

ORIGINAL ARTICLE

Patient features predicting long-term survival and health-related quality of life after radical surgery for non-small cell lung cancer

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Abstract

Background: This study presents a retrospective evaluation of patient, disease, and treatment features predicting long-term survival and health-related quality of life (HRQoL) among patients who underwent surgery for non-small cell lung cancer (NSCLC).

Methods: Between January 2000 and June 2009, 586 patients underwent surgery at the Helsinki University Hospital. The 276 patients still alive in June 2011 received two validated quality of life questionnaires (QLQ): the generic 15D and the cancer-specific EORTC QLQ-C30 + QLQ-LC13. We used binary and linear regression analysis modeling to identify patient, disease, and treatment characteristics that predicted survival and long-term HRQoL.

Results: When taking into account patient, disease, and treatment characteristics, long-term survival was quite predictable (69.5% correct), but not long-term HRQoL (R^2 between 0.041 and 0.119). Advanced age at the time of surgery, male gender, comorbidity (measured with the Charlson comorbidity index), clinical and pathological stages II-IV, and postoperative infectious complications predicted a lower survival rate. Features associated with poorer long-term HRQoL (measured with the 15D) were comorbidity, postoperative complications, and the use of the video-assisted thoracoscopic surgery (VATS) technique.

Conclusions: Long-term HRQoL is only moderately predictable, while prediction of long-term survival is more reliable. Lower HRQoL is associated with comorbidities, complications, use of the VATS technique, and reduced pulmonary function, while adjuvant therapy is associated with higher HRQoL.

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer death, with a worldwide mortality-to-incidence ratio of 0.87, indicating a truly poor prognosis.¹ The development of treatment options promises treatment for more and more patients, although the majority receive only palliative care. The primary treatment modality, especially in early stage non-small cell lung cancer (NSCLC), is radical surgery with a curative aim.² Although postoperative health-related quality of life (HRQoL) is naturally the main indicator of treatment outcome in palliative care, it has also become more important in the evaluation of curative treatment outcomes.

Numerous studies aiming to identify factors affecting postoperative HRQoL have shown varying results.^{3,4} A recent large study found that comorbidities and the use of adjuvant therapy had a significant negative effect on long-term HRQoL.³ Another study showed a significant negative effect of complications on HRQoL, while tumor stage remained a non-significant factor.⁴ Both studies found that extent of resection significantly affected HRQoL, although the effect of adjuvant chemotherapy was contradictory.^{3,4} Preoperative values for predicting postoperative outcome, such as forced expiratory volume in 1 second (FEV₁) and diffusion lung capacity for carbon monoxide (DL_{CO}), are incapable of adequately predicting postoperative HRQoL.^{2,5–7}

A common finding of numerous studies has been the significant role of preoperative HRQoL as a prognostic factor for patient survival.^{8,9} Montazeri *et al.* found preoperative HRQoL, measured with the EORTC QLQ-C30 + LC13 questionnaire, to be the most important prognostic factor for survival, although postoperative HRQoL may also have prognostic value for survival.^{10,11}

While these studies have defined singular patient, disease, and treatment factors that impact postoperative HRQoL, they have not evaluated the strength of such factors in predicting overall HRQoL. It is still important to determine patient and disease features and to create prognostic models that could serve in predicting how a treatment affects HRQoL. This determination could prove useful in preoperative patient selection to identify patients in which surgery is likely to have a negative impact.

The aim of this study was to clarify the relationship between individual patient and disease characteristics and to clarify the association of such characteristics with variance in HRQoL, as well as to create a prognostic multivariate model for predicting long-term HRQoL.

Patients and methods

Patients

We analyzed the data of patients who underwent surgery for NSCLC from January 2000 to June 2009 in our hospital. During this period, 586 patients underwent surgery, 79 with video-assisted thoracic surgery (VATS) lobectomy or segmentectomy, introduced in our hospital in 2006. Except for three cases, VATS patients had either clinical stage IA or IB disease. Patients who were still alive in June 2011 ($n = 276$) received two HRQoL questionnaires through the mail. After one month, non-respondents received another set of questionnaires and were eventually contacted by phone.

