European Journal of Cancer 52 (2016) 120–128

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Prognostic value of health-related quality of life for overall survival in elderly non-small-cell lung cancer patients

Frédéric Fiteni [a,b,c,*,1], Dewi Vernerey [a,1], Franck Bonnetain [a,c,d], Fabien Vaylet [e], Hélène Sennélart [f], Jean Trédaniel [g], Denis Moro-Sibilot [h], Dominique Herman [i], Hélène Laizé [j], Philippe Masson [k], Marc Derollez [l], Christelle Clément-Duchêne [m], Bernard Milleron [n], Franck Morin [n], Gérard Zalcman [n,o], Elisabeth Quoix [n,p], Virginie Westeel [n,q]

[a] *University Hospital of Besançon, Methodology and Quality of Life in Oncology Unit, Besançon, France*
[b] *University Hospital of Besançon, Department of Medical Oncology, Besançon, France*
[c] *EA 3181 University of Franche-Comté, Besançon, France*
[d] *Platform Quality of Life and Cancer, France*
[e] *Instruction Hospital of the Armies, Department of Pneumology, Percy-Clamart, France*
[f] *CLCC René Gaudducheau, Department of Medical Oncology, Nantes, France*
[g] *St Joseph Hospital, Department of Medical Oncology, Paris, France*
[h] *University Hospital of Grenoble, Pneumology Department, Grenoble, France*
[i] *Hospital of Nevers, Pneumology Department, Nevers, France*
[j] *Hospital of Sceaux, Pneumology Department, Sceaux, France*
[k] *Hospital of Cholet, Pneumology Department, Cholet, France*
[l] *Private Hospital, Pneumology Department, Maubeuge, France*
[m] *University Hospital of Nancy, Pneumology Department, Nancy, France*
[n] *Intergroupe Francophone de Cancérologie Thoracique (IFCT), Paris, France*
[o] *University Hospital of Caen, Pneumology Department, Caen, France*
[p] *University Hospital of Strasbourg, Pneumology Department, France*
[q] *University Hospital of Besançon, Pneumology Department, France*

Received 13 August 2015; received in revised form 20 September 2015; accepted 4 October 2015
Available online xxx

* *Corresponding author*: University Hospital of Besançon, Department of Medical Oncology, 3 Boulevard Fleming, 25000, Besançon, France. Tel.: +333 81668796.
E-mail address: fredericfiteni@gmail.com (F. Fiteni).
[1] Shared authorship.

http://dx.doi.org/10.1016/j.ejca.2015.10.004

KEYWORDS
Quality of life;
Prognostic factor;
Methodology;
Lung cancer

Abstract ***Background:*** We investigated whether the health-related quality of life (HRQoL) score is a prognostic factor for overall survival (OS) in elderly patients with advanced non-small-cell lung cancer (NSCLC).

Methods: We included 451 NSCLC patients aged 70–89 years enrolled in the Intergroupe Francophone de Cancérologie Thoracique 0501 trial, using scores of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 at baseline to investigate the prognostic value of HRQoL for OS, in addition to conventional factors. Cox regression model was used for both univariate and multivariate analyses of OS.

Results: Global health status (GH) dimension score at baseline was associated with favourable OS when adjusted for clinical, functional, and histological factors (hazard ratio [HR]: 0.986; 95% confidence interval [CI]: 0.980–0.992).

We distinguished three groups according to GH score: high (GH <46), intermediate (46 ≤GH ≤67), and low (GH >67) mortality risk. The median OS values were 14.5, 8.2, and 5.3 months in the low-, intermediate-, and high-risk categories, respectively (log-rank P <0.0001).

In the high-risk group, doublet chemotherapy was not associated with favourable OS (HR: 0.70; 95% CI: 0.49–1.003; P=0.052), whereas in the intermediate- and low-risk groups, doublet chemotherapy was associated with favourable OS (HR: 0.72; 95% CI: 0.54–0.96; P=0.023 and HR: 0.50; 95% CI: 0.30–0.84; P=0.0089, respectively).

Conclusion: This study supports the additional prognostic value of HRQoL data at diagnosis to identify vulnerable subpopulations in elderly NSCLC patients. HRQoL could thus be valuable in selecting patients who will benefit from doublet chemotherapy.

1. Background

The number of studies using health-related quality of life (HRQoL) assessment has been growing over the last decade. The Food and Drug Administration considers HRQoL to be an end-point for assessing direct clinical benefits for the patient [1–3]. Moreover, there has been evidence to suggest that assessing baseline HRQoL dimension scores in cancer patients improves the prediction of overall survival (OS) [4–9]. Quinten et al. carried out a meta-analysis involving over 10,000 cancer patients (16% lung cancer), revealing that baseline HRQoL was a prognosticator of longer survival [10]. In non-small-cell lung cancer (NSCLC) patients, several studies have demonstrated that HRQoL represents a significant prognosticator of favourable OS [6,9,11–13]. Sloan et al. prospectively observed 2,442 patients with stage I–IV NSCLC, 47% ≤65 years old and 53% >65 years old, all completing a single-item measure of overall HRQoL from the Lung Cancer Symptom Scale questionnaire within the first 6 months post-diagnosis. They demonstrated that QoL deficits at diagnosis were significantly associated with shorter OS (hazard ratio [HR]: 1.55; P < 0.001). Yet no study has specifically focused on elderly advanced NSCLC patients.

