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Early Palliative Care for Patients with Glioblastoma: A randomized phase III clinical trial (EPCOG)

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Summary

Background

Positive effects of early integration of palliative care (EIPC) have been shown for systemic solid malignant tumors. We tested the hypothesis that EIPC improves quality of life (QoL), palliative care (PC) problems and mood in glioblastoma patients and reduces caregiver burden.

Methods

This randomized, rater-blinded, controlled trial conducted in six German university medical centers included glioblastoma patients within four weeks after diagnosis (first/recurrent) and their caregivers. Patients received standard care (control) or standard care and EIPC (intervention) for 12 months. Primary outcome was change in QoL after six months measured by the trial outcome index of the FACT-Br. Data were assessed 3-monthly for up to 24 months.

Results

Between 05/2019 and 04/2021 patients were enrolled and randomized to the intervention (n=109) or control group (n=108). QoL at month six was in favor of the intervention, however not statistically significant (mean difference 4·1 with 95%-CI -4·4 to 12·6, p=0·34; intervention: n=98 (m=54/f=44); control: n=89 (m=50/f=39)). In an analysis adjusted for time of death, performed because of a significant survival difference (control superior to intervention, p=0·018), QoL was better in the intervention group (p=0·041). Secondary outcomes showed that patients significantly benefited from EIPC regarding PC problems and mood especially after intervention ended, while caregivers did not seem to benefit.

Conclusion

Provided that the survival difference is included in the analysis, EIPC improves QoL in glioblastoma patients. This, in addition to improved mood and PC problems, demonstrates that EIPC sustainably improves 'how to live' but not ‘length of life’.

Keywords

Glioblastoma, early integration of palliative care, quality of life, caregiver, sustainability

Key Points

- First randomized controlled trial on early palliative care in glioblastoma patients
- Shorter overall survival in the intervention group
- Positive effects on psychosocial, mood, palliative care, and quality of life aspects

Importance of the Study

This is the first randomized controlled trial demonstrating positive effects of EIPC on psychosocial, mood, palliative care (PC), and QoL aspects in glioblastoma patients, which has already been shown for other solid tumor entities. The effects of EIPC in our study persisted beyond the intervention period, but in contrast to other studies survival was shorter in the intervention group. Our results confirm that specialized EIPC affects "how to live" rather than "how long to live" at the end of life, in line with the PC philosophy which also focuses not on prolonging survival but on QoL. Glioblastoma patients have to be informed about their treatment options and need to balance the positive aspects of EIPC against a shorter life expectancy.

Introduction

Patients suffering from glioblastoma have not only a limited survival time with a median survival of 16-21 months,[1] but they also encounter a high symptom burden during disease progression. Their psychosocial, physical and neuropsychiatric symptoms are serious, fast developing, and life-changing, causing also a high burden for their caregivers.[2,3] Here, palliative care (PC) might be helpful in symptom control and enhancing patients´ quality of life (QoL) as well as reducing caregiver burden, especially when applied early in the disease trajectory.[2]

A positive impact of early integration of PC (EIPC) on QoL, mood and psychosocial issues has already been confirmed for systemic solid malignant tumors.[4–7] These studies influenced the guideline of the American Society for Clinical Oncology generally recommending admission to PC within eight weeks after diagnosis for all patients with advanced cancer. The current guideline of the European Association for Neuro-Oncology also recommends EIPC for gliomas.[8] However, in Germany only few glioma patients receive specialized PC at all and when they do, PC is typically delivered at a late disease stage.[9] For glioblastoma patients, beneficial effects of PC in general have been shown in cohort studies,[10,11] but contrary to other malignant tumor entities EIPC has not been tested confirmatory so far in this patient group.

The landmark study of Temel and colleagues on EIPC in non-small cell lung cancer patients found that EIPC can improve QoL and prolong survival.[4] While positive effects of EIPC on patients' QoL have also been confirmed in other RCTs in advanced cancer, effects on survival time differed between studies, reaching from equal to prolonged survival time in the EIPC intervention compared to the control group.[12,13] In studies on (EI)PC, QoL is mostly chosen as primary outcome though it is still a matter of debate whether QoL is an appropriate measurement in PC and end of life (EOL) care.[14,15]

Patients' mood, and symptom intensity[12,13] as well as caregivers' QoL can also be improved by EIPC.[6] Taking the specific symptoms and needs of glioblastoma patients into account, these important aspects should also be considered.

Therefore, the primary objective of our study was to investigate the influence of proactive EIPC on QoL of glioblastoma patients compared to standard care. Patients´ PC needs, depression and anxiety, cognitive impairment, health care use, caregiver burden as well as overall survival (OS) and sustainability were defined as secondary outcomes.

Methods

Study design

This multicenter, randomized, confirmatory, phase III, rater-blinded, parallel-group clinical trial was conducted in six university medical centers in Germany (Departments of Palliative Care and the Departments of Neurosurgery of the University Hospitals of Cologne, Aachen, Bonn (here, additionally Department of Neurooncology), Düsseldorf, Freiburg, and Munich).

The trial was conducted in compliance with the study protocol, the Declaration of Helsinki and Good Clinical Practice and has been approved by each local ethics committee (Cologne, reference 19-1024_7). The study protocol has been published previously.[16]

Patients

Patients were eligible for study participation if they had (i) a newly diagnosed glioblastoma within four weeks of diagnosis, or (ii) a recurrent glioblastoma within four weeks of diagnosis of recurrence. For each patient a caregiving person of special importance for the patients could be included (Table 1, in- and exclusion criteria).

