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Measuring symptons and functioning in glioma patients

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PART THREE

CHAPTER 6

Advance care planning (ACP) in glioblastoma patients: evaluation of a disease-specific ACP program and impact on outcomes

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Abstract

Background

The feasibility of implementing an advance care planning (ACP) program in daily clinical practice for glioblastoma patients is unknown. We aimed to evaluate a previously developed disease-specific ACP program, including the optimal timing of initiation and the impact of the program on several patient-, proxy- and care-related outcomes.

Methods

The content and design of the ACP program was evaluated, and outcomes including health-related quality of life, anxiety and depression, and satisfaction with care were measured every three months over a 15-month period.

Results

Eighteen patient-proxy dyads and two proxies participated in the program. The content and design of the ACP program was rated as sufficient. The preference for the optimal timing of initiation of the ACP program varied widely, however most of the participants preferred initiation shortly after chemoradiation. Over time, aspects of HRQoL remained stable in our patient population. Similarly, the ACP program did not decrease the levels of anxiety and depression in patients, and a large proportion of proxies reported anxiety and/or depression. The needed level of support for proxies was relatively low throughout the disease course, and the level of feelings of caregiver mastery was relatively high. Overall, patients were satisfied with the provided care over time, whereas proxies were less satisfied in some aspects.

Conclusion

The content and design of the developed disease-specific ACP program were rated as satisfactory. Whether the program has an actual impact on patient-, proxy- and care-related outcomes proxies remains to be investigated.

Introduction

The average incidence rate of glioblastoma, the most common and severe type of glioma, is approximately 3 per 100,000 persons per year[1,2]. With the introduction of multimodal treatment comprising surgery, radiotherapy and chemotherapy, the median survival of patients with glioblastoma increased but remains poor, i.e. approximately 15 months in a trial population[3].

During the disease course, many glioblastoma patients experience progressive neurological deficits such as seizures and motor deficits[4-6]. There may also be progression of cognitive dysfunction, which may subsequently interfere with the ability to make decisions about (future) care and treatment[7]. The poor median survival of glioblastoma patients in combination with the progressive neurocognitive decline warrants early involvement in treatment decision-making[8]. One way to involve patients in treatment decision-making is with advance care planning (ACP).

ACP is a process to involve patients and their proxies early in the disease trajectory in decision-making on future (palliative) care, also including end of life (EOL) care[9]. Currently, little is known about the effect of ACP on outcomes of glioblastoma patients, but it has been suggested that ACP could improve symptom control and enhance psychosocial support and EOL care planning[10]. Also, the quality of (EOL) care of patients could be improved. Previously, it has been shown that if glioma patients expressed their preferences for EOL care, these were often met[11]. Communicating their preferred place of death also resulted in more patients dying at that place[12], which was associated with dying with dignity[13]. Overall, these results suggest that ACP could potentially improve the quality of life and quality of care for glioblastoma patients.

Several ACP programs have been developed and implemented in various patient populations[9,14,15], and the effects are inconclusive. Positive effects that have been reported are empowerment, increased use of specialist palliative care and completion of advance directives, agreement between the preferred and delivered care, increased patient and family satisfaction with quality of EOL care, awareness of dying, and a reduction in stress, anxiety and depression in surviving relatives[9,14,16,17]. In contrast, other studies reported no impact of ACP on the level of health-related quality of life, patient satisfaction with care or shared decision-making, and that the delivered EOL care was not consistent with the patient's preferences[14,18].

Implementing an ACP program may be challenging. It was considered important that a program for glioblastoma should meet the demands of patients and their proxies with respect to the content of the program as well as the timing of implementation[19]. Previously, a disease-specific ACP program was developed specifically for glioblastoma patients, meaning that the content was customized for this patient population, e.g. with topics about anti-tumor and supportive treatment (e.g. corticosteroids and anti-

epileptic drugs), surrogate decision-making in case of incompetence, issues in the EOL phase (e.g. swallowing drowsiness), and caregiver burden. In addition, it was determined what the optimal timing of introduction of such a program would be. Even though the participants in that study[19] agreed on the program content, the optimal timing of introducing such a program was a matter of debate. Several patients and proxies indicated that early implementation of ACP is not preferred, however, it should also be considered that glioblastoma patients have a poor prognosis and might have a rapid decline in their cognitive functioning that could hamper decision-making later in the disease process. It was therefore suggested that the most optimal moment to offer the program was after the chemoradiation phase (approximately 3 months after the histopathological diagnosis), and that patients and proxies should be able to decide which topics are discussed.

The aim of the current study was to evaluate the previously developed ACP program in glioblastoma patients and their proxies[19], including re-evaluating the optimal timing of initiation, as well as the impact of the program on several patient-, proxy- and care-related outcomes such as health-related quality of life (HRQoL), feelings of anxiety and depression, caregiver needs and mastery, health resource utilization and satisfaction with care.

Methods

Study design and participants

This study comprised a longitudinal prospective feasibility study. Patients were eligible if they were (1) adults with a histologically confirmed glioblastoma, (2) visiting the outpatient clinic of the Haaglanden Medical Center, The Hague, a large tertiary hospital in the Netherlands, from October 2017 onwards, (3) able to understand the Dutch language, (4) considered competent to participate in an formal ACP program in a research setting as judged by the treating physician (there was no formal assessment of competence). In addition, proxies of patients that were recruited, were defined as a spouse, family member or close friend to the patient, providing most of the emotional and physical support to the patient.

Outcomes

Patients completed the cancer-specific European Organisation of Research and Treatment of Cancer (EORTC) quality of life C30 questionnaire (version 3.0) and the brain cancer-specific module, the QLQ-BN20, to assess their level of HRQoL[20-22]. Proxies

completed the Short-Form-36 to assess their level of HRQoL[23]. In addition, the Hospital Anxiety and Depression Scale (HADS) was administered to both patients and proxies to assess symptoms of anxiety and depression[24]. The Caregiver Mastery Scale[25] was administered to proxies to determine their level of mastery as informal caregivers, and the Caregiver Support and Needs Assessment Tool[26] was administered to evaluate in which areas of need the proxy required support.

To evaluate satisfaction with care, both patients and proxies completed a short-item list focusing on care in the outpatient clinic, based on items from the EORTC item library[27]. Health resource utilization of the patients was evaluated with a study-specific questionnaire. Other study-specific questionnaires were created to evaluate the content and structure of the ACP program and (changes in) wishes for treatment and EOL care over time. More detailed information on the used questionnaires can be found in Supplemental Files 1, and Supplemental Files 2-4 display the study-specific questionnaires.

Study procedures

By means of consecutive sampling, eligible patients and their proxies were invited for participation by the treating physician shortly after chemoradiation, but before adjuvant treatment, as this was considered the most optimal moment in the previous study[19] (details on the study design and patient population can be found elsewhere). If the patient and/or proxy agreed to participate, they received a study-specific folder with all topics that could be discussed within the ACP-program, which was developed in the previous study[19]. There were two scheduled ACP sessions, led by a trained facilitator (in this study the nurse specialist), which took place in the hospital. During the first session, the concept of ACP was introduced, and participants could indicate which topics they wanted to discuss in more depth. After the first session, participants were asked if they were interested in another ACP session, approximately four weeks later, in which additional questions and topics could be discussed. Patients were encouraged to complete an advance directive (AD) in their last ACP session, but this was not mandatory. During the follow-up period, patients were encouraged to contact the nurse specialist in case they had additional questions or if they wanted to inform the healthcare professionals that their wishes for treatment and EOL care had changed.

On the day of the first ACP session (i.e. baseline measurement), but prior to the actual discussion, participants were requested to complete several questionnaires (see 'outcomes'). Immediately after the ACP session(s), approximately four weeks after the baseline assessment, participants were requested to complete a questionnaire about the content and quality of the ACP program. At three months, and subsequently every three months with a maximum of 15 months follow-up, participants were also requested to complete several questionnaires related to their functioning and well-being, their perception of the quality of care received and health resource utilization

(see Figure 1 for an overview of the outcomes assessed at each time point). Approximately three months after the death of the patient, the proxy was contacted and asked to complete a questionnaire on the EOL care (these results will be reported separately). Lastly, the general practitioners (GPs) of the patients were contacted to evaluate if they were aware of the wishes of the patient and were able to act accordingly.

The study was approved by the medical ethical committee of the Haaglanden Medical Center, and all participants provided written informed consent before participation.

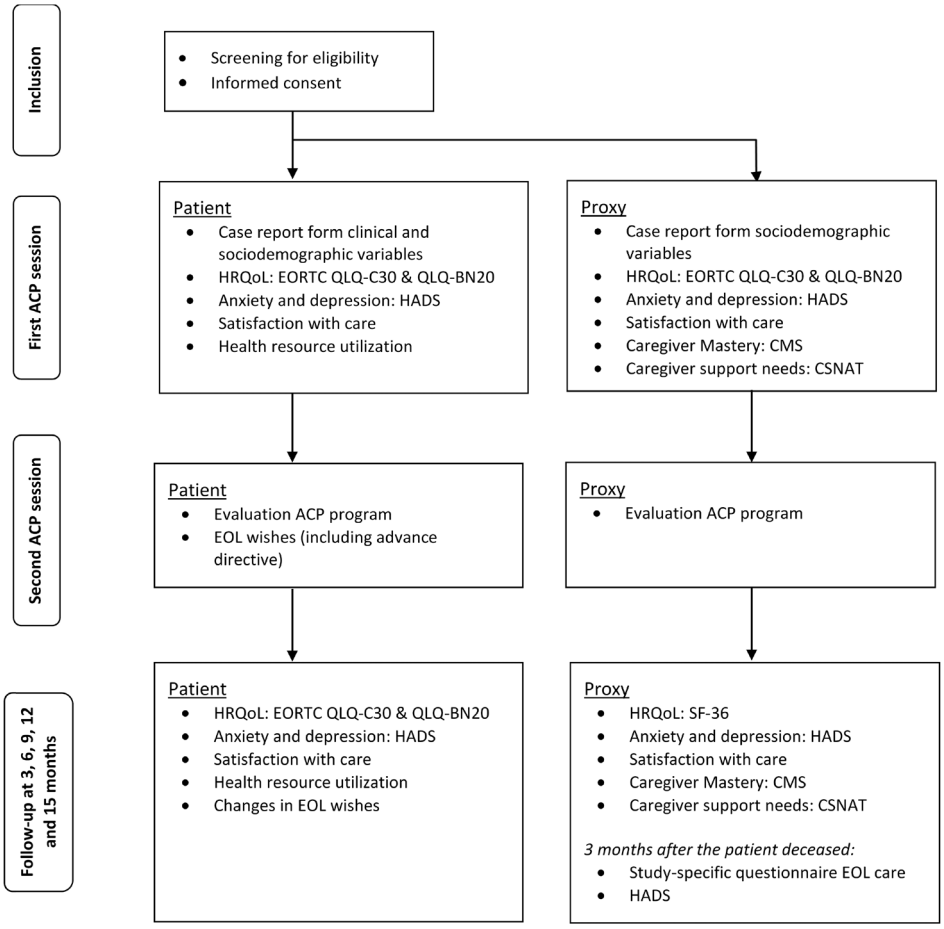

Figure 1. Overview of the assessments at each time point

Statistical analysis

Scores on the EORTC questionnaires, SF-36 and HADS were calculated according to their instruction manuals[23,28]. Due to the limited number of participants, descriptive statistics were used to describe the characteristics of the participants and the outcomes. For between and within group comparisons, students T-tests or Mann Whitney U tests were used, depending on the distribution of the tested variable. To analyze the data, IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp) was used. A p-value <0.05 was considered to be statistically significant.