We sought to investigate the additional prognostic value of baseline HRQoL assessed by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) in elderly advanced NSCLC patients treated with chemotherapy in the randomised Intergroupe Francophone de Cancérologie Thoracique (IFCT) 0501 trial.

2. Methods

2.1. Sample

The IFCT 0501 study design has been previously described [14]. Patients aged 70–89 years with stage IV NSCLC or stage III unsuitable for radical radiation therapy and performance status (PS) ≤2 were eligible for this phase III trial. They were randomly assigned 1:1 to four 28-day cycles of monthly carboplatin plus weekly paclitaxel or five 21-day cycles of single agent vinorelbine or gemcitabine, on days 1 and 8 of each cycle. Patients were stratified by centre, World Health Organization (WHO) PS score (0–1 versus 2), stage (III versus IV), and age (≤80 versus >80 years).

The protocol was approved by the *Comité de Protection des Personnes* of Ile-de-France X, Aulnay-sous-Bois, France, the trial being authorised by the French National Authority for Health. All patients provided written informed consent.

2.2. Health-related quality of life

HRQoL was assessed using EORTC QLQ-C30 questionnaire [15] at randomisation, then at 6 and 18 weeks.

The QLQ-C30 is a cancer-specific tool composed of 30 items [16–18]. Five functional scores (physical, role, cognitive, social, and emotional) have been developed, rated on a global health score ranging from 0 (worst) to 100 (best), as well as nine symptom scores (nausea, pain [PA], fatigue, dyspnoea, difficulty sleeping, anorexia, constipation, diarrhoea, and perceived financial difficulties), ranging from 0 (best) to 100 (worse).

2.3. Statistical analysis

We used means and standard deviations for continuous variables, and proportions for qualitative variables. We compared means and proportions using Student's t-test and chi-squared test, or Fisher's exact test if appropriate.

Patient characteristics were described based on the completion of baseline QoL questionnaire, ensuring that any non-random missing patient profiles were detected.

OS was defined as the time from randomisation to death from any cause. Survival was censored at last follow-up or time of analysis. OS was estimated using the Kaplan-Meier method and presented as median with 95% confidence interval (CI). Follow-up was calculated using a reverse Kaplan–Meier estimation.

The association of non-HRQoL characteristics at diagnosis and baseline HRQoL dimensions in terms of OS was assessed using univariate Cox regression analysis, followed by multivariate analysis for those exhibiting $P < 0.1$. The factors identified with a $P < 0.1$ in multivariate analysis were thereafter included in a final multivariate model with stepwise backward elimination ($P < 0.05$).

The proportionality assumption for the Cox model was verified using the log graphic method. Collinearity of baseline HRQoL scores with other covariates was examined using a multiple linear regression model.

The Hosmer and Lemeshow goodness-of-fit statistics test, adapted for survival analysis, was used to evaluate the final model's calibration.

Internal validation using a bootstrap procedure was performed to assess the final model's robustness, analysing hazard regression uncertainty for parameters involved in the final model [19].

The prognostic value of HRQoL scores added to a reference risk model, including the non-HRQoL characteristics enrolled in the final multivariate model, was evaluated using C-statistics. Harrell's C-index estimates discriminate capability, i.e. the ability to distinguish between high-risk and low-risk patients, the C-index varying from 0.5 (no discrimination) to 1 (perfect discrimination). This analysis was repeated 1000 times using bootstrap samples to derive 95% CIs for the between-model difference in C-statistics.

We used continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) to quantify the performance and net benefit of adding HRQoL scores to the reference model at 24 months post-randomisation [20,21]. The cNRI quantifies the direction of change, and the IDI the magnitude of change. When significantly greater than 0, IDI and cNRI suggest the existence of a net benefit through adding the marker of interest to the reference model.

To implement HRQoL scoring into clinical practice, we determined a cut-off value via an unsupervised method using the Q1 and Q3 interquartiles.

We performed sensitivity analyses. We first included HRQoL and clinical factors with a $P < 0.1$ in the univariate analysis using a stepwise backward elimination procedure. We then conducted a stepwise multivariate model with the treatment variable as stratification factor for the final model construction. As some data from the activities of daily living (ADL), mini-mental state (MMS), and HRQol questionnaires could have been redundant by the time of analysis, we eventually conducted a stepwise multivariable model excluding the ADL score, then the MMS score, and eventually both.

