Health-related quality of life in patients surviving non-small cell lung cancer

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ABSTRACT

Background and aims The EuroQol 5D (EQ-5D) is a standardised instrument for measuring health-related quality of life (HRQoL). It provides a utility score for health, and a self-rating of HRQoL (EQ-VAS). In this study, the EQ-5D was used to assess HRQoL in survivors of non-small cell lung cancer (NSCLC). The influence of tumour stage, adverse events, initial treatment and presence of recurrence was examined.

Methods Patients treated for NSCLC were sent a questionnaire, consisting of the EQ-5D, EQ-VAS and questions regarding adverse events. Tumour stage, date and type of initial treatment, and presence of recurrence were derived from patient files once patients had completed the questionnaire and informed consent form. Influencing factors were examined by exploring subgroups and using multiple regression analysis.

Results Of the 374 patients contacted, 260 (70%) returned a completed questionnaire. The EQ-VAS generated an average self-rated health of 69 (SD 18). The mean utility score was 0.74 (SD 0.27). Respondents with severe adverse events (dyspnoea grade $\geq$3) had statistically significantly lower utility scores than respondents without severe adverse events (median 0.52 vs 0.81; $p < 0.001$). Subgroups based on a patient's initial treatment modality revealed statistically significantly different utility scores ($p=0.010$).

Conclusion The results of the present study provide original data on HRQoL during survival of NSCLC. Adverse events were found to have a considerable impact on HRQoL. This stresses the need to search for treatment modalities that not only improve survival, but also reduce adverse events.

INTRODUCTION

Due to advanced technologies in the last decade, increasingly more options are available for treating cancer. As a consequence, decision making in choosing the best available treatment modality is becoming more complex. When deciding upon treatments, besides clinical effectiveness, effects on health-related quality of life (HRQoL) and costs are gaining importance.[1] This importance is strengthened due to the considerable increase in cancer costs over the last few years.[2 3] In cost-effectiveness analyses the additional costs of a treatment are compared with the additional health effects. In these analyses, quality-adjusted life years (QALYs) are the preferred health outcome.[4–7] QALYs are calculated by multiplying life expectancy by a value for HRQoL. To calculate QALYs it is necessary to express HRQoL as a value that is anchored on a numeric scale ranging from death (0) to perfect health (1). This value is the so-called utility score. The main advantage of using QALYs as an outcome in cost-effectiveness analyses is that it allows for comparison of the cost-effectiveness of different interventions for different indications.

Lung cancer is the leading cause of cancer death.[8 9] The prognosis of patients with lung cancer remains poor, with 5-year overall survival rates between 6% and 18%.[10] As a result, new treatments for lung cancer are continuously sought. A number of studies have elicited utility scores in non-small cell lung cancer (NSCLC), using divergent methodology.[11–16] However, these studies did not provide health utility based on the presence of severe adverse events and recurrence for patients with NSCLC. As new treatments are likely to affect the occurrence of adverse events and recurrences, it is important for decision making to know their impact on HRQoL. In the present study we therefore elicited utility scores from patients with NSCLC and examined the influence of factors such as recurrence and adverse events. Our objectives were: (1) to examine HRQoL in terms of health utility in survivors of NSCLC; (2) to examine HRQoL for subgroups of patients; and (3) to examine which factors influence HRQoL in patients with NSCLC.

METHODS

Data collection

The study population consisted of persons who were treated for NSCLC between 2004 and 2007 in the south (Maastricht region) or north (Groningen region) of The Netherlands, and who were still alive at the time of the study (2008). Patients were treated with radiotherapy, surgery, chemotherapy or a combination of these modalities.

The study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre and of the regional cancer registries. The study design was a cross-sectional survey. Patients with NSCLC treated in the past 5 years in the Maastricht or Groningen region were selected from the Netherlands Cancer Registry.[17] If patients were alive, they were sent a postal questionnaire, accompanied by a letter with general information explaining the aim of the study and a prepaid envelope to return the questionnaires. Also enclosed was an informed consent form, in which respondents agreed that additional data would be retrieved from their patient files. The additional data retrieved

were date and type of initial treatment, tumour stage at time of incidence and presence of a recurrence, either locoregional or distant, at time of completion of the questionnaire.

