European Journal of Cancer 116 (2019) 190–198

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials

Marijke Coomans [a,*], Linda Dirven [a,b], Neil K. Aaronson [c], Brigitta G. Baumert [d,e], Martin van den Bent [f], Andrew Bottomley [g], Alba A. Brandes [h], Olivier Chinot [i], Corneel Coens [g], Thierry Gorlia [j], Ulrich Herrlinger [k], Florence Keime-Guibert [l], Annika Malmström [m], Francesca Martinelli [g], Roger Stupp [n], Andrea Talacchi [o], Michael Weller [p], Wolfgang Wick [q,r], Jaap C. Reijneveld [s], Martin J.B. Taphoorn [a,b] on behalf of the EORTC Quality of Life Group and the EORTC Brain Tumor Group

[a] *Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands*
[b] *Department of Neurology, Haaglanden Medical Center, Den Haag, the Netherlands*
[c] *Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, the Netherlands*
[d] *Department of Radiation-oncology, University Hospital Bonn, Germany*
[e] *Department of Radiation Oncology (MAASTRO Clinic), and GROW (School for Oncology and Developmental Biology), Maastricht University Medical Center, Maastricht, the Netherlands*
[f] *The Brain Tumor Center, Erasmus MC Cancer Institute, Rotterdam, the Netherlands*
[g] *Quality of Life Department, European Organisation for Research and Treatment of Cancer, Brussels, Belgium*
[h] *Department of Medical Oncology, Azienda USL-IRCCS Institute of Neurological Sciences, Bologna, Italy*
[i] *Aix-Marseille Univ, APHM, CNRS, INP, Inst Neurophysiopathol, CHU Timone, Service de Neuro-Oncologie, Marseille, France*
[j] *European Organization for Research and Treatment of Cancer Headquarters, Brussels, Belgium*
[k] *Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology (CIO), University of Bonn, Bonn, Germany*
[l] *Groupe Hôpital Pitié-Salpetrière, Paris, France*
[m] *Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden*
[n] *Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*
[o] *Department of Neurosciences, Azienda Ospedaliera San Giovanni Addolorata, Roma, Italy*
[p] *Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland*
[q] *Neurology Clinic and National Centre for Tumour Diseases, University Hospital Heidelberg, Heidelberg, Germany*
[r] *German Consortium of Translational Cancer Research (DKTK), Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany*
[s] *Department of Neurology and Brain Tumour Center Amsterdam, Amsterdam University Medical Center, Amsterdam, the Netherlands*

* *Corresponding author*: Leiden University Medical Center, Department of Neurology, PO BOX 9600, 2300 RC, Leiden, the Netherlands. Fax: +31 71 524 8253.

E-mail address: m.b.coomans@lumc.nl (M. Coomans).

https://doi.org/10.1016/j.ejca.2019.05.012

Received 10 April 2019; received in revised form 13 May 2019; accepted 13 May 2019
Available online 13 June 2019

KEYWORDS
Glioma;
Health-related quality of life (HRQoL);
Prognostic factor;
Brain tumour;
Survival

Abstract ***Objective:*** Prognostic value of health-related quality of life (HRQoL) data may be important to inform patients in clinical practice and to guide clinical decision-making. Our study investigated the added prognostic value of HRQoL for overall survival (OS) and progression-free survival (PFS) in a large heterogeneous sample of glioma patients, besides known prognostic factors.

Methods: We included individual baseline data from previously published randomised controlled trials (RCTs) in glioma patients in which HRQoL was assessed through the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BN20 questionnaires. Multivariable Cox regression models (stratified for newly diagnosed versus recurrent disease) were constructed, first with clinical variables (age, sex, tumour type, performance status, allocated treatment and extent of resection) only and subsequently with HRQoL variables added, separately for OS and PFS. The added prognostic value of HRQoL was calculated using C-indices.

Results: Baseline HRQoL and clinical data from 15 RCTs were included, comprising 5217 patients. In the model including both clinical and HRQoL variables, better cognitive and role functioning and less motor dysfunction were independently associated with longer OS, whereas better role and cognitive functioning, less nausea and vomiting and more appetite loss were independently associated with prolonged PFS. However, C-indices indicated only a small prognostic improvement of the models for OS and PFS when adding HRQoL to the clinical prognostic variables (+1.1% for OS and +.7% for PFS).

Conclusion: Our findings demonstrate that several baseline HRQoL variables are independently prognostic for OS and PFS, yet the added value of HRQoL to the known clinical prognostic variables was small.