Tests were two-sided, with P-values <0.05 considered significant. The analyses were conducted using SAS 9.2 (SAS, Cary, NC) and R software (Version 2.10.1).

3. Results

3.1. Study population

Between April 2006 and December 2009, 451 patients were enrolled. The number of patients who completed the entire questionnaire at baseline was 361 (80.04%), the number of available questionnaires (i.e. with at least one QoL score that could be calculated) being 421 (93.3%). At baseline, the patients who completed the entire QoL questionnaire and those who did not were found to display similar clinical characteristics (Table 1). The baseline HRQoL scores for each dimension have been presented in Table 2. Median follow-up was 30.3 months (range: 8.6–45.2). There were 199 (88%) deaths under monotherapy versus 177 (78.6%) under doublet chemotherapy.

3.2. Association between baseline HRQoL scores and overall survival

Data pertaining to the association of clinical and HRQoL dimension scores in terms of OS is shown in Tables 3A and B. In the final model, the following characteristics were independent favourable prognosticators of OS: increasing global health status (GH) score (HR: 0.986; 95% CI: 0.980–0.992; $P < 0.0001$), PS 0–1 (HR: 0.63; 95% CI: 0.49–0.81; $P < 0.0001$), doublet chemotherapy (HR: 0.65; 95% CI: 0.52–0.80; P

Table 1
Patient characteristics according to Quality of Life Questionnaire Core 30 completion.

	Patients who completed the questionnaire at baseline (n=361)		Patients who did not complete the questionnaire at baseline (n=90)		Fisher's exact test P-value
	n	(%)	n	(%)	
Age					
<77	180	49.9	48	53	0.56
≥77	181	50.1	42	47	
Gender					
Male	270	74.8	63	70	0.35
Female	91	25.2	27	30	
Performance status					
0–1	267	74	63	70	0.15
2	93	25.7	27	30	
Unknown	1	0.3	0		
Smoking status					
Never smoked	73	20	21	23	0.51
Ever smoked	288	80	69	77	
MMS					
≤20	29	8	6	7	0.82
>20	330	91	76	84	
Unknown	2	1	8	9	
ADL					
<6	66	18	22	24	0.12
6	288	80	62	69	
Unknown	7	2	6	7	
CCI					
≤2	268	74	73	81	0.17
>2	93	26	17	19	
BMI					
≤20	43	12	9	10	0.77
20<BMI≤30	276	76	72	80	
>30	42	12	9	10	
Stage					
IIIA–IIIB	70	19	17	19	0.9
IV	291	81	73	81	
Histology					
Adenocarcinoma	184	51	45	50	0.63
Squamous	123	34	28	21	
Other	54	15	17	19	

MMS = mini-mental state score; ADL = activities of daily living score; CCI = Charlson comorbidity index; BMI = body mass index.

Table 2
Health-related quality of life scores at baseline by treatment arm.

QLQ-C30 scores	All patients (n=451)		
	N*	Mean (SD)	Median (minimum–maximum)
Global health status	420	56.8 (18.7)	58.3 (8.3–100)
Physical functioning	420	69.2 (22.5)	73.3 (0–100)
Role functioning	420	66 (34.2)	66.7 (0–100)
Emotional functioning	420	72.2 (22.6)	75 (0–100)
Cognitive functioning	421	82.4 (21.1)	82.3 (0–100)
Social functioning	411	78 (30.5)	100 (0–100)
Fatigue	420	43.5 (27.8)	33.3 (0–100)
Nausea/vomiting	421	5.5 (15.2)	0 (0–100)
Pain	420	27.9 (29.8)	16.7 (0–100)
Dyspnoea	419	44.2 (34.7)	33.3 (0–100)
Insomnia	420	28.9 (32.3)	33.3 (0–100)
Appetite loss	419	35.8 (37.2)	33.3 (0–100)
Constipation	420	25.6 (32)	0 (0–100)
Diarrhoea	417	7.5 (18.4)	0 (0–100)
Financial problems	416	4.4 (15.2)	0 (0–100)

SD = standard deviation; QLQ-C30 = Quality of Life Questionnaire Core 30.

* Number of patients with HRQoL score at baseline that can be calculated high score for a functional scale represents a *high/healthy level of functioning*, high score for the global health status/HRQoL represents a *high HRQoL*, but high score for a symptom scale/item represents a *high level of symptomatology/problems*.

<0.0001), never smoked status (HR: 0.58; 95% CI: 0.43–0.78; P=0.0003), adenocarcinoma (HR: 0.68; 95% CI: 0.50–0.93; P=0.047), increasing ADL score (HR: 0.73; 95% CI: 0.61–0.88; P=0.0011), and increasing MMS score (HR: 0.97; 95% CI: 0.94–0.99, P=0.044) (Table 4). The model's calibration was acceptable (Hosmer–Lemeshow with deciles p=0.1). The internal validation HR uncertainties reflected its robustness, especially the association between GH score and OS (Table 4).