Questionnaire

The questionnaire consisted of the EuroQol 5D (EQ-5D) and questions regarding adverse events, based on the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[18] The answers to the CTCAE questions can be translated into severity of the adverse event in terms of grades. Because the current study focuses on long-term follow-up, we examined the adverse event of dyspnoea. Severe adverse events are defined as grade ≥3.

The EQ-5D is one of the most frequently used utility measures.[19] The EQ-5D was chosen in this study because it is often used in oncology,[20] and has proven discriminative and responsive properties in lung cancer and lung disease.[14 21 22] Additionally, its use is recommended by the National Institute for Health and Clinical Excellence in the UK.[23] The five questions of the EQ-5D each represent one dimension of HRQoL (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[24] In each dimension a respondent can belong to one of three categories: no problems, moderate problems or severe problems. Combinations of these categories result in 243 permutations of health states. A regression equation defines a utility value for each of these health states. The possible values for health utility range from −0.59 (severe problems in all five dimensions) to 1 (no problems in all dimensions) on a scale where 0 represents death and 1 represents the best possible health state. Methods to derive these utility scores have been described in detail by Dolan.[25] Additionally, the EQ-5D questionnaire contains a visual analogue scale (VAS) that enables respondents to assess their health subjectively on a scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Data analysis

First, to examine health state utility in survivors of NSCLC, we calculated descriptive summary statistics for the EQ-5D utility score.

Secondly, to examine whether utility scores differed between subgroups of patients, we distinguished groups based on age, sex, treatment modality (radiotherapy, chemotherapy, surgery or a combination), tumour stage, survival time, presence of recurrence and late adverse events. For age and survival time, groups were based on whether they were below or above the median. Descriptive summary statistics were provided and normality was tested for all data using the Kolmogorov–Smirnov test. Kruskal–Wallis one-way analysis of variance and pairwise comparison tests (Mann–Whitney U) were used to explore the differences between the groups.

Thirdly, utility scores were analysed using multiple linear regression analysis to assess which variables contributed to utility. The utility score was used as the dependent variable. In cases where the dependent variable was not normally distributed, we examined the skewness and kurtosis and, if necessary, transformed the values by taking the square root to obtain acceptable distributions. Age, sex, tumour stage at time of incidence, initial treatment modality, recurrence, adverse events and survival time were considered as possible explanatory variables. Dummy variables were created to analyse the initial treatment modality. Because respondents had received divergent combinations of treatment modalities, dummy variables were included in the analysis only if at least 25 respondents had received that treatment modality. All models were fitted by backward elimination and only the final models are reported herein.

For all tests, a p value <0.05 was considered to be statistically significant. All analyses were performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Study population

From the Netherlands Cancer Registry 374 patients could be identified, of which 142 (38%) were from the southern region and 232 (62%) from the northern region. A questionnaire was sent to all these patients. Of the 374 patients, 260 (70%) gave their informed consent and returned a completed questionnaire.

Mean age was 68 years, ranging from 31 to 90 years. The majority (67%) of the respondents were male. The stage distribution included stage I in 43%, stage II in 15%, stage III in 41% and stage IV in 1% of the patients. Most patients (44%) were initially treated with surgery alone, followed by combined radiotherapy and chemotherapy in 26%, combined surgery and chemotherapy in 10%, radiotherapy alone in 9%, and other treatment strategies in 11% of the patients. At the time of completion of the questionnaire the mean survival time was 2.6 years, ranging from 0.8 to 4.8 years. Most patients (73%) had no recurrence at the time of completion, while 14% had a recurrence. Patient characteristics are presented in table 1.

