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Compliance with patient-reported outcome assessment in glioma patients: predictors for drop out

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Abstract

Background. Patient-reported outcomes are of high importance in clinical neuro-oncology. However, assessment is still suboptimal. We aimed at exploring factors associated with the probability for a) drop out of study and b) death during follow-up.

Methods. Patients were assessed twice during follow-up visits scheduled within 3 to 5 months of each other by using 3 validated patient-reported outcome measures (t1: first assessment, t2: second assessment). As "death" was seen as a competing risk for drop out, univariate competing risk Cox regression models were applied to explore factors associated with dropping out (age, gender, WHO grade, living situation, recurrent surgery, Karnofsky Performance Status, time since diagnosis, and patient-reported outcomes assessed by Distress Thermometer, EORTC-QLQ-C30, EORTC-QLQ-BN20, and SCNS-SF-34G).

Results. Two hundred forty-six patients were eligible, 173 (70%) participated. Patients declining participation were diagnosed with glioblastomas more often than with other gliomas (56% vs 39%). At t2, 32 (18%) patients dropped out, n = 14 death-related, n = 18 for other reasons. Motor dysfunction (EORTC-QLQ-BN20) was associated with higher risk for non-death-related drop out (HR: 1.02; 95% CI, 1.00–1.03; $P = .03$). Death-related drop out was associated with age (HR: 1.09; 95% CI, 1.03–1.14; $P = .002$), Karnofsky Performance Status (HR: 0.92; 95% CI, 0.88–0.96; $P < .001$), lower physical functioning (EORTC-QLQ-C30; HR: 0.98; 95% CI, 0.96–1.00; $P = .04$) and lower motor functioning (EORTC-QLQ-BN20; HR: 1.020; 95% CI, 1.00–1.04; $P = .02$).

Conclusion. Patients with motor dysfunction and poorer clinical condition seem to be more likely to drop out of studies applying patient-reported outcome measures. This should be taken into account when planning studies assessing glioma patients and for interpretation of results of patient-reported outcome assessments in clinical routine.

Key words

glioma | neuro-oncology | nonparticipation | study drop out | supportive care

The diagnosis of a glioma results in high psychosocial burden in the early phase after diagnosis, but also later on.[1–3] Maintaining quality of life and providing psychosocial and supportive care are not only major focuses of clinical neuro-oncology research,[4–10] but are also implemented in guidelines for the provision of care for these patients.[11–13] As glioma patients suffer from cognitive impairment early during the disease trajectory,[14]

adequate assessment of unmet needs, early integration of palliative care, and timely planning for end-of-life care are of high importance,[15] but also demanding to implement into clinical routine.

Patient-reported outcomes have become essential in assessing patients' quality of life and their needs in order to provide timely support.[16] These are self-report questionnaires evaluating patients' experiences with the disease, treatment-related symptoms and therapy effects focusing on quality of life,[9,17–19] distress and psychosocial burden,[20–23] as well as supportive care needs.[24] Recently, it has been shown that monitoring symptoms via patient-reported outcome measures can be very helpful for patients and even influence survival.[25,26]

However, as Taphoorn et al reported, they are far from being routinely implemented in clinical neuro-oncology.[10] Even in clinical studies applying patient-reported outcome measures, noncompliance is frequently reported, leading to a substantial selection bias and results that cannot easily be transferred to the general patient population.[8,27] Drop-out analyses can help to optimize study designs in order to avoid the above-mentioned problems with bias. Roick et al[28] reported in a large mixed cancer patient sample (53 brain tumor patients, 4%) that nonparticipation in their study was associated with higher age and advanced disease. In their cohort dropouts were more often married, contrasting the results of other studies,[29] and few had a high-level education.

Glioma patients suffer from neurocognitive deficits caused by both the disease itself and the treatment[27,30,31] and may not always be able to answer patient-reported ouctome questionnaires. Furthermore, patients undergoing chemotherapy or in poor clinical condition are often missed by patient-reported outcome assessment, but at the same time are those who could particularly benefit from early supportive care.[32,33] Therefore, we believe it to be important to assess those dropping out or declining participation in order to improve assessment, especially in glioma patients. Knowing who is at risk of dropping out could aid in providing selective guidance to minimize dropouts of studies applying patient-reported outcome measures. Furthermore, those patients dropping out of studies may also be missed by assessments in clinical routine, therefore the results could also provide information for practical clinicians useful in deciding which patients to screen more specifically.