Entering the GH score into the reference model was found to significantly improve its discriminative ability, notably its capacity to discriminate between patients who died and those who did not, as C-index statistics significantly increased from 0.66 to 0.69 (bootstrap mean difference: 0.0253; 95% CI: 0.0248–0.0259). Similarly, including the GH score into the reference model adequately reclassified patients into lower (no events) or higher (events) mortality risk, as demonstrated by a continuous net reclassification index of 0.38 (95% CI: 0.13–0.64) at 24 months post-randomisation. When adding the GH score adequately reclassified 42/68 patients (61.8%) into the 'no event' group, whereas it reclassified 196/341 patients (57.4%) into the 'event' group (Fig. 1). The IDI was 0.03 (P=0.0006). Adding the GH score to the classical risk factors improved the stratification of patients at risk of death.

The factors affecting baseline GH scores were explored using multiple linear regression. Increasing baseline GH score was associated with a PS=0–1 (P <0.0001), increasing ADL score (P=0.0061), and increasing body mass index (BMI) (P=0.023). Nevertheless, this model exhibited R^2 statistics of 12%, indicating that the GH score was not completely accounted for by PS, ADL score, and BMI.

3.3. Sensitivity analyses

In the multivariate Cox model including all variables, GH dimension score remained associated with OS (HR: 0.98; 95% CI: 0.97–0.99; P=0.0002) (Supplementary Table 1). All variables significantly influencing OS in the final model were also found to be statistically

Table 3A
Univariate and multivariate Cox regression with clinical parameters associated with overall survival.

	Number of patients	Number of events	Univariate analysis (n=451)		Multivariate analysis (n=393)	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Gender						
Male	333	282	1.00		1.00	
Female	118	95	0.77 (0.61–0.97)	0.026	1.053 (0.76–1.47)	0.76
Age (years)	451	377	0.99 (0.97–1.02)	0.60		
Treatment						
Monochemotherapy	225	199	1.00		1.00	
Doublet chemotherapy	226	178	0.64 (0.52–0.78)	<0.0001	0.61 (0.50–0.77)	<0.0001
Performance status score						
0–1	327	262	1.00		0.59 (0.46–0.75)	
2	123	114	2.10 (1.67–2.60)	<0.0001	1.00	<0.0001
Smoking status						
Never smoked	87	68	0.65 (0.50–0.84)		0.58 (0.39–0.85)	
Ever smoked	364	309	1.00	0.001	1.00	0.0034
Disease stage						
III	82	71	1.00			
IV	349	306	1.05 (0.81–1.36)	0.71		
Histology						
Adenocarcinoma	219	178	0.55 (0.41–0.73)		0.65 (0.48–0.87)	
Squamous	146	131	0.75 (0.56–1.01)		0.76 (0.56–1.03)	
Other	66	68	1.00	<0.0001	1.00	0.0015
MMS	441	377	0.96 (0.93–0.98)	0.0013	0.97 (0.94–1.00)	0.057
ADL	438	377	0.64 (0.55–0.74)	<0.0001	0.70 (0.59–0.83)	<0.0001
CCI	451	377	1.06 (0.99–1.13)	0.086	0.98 (0.96–1.01)	0.77
BMI	451	377	0.98 (0.95–1.00)	0.067	1.01 (0.94–1.09)	0.17

HR = hazard ratio; CI = confidence interval; MMS = mini-mental state; ADL = activities of daily living; CCI = Charlson comorbidity index; BMI = body mass index.

significant in this model. Only one variable, not included into the final model, significantly and negatively correlated with OS: the PA dimension score (HR: 1.004; 95% CI: 1.00–1.01; P=0.046).

In the model including treatment as stratification variable, GH score, PS 0–1, never smoked status, ADL score, and MMS score were favourably associated with OS (Supplementary Table 2).

GH score remained statistically significant in all sensitivity analyses, conducted without ADL, MMS and both scores. All other covariates significantly associated with OS in our final model were found to be statistically significant prognosticators of OS (Supplementary Tables 3–5). Physical functioning (PF) score was favourably associated with OS when the ADL score was not included.

Table 3B
Univariate and multivariate Cox regression only with health-related quality of life dimensions scores associated with overall survival.