Utility scores

Of the 260 patients who returned a completed questionnaire, 245 (94%) had completed all five questions of the EQ-5D and

Table 1 Characteristics of the study population

Characteristics		
No. of respondents	260	
Age		
Mean (SD)	68	(10)
Range		40–90
Male	175	67%
Tumour stage		
IA	56	(22%)
IB	56	(22%)
IIA	10	(4%)
IIB	30	(12%)
IIIA	47	(18%)
IIIB	59	(23%)
IV	2	(1%)
Initial treatment		
Surgery	114	(44%)
Radiotherapy and chemotherapy	68	(26%)
Surgery and chemotherapy	27	(10%)
Radiotherapy	22	(9%)
Radiotherapy, chemotherapy and surgery	19	(7%)
Radiotherapy and surgery	7	(3%)
Chemotherapy	3	(1%)
Survival time (years)		
Mean (SD)	2.59	(0.99)
Range		0.82–4.76
Recurrence at time of completion		
No	189	(73%)
Yes, local and/or regional	16	(6%)
Yes, distant metastases	20	(8%)
Unknown	35	(14%)

Values are numbers (percentages) unless stated otherwise.

could be assigned a utility score. The item 'pain/discomfort' had the most missing values (n=12), followed by 'anxiety/depression' (n=7) and self-care (n=5). The items 'mobility' and 'usual activities' each had missing values in one patient.

Mean utility was 0.74, with an SD of 0.27 (table 2). This is only slightly lower than the scores seen in individuals of similar age in the general population (UK population, 65–74 years of age: 0.78).[26] Utility scores were not normally distributed (Kolmogorov–Smirnov test, p <0.001). The EuroQol VAS generated an average self-rated health of 69 (SD 18).

Subgroup analyses

Subgroups based on the type of initial treatment revealed statistically significantly different utility scores (Kruskal–Wallis; p=0.010). Utility scores were highest for respondents treated with surgery, either alone or combined with another treatment modality (table 3). The lowest utility scores were elicited in respondents treated with radiotherapy alone.

With regard to adverse events, a total of 49 respondents reported dyspnoea grade ≥3. Respondents with severe adverse events had a statistically significantly lower utility score (median 0.52) than respondents without severe adverse events (median 0.81, p <0.001). A total of 60 respondents reported moderate (grade 2) to severe adverse events. These respondents also had a statistically significantly lower utility score (median 0.53) than respondents without adverse events (median 0.81, p <0.001).

While utility scores were higher for respondents without a recurrence than for patients with a recurrence, this difference was not statistically significant (Mann–Whitney U test, p=0.121). Utility scores of patients with a local or regional recurrence (median 0.74) were similar to those of patients with metastases (median 0.76; Mann–Whitney U test, p=0.864).

Subgroup analyses based on sex, age, tumour stage and survival time revealed no statistically significant differences.

Factors influencing health utility

In the regression model with the utility score as dependent variable, only the presence of severe adverse events and initial treatment with combined radiotherapy and chemotherapy were negatively associated with utility (explained variance 26%; table 4). Age, sex, presence of recurrence, initial treatment with surgery alone, initial treatment with combined surgery and chemotherapy, tumour stage and survival time were found not to influence the utility score.

DISCUSSION

The present study is the first to examine HRQoL in terms of health state utility among survivors of NSCLC, as well as the influence of factors such as recurrence and adverse events on health state utility. Among survivors of NSCLC, mean health state utility was 0.74 (SD 0.27). This indicates that survivors of NSCLC are on average in good health, as it is only slightly lower than the average utility score of the general population of similar age (0.78). Respondents with severe adverse events (dyspnoea grade ≥3) had statistically significantly lower utility scores than respondents without adverse events (median 0.52 vs 0.81; p <0.001). This large difference in utility scores was also present when comparing respondents with moderate to severe adverse events and respondents without adverse events (median 0.53 vs 0.81). These results stress the major impact of adverse events, even when moderate, on HRQoL. Subgroups based on initial treatment modality also revealed statistically significantly different utility scores. Respondents who had received surgery, either alone or combined, showed higher utility scores. This is likely to be related to the fact that surgery is only performed when the patient is sufficiently fit. Although patients with NSCLC in general have a lower performance status than healthy controls, patients who are treated with surgery have a higher performance status than patients who are not. Patients not treated with surgery will thus in general be in a poorer condition at baseline, and are likely to have a poorer quality of life. While utility scores were higher for respondents without a recurrence than for patients with a recurrence, this difference was not statistically significant. This was probably due to the large variance and skewness in the responses.