Results

Recruitment

A total of 31 eligible patient-proxy dyads were approached for participation between October 2017 and February 2018. Of these, 11 declined participation, four because this study was emotionally too burdensome, for two patient's their health status was too poor, two were not interested in participation, and three considered the topic of this study not relevant for their current situation. Patients who did not participate did not significantly differ from those who did participate in terms of sex (73% vs. 75% male, respectively, p=0.606), median age (65 vs. 56 years, p=0.212), median KPS score (90 vs. 80, p=0.528), and tumor type (95% vs. 91% glioblastoma IDH-wildtype, p=0.304).

Eighteen patient-proxy dyads participated in the ACP program, as well as two proxies without the patient. Therefore, aspects of the disease of a total of 20 patients were discussed. The majority of patients (75%) were male, diagnosed with glioblastoma IDH wildtype (95%), and with an unmethylated MGMT promotor (80%). The median age was 65 years (range: 45-77), with the majority of patients having a good performance status (KPS ≥70, 95%) and having no (65%) or mild (20%) cognitive symptoms. The median time since diagnosis was four months, and patients previously underwent a resection (70%) or biopsy (30%), and most patients received radiotherapy and chemotherapy (100% and 90%, respectively).

Most proxies were the partner of the patient (70%), and of female gender (75%), and they had a median age of 55 years (range:33-76). Median duration of their relationship was 36 years (range: 16-57), and most proxies (65%) were living together with the patient. See Table 1 for an overview of all baseline characteristics.

Evaluation ACP program

Patients

A total of 14/18 (78%) of the participating patients provided an evaluation of the ACP program, about one month after completion. The quality of the program was rated (on a 7-points Likert scale) as 'neither good nor poor' in 29%, and as 'somewhat good

Table 1. Sociodemographic and clinical characteristics of the participants

Baseline characteristics	Patients (n=20)	Proxies (n=20)
Age in years, median (range)	65 (45-77)	55 (33-77), *n=17*
Male sex, no. (%)	15 (75%)	5 (25%)
Educational level, no. (%)		
Low [0-4]	13 (65%)	11 (58%)
High [5-8]	6 (30%)	8 (42%)
Unknown	1 (5%)	1 (5%)
Religious, no. (%)		
Yes	8 (40%)	9 (45%)
No	9 (45%)	10 (50%)
Unknown	3 (15%)	1 (5%)
Religion important, no. (%)	n=8	n=9
Yes	5 (63%)	6 (67%)
No	2 (25%)	3 (33%)
Unknown	1 (13%	-
Tumor type, no. (%)		
Glioblastoma, IDH-wildtype	19 (95%)	-
Glioblastoma, NOS	1 (5%)	-
MGMT status, no. (%)		
Methylated	1 (5%)	-
Partial methylated	2 (10%)	-
Unmethylated	16 (80%)	-
Undetermined/missing	1 (5%)	-
KPS score, median (range)	80 (60-100)	-
≥70, no. (%)	19 (95%)	-
Cognitive status, no. (%)		
None	13 (65%)	-
Mild	4 (20%)	-
Moderate	3 (15%)	-
Severe	-	-
Time since diagnosis in months, median (range)	4 (4-8)	-
Disease status, no. (%)		
Active	2 (10%)	-
Stable	18 (90%)	-
Previous treatment, no. (%)		
Resection	14 (70%)	-
Biopsy	6 (30%)	-
Chemotherapy	20 (100%)	-
Radiotherapy	18 (90%)	-
Monoclonal antibodies	1 (5%)	-
Current treatment, no. (%)		
Chemotherapy	17 (85%)	-
Monoclonal antibodies	1 (5%)	-
No adjuvant treatment	1 (5%)	-
Relationship, no. (%)		
Partner	-	14 (70%)
Child	-	5 (25%)
Aunt	-	1 (5%)
Relationship In years, median (range)	-	36 (16-57)
Intensity contact, no. (%)		
Living together	-	13 (65%)
Daily	-	3 (15%)
Weekly	-	3 (15%)
Monthly	-	1 (5%)

to excellent' in 71%. Moreover, all patients felt that all important topics (related to the current situation, worries and fears, (supportive) treatment and preferred place of care and death[19]) were discussed, and did not identify missing topics. The acceptability of the topics, amount of provided information, number of ACP sessions, duration of the ACP session, and the functioning of the ACP facilitator were rated as acceptable to very acceptable in the large majority of cases (range: 85-100%; Figure 2A). Only one suggestion was made to improve the program, i.e. the use of a decision tree to visualize the care pathway.

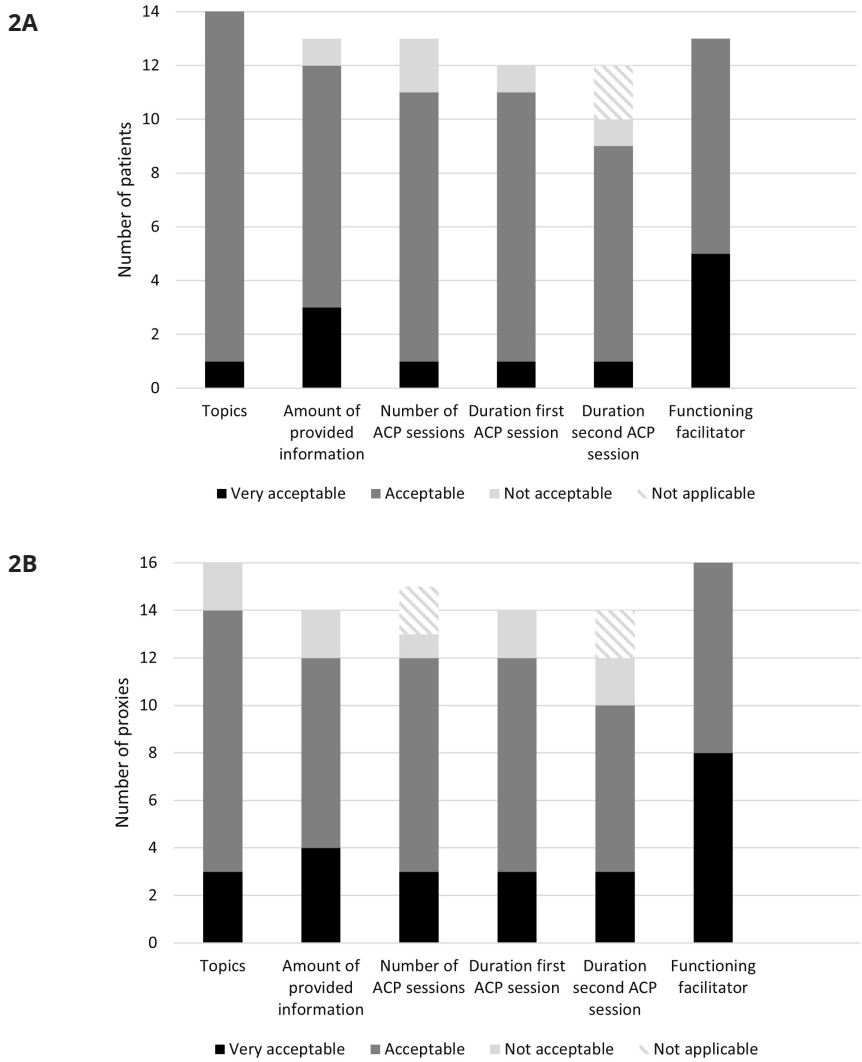

Figure 2. Acceptability of the ACP program according to patients (Figure 2A) and proxies (Figure 2B)

Responses with respect to the optimal timing of initiating the ACP program varied widely (Figure 3), with most patients preferring to introduce the program shortly after chemoradiation (about 16 weeks after the diagnosis; 5/14, 36%), during adjuvant chemotherapy (about 6 months after diagnosis; 3/14, 21%) or after adjuvant chemotherapy (about 9 months after diagnosis; 3/14, 21%).