Therefore, after having conducted an observational study in glioma patients,[34–36] we subsequently aimed to determine: 1) characteristics of patients declining participation in an observational study assessing quality of life, psychosocial burden, and supportive care needs and 2) factors associated with death and the probability to drop out of the study.

Patients and Methods

Study Design and Patient Population

The study design, feasibility, and correlation of the questionnaires have been previously reported.[34–36] In brief, inclusion criteria were the following: diagnosis of a glial cerebral tumor (according to WHO 2007[37]: astrocytoma, oligoastrocytoma, oligodendroglioma, glioblastoma); patients were affiliated with the neuro-oncological outpatient center in one of the three study centers and had to be able to understand and respond to the questions in German. All eligible patients were approached during their outpatient visit and informed about the study. After giving their informed consent, glioma patients were recruited during their outpatient visits at three study centers between March 2014 and October 2014 and assessed twice during two routinely scheduled (3 to 5 months) follow-up visits in the neuro-oncological departments. The questionnaires were administered in a paper/pencil version and filled in either by patients alone after instruction by a study group member or under guidance offered to the patients.[36] The first assessment was defined as t1, the second assessment as t2. Furthermore, clinical (eg, ongoing therapy, Karnofsky Performance Status [KPS], tumor localization and stage) and socio-demographic data of each participant were documented.

Patients were defined as *nonparticipants* if they were eligible, but declined participation after having been approached by the study team. In those patients, only age, sex, and diagnoses were assessed. *Dropouts* were defined as patients who could only be assessed at t1, but did not participate in the second assessment. Among the dropouts, we furthermore differentiated between patients who could not participate due to being deceased before the t2 assessment could take place (*death-related drop out*) and those who dropped out due to other reasons (*non-death-related drop out*). If possible, the reasons for declining further participation were assessed by the study members and documented in the database.

The study was undertaken in concordance with national law, institutional ethical standards, and the Helsinki Declaration, and the ethic commissions of all three study centers approved the study (ClinicalTrials.gov, NCT027280249).

Questionnaires

For the first assessment (t1), the Supportive Care Needs Survey Short-Form (SCNS-SF34-G), the Distress Thermometer (DT), the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30), and the brain-cancer-specific module (BN20) were used. For the second assessment (t2), the DT, EORTC-QLQ-C30 + EORTC-QLQ-BN20, and in a subgroup of patients the Supportive Care Needs Survey Screening Tool (SCNS-ST9), were applied.

The SCNS-SF34-G consists of 5 domains: health system and information, psychological, physical and daily living, patient care and support, and sexuality needs. It applies a 5-point Likert scale (1 = not applicable, 2 = satisfied, 3 = low need, 4 = moderate need, 5 = high need) to assess patients' needs applying 34 single items. A significant need for supportive care is defined as a rating of ≥ 3 for any item on the SCNS. The results are transformed into a sumscore

for every domain, ranging from 0 to 100, whereby higher values indicate higher needs for support in the respective domain. The German version was validated by Lehman et al.[24]

The SCNS-ST9 is an ultra-short screening instrument including all 5 domains and consisting of nine questions developed from the SCNS-SF34 by Girgis et al.[38] The structure of the screening instrument is similar to the SCNS-SF34-G with the same 5-point Likert scale.

The EORTC QLQ-C30 is a frequently used questionnaire that includes 30 items to assess quality of life in oncology patients in terms of function and symptom burden. Reliability and validity have been proven, and it has been translated into 85 languages. The brain module (QLQ-BN20) comprises 20 questions developed for brain tumor patients including 4 scales; 3 related to neurological deficits and 1 to future uncertainty.[9,17–19] The EORTC scale scores were calculated according to the user manual. Each scale is scored from 0 to 100, with higher scores indicating better functioning for functioning scales and worse symptoms for symptom scales.