Table 2 Utility and visual analogue scale (VAS) scores in baseline population

	Valid n	Minimum	Maximum	Median	IQR	Mean	SD
EuroQol 5D utility score	245	−0.59	1.00	0.80	0.31	0.74	0.27
EuroQol VAS	246	0	100	70	20	69	18

Table 3 Comparison of mean scores, SD, median scores and IQR according to differences in age, sex, initial treatment, tumour stage, survival time, recurrence and adverse events

		EQ-5D utility score			
	Valid N	Mean	(SD)	Median	(IQR)
Age					
<68 years	124	0.77	(0.26)	0.81	(0.31)
≥68 years	121	0.72	(0.27)	0.76	(0.19)
p Value*				0.071	
Sex					
Male	164	0.75	(0.26)	0.80	(0.31)
Female	81	0.73	(0.27)	0.76	(0.33)
p Value*				0.492	
Initial treatment modality					
Surgery alone	111	0.77	(0.25)	0.81	(0.31)
Radiotherapy and chemotherapy	63	0.69	(0.31)	0.76	(0.37)
Surgery and chemotherapy	26	0.81	(0.24)	0.85	(0.31)
Radiotherapy alone	18	0.62	(0.24)	0.69	(0.23)
Radiotherapy, chemotherapy and surgery	19	0.72	(0.22)	0.73	(0.13)
Radiotherapy and surgery	6	0.86	(0.12)	0.81	(0.22)
Chemotherapy alone	2	1.00	–	1.00	–
p Value†				0.010	
Initial tumour stage					
I	105	0.77	(0.26)	0.81	(0.31)
II	39	0.74	(0.22)	0.76	(0.16)
III	99	0.70	(0.29)	0.76	(0.26)
IV	2	0.86	(0.19)	0.86	–
p Value†				0.266	
Survival time					
<2.44 years	124	0.72	(0.27)	0.76	(0.22)
≥ 2.44 years	121	0.76	(0.26)	0.81	(0.31)
p Value*				0.073	
Recurrence					
No	177	0.76	(0.24)	0.80	(0.31)
Yes	34	0.61	(0.37)	0.76	(0.52)
p Value*				0.121	
Severe adverse events					
No	200	0.80	(0.20)	0.81	(0.31)
Yes	41	0.45	(0.33)	0.52	(0.55)
p Value*				< 0.001	

*Mann–Whitney U test.
†Kruskal–Wallis test.

Table 4 Final model of the multiple regression analysis for the utility score

	EQ-5D utility score		
	Regression model		
Independent variable	b	SE	p Value
Constant	0.820	0.018	0.000
Severe adverse events (1=yes)	−0.353	0.039	0.000
Combined radiotherapy and chemotherapy treatment (1=yes)	−0.069	0.034	0.041
	Explained variance=26%		

The only published study that also elicited EQ-5D utility scores from patients with NSCLC was a study by Trippoli *et al.*[14] They elicited utility scores in a population of 95 patients with NSCLC, and defined subgroups with regard to gender, treatment, metastases, age and time since diagnosis. In contrast to our findings, Trippoli *et al* found that the presence of metastases was a statistically significant predictor of the utility score. However, Trippoli *et al* used parametric statistics and presented only mean values and SDs. The mean difference in health state utility between patients with and without metasteses found by Trippoli *et al* (0.53 vs 0.68) is comparable with the mean difference in utility scores found in our study (0.61 vs 0.76). However, utility scores often are not normally distributed. Since this was also the case in our study, parametric statistics could not be used. The present study confirmed the findings by Trippoli *et al* that gender, age and time since diagnosis were not statistically significant predictors for the utility score. No information was provided by Trippoli *et al* on adverse events or local recurrence.