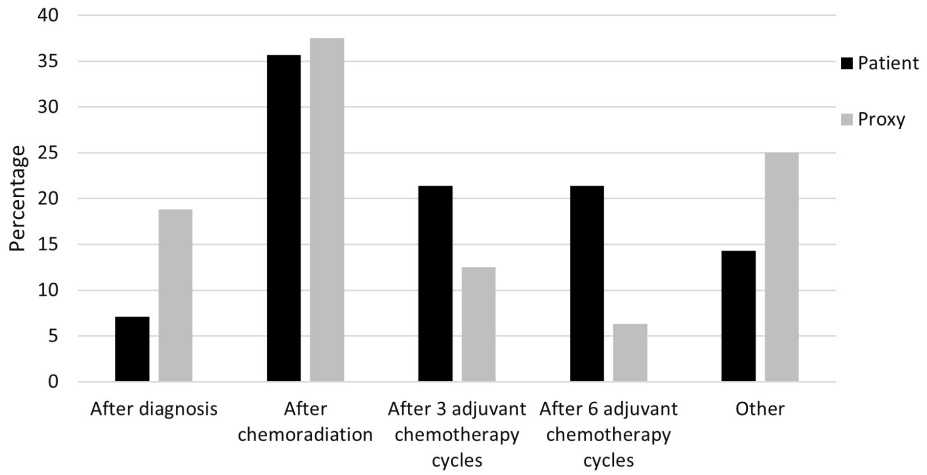

Figure 3. Preference of timing of initiation of the ACP program as rated by patients (n=14) and proxies (n=16)

Proxies

Seventeen out of 20 participating proxies (85%) provided an evaluation of the ACP program approximately one month after completion. Proxies rated the quality of the program as 'neither good nor poor' in 18% (3/17), and as 'somewhat good' to 'excellent' in 77% (13/17), with only one proxy (6%) rating the program as 'somewhat poor'. Thirteen out of sixteen (81%) of proxies indicated that all important topics were discussed, and the three proxies who indicated that not all topics were discussed did not provide information on missing topics. While the majority of proxies rated the acceptability of the topics, amount of provided information, number of ACP sessions, duration of the ACP session, and the functioning of the ACP facilitator as 'acceptable' or 'very acceptable' (range: 71-100%), there were some proxies rating some aspects (i.e. number and duration of ACP sessions) as 'not acceptable' (Figure 2B). Moreover, six patients suggested improvements for the ACP program, comprising separate sessions for patients and proxies, providing less information at once, asking participants which topics they want to discuss, and more focus on positive aspects of the disease (to maintain hope).

Similar to patients, the preference for the optimal timing of initiation of the ACP program varied widely (Figure 3). Three out of 16 proxies (19%) who provided information, preferred the time around diagnosis (shortly after surgery), 6/16 (38%) after chemoradiation (about 16 weeks after the diagnosis), 2/16 (13%) during adjuvant chemotherapy (about 6 months after diagnosis), 1/16 (6%) after adjuvant chemotherapy (about 9 months after diagnosis), and 4/16 (25%) proxies indicated that this should be flexible, and based on the wishes of the patient and proxy.

General practitioners

Eleven GPs (55%) completed the evaluation approximately 14 months after the patients/proxies started with the ACP program. Most (10/11, 91%) GPs indicated that all topics were addressed in the program. One GP reported that more information should be provided on the role of the GP during the disease trajectory. Eight GPs (73%) received the advance directive (AD) of the patients, and were aware of the content. In addition, 10/11 GPs indicated they (already) had intensive contact with the patient and proxy in which they discussed care preferences. Moreover, eight GPs indicated that it was possible to meet the wishes of the patients. Although most (64%) GPs were satisfied with the contact with the hospital, there were also some remarks. In general, the GPs felt that they were not sufficiently involved; they wished to be contacted more frequently and receive more information, with a clear transfer of information when the EOL phase starts.

Similar to patients and proxies, GPs were also not unanimous on the optimal timing of initiation of an ACP program, with 37% favoring around diagnosis, 18% immediately after chemoradiation, 9% after chemoradiation has finished, and 36% favoring an alternative time point. GPs felt that the timing should depend on the situation of the patient, but did indicate this had to be introduced as soon as possible.

Patient outcomes

Patient scores on the selected scales of the EORTC QLQ-C30 and QLQ-BN20 as well as the HADS for the baseline, 3-month and last assessment are presented in Table 2, and for all scales in Supplemental Table 1. In general, patients had significantly lower levels of functioning and more symptoms than the general population at baseline. Although the level of functioning increased between baseline and 3-months, these differences were not statistically significant. During the last assessment, the median level of physical functioning was significantly, but not to a clinically relevant extent[30], lower compared to baseline (73 vs. 80, p=0.008), while there were no significant differences for the other scales.

The median scores on the HADS anxiety and depression subscales did not differ significantly between the baseline, 3-month and last assessment (Table 2). Whereas

20% and 30% of patients reported possible anxiety and depressive disorder at baseline (score ≥8 points), respectively, this percentage was similar at the 3-month assessment (17% vs. 31%), but increased significantly to 46% and 54% at the last assessment (p=0.026 and p=0.039, respectively).

Proxy outcomes

Proxy scores on the SF-36 and HADS questionnaires at baseline, 3-months and during the last assessment are displayed in Table 3. Compared to the general population, proxies had significantly lower scores on the SF36 PCS (mean: 83 vs. 50, respectively) and MCS (mean: 69 vs. 44, respectively) at baseline. Also, proxies scored significantly lower on social functioning, mental health and vitality. At the 3-month assessment, none of the subscales or component scale scores of the SF-36 were significantly different compared to the baseline scores. At the last assessment, proxies did report significantly better physical functioning (mean: 92 vs. 84) and less bodily pain (mean: 83 vs. 77) than the baseline assessment. The median scores on the HADS anxiety and depression subscales did not differ significantly between the baseline, 3-month and last assessment. The percentage of proxies reporting possible anxiety and depressive disorder (≥8 points) changed from 56% and 29% at baseline, respectively, to 36% and 55% after three months and 39% and 39% at the last assessment.

The median CSNAT total score was similar over time, with a score of 5 out of 42 points at baseline and 3 points at both the 3-month and last assessment, indicating that the need of support was relatively low (Supplemental Table 2). In general, the need for support was higher at baseline (38% of proxies in need of at least a bit support on ≥1 item) compared to the 3-month and last assessment (28% and 26%, respectively; Supplemental Figure 1). Caregiver mastery as measured with the CMS was also similar over time, with a median score of 25 out of 35 (range 7-32) at baseline, and 27 (range: 9-33) and 26.5 (range: 9-35) at the 3-month and last assessment, with higher scores indicating less feelings of mastery (Supplemental Table 3).

Satisfaction with care

At baseline, patients rated the different aspects of care overall as 'good' to 'excellent' (mean 90%, range: 63-100%), with similar percentages at the 3-month (mean 92%, range: 70-100%) and last assessment (mean 92%, range: 82-100%; Supplemental Figures 2A-C). Only 'exchange of information between healthcare professionals' and 'provision of information about supporting organizations' were rated 'poor' at baseline by 10 and 15% of patients respectively, and 'exchange of information between healthcare professionals' was also rated as 'poor' after 3-months by 10%. The overall rating of the care received in the hospital was rated as 'good' to 'excellent' by 94% of patients at baseline, and 100% of patients at the 3-month and last follow-up (p=0.130 and p=0.274, respectively).

Table 2. Patient scores on the selected EORTC QLQ-C30 and QLQ-BN20 scales and HADS at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[29]
EORTC QLQ-C30				
Global health status				
Median (range)	67 (0-92)	63 (17-92)	58 (25-92)	
Mean (SD)	62 (27)	60 (23)	55 (22)	78 (17)*
No. of patients	18	14	15	
Physical functioning				
Median (range)	80 (13-100)	87 (20-100)	73 (8-100)*	
Mean (SD)	74 (26)	72 (28)	62 (32)	90 (15)*
No. of patients	18	13	15	
Role functioning				
Median (range)	67 (0-100)	50 (0-100)	83 (0-100)	
Mean (SD)	58 (35)	53 (35)	63 (38)	90 (15)**
No. of patients	18	13	13	
Emotional functioning				
Median (range)	71 (25-100)	88 (33-100)	67 (0-100)	
Mean (SD)	71 (23)	78 (20)	68 (28)	94 (16)**
No. of patients	18	14	15	
Cognitive functioning				
Median (range)	67 (0-100)	75 (0-100)	67 (0-100)	
Mean (SD)	66 (31)	69 (30)	67 (27)	90 (15)**
No. of patients	17	14	15	
Social functioning				
Median (range)	67 (0-100)	67 (0-100)	100 (0-100)	
Mean (SD)	68 (28)	63 (35)	73 (36)	90 (15)**
No. of patients	18	14	15	
EORTC QLQ-BN20				
Future uncertainty				
Median (range)	33 (8-92)	38 (0-100)	33 (8-100)	
Mean (SD)	39 (25)	43 (28)	42 (26)	N/A
No. of patients	18	14	14	
Communication deficit				
Median (range)	14 (0-100)	22 (0-100)	22 (0-100)	
Mean (SD)	29 (34)	35 (38)	36 (38)	N/A
No. of patients	18	14	15	
HADS				
HADS-anxiety				
Median (range)	4 (0-21)	4 (0-11)	6 (0-12)	
Mean (SD)	5 (5)	4 (3)	6 (4)	
No. of patients	15	12	13	
No. (%) score ≥8	3 (20%)	2 (17%)	6 (46%)	
HADS-depression				
Median (range)	3 (0-21)	4 (0-19)	9 (0-18)	
Mean (SD)	5 (6)	6 (6)	8 (6)	
No. of patients	17	13	13	
No. (%) score ≥8	5 (30%)	4 (31%)	7 (54%)	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Table 3. Proxy scores on the SF-36 subscales and summary scores and HADS at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[31]
SF-36				
Physical component score				
Median (range)	50 (31-65)	49 (19-60)	55 (36-61)	
Mean (SD)	50 (10)	47 (12)	53 (7)	83 (21)**[32]
No. of proxies	18	11	12	
Mental component score				
Median (range)	45 (17-62)	47 (16-62)	52 (16-61)	
Mean (SD)	44 (12)	47 (12)	44 (16)	69 (18)**[32]
No. of proxies	18	11	12	
Physical functioning				
Median (range)	95 (40-100)	90 (5-100)	95 (70-100)	
Mean (SD)	84 (21)	82 (26)	92 (10)*	85 (23)
No. of proxies	19	13	14	
Physical role functioning				
Median (range)	100 (0-100)	100 (0-100)	100 (0-100)	
Mean (SD)	75 (40)	66 (48)	77 (42)	80 (35)
No. of proxies	118	11	12	
Bodily pain				
Median (range)	74 (31-100)	62 (21-100)	92 (41-100)	
Mean (SD)	77 (25)	71 (26)	83 (22)*	81 (24)
No. of proxies	19	13	14	
Social functioning				
Median (range)	75 (25-100)	88 (13-100)	100 (25-100)	
Mean (SD)	72 (21)	67 (33)	81 (31)	85 (22)*
No. of proxies	19	13	14	
Mental health				
Median (range)	68 (8-96)	64 (4-100)	82 (4-96)	
Mean (SD)	65 (21)	61 (28)	66 (29)	76 (18)*
No. of proxies	19	13	14	
Emotional role functioning				
Median (range)	100 (0-100)	100 (33-100)	100 (0-100)	
Mean (SD)	70 (41)	81 (26)	72 (36)	83 (33)
No. of proxies	18	12	13	
Vitality				
Median (range)	70 (5-80)	55 (5-85)	66 (5-95)	
Mean (SD)	55 (27)	53 (26)	59 (27)	69 (19)*
No. of proxies	19	13	14	
General health perceptions				
Median (range)	67 (30-92)	67 (30-92)	72 (25-97)	
Mean (SD)	64 (18)	62 (20)	66 (23)	71 (21)
No. of proxies	19	13	14	