	Number of patients	Number of events	Univariate analysis (n=451)		Multivariate analysis (n=451)	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Global health status	420	377	0.98 (0.98–0.99)	<0.0001	0.986 (0.98–0.992)	<0.0001
Physical functioning	420	377	0.98 (0.98–0.99)	<0.0001	0.989 (0.984–0.995)	0.0003
Role functioning	420	377	0.99 (0.987–0.993)	<0.0001	0.994 (0.991–0.998)	0.001
Emotional functioning	420	377	0.989 (0.989–0.998)	0.0055	0.996 (0.991–1.000)	0.068
Cognitive functioning	421	377	0.992 (0.987–0.997)	0.0011	0.996 (0.991–1.001)	0.12
Social functioning	411	377	0.993 (0.989–0.996)	<0.0001	0.997 (0.993–1.001)	0.12
Fatigue	420	377	1.011 (1.007–1.015)	<0.0001	1.007 (1.003–1.011)	0.0012
Nausea and vomiting	421	377	1.003 (0.996–1.010)	0.40		
Pain	420	377	1.010 (1.006–1.013)	<0.0001	1.007 (1.003–1.011)	0.0003
Dyspnoea	419	377	1.007 (1.004–1.010)	<0.0001	1.004 (1.000–1.007)	0.031
Insomnia	420	377	1.003 (1.000–1.006)	0.0983	1.002 (0.998–1.005)	0.33
Appetite loss	419	377	1.007 (1.004–1.010)	<0.0001	1.005 (1.001–1.008)	0.006
Constipation	420	377	1.004 (1.000–1.007)	0.025	1.002 (0.999–1.006)	0.22
Diarrhoea	417	377	1.004 (0.998–1.009)	0.23		
Financial difficulties	416	377	1.005 (0.998–1.012)	0.14		

HR = hazard ratio; CI = confidence interval.

Table 4
Clinical and health-related quality of life dimension scores associated with overall survival.

	Number of patients	Number of events	HR (95% CI)	P-value
GH	420	377	0.986 (0.980–0.992)	<0.0001
Treatment				
Monochemotherapy	225	199	1.00	
Doublet chemotherapy	226	198	0.65 (0.52–0.80)	<0.0001
Performance status score				
0–1	327	262	0.63 (0.49–0.81)	
2	123	114	1.00	0.0003
Smoking status				
Never smoked	87	68	0.58 (0.43–0.78)	
Ever smoked	264	309	1.00	0.0003
Histology				
Adenocarcinoma	219	178	0.68 (0.50–0.93)	
Squamous	146	131	0.80 (0.58–1.01)	
Other	66	68	1.00	0.047
MMS	441	377	0.97 (0.94–1.00)	0.043
ADL	438	377	0.81 (0.66–0.99)	0.0011

HR = hazard ratio; CI = confidence interval; GH = global health score; MMS = mini-mental state; ADL = activities of daily living.

3.4. Proposal for implementing HRQoL

When using the interquartile ranges (GH $\leq$46, 46<GH<67, and GH $\geq$67), GH score remained associated with OS in stepwise multivariable Cox regression (P <0.0001) (Table 5). We thus distinguished three groups, categorised as high (GH <46), intermediate (46$\leq$GH$\leq$67), or low (GH >67) mortality risk. Median OS values were 5.3, 8.2, and 14.5 months in the low-, intermediate-, and high-risk groups, respectively (log-rank P <0.0001) (Fig. 2).

In the high-risk subgroup, doublet chemotherapy was not associated with favourable OS (HR: 0.70; 95% CI: 0.49–1.003; P=0.052). In the intermediate- and low-risk groups, doublet chemotherapy was associated with favourable OS (HR: 0.72; 95% CI: 0.54–0.96; P=0.023, and HR: 0.50; 95% CI: 0.30–0.84; P=0.0089, respectively).

4. Discussion

To our knowledge, this is the first analysis of HRQoL data derived from the EORTC QLQ-C30 questionnaire as prognostic markers of OS in elderly advanced NSCLC patients. Based on our data, the GH dimension score provided significant value in addition to PS, treatment type, smoking status, histology, and both ADL and MMS scores.

This is in line with other studies investigating HRQoL in NSCLC patients [6,14–16]. Sloan et al. [12] and Jacot et al. [13] demonstrated that overall HRQoL deficits, at lung cancer diagnosis, were significantly associated with poor OS (HR: 1.55; P <0.001 and 2.20; P <0.001, respectively). Yet these studies did not take account of disease stage or age.

Among the Charlson comorbidity index (CCI), MMS score, and ADL score, no geriatric index has been found to be able to guide thoracic oncologists in decision-making for elderly NSCLC patients. In our final model including GH, the MMS and ADL scores were both associated with OS, whereas CCI was not, as previously-published [14]. Our results indicate that HRQoL by the EORTC QLQ-C30 questionnaire could provide a useful tool, the GH score being statistically significant in all sensitivity analyses. Moreover, with PF being statistically associated with OS in the model without ADL, these results suggest that the EORTC QLQ-C30 questionnaire could even surpass the ADL score, reflecting the same characteristics while adding the global GH evaluation. The collinearity of baseline HRQoL scores with other covariates was examined using a multiple linear regression model. This model exhibited R^2 statistics of 12%, indicating that the GH score was much more than a simple amalgamation of PS, ADL score and BMI. Moreover, the PS and ADL scores are evaluated by the physician rather than being self-reported. Therefore, the use of the HRQoL questionnaire could limit the interpretation by the physicians. Finally, the idea would be to use only the HRQoL questionnaire rather than two or more questionnaires (ADL, MMS etc) for the geriatric evaluation to help physicians in their decision-making, which is often difficult in elderly patients with lots of comorbidities.

