coronary intervention). Hypertension was defined as a history of high blood pressure requiring medication. Congestive heart disease was defined as a history of heart failure or a left ventricular ejection fraction less than 0.5. Diabetes mellitus was defined as diabetes requiring insulin or oral anti-diabetic medication. Peripheral vascular disease was defined as a history of claudication, carotid stenosis, or abdominal aneurysm. Cerebrovascular disease was defined as a history of stroke or transient ischemic attack. The extent of resection was divided into two groups: Pneumonectomy and lobectomy/sublobar resection. Tumor stage was divided into two groups: stage I and stage II-III. Smoking status was divided into three categories; current, former and never smoker. Current smoker was defined as an active smoker or a person who had stopped smoking within one year of surgery. Former smoker was defined as a previous smoker who had stopped smoking more than one year before surgery. Never smoker was defined as a person who had never been an active smoker. If the patients had any complications, they were classified as "Complication: Yes"; otherwise, they were classified as "Complication: No." A complication was defined as any of the following postoperative problems: new-onset atrial fibrillation, prolonged air leak (i.e. chest tubes in place for more than five days), pneumonia, reintubation, reoperation, or a hospital stay of eight days or more.

Results

Study population and survival

A baseline SF-36 questionnaire was completed by 170 patients. Six months after surgery, 11 patients had died, while 18 patients did not return the follow-up questionnaire. Thus, the study population consisted of 141 patients who completed the SF-36 questionnaire six months after surgery. The response-rate was 89% (141/159). The clinical variables of the study population are shown in Table I. After a median follow-up time of 4.0 years, 35 deaths had occurred. Survival in patients with a minimum follow-up time of six months was 94% (133 at risk) at one year, 87% (123 patients at risk) at two years, and 77% (70 at risk) at four years.

Table I. Pre- and postoperative characteristics, tumor stage, and histopathology.

	n = 141	
Variable	Mean or No. of patients	SD or %
Age (years)	66.6	9.1
Women	76	54
Comorbidities*	71	50
Smoking status**		
Current smoker	56	40
Former smoker	65	46
Never smoker	20	14
Operation		
Pneumonectomy	17	12
Lobectomy	117	83
Thoracotomy, sublobar resection	5	4
VATS	2	1
Complications***	30	21
Stage I	106	75
Stage II–III	35	25
Histopathology		
Adenocarcinoma	94	67
Squamous cell carcinoma	20	14
Carcinoid	15	11
Other	12	9

SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

*Comorbidity was defined as the presence of any of the following factors: ischemic heart disease, hypertension, congestive heart disease, diabetes mellitus, peripheral vascular disease, or cerebrovascular disease.

**Smoking status was divided into three categories. Current smoker was defined as an active smoker or a person who had stopped smoking within one year prior to surgery. Former smoker was defined as a previous smoker who had stopped smoking more than one year before surgery. Never smoker was defined as a person who had never been an active smoker.

***Complications were defined as any of the following: new-onset atrial fibrillation, prolonged air leak (i.e. chest tubes in place for more than five days), pneumonia, reintubation, reoperation, or hospital stay of eight days or more.

Associations between SF-36 scores six months after surgery and survival

The mean SF-36 summary and subscale scores are shown in Table II. The Cox proportional hazard Model 1 was adjusted for age, gender, comorbidities, extent of resection, tumor stage, smoking status, and postoperative complications. Model 2 was additionally adjusted for the corresponding baseline SF-36 scores. There was a significant association between the SF-36 physical component summary score and survival, with a hazard ratio for a 10-point increment on the 0–100 scale of 0.649 (95% CI 0.450–0.937; $p = 0.021$). The SF-36 mental component summary score was also significantly associated with survival, with a hazard ratio for a 10-point increment on the 0–100 scale of 0.701 (95% CI 0.519–0.946; $p = 0.020$). Adding corresponding baseline SF-36 scores to the model gave practically unchanged hazard ratios, as shown in Model 2 (Table III).

Associations between "Better" versus "Worse" Short Form 36 scores than the age- and gender-matched normal Swedish population six months after surgery and survival

Compared to the age- and gender-matched normal population, 71% of the patients in the study had a lower SF-36 physical component summary score, while 68% had a lower mental component summary score six months after surgery for lung cancer. The patients were divided into two groups for each SF-36 summary or subscale score; a patient was categorized as "Better" if the SF-36 score was higher than the age- and gender-matched normal Swedish population, otherwise as "Worse." For the physical component summary score, there were 28 deaths in the group categorized as "Worse," and seven deaths occurred in the group categorized as "Better." For the mental component summary score, there were 29 deaths in the group categorized as "Worse," and six deaths occurred in the group categorized as "Better." Having a worse physical component summary score six months after surgery compared to the mean of the age- and gender-matched normal population was not significantly associated with a higher risk for death (hazard ratio 1.74, 95% CI 0.71–4.28; $p = 0.22$). However, a worse mental component summary score six months after surgery compared to the mean of the age- and

Table II. Short Form 36 summary and subscale scores six months after surgery in the study population and in the age- and gender-matched normal Swedish population.