Quality of life instruments

We measured HRQoL with two self-administered quality of life questionnaires (QLQ): the 15D and the EORTC QLQ-C30 + LC13.^{12,13} The 15D is a generic HRQoL instrument consisting of 15 individual functional dimensions, each of which contains five ordinal levels. We used a set of population-based preference or utility weights to calculate from the health state descriptive system (questionnaire) the single index score (15D score), representing overall HRQoL on a scale from zero (death) to one (full health), and the dimension level values, reflecting a good state of function relative to no problems in the dimension (=1) and to death (=0). A recent study determined the minimal important difference (MID) in the 15D score (representing overall HRQoL) to be 0.015.¹⁴

The QLQ-C30 is a disease-specific HRQoL instrument used for oncology patients, and the LC13 is its lung cancer-

specific supplementary module; both have a score scale ranging from 0 to 100, a high score reflecting either a good state of function or a high intensity of symptoms. Maringva *et al.* determined a MID global QoL score of 9.4 for better or 4.4 for worse.¹⁵

A total of 230 patients replied to the 15D questionnaire, and 221 patients to both the 15D and EORTC QLQ-C30 + LC13 questionnaires. Our previous article describes the questionnaires in more detail.¹⁶

Statistical analysis

We determined Pearson's correlation coefficients in order to identify significant correlations between variables included in the analyses and considered a P value < 0.05 statistically significant. We used SPSS version 21.0.0 to analyze the data (IBM Corp., Armonk, NY, USA).

We used binary logistic regression models (with forward logistic regression as the method) to predict the probability of death by the time of the study. The first model included preoperative patient and disease variables, and the second model included perioperative variables. Model 1 included the surgical technique, as the surgeons chose it before surgery.

We used a nearly identical approach in an effort to identify factors that significantly influence long-term HRQoL. The difference was that we used both stepwise (the rules for taking a new variable into the model were less strict than in the binary logistic regression models noted above) and backward methods to build our models. With a similar model, using the stepwise method, we identified factors that statistically significantly affected the most severely impaired 15D dimensions. The coefficients represent the mean change in HRQoL scores per unit change in the given predictor variable. For the categorical variables, the change is compared with the alternatively prevailing situation. For the VATS technique, the change is compared with thoracotomy as the surgical technique. For squamous cell carcinoma, for example, the change is given compared with adenocarcinoma as the histological finding.

The Ethics Committee of the Helsinki University Hospital approved this protocol.

Results

Study population

By June 2011, 301 (51.4%) patients had died. We were unable to obtain data on seven patients, as these patients did not attend follow-up at our institution. In the beginning, we excluded 48 patients from the analyses because of insufficient data; an additional seven patients were excluded during the analysis stage for this same reason. In total, we included survival data on 524 patients. A total of 221 patients completed

Table 1 Patient characteristics

	All patients (n = 524)	Respondents (n = 230)	Thoracotomy† (n = 188)	VATS (n = 42)
	Mean ± SD or N (%)			
Age	65.1 ± 8.8	63.0 ± 8.7	62.1 ± 8.4	66.9 ± 8.9
Women	201 (37.9)	108 (47.0)	82 (43.6)	26 (61.9)
CCI score				
0	292 (55.0)	136 (59.1)	119 (63.3)	17 (40.5)
1	133 (25.0)	55 (23.9)	43 (22.9)	12 (28.6)
2	76 (14.3)	29 (12.6)	18 (9.6)	11 (26.2)
3	24 (4.5)	9 (3.9)	7 (3.7)	2 (4.8)
≥ 4	6 (1.1)	1 (0.4)	1 (0.5)	0
FEV1%	76.2 ± 18.5	77.0 ± 18.7	77.0 ± 18.4	77.1 ± 20.5
SPY	42.1 ± 19.2	41.5 ± 19.2	41.5 ± 19.6	41.2 ± 17.5
Clinical stage				
IA	168 (31.6)	92 (40.0)	60 (31.9)	32 (76.2)
IB	119 (22.4)	49 (21.3)	39 (20.7)	10 (23.8)
IIA	10 (1.9)	5 (2.2)	5 (2.7)	0
IIB	138 (26.0)	46 (20.0)	46 (24.5)	0
IIIA	51 (9.6)	20 (8.7)	20 (10.6)	0
IIIB	43 (8.1)	18 (7.8)	18 (9.6)	0
IV	2 (0.4)	0	0	0
Operation				
Pneumonectomy	60 (11.3)	18 (7.8)	18 (9.6)	0
Lobectomy	408 (76.8)	182 (79.1)	147 (78.2)	35 (83.3)
Sleeve	31 (5.8)	13 (5.7)	13 (6.9)	0
Sub-lobar	32 (6.0)	17 (7.4)	10 (5.3)	7 (16.7)
Neoadjuvant therapy	61 (11.5)	25 (10.9)	25 (13.3)	0
Adjuvant therapy	91 (17.1)	37 (16.1)	35 (18.6)	2 (4.8)
Histology				
Adenocarcinoma	273 (51.4)	124 (53.9)	94 (50.0)	30 (71.4)
Squamous cell carcinoma	197 (37.1)	83 (36.1)	72 (38.3)	11 (26.2)
Large cell carcinoma	30 (5.6)	8 (3.5)	7 (3.7)	1 (2.4)
Undifferentiated	31 (5.8)	15 (6.5)	15 (8.0)	0
Pathological stage				
IA	153 (28.8)	89 (38.7)	61 (32.4)	28 (66.7)
IB	150 (28.2)	70 (30.4)	60 (31.9)	10 (23.8)
IIA	20 (3.8)	11 (4.8)	9 (4.8)	2 (4.8)
IIB	99 (18.6)	37 (16.1)	37 (19.7)	0
IIIA	68 (12.8)	14 (6.1)	12 (6.4)	2 (4.8)
IIIB	39 (7.3)	9 (3.9)	9 (4.8)	0
IV	2 (0.4)	0	0	0
Complication	167 (31.5)	48 (20.9)	43 (22.9)	5 (11.9)
Recurrence	208 (39.2)	25 (10.9)	22 (11.7)	3 (7.1)