The DT is a self-report screening instrument evaluating psychological distress using a visual analogue scale from 0 to 10.[20] It also consists of 40 items assessing financial, physical, emotional, and spiritual concerns by a problem list. Higher scores indicate higher levels of distress and a score of 6 on the visual analogue scale is recommended as a cut-off for a clinically significant level of distress in brain tumor patients.[21,22,39]

Definition of Outcomes and Statistical Analysis

Outcomes were 1) nonparticipation (descriptive) and 2) discontinuing the assessment during the study due to either a) non-death-related drop out or b) death-related drop out (explorative). For the first outcome, clinical data from patients consenting to participate in the study and those declining participation were compared (KPS, histopathological diagnosis, adjuvant treatment). Clinical data were derived from hospital records and compared using descriptive analysis. For the second outcomes, clinical data as described above and results from the aforementioned questionnaires were compared using explorative analyses.

For analyses of the second outcomes we used competing risk Cox regression models assuming that "death" of a patient is competing with "drop out." Restricted by the number of events of deaths and drop outs we used univariate models only. Predictors for death were evaluated by univariate Cox regression models. Only variables that had at least 5 observations in each factor level were explored. Thus, the following variables were tested for association with non-death-related drop out: age (years), sex (male vs female), living situation (in relationship vs single), WHO grade (low-grade glioma [WHO grade I and II] vs high-grade glioma [WHO grade III and IV]), eloquent tumor location (yes vs no), ongoing chemotherapy (yes vs no), surgery for recurrent tumor (yes vs no), Karnofsky index (%), time since diagnoses (years), distress (≥6 vs. <6), selected subscales of the EORTC QLQ-C30 and QLQ-BN20 (global quality of life, physical functioning, cognitive functioning, future uncertainty, motor dysfunction), and the 5 dimension scores of the SCNS-SF34. The EORTC scales, which were considered most important in this context, were preselected in order to restrict problems related to multiple testing. The same variables were tested for death-related drop out, except for living situation, WHO grade, and chemotherapy due to insufficient number of observations.

Sensitivity analyses were performed using multinomial logistic regression models comparing non-death-related drop out and death-related drop out vs participation at t2.

Descriptive statistics and multinomial regression analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York, USA). Competing-risk Cox regression analyses were performed using R Version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants and Nonparticipants at t1

Two hundred forty-six patients were eligible for our study. Informed consent was given by 173 (70%) patients. The 73 patients (30%) who declined to participate gave the following reasons: unclear / not stated (n = 26, 35%), fear of personal questions/unable for mental reasons (n = 22, 30%), not interested (n = 18, 25%), time constraints (n = 5, 7%), or already participating in another study (n = 2, 3%). Among patients declining to participate in the screening, the proportion of those with glioblastomas was considerably higher than those with lower grade tumors (56% vs 39%, $P = .02$) and there was a slight male preponderance (56% vs 53%, $P = .67$) than patients who participated.

The male-to-female ratio of the participating patients was 1:1, and the mean age was 51 years (nonparticipants, 56 years). The majority of patients had a primary diagnosis of a high-grade glioma (participants: WHO grade III: 43% and WHO grade IV: 39% vs nonparticipants: WHO grade III: 34% and WHO grade IV: 56%). Most of the participating patients (87%) had a KPS ≥70, with a mean of 81.4 (SD = 13.4). The median time since diagnosis was 33.6 months. Socio-demographic details of participants are provided in Table 1.