1. Introduction

Health-related quality of life (HRQoL) is an important end-point, both in clinical practice and in clinical trials in oncology. In clinical trials, HRQoL data may contribute to determine the net clinical benefit of a treatment strategy. In clinical practice, HRQoL data may provide important information on the patients' functioning during the course of disease and guide tailored treatment [1,2]. This is particularly important in patient populations where survival is relatively short and where cure is not possible. HRQoL is therefore relevant for patients with gliomas, the most common malignant primary brain tumour in adults [3].

One important feature of HRQoL data may be its potential prognostic value for survival. Clinical variables such as age and performance status (PS) have proven to be important prognostic factors for overall survival (OS) in glioma patients, and recent studies have shown that HRQoL is an independent prognostic marker for survival in various other cancer populations [4–6]. If demonstrated to be an independent prognostic factor in glioma, HRQoL data could be used in clinical practice to inform patients, facilitate decision-making and ultimately to improve outcomes. In addition, HRQoL could be used as a stratification variable in future clinical trials [7].

The few studies investigating HRQoL as a prognostic factor for survival in glioma patients reported disparate results [8–10]; in glioblastoma and anaplastic oligodendroglioma patients, the specific HRQoL scales that were found to be of prognostic importance differed between studies, and the predictive ability of the models showed only modest improvement when adding HRQoL scales to known clinical predictors [8,9]. These findings may, in part, reflect methodological issues such as small sample sizes, missing baseline data and statistical techniques chosen to analyse the data. Moreover, prognostic models in glioma research focused on OS as end-point. In glioma, progression-free survival (PFS) may also be a relevant outcome, which can be seen as a surrogate end-point for measuring treatment efficacy [11]. With this knowledge, it seems most appropriate to assess the prognostic value of HRQoL for both OS and PFS. Additionally, a prognostic model should include the recent changes in classification of tumour types involving molecular markers [12,13]. The added prognostic value of HRQoL in such a model has not yet been investigated.

The aim of the present study was to investigate the added prognostic value of HRQoL for OS and PFS in a large, heterogeneous sample of glioma patients above and beyond the known prognostic factors.

2. Methods

2.1. Study sample

This study is part of the CODAGLIO (i.e. COmbining clinical trial Data sets in GLIOma) project, in which a database was created including HRQoL data (assessed with the European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30, version 3.0 [14], and the brain cancer-specific QLQ-BN20 [15], both showing robust psychometric properties) of individual glioma patients from 15 previously published phase II and III randomised controlled trials (RCTs) (Supplementary file 1).

2.2. Prognostic variables

Besides HRQoL (see supplementary file 2 for details on HRQoL assessment), other sociodemographic and clinical variables previously recognised as prognostic for OS that were available in all included RCTs were collected: tumour type (World Health Organisation [WHO] grade II or III astrocytoma, oligodendroglioma and oligoastrocytoma [all classified as non-glioblastoma] or grade IV [glioblastoma]), age, sex, disease stage (newly diagnosed versus recurrent), WHO PS (0 versus 1 versus 2), prior resection (yes versus no) and allocated treatment (radiotherapy [RT monotherapy], chemotherapy [chemomonotherapy], angiogenesis inhibitors [angiomonotherapy], tumour-treating fields [TTF monotherapy], radiotherapy and chemotherapy combined [RT and chemo], radio and angiogenesis inhibitors combined [RT and angio], radiotherapy combined with chemotherapy and angiogenesis inhibitors [RT and chemo and angio] and chemotherapy and TFF combined [chemo and TTF]). Prior resection was classified into yes/no because information on the extent of resection (biopsy, partial or gross total resection) was not available for all patients. Therefore, we classified both partial and complete resection as resected, and biopsy as not resected. Owing to the variety of treatments that were used in the different RCTs, treatments were categorised based on type and combination (e.g. lomustine, irinotecan, combined procarbazine, lomustine and vincristine and temozolomide were all classified as chemotherapy). Moreover, subgroup analyses were carried out in patients with data on use of corticosteroids and antiepileptic drugs (AEDs) at baseline and in patients with data on molecular parameters (Supplementary file 2 for details).