†Respondents grouped according to surgical technique applied. CCI, Charlson comorbidity index; FEV1 %, forced expiratory volume in 1 second (FEV1) percentage of the predicted value; SD, standard deviation; SPY, smoke pack-years (given for smokers); VATS, video-assisted thoracoscopic surgery.

both HRQoL questionnaires, while nine answered only the 15D questionnaire. Patient characteristics are listed in Table 1. The median follow-up time among the respondents was 4.85 years (range 2.01–11.13). About 88% of the patients were smokers. Noted postoperative complications among the respondents included bleeding in five (2.2%), infection in 20 (8.7%), cardiac events in two (0.9%), prolonged air leak in 12 (5.2%), and other complications in 14 patients (6.1%). A total of 48 respondents experienced complications (20.9%); five of these had two separate complications. In these patients, only

the first complication was included in the analyses. Twenty-five respondents experienced recurrence with a mean time to recurrence of 38 ± 24 months. The correlation between recurrence status and total HRQoL, however, showed no statistical significance.

Survival

One, two, and five-year survival rates after surgery were 84.5%, 73.2%, and 51.2%, respectively. Features included in

Table 2 Variables included in the multivariate analyses and results for the probability of death at the time of the study (*n* = 524)

	Mean ± SD or N (%)	Probability of death	
		Mod 1 Coefficient (Sig.)	Mod 2
Percentage predicted correctly		67.9	69.5
Constant		−5.70	−5.76
Preoperative features			
Time since operation (months)	81.2 ± 33.2	0.021 (0.001)	0.021 (0.001)
Age at operation	65.1 ± 8.8	0.056 (0.001)	0.052 (0.001)
Male	330 (62.1)	0.442 (0.027)	0.488 (0.016)
SPY†	42.1 ± 19.2		
CCI score	0.72 ± 1.0	0.238 (0.026)	0.242 (0.029)
FEV1%	76.2 ± 18.5		
Clinical stages II-IV†	245 (46.1)	0.546 (0.006)	
Neoadjuvant therapy	61 (11.5)		
VATS	68 (12.8)		
Perioperative features			
Lobectomy or segmentectomy	394 (74.2)		
Stages II-IV†	228 (42.9)		0.902 (0.001)
Squamous cell carcinoma‡	197 (37.1)		
Large cell or undifferentiated carcinoma‡	61 (11.5)		
Adjuvant chemotherapy	77 (14.5)		
Adjuvant radiotherapy	14 (2.6)		
Complications			
Bleeding	15 (2.8)		
Air leak	29 (5.5)		
Infection	59 (11.1)		0.837 (0.013)
Cardiac	16 (3.0)		1.93 (0.070)
Other	48 (9.0)		

†Compared to stage I; ‡compared to adenocarcinoma. CCI, Charlson comorbidity index; FEV1%, forced expiratory volume in 1 second (FEV1) percentage of the predicted value; SD, standard deviation; SPY, smoke pack-years (given for smokers); VATS, video-assisted thoracoscopic surgery; SD, standard deviation.

the analyses for patient survival and the results are listed in Table 2.