Subgroup analyses suggested the baseline GH score to be a predictor of treatment effect, with 46 being the cut-off value. The ESOGIA-Groupe Français de Pneumo-Cancérologie 0802 trial assessed the integration of the comprehensive geriatric assessment (CGA) in treatment-decision-making in stage IV NSCLC patients over 70 years old [22]. The study failed to prove the superiority of a CGA-based strategy compared to PS-guided strategy of treatment allocation in terms of time to treatment failure. CGA has never

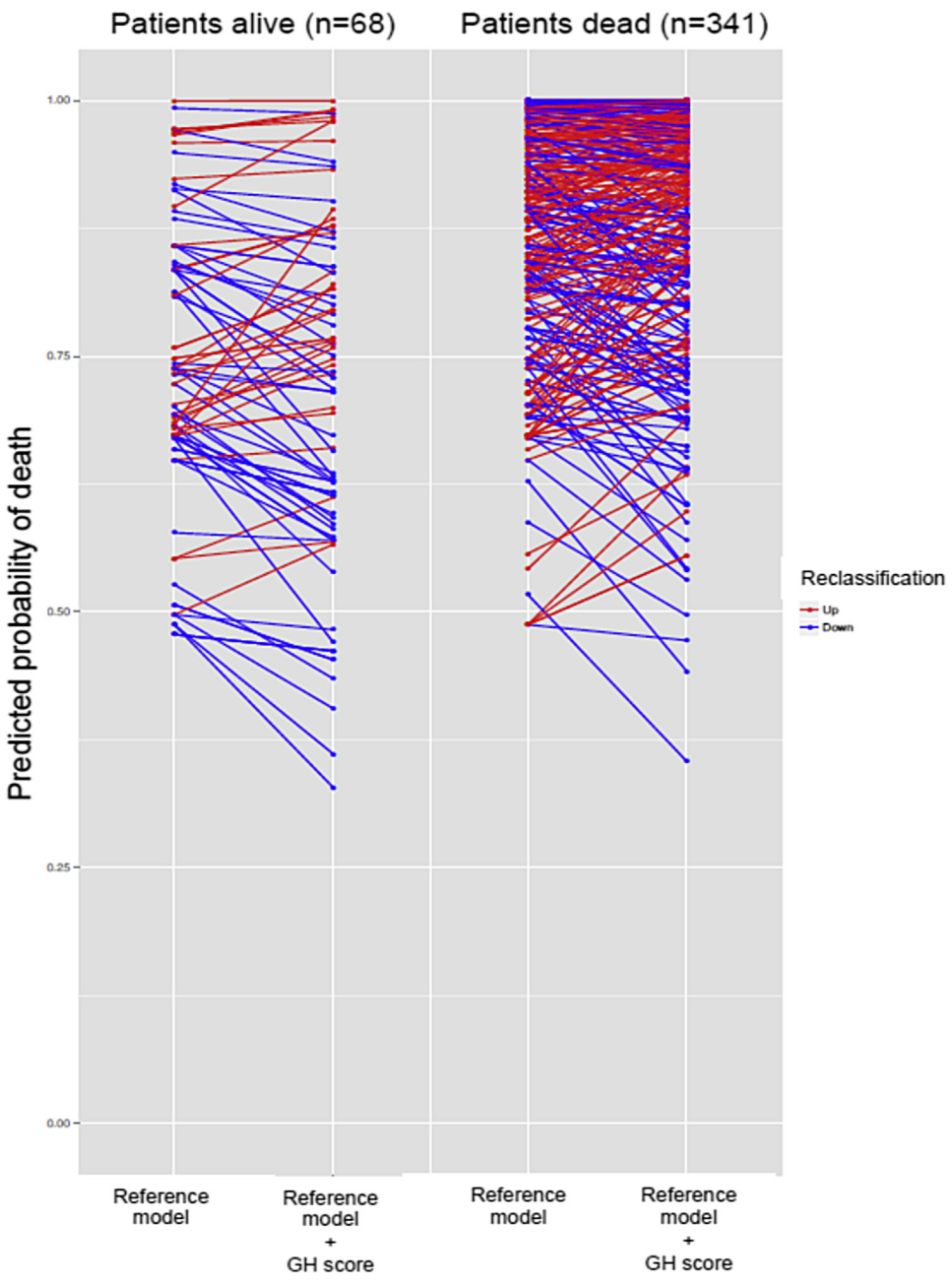

Fig. 1. Additive value of the GH dimension score for reclassifying mortality risk at 24 months post-randomisation (continuous net reclassification improvement). Blue lines in patients who did not die indicate that the GH score had the correct (downward) influence on risk prediction (42/68 = 61.8%). Conversely, red lines in patients who died indicate a correct (upward) change in risk assessment when using GH score (196/341 = 57.4%). GH = global health.