Table 3. Continued

	Baseline	Month 3	Last assessment	General population[31]
HADS				
HADS-anxiety				
Median (range)	9 (2-19)	5 (3-18)	6 (0-18)	
Mean (SD)	9 (5)	8 (6)	8 (6)	
No. of proxies	18	11	13	
No. (%) score ≥8	10 (56%)	4 (36%)	5 (38%)	
HADS-depression				
Median (range)	4 (0-20)	8 (0-202)	4 (0-20)	
Mean (SD)	6 (5)	8 (6)	7 (6)	
No. of proxies	17	11	13	
No. (%) score ≥8	5 (29%)	6 (54%)	5 (38%)	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Proxies were in some respects less satisfied with the provided care than patients, with 78% (range: 40-100%) still rating the care as 'good' to 'excellent' at baseline, and 87% at both the 3-month and last assessment (Supplementary Figures 3A-C). Particularly at baseline, 7/16 items were rated as poor by 5-20% of proxies, with 'the information provided on the overall supportive services available' rated as worst. This was the only item that was rated as 'poor' by 8% of proxies at the 3-month and last assessment. The overall rating of the care received in the hospital was rated as 'good' to 'excellent' by 90% of proxies at baseline, and 92% and 100% of patients at the 3-month and last follow-up, respectively (p=0.130 and p=0.02, respectively).

Health resource utilization

All patients had at least basic health insurance, with the majority (15/18, 83%) having additional insurances. Overall, health care usage was higher in the three months before baseline compared to the three months before the last assessment. The majority of patients had contact with the general practitioner (10/17, 59%), specialist in the hospital (16/17, 94%; mainly the neurologist) or other health care professionals (7/18, 39%; occupational therapist, physical therapist, psychologist, speech therapist, or massage therapist) in the three months before the baseline assessment. These percentages were 71% (10/14), 60% (9/15), and 20% (3/15) in the three months for the last assessment, respectively. None of the patients was treated in an inpatient clinic for medical or psychological problems in the three months before baseline, while one patient (1/14, 7%) was admitted to a rehabilitation center. In the three months before the baseline assessment, 41% (7/17) patients visited the emergency department for various reasons, and 50% (9/18) of patients was admitted to a hospital, while these

percentages were 13% and 13% in the three months before the last assessment. Lastly, the majority (14/18, 78%) of patients used medication (corticosteroids, anti-epileptic drugs and/or chemotherapy) in the three months before baseline, while this was 80% (13/15) at the last assessment.

Discussion

In this study we evaluated the previously developed disease-specific ACP program in glioblastoma patients and their proxies, including the optimal timing of initiation and the impact of the program on several patient-, proxy- and care-related outcomes. The large majority of patients and proxies rated the different aspects of the ACP program (such as the topics, number of sessions, duration of the session, functioning of the facilitator) as 'acceptable', and the overall quality was rated as 'somewhat good' to 'excellent' by most participants. These results suggest that the content and design of the currently available ACP program is sufficient. Some participants made suggestions for improvements, such as separate sessions for patients and proxies, providing less information at once, which could be considered on an individual basis, depending on the available time and resources. One of the reasons that participants in our study may have appreciated the program is that their treating nurse specialists were the facilitators, as previous research has shown that most patients prefer to have ACP discussions with their primary care physicians instead of surgeons or medical oncologists, because of trust and familiarity[33]. A similar relationship is expected between the patient and nurse specialist. Aspects that are important to include in ACP conservations are cultural aspects, taking sufficient time for the ACP conversations, and guiding patients in documenting their wishes. Still, about one third of the eligible patients did not want to participate for various reasons, of which being emotionally overwhelmed was the most common reason to decline[33]. A systematic review on experiences of patients with life-threatening or life-limiting diseases with ACP reported that, although patients also experienced benefits, ACP can be accompanied by unpleasant feelings[34]. The most important negative emotion was being confronted with having a life-limiting disease. It was suggested that the emotional burden could be lessened by introducing the program in group sessions[34]. In our ACP program, we aimed to reduce the emotional burden for patients and proxies by having them decide which topics they want to discuss. Even if not addressed, by presenting topics that could become an issue in the future (e.g. palliative sedation), we tried to trigger patients to at least think about these topics. A major limitation is that we did not record which topics were eventually discussed by the participants during the ACP sessions.

Similar to the results from the developmental phase[19], the preference for the optimal

timing of initiation of the ACP program varied widely. Although about one third of the participants in our study indicated that the program should be initiated shortly after chemoradiation, a large proportion suggested that the program should be initiated later in the disease trajectory. In studies in other populations, patients indicated that the optimal timing for the initiation of ACP was as early as possible[33,34], as they found it desirable to receive all relevant information as soon as possible and that it is better to deal with these issues in reasonable health. Early initiation of ACP is also considered important for glioblastoma patients, as they have an incurable disease and may experience a rapid decline in their cognitive functioning, hampering decision-making[7]. Neverthless, an important barrier for participation in such a program may be prognostic awareness, as about half of brain tumors patients is not fully aware of their poor prognosis[5]. The GPs participating in our study confirmed that it is important to offer ACP as soon as possible. Despite the variation in preference of optimal timing of initiation of the ACP program, we suggest to offer the program shortly after the chemoradiation before patients are cognitively too impaired, and mention the availability of the program in later disease stages (i.e. after 3 and 6 adjuvant chemotherapy cycles) to patients who declined before. Early initiation of such a program also allows that topics can be discussed at different moments in the disease course.

As also previously found, patients in our study had significantly lower levels of functioning and more symptoms compared to the general population[35,36]. Over time, aspects of HRQoL remained stable in our patient population. In the literature, the impact of ACP on HRQoL aspects was found to be contradictory. One large international RCT in 1117 patients with advanced cancer also did not find any impact of ACP on the level of HRQoL[14], while other studies found that the level of HRQoL was improved by introducing an ACP program[16,37]. Although glioblastoma patients typically experience a deterioration in HRQoL during the disease course[38-40], we cannot determine whether the ACP program helped to prevent this deterioration. Similarly, contrary to our expectations[16], the ACP program did not decrease the levels of anxiety and depression in patients over time. Instead, the number of patients with a possible anxiety or depression disorder was larger during the last assessment compared to baseline, which can be related to the progressive nature of the disease. The non-randomized study design, the possible selection of patients, and the small number of recruited patients and drop-out over time hampers to draw meaningful conclusions, warranting further investigation of the effectiveness of an ACP program on patient and proxy outcomes. It could also be argued that the currently used outcomes are not the most suitable for evaluating the impact of an ACP program, as these are influenced by many other aspects such as anti-tumor treatment, cognitive deterioration and societal and environmental factors. Currently, there is no consensus on the optimal outcome measure to evaluate the impact of an ACP program, and it is hypothesized that the

benefits of ACP are mainly related to the relational domain[14]. Perhaps mastery is a more suitable outcome, reflecting the belief that one is able to influence or control life events and that one is competent or effective in managing those events in order to produce desired outcomes[25]. Besides patient-related outcomes, outcomes related to the provided care and quality of care should also considered important, such as health care utilization and the use of anti-tumor treatment in the EOL stage.

Another outcome that was evaluated in this study is satisfaction with care. Overall, patients were satisfied with the provided care over time, whereas proxies were less satisfied. Particularly the exchange of information between healthcare professionals and the provision of information on support services were rated as poor. Provision of information could be enhanced by appointing a dedicated case manager or primary nurse, who could regularly ask patients and proxies about which information is needed[41] and who may facilitate the communication between different healthcare professionals in different settings (e.g. hospital and GP practice). Nevertheless, it should be recognized that in the international RCT described by Korfage et al.[14], but also in other studies[17], ACP did not have an impact on the perceived satisfaction with care. There is evidence though, that patients who participated in ACP conversations were more likely to receive palliative care and were more likely to have their preferences documented[14]. This was also observed in our study, in which most patients did document their wishes, which were also communicated to the GPs. The GPs indicated that these wishes could be met in 72%. It is unknown, however, whether this high rate of documented wishes is due to the ACP program, or due to the fact that this is a highly motivated population. Nevertheless, a previous study in glioblastoma patients has shown that patients who expressed their wishes more often died with dignity[13]. These findings suggest that some aspects of care can be improved with ACP.

Not only glioblastoma patients are affected by the disease and its treatment, but also their proxies. Caregivers are challenged to solve problems and make decisions when care changes, and not all of them are prepared for this[42]. We found that proxies reported significantly lower scores in the physical and mental domains compared to the general population, and a large proportion of proxies reported anxiety and/or depression during the disease course. These results emphasize the impact of the disease on the proxies' functioning and well-being. Over time, some aspects of HRQoL improved for proxies, such as better physical functioning and less bodily pain, suggesting that proxies became better in coping with the situation. We found that the needed level of support was relatively low throughout the disease course, and the level of feelings of caregiver mastery were relatively high. In general, the caregiver burden can be decreased by providing information and concrete advice[42,43], offering guidance[43], improving the communication between patients, proxies and their healthcare professionals[42], and by offering psychosocial support[42]. Several interventions are available to improve the knowledge of patients and caregivers[44], improve the caregivers'

level of social support, e.g. by offering support services[45], or establish caregiver mastery through a psychological intervention[46]. Although we did not find a change in outcomes for proxies over time in this non-randomized prospective study, it is premature to conclude that ACP does not have an impact at all. A previous controlled study in older people did find that relatives who received ACP had less stress, anxiety and depression compared to those that had not[16]. This underlines that a controlled study is needed to draw definite conclusions on the impact of ACP on the well-being of proxies.