Quality of life

Differences in 15D scores between our respondents and the age and gender-standardized general population appear in our previous article.¹⁶ The respondents had significantly lower mean 15D scores and showed statistically significantly deteriorated function in regard to mobility, breathing, usual activities, depression, distress, and vitality compared with the general population. The most severe HRQoL impairment occurred in breathing and mobility. The same article reported the QLQ-C30 results for our respondents and showed lower scores among the respondents on the global QoL item.

Features predicting patients’ long-term HRQoL are detailed in Table 3. The results were virtually identical for both methods, so for clarity we provide only the results from the stepwise analysis.

The characteristics that demonstrate a statistically significant effect on the 15D dimensions most severely impaired

among the respondents (i.e. breathing and mobility) are detailed in Table 4.

Discussion

This study has demonstrated the poor predictability of long-term HRQoL based on common preoperative clinical factors. This trend was also observed in a previous study, where baseline HRQoL rather than preoperative clinical features was the most significant predictive factor for postoperative short-term HRQoL in patients treated surgically.¹⁷ However, surgery for NSCLC seldom corrects or alleviates symptoms, as patients are usually asymptomatic; surgery may even cause significant disease burden in itself.

Some previous studies have shown that comorbidities have no significant impact on long-term HRQoL.^{5,18} This difference may stem from the varied methods of categorizing patients based on the extent of their comorbidity: Paull *et al.* used subgroups comprising patients with Charlson comorbidity index (CCI) scores between 0 and 2 and scores > 2, while Balduyck *et al.* categorized their patients into sub-

Table 3 Features predicting long-term HRQoL among respondents ($n = 230$)

	Mean \pm SD or N (%)	15D score		EORTC QLQ-C30 Global health status	
		Model 1	Model 2	Model 1	Model 2
Adjusted R square		0.060	0.119	0.041	0.088
		Coefficient (Sig.)			
Constant		0.798	0.854	52.5	54.2
Preoperative features					
Time since operation (months)	70.0 \pm 29.4		-0.001 (0.041)		
Age at operation	63.0 \pm 8.7				
Male	122 (53.0)				
SPY	41.5 \pm 19.2				
CCI score	0.63 \pm 0.88	-0.028 (0.001)	-0.030 (0.001)	-3.32 (0.067)	-3.23 (0.068)
FEV1%	77.0 \pm 18.7	0.001 (0.090)	0.001 (0.087)	0.208 (0.015)	0.179 (0.032)
Neoadjuvant	25 (10.9)				
Clinical stage II-IV†	90 (39.1)				
VATS	42 (18.7)		-0.044 (0.031)		
Intraoperative features					
Pathological stage II-IV†	71 (30.9)				
Squamous-cell carcinoma‡	83 (36.1)				
Large-cell or undifferentiated carcinoma‡	23 (10.0)				
Lobar or minor resection	179 (77.8)				
Adjuvant chemotherapy	32 (13.9)				10.9 (0.010)
Adjuvant radiotherapy	5 (2.2)				
Complications					
Bleeding	5 (2.2)		-0.071 (0.140)		-20.6 (0.040)
Air leak	12 (5.2)		0.056 (0.085)		
Infection	17 (7.4)		-0.069 (0.012)		-8.88 (0.111)
Cardiac	1 (0.4)				
Other	13 (5.7)		-0.063 (0.044)		

†Compared to stage I; ‡compared to adenocarcinoma. CCI, Charlson comorbidity index; FEV1%, forced expiratory volume in 1 second (FEV1) percentage of the predicted value; HRQoL, health-related quality of life; SD, standard deviation; SPY, smoke pack-years (given for smokers); VATS, video-assisted thoracoscopic surgery; SD, standard deviation.

groups with CCI scores of 0, 1–2, 3–4 and ≥ 5 .^{5,18} In our study, the presence or absence of comorbidity was one of the strongest predictors of HRQoL, emphasizing the importance of this patient feature as a predictive factor for long-term post-operative HRQoL.