proven able to predict treatment efficacy in elderly lung cancer patients, meaning that HRQoL could represent a better tool to identify patients likely to benefit from doublet chemotherapy. However, further research is warranted to validate the questionnaire's predictive value and to define cut-off values.

Our study displayed several limitations. First, the specific lung cancer module QLQ-LC13 questionnaire, which could have improved the HRQoL's prognostic value, was not employed. Secondly, data must be replicated using external validation study and confirmed in a prospectively recruited cohort. Furthermore, the Instrumental Activities Daily Living index, which explores patients' ability to use public transportation, telephone, drive, etc., was not administered. Finally, our study was not designed to predict the treatment type to be given to the patients, based on HRQoL score.

Our study provides evidence of the additional prognostic value of HRQoL data to identify vulnerable elderly NSCLC subpopulations. The EORTC QLQ-C30

Table 5
Clinical and health-related quality of life dimension scores associated with overall survival using the Q1 and Q3 interquartiles of global health score.

	Number of patients	Number of events	HR (95% CI)	P-value
GH <46	136	123	1.00	<0.0001
46 ≤GH ≤67	228	193	0.42 (0.31–0.59)	
GH >67	87	61	0.67 (0.53–0.85)	
Treatment				
Monochemotherapy	225	199	1.00	
Doublet chemotherapy	226	198	0.64 (0.52–0.79)	<0.0001
Performance status score				
0–1	327	262	0.66 (0.51–0.84)	
2	123	114	1.00	0.0003
Smoking status				
Never smoked	87	68	0.58 (0.44–0.77)	
Ever smoked	264	309	1.00	0.0003
Histology				
Adenocarcinoma	219	178	0.67 (0.50–0.89)	
Squamous	146	131	0.77 (0.57–1.05)	
Other	66	68	1.00	0.025
MMS	441	377	0.97 (0.95–1.01)	0.059
ADL	438	377	0.73 (0.61–0.87)	0.0003

HR = hazard ration; CI = confidence interval; GH = global health score; MMS = mini-mental state; ADL = activities of daily living.

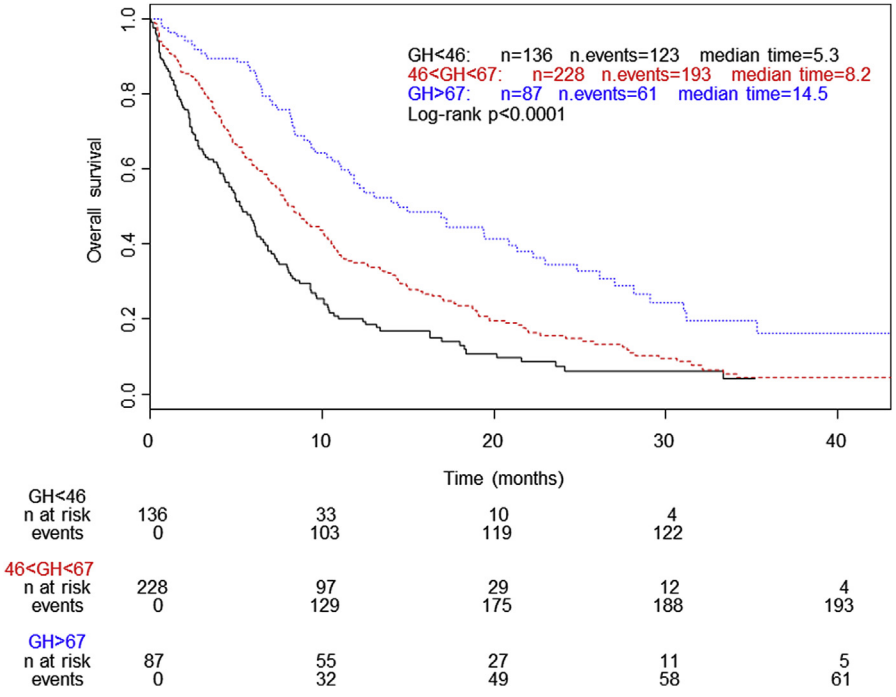

Fig. 2. Kaplan–Meier survival curves according to GH score. GH = global health.

questionnaire could constitute a valuable tool for selecting patients likely to benefit from doublet chemotherapy.