2.3. Statistical analysis

All patients with a completed baseline HRQoL form were included in the analyses. OS was measured from the date of randomisation until the date of death (i.e. event) or the date of last contact (determined at the time of the database lock, separately for each individual RCT; i.e. censored patients) and was estimated using the Kaplan–Meier method. PFS was measured from the date of randomisation until the date of progression or death (i.e. events) or date of last contact (determined at the time of the database lock, separately for each individual RCT, i.e. censored patients). In all included RCTs, progression was defined by means of the Response Assessment in Neuro-Oncology (RANO) Criteria or MacDonald criteria [16,17]. The log-rank test was used to compare survival distributions. To evaluate if there were differences between patients with and without a HRQoL form (i.e. selection bias), several clinical characteristics were compared using the Chi-square test for categorical data and independent Student t-tests for continuously distributed variables.

The construction of the final prognostic models was based on two steps. First, univariable Cox proportional hazard (CPH) models were constructed to assess the association between each independent variable (tumour type, age, sex, prior resection, WHO PS and all HRQoL scales/items) and OS and PFS. Hazard ratios and their corresponding 95% two-sided confidence intervals (CIs) were calculated [18]. Subsequently, multivariable CPH models, separately for OS and PFS, were constructed, including those variables that exhibited $P < .10$ in univariable analysis. The models were stratified for disease stage (newly diagnosed versus recurrent). First, proportional hazard assumptions for the Cox models were assessed graphically, and potential multicollinearity was investigated with Spearman-rank correlation coefficients. Next, a stepwise backward model was applied to eliminate non-significant parameters ($P < .0$ for inclusion and $P > .10$ for exclusion). The model was first carried out with the sociodemographic/clinical variables only ('clinical model') and subsequently with the sociodemographic/clinical variables and HRQoL scales ('clinical + HRQoL model'). The purpose of this second model was to assess the potential benefit of adding baseline HRQoL scores to the sociodemographic/clinical factors to predict survival more accurately. Performance of the two final multivariable models (one for OS and one for PFS) was assessed with Harrell's concordance-index (C-index) [19], which estimates the probability of concordance between predicted and observed responses. Finally, internal validation of the models was carried out by comparing the C-indices of 1000 bootstrap replications [20].

Finally, these steps were repeated in subgroups of patients. Analyses were performed using IBM SPSS, version 23.0 [21], while the calculation of C-indices and the validation of the models were performed with R [22] using the rms package [23].

3. Results

Individual patient data were obtained from 15 international RCTs including a total of 6048 patients.

3.1. Data collection and baseline characteristics

Baseline HRQoL data were available for 86% (5217/6084) of the patients (Table 1). Patients who completed a baseline HRQoL questionnaire were younger (mean age 53 versus 55 years), had a better WHO PS (WHO = 0 in 38% versus 29%) and had undergone resection more often (74% versus 62%) than patients who did not complete the baseline HRQoL assessment. There was also a significant difference in survival time: patients who completed a HRQoL baseline form had longer OS than patients without a baseline form (median 18.0 months, 95% CI [17.3–18.7] versus median 14.7 months, 95% CI [13.3–16.1], $p < .001$). Similarly for PFS, patients with a baseline form had longer PFS than patients without a baseline form (8.3 months, 95% CI [7.9–8.7] versus 5.3 months, 95% CI [4.7–5.9], $p < .001$).

3.2. Clinical model

Results of the univariable analyses showed that all clinical variables and the majority of the HRQoL variables were associated with longer OS and PFS (see Supplementary file 3 for details). In the multivariable models for OS and PFS including the clinical variables only, female sex, a younger age, non-glioblastoma tumour type, a better WHO PS, resection and allocated treatment other than radiotherapy alone were independently associated with longer OS and PFS (Tables 2 and 3).

3.3. Clinical and HRQoL model

In the multivariable models including both the clinical and HRQoL variables, all clinical variables remained significantly prognostic for OS and PFS. Among the HRQoL variables, better role and cognitive functioning and less motor dysfunction were associated with longer OS (Table 2), and better cognitive functioning, less nausea and vomiting and more appetite loss were associated with longer PFS (Table 3).

3.4. Predictive accuracy

The validated C-index for the model predicting OS with both the clinical and HRQoL variables was reasonable and similar in predicting survival to the model with the clinical variables only (C = .721 versus C = .716, respectively) (Table 4). This represents a relative gain in predictive accuracy of 1.1% (see Table 4 for the calculation). Similar results were found for PFS, with predictive abilities of C = .683 and C = .679 for the clinical model and clinical + HRQoL model, respectively. The added value of the HRQoL scales in this model was also small (.7%).