Table 4 Features that statistically significantly affect moving and breathing on the 15D questionnaire ($n = 230$)

	Moving	Breathing
Adjusted R square	0.103	0.117
	Coefficient (Sig.)	
Constant	0.863	0.595
Time since operation (months)	-0.001 (0.001)	
CCI score	-0.049 (0.001)	
Other complications	-0.099 (0.048)	
FEV1%		0.003 (0.003)
SPY		-0.002 (0.041)

CCI, Charlson comorbidity index; FEV1%, forced expiratory volume in 1 second (FEV1) percentage of the predicted value; SPY, smoke pack-years (given for smokers).

According to current understanding, preoperative FEV₁ value is a useful predictor of the quantitative outcome of surgery, especially when expressed as a percentage of the normal value, but fails to predict long-term HRQoL with sufficient accuracy.^{2,7,19–21} Nevertheless, the statistically significant influence of FEV₁ status on QLQ-C30 global health status (Table 2) and on the 15D dimension of breathing (Table 3) observed in this study indicates that preoperative FEV₁ may also be a predictive factor for HRQoL. Other researchers have made similar observations.²²

Postoperative complications seemed to significantly impact patients' long-term survival and HRQoL. The presence or absence of comorbidity did not correlate with the occurrence of postoperative complications, but advanced age (≥ 70 years) at the time of surgery ($n = 176$) correlated significantly with the risk of complications. Complications seem to affect patients' HRQoL much longer than previous studies have reported.²⁰ Future studies should aim to examine this relationship between complications and long-term survival and HRQoL in more detail and particularly focus on finding potential factors capable of predicting the high risk for complications.

Our surprising and seemingly illogical finding of the negative effect of the VATS technique on long-term HRQoL contradicts the results of previous studies; however, our finding may be biased because of the retrospective nature of our study.²³ In a previous study, our group found that patients who underwent surgery with the VATS technique were older, had more comorbidities, and poorer absolute pulmonary function.²⁴ The main characteristics of the two groups appear in Table 1. The use of VATS showed no correlation with the occurrence of complications or possible progression of the disease. In the absence of data on baseline HRQoL – the strongest predictive factor for long-term HRQoL – factors mimicking its effect gain more power. Comorbidities showed a strong negative effect on HRQoL and correlated positively with the probability of using VATS as a surgical technique. This indicates that patients who underwent surgery with VATS may have had poor HRQoL even before the surgery, and the set of variables we included in the analyses failed to account for this bias.

The use of VATS also correlated strongly with time since surgery, age at the time of surgery, disease stage, and the extent of resection, all of which is understandable. We tried to minimize the effect of such correlations by replacing the variables with new ones derived from previous variables or by removing correlating variables from the analyses, but doing so failed to alter the results. For example, replacing the variables of clinical stage and use of the VATS technique with a hybrid variable for separating patients with stage I disease and who underwent surgery with VATS from the rest of the patients had no significant effect on the results. Thus, we decided to include the primary clinical variables in the tables in order to enable clear evaluation of the results.

An important finding was the statistically and clinically significant positive effect of adjuvant therapy on HRQoL when measured with QLQ-C30 (Table 2). Numerous studies have earlier reported that adjuvant therapy has either a negative effect or no effect at all on HRQoL, while still emphasizing the fact that clinicians should not be discouraged from using adjuvant therapy, as it is only associated with a moderate decline in HRQoL.^{4,5,20}

The five-year survival in our patient group (51.2%) was comparable to other studies (42%–47%),^{25,26} Our observation that advanced age at the time of surgery had no influence on long-term HRQoL supports the prevalent opinion that advanced age shows no correlation with a steeper decline in long-term postoperative HRQoL.^{27,28}

Limitations

As noted above, baseline HRQoL prior to treatment would have been a key variable in the model for predicting long-term HRQoL. The absence of this knowledge probably significantly lowered the explanatory power of our model. It

may also have led to bias, as factors indicating or correlating with possible lower preoperative HRQoL, such as the CCI score and use of VATS, may carry too much weight in the analyses or have inappropriately negative coefficients. One limitation of the results regarding the use of the VATS technique was its introduction into practice in our hospital in 2006 (i.e. in the middle of the study period). The long period during which our patients underwent surgery also raises difficulties in the analyses and may lead to significant bias.

Conclusion

In conclusion, because objective clinical measurements seem to play such a small role in predicting HRQoL, patients should systematically receive information about possible declines in long-term HRQoL. Moreover, clinicians should employ every measure available to avoid complications, as such complications can significantly compromise long-term HRQoL.

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Disclosure

No authors report any conflict of interest.

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