In conclusion, the developed disease-specific ACP program is rated as acceptable by patients and proxies, suggesting that its current format is sufficient. Although not designed to evaluate the effectiveness of an ACP program on patient and proxy outcomes, the preliminary results of this feasibility study did not show an impact. To draw definite conclusions on the effect of ACP on outcomes of glioblastoma patients and their proxies, an international follow-study is needed, allowing to investigate cultural influences. Important aspects to consider in such a study are the most optimal design, the primary endpoint and the timing of introduction of an ACP program.

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Supplemental Table 1. Patient scores on the all EORTC QLQ-C30 and QLQ-BN20 scales at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[29]
EORTC QLQ-C30				
Global health status				
Median (range)	67 (0-92)	63 (17-92)	58 (25-92)	
Mean (SD)	62 (27)	60 (23)	55 (22)	78 (17)*
No. of patients	18	14	15	
Physical functioning				
Median (range)	80 (13-100)	87 (20-100)	73 (8-100)*	
Mean (SD)	74 (26)	72 (28)	62 (32)	90 (15)*
No. of patients	18	13	15	
Role functioning				
Median (range)	67 (0-100)	50 (0-100)	83 (0-100)	
Mean (SD)	58 (35)	53 (35)	63 (38)	90 (15)**
No. of patients	18	13	13	
Emotional functioning				
Median (range)	71 (25-100)	88 (33-100)	67 (0-100)	
Mean (SD)	71 (23)	78 (20)	68 (28)	94 (16)**
No. of patients	18	14	15	
Cognitive functioning				
Median (range)	67 (0-100)	75 (0-100)	67 (0-100)	
Mean (SD)	66 (31)	69 (30)	67 (27)	90 (15)**
No. of patients	17	14	15	
Social functioning				
Median (range)	67 (0-100)	67 (0-100)	100 (0-100)	
Mean (SD)	68 (28)	63 (35)	73 (36)	90 (15)**
No. of patients	18	14	15	
Fatigue				
Median (range)	39 (0-100)	50 (22.2-100)	33 (0-100)	
Mean (SD)	48 (29)	52 (26)	43 (31)	17 (20)**
No. of patients	18	14	15	
Nausea and vomiting				
Median (range)	0 (0-33.3)	0 (0-33)	0 (0-100)	
Mean (SD)	8 (12)	6 (11)	20 (32)	2.7 (10)
No. of patients	18	14	15	
Pain				
Median (range)	16.7 (0-67)	0 (0-50)	0 (0-67)	
Mean (SD)	19 (22)	10 (17)	12 (19)	15 (22)
No. of patients	18	14	15	
Dyspnea				
Median (range)	0 (0-67)	0 (0-33)	0 (0-67)	
Mean (SD)	9 (19)	13 (17)	16 (25)	7.1 (17)
No. of patients	18	13	15	
Insomnia				
Median (range)	33 (0-100)	0 (0-100)	33.3 (0-100)	
Mean (SD)	31 (33)	19 (31)	27 (31)	14 (23)*
No. of patients	18	14	15	
Appetite loss				
Median (range)	0 (0-67)	0 (0-100)	0 (0-67)	
Mean (SD)	19 (29)	17 (28)	20 (25)	3.3 (12)*
No. of patients	17	14	15	
Constipation				
Median (range)	0 (0-100)	16.7 (0-67)	33.3 (0-67)	
Mean (SD)	20 (32)	21 (25)	22 (24)	4.8 (14)
No. of patients	18	14	15	

Supplemental Table 1. Continued

	Baseline	Month 3	Last assessment	General population[29]
Diarrhea				
Median (range)	0 (0-67)	0 (0-33.3)	0 (0-33)	
Mean (SD)	9 (22)	5 (12)	7 (14)	3.9 (14)
No. of patients	18	14	14	
Financial difficulties				
Median (range)	0 (0-100)	0 (0-100)	0 (0-100)	
Mean (SD)	19 (31)	24 (33)	20 (30)	3.1 (13)*
No. of patients	18	14	15	
EORTC QLQ-BN20				
Future uncertainty				
Median (range)	33 (8-92)	38 (0-100)	33 (8-100)	
Mean (SD)	39 (25)	43 (28)	42 (26)	N/A
No. of patients	18	14	14	
Visual deficits				
Median (range)	6 (0-100)	22 (0-100)	28 (0-100)	
Mean (SD)	24 (31)	25 (28)	31 (30)	N/A
No. of patients	18	14	14	
Motor dysfunction				
Median (range)	17 (0-78)	11.1 (0-83)	22 (0-67)	
Mean (SD)	23 (24)	25 (29)	21 (20)	N/A
No. of patients	18	14	15	
Communication deficit				
Median (range)	14 (0-100)	22 (0-100)	22 (0-100)	
Mean (SD)	29 (34)	35 (38)	36 (38)	N/A
No. of patients	18	14	15	
Headache				
Median (range)	0 (0-33)	0 (0-33)	0 (0-100)	
Mean (SD)	6 (13)	10 (16)	16 (28)	N/A
No. of patients	18	14	15	
Seizures				
Median (range)	0 (0)	0 (0-33)	0 (0-33)	
Mean (SD)	0 (0)	2 (9)	2 (9)	N/A
No. of patients	18	14	15	
Drowsiness				
Median (range)	0 (0-100)	33.3 (0-100)	33.3 (0-100)	
Mean (SD)	28 (28)	28 (33)	29 (29)	N/A
No. of patients	18	13	14	
Hair loss				
Median (range)	0 (0-100)	0 (0-100)	0 (0-100)	
Mean (SD)	25 (36)	19 (31)	13 (30)	N/A
No. of patients	17	14	15	
Itchy skin				
Median (range)	0 (0-100)	0 (0-67)	0 (0-67)	
Mean (SD)	15 (31)	14 (22)	13 (21)	N/A
No. of patients	18	14	15	
Weakness of legs				
Median (range)	17 (0-100)	0 (0-67)	0 (0-33)	
Mean (SD)	31 (37)	18 (26)	11 (16)	N/A
No. of patients	18	13	15	
Bladder control				
Median (range)	0 (0-100)	0 (0-66.7)	0 (0-100)	
Mean (SD)	19 (31)	14 (22)	21 (31)	N/A
No. of patients	18	13	14	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Supplemental Table 2. Scores on the items of the Carer Support Needs Assessment Tool (CSNAT) at baseline and the 3-month and last assessment

	Baseline	Month 3	Last assessment
1) Understanding your relative's illness			
Median (range)	0 (0-3)	0 (0-3)	0.5 (0-3)
Mean (SD)	0.7 (0.9)	0.5 (0.9)	0.6 (0.8)
No. of proxies	18	13	14
2) Having time to yourself in the day			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.7 (1)	0.3 (0.5)	0.2 (0.4)
No. of proxies	17	12	13
3) Managing your relative's symptoms			
Median (range)	1 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.9 (1)	0.3 (0.5)	0.3 (0.4)
No. of proxies	18	12	13
4) Your financial, legal or work issues			
Median (range)	0 (0-3)	0 (0-2)	0 (0-2)
Mean (SD)	0.7 (1)	0.5 (0.8)	0.5 (0.8)
No. of proxies	18	13	13
5) Providing personal care for your relative			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.4 (0.9)	0.3 (0.5)	0.2 (0.4)
No. of proxies	16	12	12
6) Dealing with your feelings and worries			
Median (range)	1 (0-3)	0 (0-1)	0 (0-2)
Mean (SD)	0.8 (1)	0.5 (0.5)	0.6 (0.8)
No. of proxies	17	11	13
7) Knowing who to contact if you are concerned about your relative			
Median (range)	1 (0-3)	0.5 (0-2)	0 (0-2)
Mean (SD)	1.1 (1.1)	0.8 (0.9)	0.4 (0.9)
No. of proxies	18	12	14
8) Looking after your own health (physical problems)			
Median (range)	0 (0-2)	0 (0-0)	0 (0-1)
Mean (SD)	0.3 (0.7)	0 (0)	0.2 (0.4)
No. of patients	16	10	13
9) Equipment to help take care for your relative			
Median (range)	0 (0-2)	0 (0-1)	0 (0-1)
Mean (SD)	0.6 (0.7)	0.3 (0.5)	0.2 (0.4)
No. of proxies	16	12	13
10) Your beliefs or spiritual concerns			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.3 (0.8)	0.1 (0.3)	0.1 (0.4)
No. of proxies	18	12	14
11) Talking with your relative about his or her illness			
Median (range)	0 (0-3)	0 (0-2)	1 (0-2)
Mean (SD)	0.6 (0.9)	0.4 (0.7)	0.7 (0.8)
No. of proxies	18	12	13
12) Practical help in the home			
Median (range)	0 (0-3)	0 (0-2)	0 (0-1)
Mean (SD)	0.7 (1)	0.2 (0.6)	0.2 (0.4)
No. of proxies	17	12	13

Supplemental Table 2. Continued

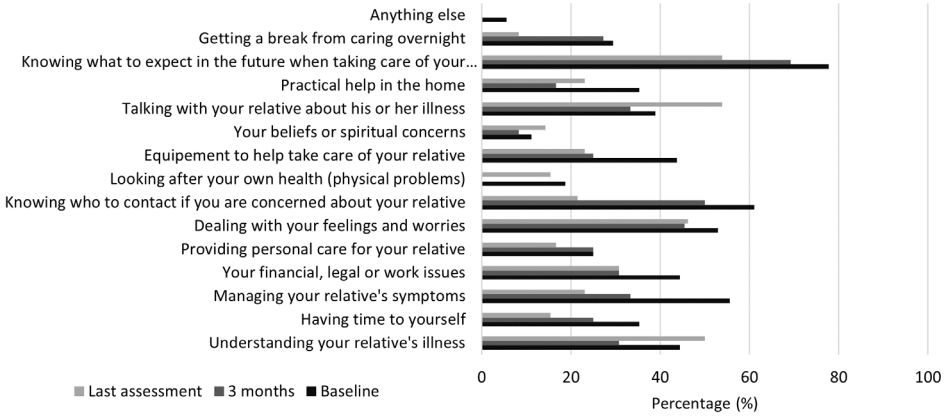
	Baseline	Month 3	Last assessment
13) Knowing what to expect in the future when taking care of your relative			
Median (range)	2 (0-3)	1 (0-3)*	1 (0-3)
Mean (SD)	1.5 (1)	0.9 (0.9)	0.9 (1.1)
No. of proxies	18	13	13
14) Getting a break from caring overnight			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.5 (0.9)	0.3 (0.5)	0.1 (0.3)
No. of proxies	17	11	12
15) Anything else			
Median (range)	0 (0-2)	0 (0-0)	0 (0-0)
Mean (SD)	0.1 (0.5)	0 (0)	0 (0)
No. of proxies	18	5	8
Total CSNAT score			
Median (range)	5 (0-37)	3 (0-14)	3 (0-14)
Mean (SD)	7.7 (9.9)	4.6 (4.5)	4.9 (4.5)
No. of proxies	13	9	11