3.5. Subanalyses

Results of the subanalyses (Supplementary file 3) including patients with data on AEDs and corticosteroids showed that in addition to the clinical variables, lower levels of fatigue and motor dysfunction were prognostic for longer OS, and better role functioning, less appetite loss and weakness of the legs were prognostic for longer PFS. With regard to the subgroup including the WHO 2016 tumour classification and O^6-methylguanine-DNA methyltransferase promotor methylation status, worse emotional functioning, less fatigue and less nausea and vomiting were prognostic for longer OS, and only less nausea and vomiting was prognostic for longer PFS. C-indices were similar to the 'original' models.

4. Discussion

We studied the added value of baseline HRQoL as prognostic indicator for OS and PFS in a large, heterogeneous sample of glioma patients by pooling individual HRQoL and sociodemographic/clinical data from previously conducted RCTs, controlling for known prognostic factors. Although this sample represents a large proportion of the glioma patient population regarding sex, age and type of tumour, the patients included in our analysis had a relatively good PS, indicating selection bias, likely driven by stringent inclusion criteria for RCTs [24]. Moreover, patients who completed a baseline form (86%) had a better OS and PFS than those who did not, reflecting a selection bias in the available sample of trial patients.

The prognostic value of known clinical parameters was confirmed in this study; younger and female patients, those with a better PS, a non-glioblastoma tumour type (irrespective of further tumour histology) and patients who underwent resection and were treated with other treatment regimens than radiotherapy alone had both significantly longer OS and PFS. Of note, we did not include interaction effects, hampering estimation of survival for specific subgroups

Table 1
Baseline sociodemographic and clinical characteristics of the patients included in the RCTs, separately for those with and without completed baseline health-related quality of life forms.

	All patients (n = 6084)	HRQoL present (n = 5217)	HRQoL absent (n = 867)	P-value
	n (%)	n (%)	n (%)	
Sex				
Male	3710 (61)	3211 (62)	499 (58)	.165
Female	2351 (39)	2005 (38)	346 (40)	
Missing	23 (0)	1 (0)	22 (3)	
Age (mean, SD)	53 (13)	53 (13)	55 (13)	<.001*
Histology				
Non-glioblastoma	1762 (29)	1501 (29)	261 (30)	.423
Glioblastoma	4322 (71)	3716 (71)	606 (70)	
Disease stage				
Newly diagnosed	4968 (82)	4330 (83)	638 (74)	<.001*
Recurrent	1116 (18)	887 (17)	229 (26)	
WHO PS				
WHO 0	2257 (37)	2006 (38)	251 (29)	<.001*
WHO 1	3015 (50)	2587 (50)	428 (49)	
WHO 2	756 (12)	604 (12)	152 (18)	
Missing	56 (1)	20 (0)	36 (4)	
Allocated treatment				
RT alone	1349 (22)	1105 (21)	244 (28)	<.001*
Chemo alone	1107 (18)	840 (16)	267 (31)	
Angio alone	126 (2)	106 (2)	20 (2)	
RT and chemo	1633 (27)	1455 (28)	178 (21)	
RT and chemo and angio	834 (14)	807 (15)	27 (3)	
Chemo and angio	444 (7)	360 (7)	84 (10)	
TTF alone	120 (2)	107 (2)	13 (2)	
Chemo and TTFields	466 (8)	434 (8)	32 (4)	
Missing	5 (0)	3 (0)	2 (0)	
Surgical status				
Resected	4379 (72)	3845 (74)	534 (62)	<.001*
Not resected	1523 (25)	1221 (23)	302 (35)	
Missing	182 (3)	151 (3)	31 (4)	
Use of AEDs				
No	1337 (22)	1134 (22)	203 (23)	.033*
Yes	1566 (26)	1371 (26)	195 (23)	
Missing	3181 (52)	2712 (52)	469 (54)	
Use of steroids				
No	3182 (52)	2754 (53)	428 (49)	.807
Yes	2329 (38)	2021 (39)	308 (36)	
Missing	573 (9)	442 (9)	131 (15)	
IDH status				
IDH-mutant	463 (8)	396 (8)	67 (8)	<.001*
IDH-wildtype	875 (14)	804 (15)	71 (8)	
Missing	4746 (78)	4017 (77)	729 (84)	
1p/19q status				
Codeleted	214 (4)	175 (3)	39 (4)	<.001*
Non-codeleted	1485 (24)	1338 (26)	147 (17)	
Missing	4385 (73)	3704 (71)	681 (79)	
MGMT status				
Methylated	1657 (27)	1483 (28)	174 (20)	<.001*
Unmethylated	1634 (27)	1462 (28)	172 (20)	
Missing	2783 (46)	2272 (44)	521 (60)	

WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumour-treating fields; HRQoL, health-related quality of life; IDH, isocitrate dehydrogenase mutations; MGMT, O^6-methylguanine-DNA methyltransferase promotor methylation.