	Study population		Reference group	
Variable	Mean	SD	Mean	SD
SF-36 summary scores				
Physical component	38.2	10.6	43.6	3.5
Mental component	42.8	12.8	50.7	1.7
SF-36 subscale scores				
Physical functioning	62	25	74	9
Physical role functioning	30	40	67	11
Bodily pain	66	26	68	4
General health	55	21	67	5
Vitality	53	23	66	6
Social functioning	71	28	86	4
Emotional role functioning	52	45	78	8
Mental health	66	23	80	4

SD, standard deviation.

gender-matched normal population was significantly associated with a higher risk for death (hazard ratio 2.90, 95% CI 1.18–7.17; $p = 0.02$) (Table IV).

Discussion

This prospective population-based cohort study showed that impaired quality of life, assessed by SF-36 six months after thoracic surgery for lung cancer, was associated with an increased risk of mortality. After adjustments for age, gender, comorbidities, extent of resection, tumor stage, smoking status, postoperative complications, and the corresponding baseline SF-36 scores, both the physical and mental component summary scores remained independent predictors of long-term survival. We also found that having a worse mental aspect of quality of life six months after surgery, compared to a matched normal population, was associated with a three-fold increased risk of death.

The longitudinal, prospective, population-based design and the high response rate contributed to the strengths of this study. No patient was lost during follow-up and survival status was 100% complete because of the high-quality national Total Population Register (Statistics Sweden). We used a validated instrument to assess health-related quality of life and were able to perform comparisons to the general population. The population-based study design improved the external validity (generalizability) of the study, and we therefore expect our findings to apply to other patients who underwent lung cancer surgery. A loss of information, to some extent, was due to the categorization of some clinical variables.

A review article, based on an analysis of clinical trials, evaluated data linking baseline patient reported outcomes to survival in patients with cancer [1]. Despite a large disparity between studies, there was a remarkable agreement in support of the hypothesis of a relationship between patient reported outcomes and survival. The conclusion was that patient reported outcomes provided distinct prognostic information beyond standard clinical measures. Further evidence for the prognostic value of a specific patient reported outcome (i.e. quality of life data derived from a single instrument) was provided in a cancer meta-analysis

Table III. Hazard ratios for associations between a 10-point difference in the Short Form 36 summary and subscale scores six months after surgery and survival. A hazard ratio below 1 indicates that lower Short Form 36 scores are associated with a higher risk for death.

	Model 1*			Model 2**		
Variable	HR	95% CI	p	HR	95% CI	p
SF-36 summary scores						
Physical component	0.649	0.450–0.937	0.021	0.662	0.447–0.981	0.040
Mental component	0.701	0.519–0.946	0.020	0.670	0.490–0.916	0.012
SF-36 subscale scores						
Physical functioning	0.772	0.663–0.900	0.001	0.720	0.606–0.855	<0.001
Physical role functioning	0.912	0.819–1.016	0.095	0.921	0.820–1.034	0.164
Bodily pain	0.915	0.801–1.046	0.193	0.901	0.787–1.033	0.134
General health	0.759	0.627–0.917	0.004	0.745	0.600–0.924	0.008
Vitality	0.864	0.731–1.021	0.086	0.861	0.725–1.023	0.089
Social functioning	0.785	0.696–0.885	<0.001	0.785	0.692–0.891	<0.001
Emotional role functioning	0.947	0.871–1.029	0.198	0.931	0.852–1.018	0.116
Mental health	0.794	0.669–0.943	0.009	0.765	0.639–0.914	0.003

CI, confidence interval; HR, hazard ratio; SF-36, Short Form 36.

*Adjusted for age, gender, comorbidities, extent of resection, smoking status, tumor stage, and postoperative complications.

**Adjusted for age, gender, comorbidities, extent of resection, smoking status, tumor stage, postoperative complications, and corresponding baseline SF-36 summary or subscale scores.

Table IV. Associations between "Better" versus "Worse" Short Form 36 scores than the age- and gender-matched normal Swedish population six months after surgery and survival. A hazard ratio above 1 indicates that having a lower Short Form 36 score compared to the matched normal population is associated with a higher risk for death.