Drop out at t2

One hundred forty-one patients participated in the follow-up analysis (t2), which was performed during the consecutive outpatient visit (initially planned 3 to 5 months after the first assessment [mean = 4.8 months; range, 1.4–13.8 months]). Drop out was either death-related (n = 14, 44%) or non-death-related (n = 18, 56%). For patients alive at t2, reasons for not having a t2 assessment included: "not interested in a second assessment" (n = 9, 50%), "assessment too time-consuming" (n = 5, 28%), or "unclear" (n = 4, 22%). The proportion of patients with a high-grade glioma was higher in the patient sample who dropped out due to death than those who dropped out due to other reasons (death: 100% vs other reasons: 67%). Furthermore, more of the dropped out patients were under chemotherapy at

Table 1 Clinical and demographic data of the patient sample (participants and dropouts are shown separately) and results of psychosocial assessment using the Distress Thermometer, the EORTC-QLQ-C30 and EORTC-QLQ-BN20, and the SCNS SF34-G at t1 are displayed

	Total study sample (t1) n = 173 (100%)	Patients with complete follow-up (t1 and t2) n = 141 (82%)	Patients without follow-up (no t2) n = 32 (19%)	
			deceased n = 14 (8%)	dropout (non-death-related) n = 18 (10%)
Time since t1 in months				
Mean (SD, Min–Max)	5.3[4] (2.5, 1.4–13.8)	5.3[1] (2.6, 1.4–1.3)	5.6[2] (3.7, 1.6–13.8)	5.0[3] (0.0, 5.0–5.0)
Median, Q1–Q3	5.0 (3.2–6.2)	4.8 (3.1–6.7)	3.7 (2.9–9.0)	5.0 (5.0–5.0)
Age in years*				
Mean (SD, Min–Max)	51 (14, 21–78)	50 (14, 21–78)	62 (12, 37–76)	51 (13, 29–75)
Sex n (%)				
male	92 (53)	72 (51)	8 (57)	12 (67)
female	81 (47)	69 (49)	6 (43)	6 (33)
Living situation*, n (%)				
single	39 (22)	30 (21)	2 (14)	7 (39)
in relationship	124 (72)	102 (72)	12 (86)	10 (56)
unknown	10 (7)	9 (7)	-	1 (5)
WHO grade*, n (%)				
LGG (WHO I and II)	32 (19)	26 (18)	-	6 (33)
HGG (WHO III and IV)	141 (81)	115 (82)	14 (100)	12 (67)
Tumor localization I*, n (%)				
frontal	75 (43)	68 (48)	3 (21)	4 (22)
temporal	48 (28)	38 (27)	7 (50)	3 (17)
parietal	23 (13)	18 (13)	3 (21)	2 (11)
occipital	12 (7)	6 (4)	1 (7)	5 (28)
other	15 (9)	11 (8)	-	4 (22)
Tumor localization II *, n (%)				
eloquent	87 (50)	71 (50)	8 (57)	8 (44)
non eloquent	85 (49)	69 (49)	6 (43)	10 (56)
n.a.	1 (1)	1 (1)	-	-
Extent of resection, n (%)				
subtotal resection/biopsy	68 (39)	55 (39)	10 (71)	3 (17)
complete resection	102 (59)	83 (59)	4 (29)	15 (83)
n.a.	3 (2)	3 (2)	-	-
Ongoing chemotherapy*, n (%)				
yes	63 (36)	44 (31)	11 (79)	8 (44)
no	110 (64)	97 (69)	3 (21)	10 (56)
Surgery for recurrent tumor*, n (%)				
yes	56 (32)	45 (32)	6 (43)	5 (28)
no	117 (68)	96 (68)	8 (57)	13 (72)
Karnofsky Peformance Status (KPS)*				
Median (SD, range)	90 (40–100)	90 (40–100)	70 (60–90)	90 (10–100)
KPS < 70, n (%)	18 (10.4)	7 (5.0)	4 (22.2)	7 (50.0)
KPS ≥ 70, n (%)	151 (87.3)	130 (92.2)	14 (77.8)	7 (50.0)
n.a.	4 (2.3)	4 (2.8)	-	-
Time since diagnosis in months*				
Mean (SD, range)	46 (49, 2–278)	52 (54, 28–279)	31 (41, 2–125)	60 (55, 4–173)