**p-value<0.05 compared to the baseline score*

Supplemental Table 3. Scores on the different items of the Caregiver Mastery Scale at baseline and the 3-month and last assessment

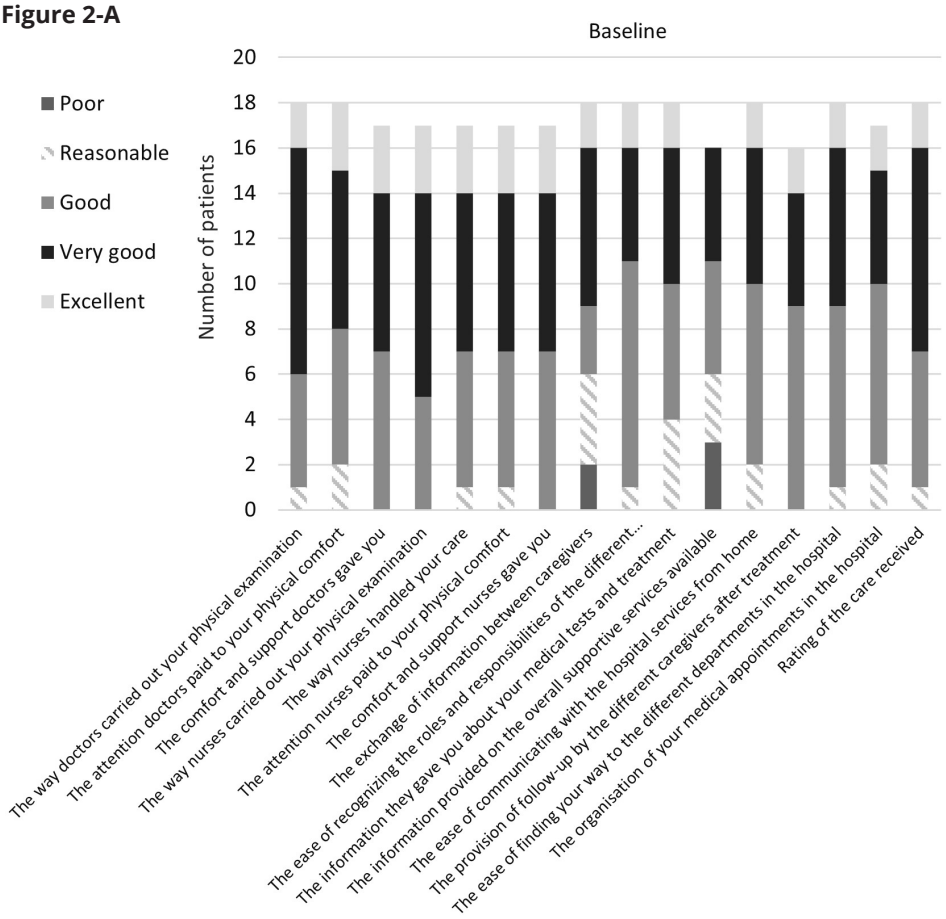
	Baseline	Month 3	Last assessment
1) You are usually certain about what to do in caring for your partner			
Median (range)	2 (1-15)	2 (1-4)	2 (1-4)
Mean (SD)	1.9 (0.9)	0.5 (0.9)	2.1 (1.1)
No. of proxies	18	13	14
2) No matter what you do as a caregiver, it never seems to be enough			
Median (range)	4 (1-4)	4 (1-5)	4 (1-5)
Mean (SD)	3.5 (0.9)	3.9 (1.1)	3.9 (1.1)
No. of proxies	18	13	14
3) In general, you are able to handle most problems in the care of your partner			
Median (range)	2 (1-5)	2 (1-5)	2 (1-5)
Mean (SD)	2.2 (1.1)	2.1 (1.1)	1.9 (1.0)
No. of proxies	18	13	14
4) You are not doing as well as you like as a caregiver			
Median (range)	4 (1-5)	4 (2-5)	4 (2-5)
Mean (SD)	3.7 (1.0)	3.9 (0.7)	3.9 (0.9)
No. of proxies	17	13	14
5) You feel that you have a great deal influence over the things that happen in caregiving			
Median (range)	2 (2-5)	2 (1-5)*	2 (1-5)
Mean (SD)	2.8 (1.1)	2.3 (1.3)	2.6 (1.4)
No. of proxies	17	13	14
6) You belief you are mastering most of the challenges in caregiving			
Median (range)	4 (1-5)	4 (1-5)	4 (1-5)
Mean (SD)	3.4 (1.2)	3.3 (1.3)	3.4 (1.3)
No. of proxies	18	13	14
7) You have lost some control of your life since your partner's illness			
Median (range)	2.5 (1-5)	2 (1-5)	2 (1-5)
Mean (SD)	2.8 (1.2)	2.5 (1.1)	2.4 (1.2)
No. of proxies	18	12	14
Total CMS score			
Median (range)	25 (7-32)	27 (9-33)	26.5 (9-35)
Mean (SD)	24.9 (5.6)	26.2 (6.1)	26.2 (6.5)
No. of proxies	17	13	14

*p-value<0.05 compared to the baseline score



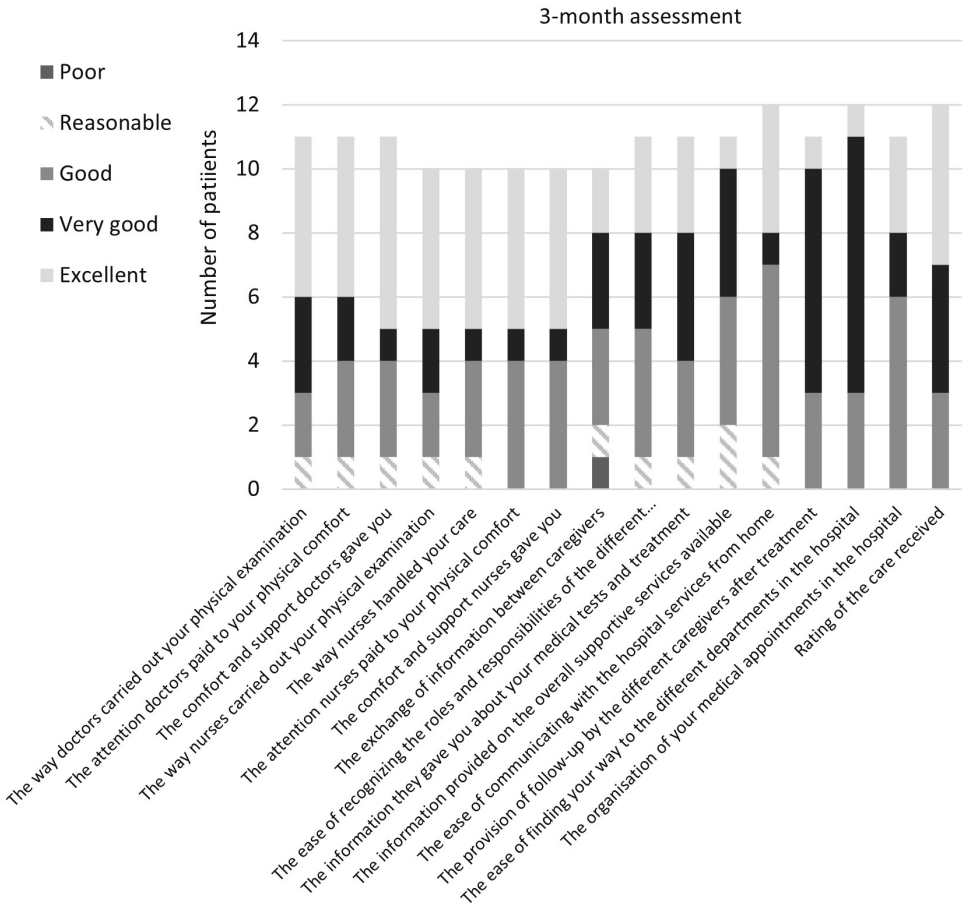
Supplemental Figure 1. The percentage of proxies indicating at least 'a bit more' need in support of different aspects as assessed with the CSNAT