(e.g. glioblastoma patients who were treated with radiotherapy only). Nevertheless, several HRQoL parameters provided independent prognostic information in addition to the known clinical variables, confirming previous results in glioma patients [8–10]. Although the C-index scores indicated that adding HRQoL parameters to the prognostic model did improve the model, the added value was small (1.1% for OS and .7% for PFS). These results confirm previous results in glioblastoma patients in which HRQoL calculated with the C-index was found to add 1.4% to the clinical variables for OS [8]. Overall, the predictive accuracy in our

Table 2
Multivariable Cox proportional hazard models for overall survival, one including clinical data only and one model including both clinical and HRQoL data.

	Cox model for clinical data		Cox model for clinical and HRQOL data	
	HR death (95% CI)[a]	P-value	HR death (95% CI)[a]	P-value
Clinical variables				
Female (ref)	ref		ref	
Male	1.22 (1.13–1.31)	<.001*	1.28 (1.18–1.39)	<.001*
Age[c]	1.03 (1.02–1.03)	<.001*	1.03 (1.02–1.03)	<.001*
Non-glioblastoma (ref) Glioblastoma	ref 3.44 (3.01–3.90)	<.001*	ref 3.65 (3.17–4.13)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.37 (1.26–1.49)	<.001*	1.29 (1.18–1.42)	<.001*
WHO PS 2	2.00 (1.78–2.26)	<.001*	1.62 (1.41–1.87)	<.001*
Resected (ref)	ref		ref	
Not resected	1.46 (1.32–1.61)	<.001*	1.48 (1.33–1.64)	<.001*
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	.65 (.56–.76)	<.001*	.67 (.57–.79)	<.001*
Trt: Angio alone	.50 (.35–.71)	<.001*	.48 (.33–.69)	<.001*
Trt: RT and chemo	.64 (.57–.71)	<.001*	.62 (.55–.70)	<.001*
Trt: RT and chemo and angio	.50 (.44–.57)	<.001*	.50 (.44–.68)	<.001*
Trt: Chemo and angio	.40 (.30–.55)	<.001*	.37 (.27–.51)	<.001*
Trt: TTF alone	.79 (.58–1.07)	.132	.75 (.55–1.04)	.083*
Trt: Chemo and TTFields	.45 (.39-.52	<.001*	.47 (.40–.55)	<.001*
HRQoL variables				
Role functioning[c]	–	–	.99 (.99–.99)	.037*
Cognitive functioning[c]	–	–	.99 (.99–.99)	.002*
Motor dysfunction[c]	–	–	1.00 (1.00–1.01)	.026*

HR, hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumour-treating fields; HRQoL, health-related quality of life; ref, reference group in analysis. [a]Significant HRQoL variables are presented. [c]Continuous variable. *Statistically significant.
Models are stratified for disease stage (newly diagnosed/recurrent).
[a]HRs reflect the probability for the event death. HRs of >1 suggest and increased risk of death compared to the reference category, HRs <1 suggest a smaller risk.

study was reasonable for OS (C-index of .716) and slightly less accurate for PFS (C-index of .679), again comparable to previous studies in glioma patients with C-indices including the clinical and HRQoL variables of .63, .65 and .77 for OS [8–10]. Although similar compared to previous studies in glioma patients, the added value was smaller compared to studies including other cancer patients. In two studies including patients from 11 to 18 different cancer sites, the added value was found to be 5% and 6%, respectively [6,25]. Glioma patients may entail a specific group of patients, as they do not only have cancer but also a progressive neurological disease. Although we included items and scales as measures with the brain tumour-specific QLQ-BN20 module for this purpose, of which some items/scales were independently prognostic for OS (e.g. motor dysfunction), this did not increase the added prognostic value. Because HRQoL added little prognostic information to the clinical variables, further validation and calibration of these models was not considered meaningful.