Table 1 Continued

	Total study sample (t1) n = 173 (100%)	Patients with complete follow-up (t1 and t2) n = 141 (82%)	Patients without follow-up (no t2) n = 32 (19%)	
			deceased n = 14 (8%)	dropout (non-death-related) n = 18 (10%)
Median, Q1–Q3	34 (10–70)	35 (14–69)	13 (8–34)	47 (7–95)
< 3 years, n (%)	89 (51)	71 (50)	11 (79)	7 (39)
≥ 3 years, n (%)	76 (44)	65 (46)	3 (21)	8 (44)
n.a.	8 (5)	5 (4)	-	3 (17)
Value of Distress Thermometer*				
Mean (SD, range)	4.6 (2.7; 0.0–10.0)	4.6 (2.8; 0.0–10.0)	5.2 (2.3; 0.0–9.0)	4.4 (2.5; 0.0–8.0)
< 6 (n, %)	109 (63)	88 (62)	9 (64)	12 (67)
≥ 6 (n, %)	57 (33)	46 (33)	5 (36)	6 (33)
n.a.	7 (4)	7 (5)	-	-
Selected EORTC-QLQ-C30 and EORTC-QLQ-BN20 Scores*, Mean (SD)				
C30 Global Health Status/QoL	61.0 (22.7)	62.1 (23.0)	54.2 (22.3)	57.9 (20.9)
C30 Physical functioning	74.7 (25.6)	77.1 (24.8)	56.2 (28.8)	70.4 (24.2)
C30 Emotional functioning	59.4 (27.4)	59.3 (28.2)	59.5 (23.3)	60.3 (24.9)
C30 Cognitive functioning	63.0 (32.5)	64.0 (32.5)	50.0 (33.3)	65.7 (31.4)
BN20 Future uncertainty	39.3 (29.2)	38.8 (29.9)	38.8 (25.9)	43.8 (27.3)
BN20 Motor dysfunction	25.0 (27.2)	21.6 (26.1)	42.9 (31.4)	36.4 (25.2)
SCNS-SF34G Scores*				
Physical and daily living needs Mean (SD)	19.2 (21.4; 0.0–83.3)	19.8 (22.7)	14.7 (13.9)	18.1 (14.8)
Median (Q1 – Q3)	12.5 (0.0–25.0)	12.5 (0–29.2)	12.5 (4.2–22.9)	16.7 (7.3–26.0)
Psychological needs Mean (SD)	26.9 (27.8; 0.0–95.0)	27.4 (28.6)	25.7 (27.9)	24.3 (22.8)
Median (Q1 – Q3)	17.5 (5.0–45.0)	17.5 (5.0–46.3)	12.5 (1.3–48.8)	11.3 (5.0–45.0)
Patient care and support needs Mean (SD)	10.5 (19.1; 0.0–93.8)	10.2 (18.3)	10.7 (24.3)	13.0 (21.7)
Median (Q1 – Q3)	0.0 (0.0–12.5)	0.0 (0–12.5)	0.0 (0.0–10.9)	0.0 (0.0–21.9)
Health system and information needs Mean (SD)	22.1 (27.3; 0.0–100.0)	22.2 (27.4)	13.5 (19.8)	27.0 (30.7)
Median (Q1 – Q3)	11.4 (0.0–36.4)	11.0 (0.0–36.4)	4.5 (2.3–19.3)	15.9 (0.0–53.3)
Sexuality needs Mean (SD)	13.4 (21.8; 0.0–100.0)	14.6 (22.5)	5.8 (14.2)	9.8 (21.1)
Median (Q1 – Q3)	0.0 (0.0–16.7)	0.0 (0.0–25.0)	0.0 (0.0–4.2)	0.0 (0.0–12.5)

*Socio-demographic/clinical status information and results of questionnaires at t1
[1]Time to t2
[2]Time until death
[3]Time until drop out, censored after 5 months
[4]Time to event (t2/Death/Censoring)
HGG, high-grade glioma; LGG, low-grade glioma

t1 (death: 79% vs no t2: 44%) and presented with a poorer clinical condition (death: mean KPS at t1 = 67, range 60–90 vs no t2: mean KPS at t1 = 80, range 60–100). Baseline DT score was higher among deceased vs not-deceased drop-outs (mean 5.2 ± SD 2.3 vs 4.4 ± SD 2.5). These data are provided in more detail in Table 1.