Figure 2-A



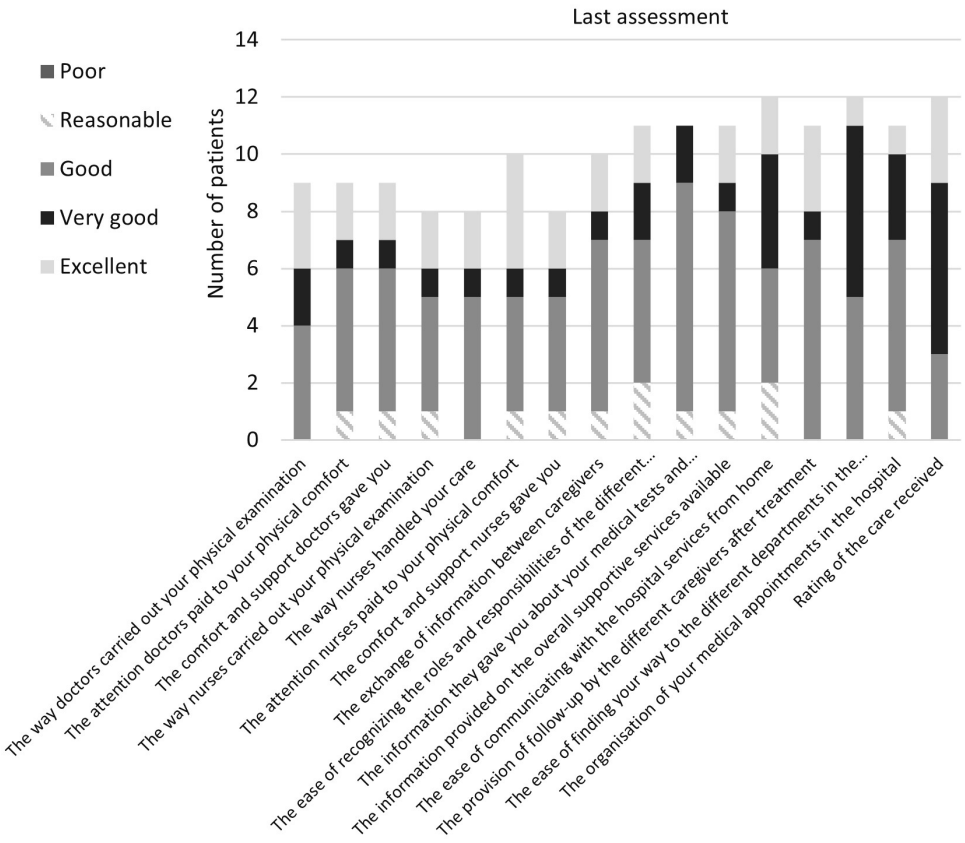
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 2-B



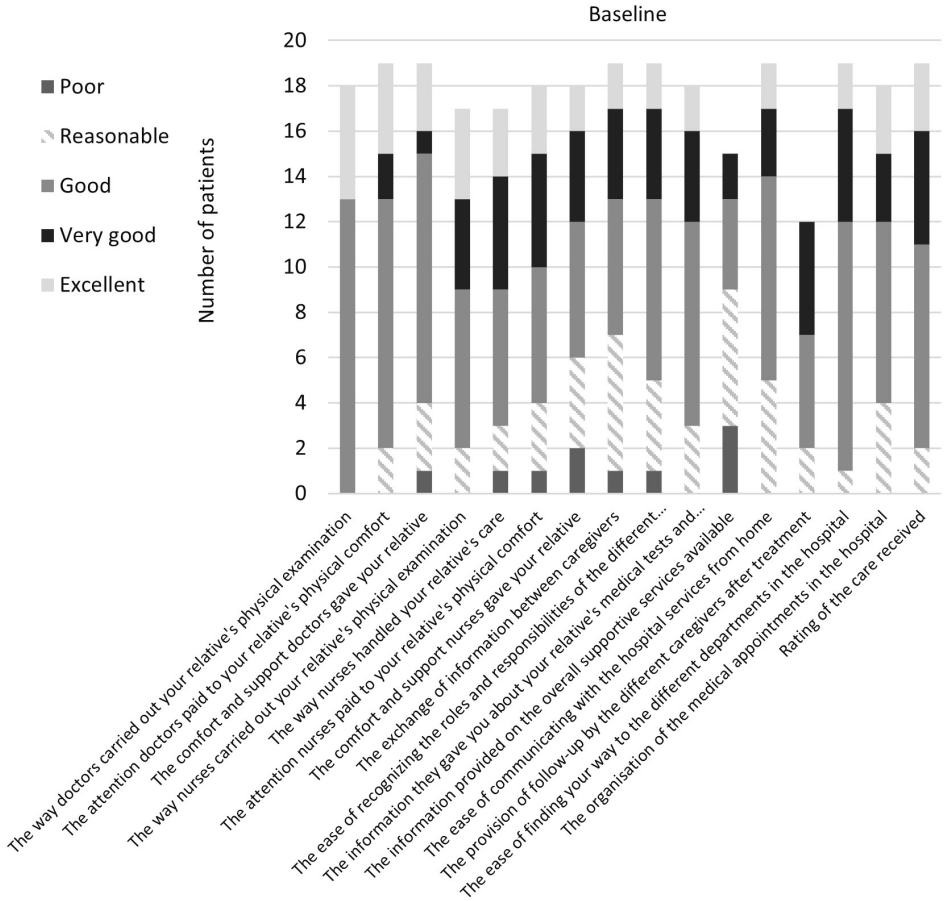
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 2-C



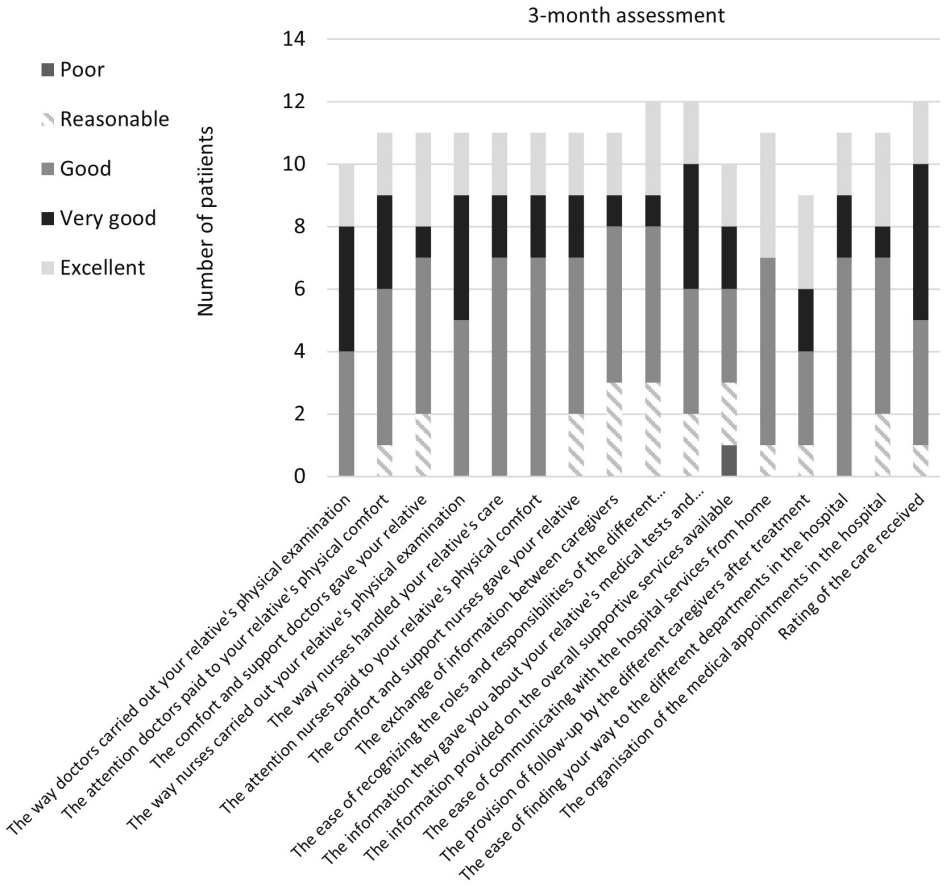
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 3-A



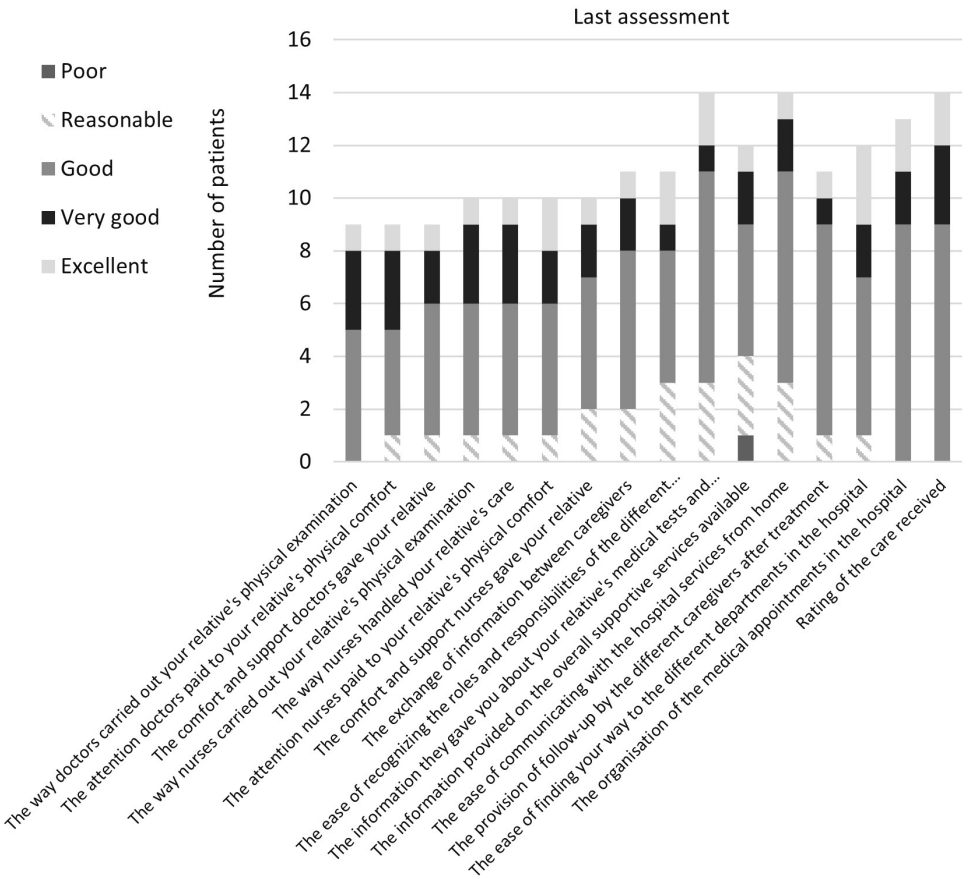
Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Figure 3-B



Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Figure 3-C



Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Supplemental File 1.