Conflict of interest statement

Frédéric Fiteni declares no conflict of interest. Dewi Vernerey declares no conflict of interest. Franck Bonnetain reports grants and personal fees from ROCHE, grants, personal fees and non-financial support from NOVARTIS, personal fees from MERCK SERONO, and personal fees from NESTLE. Fabien Vaylet declares no conflict of interest. Hélène Sennelart declares no conflict of interest. Jean Tredaniel declares no conflict of interest. Denis Moro-Sibilot declares participation to Roche, Eli Lilly, AstraZeneca, Novartis, Pfizer, Boehringer Ingelheim, Amgen, and BMS boards. Dominique Herman declares no conflict of interest. Hélène Laizé declares no conflict of interest. Philippe Masson declares no conflict of interest. Marc Derollez declares no conflict of interest. Christelle Clément-Duchêne declares no conflict of interest. Bernard

Milleron received personal fees outside the submitted work from AstraZeneca, BMS, Chugai, Lilly and Roche. Franck Morin declares no conflict of interest. Gérard Zalcman declares no conflict of interest. Elisabeth Quoix declares no conflict of interest. Virginie Westeel declares no conflict of interest.

Funding

Funding was received from Ligue Contre Le Cancer and Intergroupe Francophone de Cancérologie Thoracique.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.10.004.

References

[1] Beitz J, Gnecco C, Justice R. Quality-of-life end points in cancer clinical trials: the U.S. food and drug administration perspective. J Natl Cancer Inst Monogr 1996;20:7–9.
[2] Johnson JR, Temple R. Food and drug administration requirements for approval of new anticancer drugs. Cancer Treat Rep 1985;69(10):1155–9.
[3] Fiteni F, Westeel V, Pivot X, Borg C, Vernerey D, Bonnetain F. Endpoints in cancer clinical trials. J Visc Surg 2014;151(1):17–22.
[4] Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. Health Qual Life Outcomes 2009;7:102.
[5] Eton DT, Fairclough DL, Cella D, Yount SE, Bonomi P, Johnson DH. Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592. J Clin Oncol 2003;21(8):1536–43.
[6] Djärv T, Metcalfe C, Avery KN, Lagergren P, Blazeby JM. Prognostic value of changes in health-related quality of life scores during curative treatment for esophagogastric cancer. J Clin Oncol 2010;28(10):1666–70.
[7] Luoma ML, Hakamies-Blomqvist L, Sjöström J, Pluzanska A, Ottoson S, Mouridsen H, et al. Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer. Eur J Cancer 2003;39(10):1370–6.
[8] Movsas B, Moughan J, Sarna L, Langer C, Werner-Wasik M, Nicolaou N, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol 2009;27(34):5816–22.
[9] Fielding R, Wong WS. Quality of life as a predictor of cancer survival among Chinese liver and lung cancer patients. Eur J Cancer 2007;43(11):1723–30.
[10] Quinten C, Coens C, Mauer M, Comte S, Sprangers MA, Cleeland C, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol 2009;10(9):865–71.
[11] Efficace F, Bottomley A, Smit EF, Lianes P, Legrand C, Debruyne C, Schramel F, et al. Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. Ann Oncol 2006;17(11):1698–704.
[12] Sloan JA, Zhao X, Novotny PJ, Wampfler J, Garces Y, Clark MM, et al. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. J Clin Oncol 2012;30(13):1498–504.
[13] Jacot W, Colinet B, Bertrand D, Lacombe S, Bozonnat MC, Daurès JP, et al. Quality of life and comorbidity score as prognostic determinants in non-small-cell lung cancer patients. Ann Oncol 2008;19(8):1458–64.
[14] Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavolé A, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378(9796):1079–88.
[15] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.
[16] Ringdal GI, Ringdal K. Testing the EORTC Quality of Life Questionnaire on cancer patients with heterogeneous diagnoses. Qual Life Res 1993;2(2):129–40.
[17] Anderson RT, Aaronson NK, Wilkin D. Critical review of the international assessments of health-related quality of life. Qual Life Res 1993;2(6):369–95.
[18] Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol 1995;13(5):1249–54.
[19] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(4):361–87.
[20] Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. Clin Chem Lab Med 2010;48(12):1703–11.
[21] Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23(13):2109–23.
[22] Corre R, Chouaid C, Barlesi F, Le Caer H, Dansin E, Vergnenegre A, et al. Study ESOGIA-GFPC 08–02: phase III, randomized, multicenter trial involving subjects over age 70 with stage IV non-small cell lung cancer and comparing a "classical" strategy of treatment allocation (dual-agent therapy based on carboplatin or monotherapy with docetaxel alone), based on performance status and age, with an "optimized" strategy allocating the same treatments according to a simplified geriatric screening scale, plus a more thorough geriatric evaluation if necessary. Paper presented at the 2011 ASCO Annual Meeting. Available at: http://meetinglibrary.asco.org/content/83335-102.