Variable	Better* than reference group No. of patients (%)	Worse* than reference group No. of patients (%)	Model 3** HR	95% CI	p
SF-36 summary scores					
Physical component	41 (29)	100 (71)	1.74	0.71–4.28	0.22
Mental component	45 (32)	96 (68)	2.90	1.18–7.17	0.02
SF-36 subscale scores					
Physical functioning	55 (39)	86 (61)	5.23	1.72–15.9	0.004
Physical role functioning	33 (23)	108 (77)	2.61	0.88–7.78	0.08
Bodily pain	69 (49)	72 (51)	1.41	0.68–2.91	0.35
General health	45 (32)	96 (68)	1.57	0.64–3.84	0.32
Vitality	47 (33)	94 (67)	2.52	0.97–6.55	0.06
Social functioning	54 (38)	87 (62)	2.24	0.98–5.10	0.06
Emotional role functioning	58 (41)	83 (59)	2.13	0.96–4.73	0.06
Mental health	48 (34)	93 (66)	2.97	1.17–7.52	0.02

CI, confidence interval; HR, hazard ratio; SF-36, Short Form 36.

*A patient was categorized as "Better" if the SF-36 score was higher than the age- and gender-matched normal Swedish population, otherwise as "Worse."

**Adjusted for age, gender, comorbidities, extent of resection, smoking status, tumor stage, postoperative complications.

[13], which showed additional prognostic value of quality of life data to that of clinical and socio-demographic factors for survival estimation. The association between pretreatment/baseline health-related quality of life and survival has been shown in several other disorders apart from the field of oncology [2–5].

Gotay and co-workers present several possible explanations for the consistent observation that patient reported outcomes (including self-reported health-related quality of life) are associated with survival [1,23,24]. The SF-36, and other validated quality of life instruments, could possibly use more sensitive response scales, and thus be able to detect smaller changes regarding patient health status earlier than standard clinical measures. Another explanation may be that compliance with recommended therapy is stronger in patients with high quality of life, which presumably could have an impact on long-term survival. Also, the individual and subjective perception of functional, physical, or mental status may be intimately connected with survival.

However, the question remains whether aspects of health-related quality of life can predict survival after lung cancer surgery. In a previous study [17], we found that baseline SF-36 quality of life scores provided prognostic information regarding long-term survival, and those changes in both the physical and mental SF-36 summary scores from baseline to six months after surgery were important independent risk factors for mortality.

The association between post-treatment quality of life and long-term survival has been analyzed in populations with various diseases [11,14–16]. Although the assessments of quality of life were performed using different instruments, the reported results were congruent and indicated a strong relationship between post-treatment quality of life scores and survival. Two large studies of patients with breast cancer [14] and prostate cancer [11] clearly demonstrated significant associations between quality of life measures at 6–12 months post-treatment and long-term survival.

It has been speculated that quality of life measurements are detecting subclinical recurrences of cancer before disease progression is evident by other measures. Therefore, it has been suggested that serial measurements of quality of life could be used as a surveillance method, and negative changes in quality of life could be useful for clinical decision making. Measurements of health-related quality of life have repeatedly and in diverse clinical settings demonstrated complementary information to standard clinical parameters because they address different aspects of a patient's physical and mental wellbeing and functioning. Health-related quality of life seem to be a responsive indicator for survival, and for that reason, it may be rational to include assessment of quality of life into clinical trials.

The prognostic value of post-treatment quality of life after surgery has also been studied [15,16]. A report from the Cleveland Clinic showed that lower functional health-related quality of life six months after cardiac surgery was predictive of reduced long-term survival [15]. This may also indicate that the degree of functional recovery was directly related to survival. Regrettably, the instrument that was used in their study did not capture the mental aspect of quality of life. In a Swedish nationwide prospective study of patients who underwent surgery with curative intent for esophageal cancer, it was found that assessment of specific quality of life items six months after esophageal cancer surgery could be used as predictors of survival [16]. The items included physical function and global quality of life, among other measures.

Our findings suggest that SF-36 physical and mental summary scores six months after surgery for lung cancer provide important information regarding prognosis. In clinical practice, it would be both easy and inexpensive to implement a quality of life assessment six months after surgery. The mental component summary score could be compared to that of an age- and gender-matched reference population, and a lower score would indicate a three-fold increased risk for death. However, the question still remains as to how one can effectively translate information from quality of life measurements into clinical practice. Furthermore, there is very little understanding regarding the mechanics behind the relationship between quality of life assessments and survival, and explanatory mechanisms remain to be identified. Further study is also warranted to determine if efforts to improve health-related quality of life also increase survival.

Conclusion

In conclusion, we found that quality of life as assessed by SF-36 six months after thoracic surgery for lung cancer was prognostic for long-term survival. Both physical and mental aspects of quality of life were independently associated with a higher risk for death after adjustment for confounding factors. We also found that having a worse mental aspect of quality of life six months after surgery, compared to a matched normal population, was associated with a three-fold increase in the risk of death.

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