Role and cognitive functioning were the only two HRQoL variables that were independently prognostic for both OS and PFS. Other studies including different types of glioma patients also found that baseline cognitive complaints, as measured with the EORTC QLQ-C30 cognitive functioning scale or objective cognitive functioning measured with a neuropsychological test battery or the Mini-Mental State Examination, were prognostic for OS [8,9,26–30]. Cognitive impairment might be an early indicator of tumour progression which may not (yet) be visible or detected on scans [31]. Another explanation could be that patients' cognitive complaints act as a proxy for tumour volume, which was not included as a covariate in our study but is associated with survival [32]. The finding that role functioning was an independent prognostic variable for OS did not replicate earlier brain tumour studies but might be indicative of the impact of the disease on functioning in daily life. Indeed, role functioning was also found to be prognostic in, for example, testicular cancer patients, where the disease similarly strikes at a younger age compared with other cancers, affecting the working life of patients and therefore the role functioning of these patients [6]. Other HRQoL variables that were prognostic in our study were motor dysfunction (for OS), nausea and vomiting and appetite loss (for PFS). These symptoms may be an indicator of the severity of the disease.

Table 3
Multivariable Cox proportional hazard models for progression-free survival, one including clinical data only, and one model including both clinical and HRQoL data.

	Cox model for clinical data		Cox model for clinical and HRQOL data	
	HR progression (95% CI)[a]	P-value	HR progression (95% CI)[a]	P-value
Clinical variables				
Female (ref)	ref		ref	
Male	1.18 (1.11–1.26)	<.001*	1.19 (1.11–1.27)	<.001*
Age[c]	1.01 (1.01–1.01)	<.001*	1.01 (1.01–1.01)	<.001*
Non-glioblastoma (ref) Glioblastoma	ref 3.23 (2.90–3.60)	<.001*	ref 3.29 (2.93–3.69)	<.001*
WHO PS 0 (ref)	ref		ref	
WHO PS 1	1.25 (1.16–1.34)	<.001*	1.22 (1.13–1.32)	<.001*
WHO PS 2	1.40 (1.25–1.57)	<.001*	1.28 (1.13–1.45)	<.001*
Resected (ref)	ref	.001*	ref	.004*
Not resected	1.67 (1.07–1.27)		1.14 (1.04–1.25)	
Trt: RT alone (ref)	ref		ref	
Trt: Chemo alone	1.06 (.93–1.20)	.396	1.14 (1.00–1.30)	.059
Trt: Angio alone	.70 (.53–.92)	.009*	.72 (.55–.95)	.020*
Trt: RT and chemo	.70 (.63–.78)	<.001*	.73 (.65–.82)	<.001*
Trt: RT and chemo and angio	.50 (.44–.56)	<.001*	.52 (.45–.59)	<.001*
Trt: Chemo and angio	.56 (.45–.70)	<.001*	.58 (.46–.74)	<.001*
Trt: TTF alone	.70 (.53–.93)	.015*	.72 (.54–.96)	.027*
Trt: Chemo and TTFields	.92 (.80–1.06)	.245	.99 (.86–1.15)	.894
HRQoL variables				
Role functioning[c]	–	–	.99 (.99–.99)	.010*
Cognitive functioning[c]	–	–	.99 (.99–.99)	.032*
Nausea and vomiting[c]	–	–	1.00 (1.00–1.01)	.010*
Appetite loss[c]	–	–	.99 (.99–.99)	.011*

HR, hazard ratio; CI, confidence interval; WHO PS, World Health Organisation Performance Status; Trt, allocated treatment; RT, radiotherapy; chemo, chemotherapy; Angio, angiogenesis inhibitor; TTF, tumour-treating fields; HRQoL, health-related quality of life; ref, reference group in analysis. [a]Significant HRQoL variables are presented. [c]Continuous variable. *Statistically significant.
Models are stratified for disease stage (newly diagnosed/recurrent).
[a]HRs reflect the probability for the event progression. HRs of >1 suggest and increased risk of progression compared with the reference category, HRs <1 suggest a smaller risk.

In the subgroup analyses including AEDs and corticosteroid use or the molecular markers, all known clinical variables remained prognostic for OS and PFS. In contrast, HRQoL variables varied across subgroups: other functioning scales and symptoms were of prognostic value in the subgroup models compared with the 'original model'. Moreover, some HRQoL variables were unexpectedly prognostic for PFS and OS, i.e. more appetite loss for prolonged PFS in the main analysis and worse emotional functioning for prolonged OS in the subanalysis including the molecular markers. These findings imply that although the clinical variables appeared to be robust prognostic markers, the prognostic value of the HRQoL variables depended on the subgroups. For the subgroup analysis including the molecular markers, assessment period may also be a factor, as the patients for whom data on molecular markers were available were included in more recent RCTs. We also considered using the HRQoL summary score [33] instead of all individual scales/items; however, the summary score consists of items of the EORTC QLQ-C30 only and does not include the brain tumour–specific items/scales included in the EORTC QLQ-BN20. Taken together, our results suggest that the role of HRQoL data in predicting prognosis is limited and not useful for stratification in future clinical trials, as it is unclear which variables should be assessed and included.