In a study by Ko *et al*, utility scores were calculated using the Health Activities and Limitations Index.[11] The authors found a mean utility score of 0.66 (SD 0.24) for 12 patients with lung cancer who were diagnosed 1–5 years earlier. Yabroff *et al* also used the Health Activities and Limitations Index to elicit utility scores in several cancer types and other chronic conditions, including 55 patients with lung cancer in the continuing phase of care.[12] This group reported a mean utility score of 0.69 (95% CI 0.64 to 0.74). A study by Manser *et al* derived utility scores from 90 patients with NSCLC, using the Assessment of Quality of Life instrument.[13] Utility scores were calculated specifically for tumour stage and for operable and inoperable patients; both factors were found not to influence utility. Overall, the results of the present study are similar to these other studies examining utility in patients with NSCLC. However, these studies did not examine the influence of recurrences and adverse events.

Regarding adverse events, our results confirm the recently published results of Doyle *et al*[15] and Nafees *et al.*[16] These two publications, based on one study, concluded that severe adverse events heavily influence health state utility of patients with NSCLC. However, the study focused on advanced metastatic lung cancer, and elicited preferences from the general population for health states that were developed by a limited number of experts. In contrast, the present study focused on all patients with NSCLC who have survived their disease, and elicited health states directly from the patients themselves, which were subsequently transformed into utility scores using frequently used scoring functions. Despite the differences in methodology, the present study confirms the conclusion that severe adverse events heavily influence health state utility of patients with NSCLC. While suspicion was raised that the EQ-5D would lack sensitivity to reflect changes in symptom status of patients with NSCLC,[15] the results of the present study weaken this suspicion.

The current study has a number of potential limitations. First, our sample consisted of 260 responders. Although this was sufficient for most (subgroup) analyses, it resulted in some small subgroups based on initial treatment modality. However, despite these small samples, a statistically significant difference was found. The goal of the present study was to explore which factors influence HRQoL in NSCLC survivors. The design of our study was not intented and will not be appropriate to answer more specific questions. Interesting topics for future research would be, for example, whether different types and regimens of chemotherapy affect HRQoL, and whether different causes of adverse events affect HRQoL. Secondly, adverse events were self-reported by the respondents instead of by the physician. Although it is known that self-reported adverse events based on the CTCAE are feasible and show high agreement with physician-reported adverse events,[27] it would be interesting to examine the relationship between self-reported adverse events, physician-reported adverse events and health state utility in a future study. Thirdly, the high percentage of patients treated with surgery and the high percentage of patients with stage I NSCLC indicates that our population was a relatively 'healthy' sample. While this is expected since patients with lower stages and/or patients who receive surgery are more likely to survive their disease, some non-responder bias may have been present which may have overestimated HRQoL.

From a recently published review it was concluded that in NSCLC high-quality economic evaluations are lacking.[28] Because much evidence is available on effectiveness, economic evaluation using decision-analytic modelling may well offer a good solution. Decision-analytic modelling is a tool to synthesise available evidence from different sources to inform decision making.[29 30] In such a model, data on HRQoL can be combined with data on costs and effectiveness in order to examine the cost-effectiveness of a treatment.[31] The current study provides original data on utility scores among patients with NSCLC who have survived their disease. These results can be of important use in future cost-effectiveness modelling studies and decision making regarding treatments in NSCLC.[20] Furthermore, the results emphasise the considerable influence of adverse events on HRQoL. This indicates that when a new treatment is able to reduce the occurrence of adverse events, it will gain a significant number of QALYs. This finding stresses the importance of searching for treatments that not only improve survival, but can also reduce the occurrence of adverse events.

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Competing interests None.

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