Predictors for Drop out and Death

The results of the competing risk models are provided in Table 2. In our patient sample, only "poorer motor functioning" (motor functioning scale, EORTC QLQ-BN20) was associated with dropping out of the study (HR: 1.02; 95%

Table 2 Univariate competing risk Cox regression models identifying predictors for non-death-related drop out

	"drop out" assuming "death" as a competing risk		
	Hazard Ratio	95% Confidence Interval	*P* value
Age in years	1.02	0.98–1.06	.37
Sex			
male	1.91	0.72–5.08	.20
female	1.00		
Living situation			
in relationship	0.44	0.17–1.16	.10
single	1.00		
WHO grade			
LGG (WHO I and II)	1.50	0.56–4.00	.42
HGG (WHO III and IV)	1.00		
Eloquent tumor location			
yes	1.18	0.46–2.98	.73
no	1		
Ongoing chemotherapy			
yes	2.40	0.95–6.08	.07
no	1		
Surgery for recurrent tumor			
yes	1.19	0.43–3.34	.74
no	1		
Karnofsky Index in percent	0.99	0.96–1.03	.71
Time since diagnosis in years	1.00	1.00–1.00	.83
Value on Distress Thermometer			
≥ 6	1.04	0.39–2.77	.94
< 6	1		
Selected EORTC-QLQ-C30 and EORTC-QLQ-BN20 scales			
C30 Global Health Status/QoL	1.00	0.97–1.01	.42
C30 Physical functioning	0.99	0.97–1.00	.20
C30 Emotional functioning	1.00	0.98–1.02	.96
C30 Cognitive functioning	1.00	0.99–1.02	.74
BN20 Future uncertainty	1.01	1.00–1.03	.17
BN20 Motor dysfunction	1.02	1.00–1.03	.03
SCNS-SF34G scores			
Physical and daily living needs	1.00	0.98–1.02	.91
Psychological needs	1.00	0.98–1.02	.87
Patient care and support needs	1.01	0.99–1.03	.45
Health system and information needs	1.01	0.99–1.02	.22
Sexuality needs	1.00	0.96–1.02	.41

HGG, high-grade glioma; LGG, low-grade glioma

CI, 1.00–1.03; *P* = .03). Furthermore, "being under chemotherapy" hinted at a higher risk for dropping out (HR: 2.40; 95% CI, 0.95–6.08; *P* = .07), but did not reach statistical significance.

Predictors for drop out due to death were "higher age" (HR: 1.09; 95% CI, 1.03–1.14; *P* = .002), "lower Karnofsky Performance Status" (HR: 0.92; 95% CI, 0.88–0.96; *P* < 0.001), "lower physical functioning" (physical functioning scale, EORTC-QLQ-C30; HR: 0.98; 95% CI, 0.96–1.00; *P* = .04), and "lower motor functioning" (motor dysfunction, EORTC-QLQ-BN20; HR: 1.020; 95 CI%, 1.00–1.04; *P* = .02). "Time since diagnosis in years" was not found to be associated with drop out or death (HR: 1.00; 95% CI, 1.00–1.00, *P* = .83). Further results are displayed in Table 3. The sensitivity

Table 3 Univariate Cox regression models exploring predictors for drop out due to death

	Drop out due to death[1]		
	Hazard Ratio	95% Confidence Interval	*P* value
Age in years	1.09	1.03–1.14	<.01
Sex			
male	1.04	0.35–3.12	.94
female	1.00		
Eloquent tumor location			
yes	1.81	0.59–5.56	.30
no	1.00		
Surgery for recurrent tumor			
yes	2.59	0.85–7.9	.09
no			
Karnofsky Index in percent	0.92	0.88–0.96	<.001
Time since diagnosis in months	0.99	0.97–1.0	.09
Value of Distress Thermometer			
≥ 6	1.35	0.44–4.2	.60
<6			
Selected EORTC QLQ-C30 and EORTC QLQ-BN20 scales			
C30 Global Health Status/QoL	0.99	0.96–1.01	.28
C30 Physical functioning	0.98	0.96–1.00	.04
C30 Emotional functioning	1.00	0.98–1.03	.75
C30 Cognitive functioning	0.99	0.97–1.01	.21
BN20 Future uncertainty	1.00	0.98–1.02	1.00
BN20 Motor dysfunction	1.02	1.00–1.04	.02
SCNS-SF34G scores			
Physical and daily living needs	0.99	0.95-1.01	.34
Psychological needs	1.00	0.98–1.02	.89
Patient care and support needs	0.99	0.96–1.02	.56
Health system and information needs	0.97	0.93–1.01	.10
Sexuality needs	0.97	0.92–1.02	.19