Detailed description of the outcome measures

Health-related quality of life

To assess the patients' level of HRQoL, the European Organisation of Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30, version 3.0) and brain cancer module (QLQ-BN20) were used[1-3]. The EORTC QLQ-C30 is a cancer-specific questionnaire comprising 30 items, resulting in five functional scales (physical, cognitive, emotional, role and social functioning), three symptom scales (fatigue, pain, nausea and vomiting), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and a global health status score. The brain-specific QLQ-BN20 comprises 20 items, resulting in four symptom scales (visual disorder, motor dysfunction, future uncertainty and communication deficit) and seven symptoms assessed with a single item (headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs and bladder control). All items are scored on a 4-point Likert scale ranging from 'not at all' to 'very much', except for the items of the global health status score, which are scored on a 7-point Likert scale ranging from 'very poor' to 'excellent'. As specified in the EORTC scoring manual, raw item scores were aggregated and transformed into a linear scale ranging from 0 to 100. A higher score for the functioning scales represents better functioning, while a higher score for symptom scales represents worse functioning or a higher level of symptoms[4]. Differences in mean scale scores of at least 10 points were deemed clinically relevant for scales of the QLQ-BN20[5,6], while scale-specific minimal important differences (MIDs) were available for most of the scales of the QLQ-C30[7].

To assess the proxies' level of HRQoL, we used the Short-Form (SF)-36 questionnaire. This questionnaire consists of 36 items, organized into eight multi-item scales, assessing physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. In addition, the SF-36 yields two higher order component scores, the physical component score (PCS) and mental component score (MCS). A higher score represents better functioning[8]. As no MIDs were available for proxies, we set the MCID for the SF-36 domains also at 10 points, as the majority of reported MCIDs for the different domains were <10 points[9]. For the mental and physical component scales, MCIDs were set at 4.6 points and 3.0 points, respectively[10].

Anxiety and depression

To determine the level of anxiety and depressive symptoms in both patients and proxies, the Hospital Anxiety and Depression Scale (HADS) was used[11]. This

questionnaire comprises 14 items, resulting in an anxiety subscore and depression subscore. The total score ranges between 0 and 21 for each subscale, and a higher score indicates more problems. A score on a subscale ≥8 was considered indicative for borderline anxiety or depression[12].

Caregiver mastery

The Caregiver Mastery Scale was used to assess the level of mastery of the caregiver[13], i.e. the combined effects of the informal caregiver's self-perception and actual ability to successfully perform the activities of providing care. This questionnaire consists of seven statements for which the caregiver can indicate their perception on how well they were able to provide the necessary care. Scores are provided on a 5-point Likert-scale ranging from 'completely agree' to 'not agreeing at all'. Scores for each statement are added and a total score (range: 7-35) is calculated. A higher score indicates less feelings of mastery.

Caregiver support needs

The Care Support Needs Assessment Tool (CSNAT) was used to assess in which areas of need the informal caregiver requires support[14]. The questionnaires consists of 14 domains (i.e. broad areas of need, such as practical help at home or dealing with feelings and worries) in which carers commonly say they require support. All questions are scored on a 4-point Likert scale ranging from 'no', to 'a bit more', 'more' and 'much more' (scores 0-3). Scores on each item are added and a total score (range: 0-42) is calculated. A higher score indicates a higher need of support.

Satisfaction with care

A short-item list was created with items from the EORTC item library[15]. Most items were adapted from the EORTC PATSAT[16], which includes an outpatient module. Items were scored on a 5-point Likert scale ranging from 'bad' to 'excellent'. As specified in the EORTC scoring manual, raw item scores were aggregated and transformed into a linear scale ranging from 0 to 100[4]. A higher score indicates higher satisfaction with care. Both the patient and the proxy completed this questionnaire (see Supplemental File 3 for the selected questions).

Health resource utilization

A study-specific questionnaire (see Supplemental File 4) was created to assess health resource utilization of glioblastoma patients. In this questionnaire, the number (and days) of hospitalizations and consultations with healthcare providers (specialist, general practitioner, other medical providers) was collected, as well as used drug therapy.

Evaluation ACP program

Another study-specific questionnaire (see Supplemental File 5) was used to evaluate the content and structure of the ACP program. The patients and proxies assessed the overall quality of the program, as well as the quality of the facilitator. In addition, the topics and quantity of provided information were evaluated, the number and duration of the ACP sessions, and suggestions to improve the ACP program were requested.

The general practitioner of each patient also received an evaluation questionnaire, in which they also had to rate the timing, topics and quality of the ACP program. In addition, they were asked to indicate if they received an AD of the patient, if they were aware of the wishes of the patient in another way, if they were able to comply with these wishes, and whether the contact with the treating physicians in the hospital was satisfactory.

Patient wishes

To assess patient's wishes with EOL care, information on the number of completed ADs, changes in ADs over time, changes in wishes and preferred place of care/death were collected by the nurse practitioner, based on conversations with the patient during the follow-up period.

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Supplemental File 2.

Questions to measure satisfaction with care (patient version as example)

		Poor	Fair	Good	Very good	Excellent
How would you rate the doctors with respect to:						
1.	The way they carried our your physical examination (took your temperature, felt your pulse, etc.)?	1	2	3	4	5
2.	The attention they paid to your physical comfort?	1	2	3	4	5
3.	The comfort and support they gave you?	1	2	3	4	5
How would you rate the nurses with respect to:						
4.	The way they carried our your physical examination (took your temperature, felt your pulse, etc.)?	1	2	3	4	5
5.	The way they handled your care (gave your medicines, performed injections, etc.)?	1	2	3	4	5
6.	The attention they paid to your physical comfort?	1	2	3	4	5
7.	The comfort and support they gave you?	1	2	3	4	5
How would you rate the services and healthcare organisations with respect to:						
8.	The exchange of information between caregivers?	1	2	3	4	5
9.	The ease of recognizing the roles and responsibilities Of the different caregivers (doctors, nurses, physiotherapists psychologists, etc.) involved in your care?	1	2	3	4	5
10.	The information they gave you about your medical tests and treatment?	1	2	3	4	5
11.	The information provided on the overall support services available (social, psychological, physiotherapy dietitian services, support groups, etc.)?	1	2	3	4	5
12.	The ease of communicating with the hospital services from home?	1	2	3	4	5
13.	The provision of follow-up by the different caregivers (doctors, nurses, physiotherapists, psychologists, etc.) after treatment?	1	2	3	4	5
14.	The ease of finding your way to the different departments in the hospital?	1	2	3	4	5
15.	The organization of your medical appointments in the hospital?	1	2	3	4	5
16.	How would you rate the care you received?	1	2	3	4	5

Supplemental File 3.

Study-specific questionnaire to measure health resource utilization

1) In the last three months, have you contacted your general practitioner?

☐ No

☐ Yes, ☐☐☐ contact(s)

(Please sum all contacts, including contacts by phone)

2) In the last three months, did you have contact with a doctor in the hospital, without being admitted to the hospital?

(Examples of doctors are the neurologist, medical oncologist, neurosurgeon or rehabilitation specialist)

☐ No

	Doctor	Number of contacts
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐

3) In the last three months, have you contacted other healthcare professionals?

(Examples of other healthcare professionals are physiotherapists, occupational therapists, psychotherapists, social workers, alternative medicine practitioners, psychiatrists, or psychologists)

☐ No

	Healthcare professional	Number of contacts
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐

4) In the last three months, have you received half-days or full days treatment for medical / psychological problems? A half-day or full-day treatment can vary from half a day to 5 days a week.

(Please sum all half-days and full days)

☐ No

☐ Yes, namely: ☐☐☐**,**☐☐ day(s)

In what kind of institution did you receive this care?
☐ University hospital
☐ Municipal hospital
☐ Psychotherapeutic institution
☐ Rehabilitation center
☐ Other institution, namely:_____

5) In the last three months, have you been admitted to a healthcare institution?
(This means at least one night in for example a hospital, nursing home, hospice, rehabilitation center)
☐ No
☐ Yes, namely ☐☐☐ times

In what kind of institution did you receive this care?
☐ University hospital
☐ Municipal hospital
☐ Psychotherapeutic institution
☐ Rehabilitation center
☐ Hospice
☐ Nursing home
☐ Other institution, namely:_____

6) In the last three months, did you visit the emergency department?
☐ No
☐ Yes, namely: ☐☐☐ times

Reason: _____
_____
_____
_____
_____

7) In the last three months, have you called the medical team (e.g. general practitioner, doctor in the nursing home or hospice, doctor in the hospital, psychiatrist, psychologist, nurse in the hospital, social worker) for information?
☐ No
☐ Yes, namely ☐☐☐ times

8) In the last three months, have you used medication?
*(Do **not** count the medicines that you received during a hospital stay, and neither count products such as contraception, vitamin supplements or alternative medicines)*

☐ No
☐ Yes, ☐☐☐ namely

Medicin (name or description	Dose*	Number of times a day	Number of days in the past 4 weeks

**If you do not know the dose, you can omit this question*

9) Do you have health insurance?

☐ Basic health insurance
☐ Basic health insurance + additional options
☐ Not insured

Supplemental File 4.

Study specific questionnaire to evaluate the ACP program (patient and proxy version)

1. In your opinion, what is the optimal time during the disease course to introduce the ACP program?
☐ After diagnosis (shortly after the operation)
☐ After chemoradiation (approximately 12-16 weeks after diagnosis)
☐ After 3 adjuvant chemotherapy (approximately 6 months after diagnosis)
☐ After 6 adjuvant chemotherapy cycles (approximately 9 months after diagnosis)
☐ Other, namely: _____
_____
_____
_____

2. How would you rate the quality of the ACP program?

1	2	3	4	5	6	7
Poor			Neutral			Excellent

3. What is your opinion about the topics that are discussed within the ACP sessions?
☐ All important topics are discussed.
☐ Topics are missing, namely: _____
_____
_____
_____

4. Was the ACP program acceptable?

	Very acceptable	Acceptable	Not Acceptable	Not applicable
a) Topics	☐	☐	☐	☐
b) Amount of provided information	☐	☐	☐	☐
c) Number of ACP sessions	☐	☐	☐	☐
d) Duration first ACP session	☐	☐	☐	☐
e) Duration second ACP session	☐	☐	☐	☐
f) Functioning facilitator	☐	☐	☐	☐
g) Other, namely:	☐	☐	☐	☐

5. Were there aspects that you encountered during the ACP sessions which you would suggest to change?

☐ No

☐ Yes, namely: _____

_____

_____

_____

Thank you for completing this questionnaire. Below you can provide additional comments.

_____

_____

_____

_____

_____

_____

_____

_____

_____