Although the added prognostic value of HRQoL was small, HRQoL remains an important outcome in both clinical trials and practice. In clinical trials, HRQoL assessment is important to determine the net clinical benefit of a new treatment strategy [34]. In clinical practice, HRQoL assessments are important in monitoring patients' functioning over time and in informing patients and clinicians about the effect of the tumour and treatment on symptoms, functioning and quality of life. In addition, rather than baseline HRQoL data, a change in HRQoL from baseline during treatment, reflecting the impact of treatment on HRQoL, may be of more prognostic value and should be further investigated to inform patients in clinical practice on the impact of treatment [35]. However, it is important to also include data on treatment compliance, as this may also be related with more adverse events [36]. With regard to the selection bias toward a healthier population, in other cancer populations, it has been shown that in centres participating in clinical trials with high HRQoL compliance rates, survival rates are higher as well [37]. Whether this reflects solely

Table 4
Performance and internal validation of the multivariable Cox proportional hazard models for overall survival (OS) and progression-free survival (PFS).

Model	n	c-index	Bootstrapped c-index (mean from 1000 bootstraps)	Optimism[a] (%)	Added value[b] (%)
Main analysis					
OS: clinical model	4944	.7172	.7157	.002	–
OS: clinical + HRQoL model	4396	.7254	.7213	.004	1.1%
PFS: clinical model	5018	.6805	.6793	.001	–
PFS: clinical + HRQoL model	4458	.6863	.6828	.004	.7%
Sub analysis					
OS: clinical model + AEDs, steroids	2292	.7069	.7028	.004	–
OS: clinical + HRQoL model + AEDs, Steroids	2069	.7166	.7054	.011	.5%
PFS: clinical model + AEDs, steroids	2321	.7058	.7032	.003	–
PFS: clinical + HRQoL model + AEDs, Steroids	2093	.7099	.7021	.008	-.2%
OS: WHO 2016 classification + MGMT: clinical model	1748	.6962	.6877	.009	–
OS: WHO 2016 classification + MGMT: clinical + HRQoL model	1503	.7142	.6970	.017	1.8%
PFS: WHO 2016 classification + MGMT: clinical model	1765	.6865	.6800	.007	–
PFS: WHO 2016 classification + MGMT: clinical + HRQoL model	1518	.6979	.6835	.014	.7%

AEDs, antiepileptic drugs; HRQoL, health-related quality of life; WHO, World Health Organisation; MGMT, O^6-methylguanine-DNA methyltransferase promotor methylation.
[a] Measure of internal validation: c-index minus the bootstrapped c-index.
[b] Added value of the bootstrapped c-index of the clinical + HRQoL model compared with the clinical mode. The added value is calculated using the formula: ((clinical+HRQoL model − .5)/(.5) (*100) - (clinical model − .5)/(.5) (*100)).

the patient's health status or the level of care is currently unknown.

In conclusion, this study investigated the added prognostic value of HRQoL to the known clinical variables in a large heterogeneous sample of glioma patients. Although some HRQoL parameters were independently prognostic for survival, the added value of baseline HRQoL to the known clinical prognostic variables was small. Thus, although HRQoL has proven to be an important outcome in glioma patients for various purposes, HRQoL adds little for prognostic purposes.

Conflict of interest

None related to the content of this manuscript.

Funding

This study was funded with a grant from The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group.

Grant application number

CODAGLIO v1 005 2015.

Authorship

B.B., M.B., A.A.B., O.C., U.H., F.K.G., A.M., R.S., M.W. and W.W. were the principal investigators of the RCTs for which the data were originally collected and were involved in data collection. In addition, J.R. and M.T. were also involved in data collection in several RCTs. All authors were involved in the conceptualisation of this study. M.C. and L.D. performed the statistical analysis and wrote the first draft of the manuscript. All authors have been involved in the revision of the manuscript and have read and approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.012.

References

[1] Aaronson NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al. Compromised health-related quality of life in patients with low-grade glioma. J Clin Oncol 2011;29:4430–5.

[2] Dirven L, Aaronson NK, Heimans JJ, Taphoorn M. Health-related quality of life in high-grade glioma patients. Chin J Canc 2014;33:40–5.