[1] The following factors were not tested for association with death-related drop out due to insufficient number of observation in the respective factor levels: living situation, WHO grade, and chemotherapy

analyses revealed similar results and showed sufficient robustness of our regression models (supplemental table 1).

Discussion

Patient-reported outcome measures have become an essential part of assessing patients' symptoms, including quality of life, distress, and need for supportive care, and should be implemented into clinical routine.[12,15,16,22,40] However, implementation is complicated due to several factors. Patients in very poor clinical condition are not able to undergo psychosocial assessment by patient-reported outcome measures even in a study environment,[41] some questionnaires are too demanding, and if assessments are performed too often, patients can be irritated.[36,42–45] In our analyses we showed that patients with glioblastomas seemed to be more likely to decline study participation. In the death-related drop out group, a higher proportion of patient had high-grade glioma, were under chemotherapy at t1, and were in poorer clinical condition at t1. Motor dysfunction (EORTC-QLQ-BN20) was associated with possible non-death-related drop out of our study, while KPS, age, physical functioning (EORTC-QLQ-C30), and motor dysfunction (EORTC-QLQ-BN20) were associated with death related drop out. However, needs of support or distress of the patients at the initial screening were not related to drop out, probably indicating that patients discontinuing the study are as distressed by their disease and in need of support as those screened twice. In the following sections, we address and elaborate on the above-stated points.

Participants and Decliners of the Study

Due to the inclusion and exclusion criteria for this study (eg, understanding the applied questionnaires and being able to fill in the questionnaires), the assessment evaluated only a certain (fitter) proportion of the neuro-oncology patients at the study centers, leading to biased results and likely underrepresenting the needs and concerns in more severely affected patients. This is a widespread problem throughout the study landscape for patients with high-grade gliomas. For example, in a study by Halkett et al evaluating a homogenous population of patients with high-grade gliomas undergoing combined radiation and chemotherapy, only 127 out of 165 eligible patients gave informed consent and 116 could be assessed using patient-reported outcomes in this relatively early phase of the disease right after surgery under radiochemotherapy.[46] Reasons given for nonparticipation were similar to those found in our study and included physical and emotional burden, not interested, patient admitted to hospital, or unable to complete questionnaires due to cognitive deficits. Overall, patients declining participation in our study stated similar reasons as those who participated but declined the second assessment, but additionally were afraid of questions being too personal. However, several strategies exist to overcome the problem of nonparticipation,[30,47] eg, by assessing needs through semistructured interviews despite the inherent time constraint.[48] Furthermore, the fact that the group of patients declining participation showed a considerably higher proportion of patients with glioblastoma, indicates that these patients are probably too burdened by the disease to participate in a lengthy paper and pencil screening requiring prolonged concentration, but could maybe have been assessed by interviews, shorter assessments, or new approaches such as cell-phone-based daily assessments.[49] It is well known that the patients in clinical studies who are more burdened by the disease tend to refuse quality-of-life assessments or screening procedures more often.[28,50,51]

Dropouts and Factors for Dropping Out of the Study

In general, the number of dropouts observed in this study is relatively low in comparison to others, which may be due to the second assessment being scheduled during a routine follow-up without additional visiting requirements for the patients (scheduled after 3 to 5 months). Furthermore, the setting may have been beneficial with a highly motivated study group, including trained study nurses and medical students carrying out the instructions on how to fill in the questionnaires without the often-encountered time pressure of routine practice. Furthermore, all neuro-oncological study centers ensure a high personnel continuity during their clinical routine, increasing patient compliance. As this was an observational study, it is possible that the intervention was not perceived by the patients as to be very burdening and patients received attention from their physicians, possibly leading to a high compliance. However, the time to the second assessment was highly variable. Therefore, several patients had a longer period to become a dropout due to death, probably leading to an artificially lower number of non-death-related drop outs. One reason for the high variance of t2 is that some patients with low-grade gliomas were included. However, due to the small subgroup of patients who dropped out, the results have to be interpreted with caution.

The number of patients with high-grade gliomas was higher in the death-related drop out patient sample (n = 14,100%) compared with those patients who participated at t2 (n= 115 out of 141, 82%), but was similar in the complete drop out patient sample (26 of 32, 81%). Irrespective of histological diagnoses, patients reaching a certain clinical condition were also at risk of withdrawal from the study, as the competitive regression analyses yielded "motor functioning" to be associated with dropping out. Others have reported similar data with regard to neurocognitive and physical functioning, underlining that—although we report here results of an observational study—the feasibility of psychosocial screening in glioma patients in routine clinical practice will be challenging, which should be further addressed.[31,52]

The main reason for discontinuing the study was "death," especially for older patients and patients in a poorer physical condition, who were at higher risk of dying during the observational period. However, DT and needs for support were similar in both patient groups at t1. Therefore, in our opinion psychosocial support should be offered to patients at risk of needing further support in an easily accessible fashion even if further patient-reported outcome assessment is refused or not possible due to decline in clinical condition.[33,53] In this situation the "assessment" should be part of the physician–patient consultation and should also include caregivers by directly asking questions with regard to the needs for support and provision of support measure, eg, referral to social workers, psycho-oncologists, and palliative care medicine.

Limitations of the Study

Of note, although the data were acquired in a prospective manner, this analysis was done as posthoc analysis. The timing of t2 was more heterogeneous (1 to 13 months) than planned in the study protocol (3 to 5 months). The follow-up visits differed in our patient sample due to variability in diagnoses (low-grade gliomas were included). Dropouts were censored at 5 months for the regression analysis as the exact date of drop out was not available for all. Thus, the time under risk for drop out or participation at t2 may differ to some extent. However, sensitivity analyses using multinomial logistic regression, which did not take into account the underlying time structure, confirmed the results of the Cox analyses.

Reasons for opt-out or for discontinuing the study were not documented in all nonparticipants and dropouts. We do not know if those patients actively declined further participation or not. However, as no patients were lost to follow-up, we can exclude that nonparticipation occurred due to practical reasons, such as distance to the home or other socio-demographic factors.

Overall and within the competing outcomes of "death" and "drop out," we observed a small number of events (n = 18 and n = 14, respectively). Therefore, multivariable analyses were not possible and the statistical power was restricted. In order to restrict the problem of multiple testing we also tried to limit the number of tested explanatory

variables and performed variable selection on a content-driven a priori basis. Still, multiple variables were assessed. Without a correction for multiple testing and without multivariable analysis (not possible due to the limited number of dropouts) we must take into account that the results may be by chance and cautiously interpret them, as type I error may not be excluded in an explanatory analyses setting without adjustment of *P* values.

Even though we conclude that patient-reported outcome assessment may be too burdensome in particular patients with gliomas and that implementation in clinical routine may remain challenging, some patients may have declined participation because it was designed as a study requiring informed consent. It may be that handing out questionnaires as a routine without the need to read, understand, and sign consent forms might be more accepted by patients. However, this hypothesis needs further evaluation.

Conclusion

Our results indicate that patients with lower motor functioning and in worse clinical condition seem to be more likely to drop out of studies applying patient-reported outcome measures. Therefore, this should be taken into account when planning studies with glioma patients and interpreting the results of patient-reported outcmoe assessments in clinical routine. Furthermore, when screening is declined or not possible due to a poorer clinical condition, neuro-oncologists should provide psychosocial support to these patients in a low-threshold manner.

Supplementary Material

Supplementary data are available at *Neuro-Oncology Practice* online.

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