[3] Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain

and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol 2018;20:iv1–86.
[4] Efficace F, Biganzoli L, Piccart M, Coens C, Van Steen K, Cufer T, et al. Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. Eur J Cancer 2004;40:1021–30.
[5] Maisey N, Norman A, Watson M, Allen M, Hill M, Cunningham D. Baseline quality of life predicts survival in patients with advanced colorectal cancer. Eur J Cancer 2002;38:1351–7.
[6] Quinten C, Martinelli F, Coens C, Sprangers MA, Ringash J, Gotay C, et al. A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites. Cancer 2014;120:302–11.
[7] Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 2008;26:1355–63.
[8] Mauer M, Stupp R, Taphoorn M, Coens C, Osoba D, Marosi C, et al. The prognostic value of health-related quality-of-life data in predicting survival in glioblastoma cancer patients: results from an international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. Br J Canc 2007;97:302–7.
[9] Mauer ME, Taphoorn MJ, Bottomley A, Coens C, Efficace F, Sanson M, et al. Prognostic value of health-related quality-of-life data in predicting survival in patients with anaplastic oligodendrogliomas, from a phase III EORTC brain cancer group study. J Clin Oncol 2007;25:5731–7.
[10] Paquette B, Vernerey D, Chauffert B, Dabakuyo S, Feuvret L, Taillandier L, et al. Prognostic value of health-related quality of life for death risk stratification in patients with unresectable glioblastoma. Cancer Med 2016;5:1753–64.
[11] Lamborn KR, Yung WA, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 2008;10:162–70.
[12] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20.
[13] Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol 2009;27:5743–50.
[14] 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;85:365–76.
[15] Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer 2010;46:1033–40.
[16] Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963–72.
[17] Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8:1277–80.
[18] Kirkwood BR, Sterne JA. Essential medical statistics. John Wiley & Sons; 2010.
[19] Harrell FE, Lee KL, Mark DB. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[20] Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med 1992;11:2093–109.
[21] Released I. IBM SPSS statistics for windows. 20. Armonk, NY: IBM Corp; 2013.
[22] Team RCR. A language and environment for statistical computing. 2013.
[23] Harrell Jr FE. Rms: regression Modeling Strategies. R package version 4.0-0. City. 2013.
[24] Dirven L, Reijneveld JC, Aaronson NK, Bottomley A, Uitdehaag BM, Taphoorn MJ. Health-related quality of life in patients with brain tumors: limitations and additional outcome measures. Curr Neurol Neurosci Rep 2013;13:359.
[25] Ediebah DE, Quinten C, Coens C, Ringash J, Dancey J, Zikos E, et al. Quality of life as a prognostic indicator of survival: a pooled analysis of individual patient data from canadian cancer trials group clinical trials. Cancer 2018;124:3409–16.
[26] Klein M, Postma T, Taphoorn M, Aaronson N, Vandertop W, Muller M, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. Neurology 2003;61:1796–8.
[27] Meyers CA, Hess KR, Yung WA, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol 2000;18:646.
[28] Johnson DR, Sawyer AM, Meyers CA, O'neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro Oncol 2012;14:808–16.
[29] Brown PD, Buckner JC, O'Fallon JR, Iturria NL, O'Neill BP, Brown CA, et al. Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. Int J Radiat Oncol Biol Phys 2004;59:117–25.
[30] Gorlia T, van den Bent MJ, Hegi ME, Mirimanoff RO, Weller M, Cairncross JG, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE. 3. Lancet Oncol 2008;9:29–38.
[31] Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol 2004;3:159–68.
[32] Kreth FW, Faist M, Rossner R, Volk B, Ostertag CB. Supratentorial World Health Organization grade 2 astrocytomas and oligoastrocytomas: a new pattern of prognostic factors. Cancer 1997;79:370–9.
[33] Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol 2016;69:79–88.
[34] Dirven L, Armstrong TS, Taphoorn MJ. Health-related quality of life and other clinical outcome assessments in brain tumor patients: challenges in the design, conduct and interpretation of clinical trials. Neurooncol Pract 2015;2:2–5.
[35] Beer TM, Miller K, Tombal B, Cella D, Phung, Holmstrom S, et al. The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: exploratory analyses of AFFIRM and PREVAIL studies. Eur J Cancer 2017;87:21–9.
[36] Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf 2014;13(Suppl 1):S41–55.
[37] Greimel E, Kristensen GB, van der Burg ME, Coronado P, Rustin G, del Rio AS, et al. Quality of life of advanced ovarian cancer patients in the randomized phase III study comparing primary debulking surgery versus neo-adjuvant chemotherapy. Gynecol Oncol 2013;131:437–44.