Gender data were collected via self-report by the participants; each of the participants could define themselves as either male or female.

Study participants were enrolled within the neurosurgery/neurooncology department on the ward or in the outpatient clinic via a first eligibility check by the study nurse and a final decision on eligibility as well as study enrollment by the treating neurosurgeon/neurooncologist. Written informed consent was provided by all participants (patients/caregivers).

Randomization and masking

Randomization consisted of two steps: (i) “Montreal Cognitive Assessment (MoCA)[17] - randomization” before baseline assessment to assign predefined MoCA-sequences for each patient; (ii) Randomization of patients and caregivers to the intervention or control group (see Procedures) after completed baseline assessment. A 24/7 readily accessible internet-based tool (ALEA 3.0; ALEA Clinical Services BV, Abcoude, NL) was used by an unblinded team member who informed the participants about their allocation to the trial arm, but was not further involved in data collection or analysis. Patients were assigned to treatment groups (ratio 1:1) according to permuted blocks of varying length. Randomization was stratified by study site, time point of PC intervention (initial diagnosis or recurrence), and caregiver availability (i.e., 24 strata in total). The allocation sequence was created using ALEA.

The researchers responsible for the outcome assessments and the statistician performing the statistical analysis were blinded to the study arm. Study participants were asked not to tell the assessment researchers whether they were in the intervention or control group. The status of the researchers’ blindness was noted after each visit.

Procedures

In the control as well as in the intervention group patients and their caregivers received "optimized" standard care, consisting of regular visits to the neurosurgery/neuro-oncology outpatient clinic every three months (±1 week) as well as treatment and routine assessments following the international guideline standards valid at the time of the study.[18] Optimization of the standard care was achieved by regular assessments of the patients' QoL at each regular clinic visit using the Functional Assessment of Cancer–Brain (FACT-Br) questionnaire.[19] Thereby, primary treating physicians were able to detect and react to patients' current needs in a timelier and more frequent manner, e.g., by initiating already existing PC support also in the control group at any time ("reactive" approach).

In the intervention group patients received specialized PC over a period of 12 months in addition to the optimized standard care in a "proactive" manner, i.e., irrespective of their current needs. PC was provided monthly on a regular and structured basis by a team consisting of a PC physician and a PC social worker (EIPC team). Every 3 months (±1 week) a fixed face-to-face contact with the EIPC team was scheduled at the day of the patients´ visit to the neurosurgery/neuro-oncology outpatient clinic (please see Figure 1 in the study protocol for further details).[16] Moreover, patients were contacted by the EIPC team by telephone every month between the clinic visits. Face-to-face contact could also be replaced by a telephone contact or contact with the caregivers if patients were too ill to come to the clinic or a clinic visit was not possible due to the Covid-19 pandemic. The intervention was strictly provided following a PC manual including the topics pain and symptom management, psychosocial and spiritual support, assistance in treatment decisions like determining treatment goals, advance care planning and support in care planning (details published elsewhere[16]).

Outcome study data were assessed at baseline and then 3-monthly until month 12 during personal meetings at the patient´s home/whereabouts; slightly delayed to the routine clinical visits (within 2 weeks). If patients were not able to speak for themselves (self-assessment) or felt overburdened, caregivers were asked to complete the question forms together with the patients (joint-assessment) or for/instead of the patients (proxy-assessment; proxy-patient perspective). From month 12 onwards, a 3-monthly follow-up assessment was conducted via telephone until month 24 or until death/end of study participation (12 months follow-up to study the maintenance/sustainability of EIPC). Telephone assessments were also possible during the intervention period, when a personal meeting was not possible due to the Covid-19 pandemic.

Outcomes

Primary outcome

The primary objective of the study was to determine the QoL of patients with glioblastoma after six months when receiving proactive EIPC compared to standard care. Patients´ QoL was assessed in each study center by the specific module for brain tumor patients of the FACT (FACT-Br)[19] following Temel and colleagues.[4] Changes in QoL (post value minus baseline) were analyzed by the Trial Outcome Index (TOI, 37 items scored 0-4, range 0-148, high TOI means high QoL) which is the sum of scores on the FACT-Br subscales (brain-specific (Br1-21, NTX6, An10), physical well-being (GP1-7) and functional well-being (GF1-7)) from baseline to six months of treatment.

Secondary outcomes

Following secondary outcomes were included at baseline and months 3-24 (3-monthly, sustainability): Quality of Life (Functional assessment of cancer therapy – Brain (FACT-Br))[19] including its subscores physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), brain-specific subscale (BRCS), FACT-General (FACT-G) and FACT-Br (FACT-G + BRCS); patients' PC needs (Integrated Palliative care Outcome Scale (IPOS-total))[20,21] including its subscores gastrointestinal symptoms (IPOS-GS), physical symptoms (IPOS-PS) and psychological and practical issues, communication (IPOS-PP); patients' depression and anxiety (Hospital Anxiety and Depression scale (HADS-total))[22] including its subscores anxiety (HADS-A) and depression (HADS-D); patients' cognitive impairment (MoCA)[17]; caregiver burden (Zarit Burden Interview, short version (12 questions; ZBI-12-total))[23,24] including the subscores burden (ZBI-burden) and guilt (ZBI-guilt), adapted by Ballesteros and colleagues[25]; health care use (number of procedures and proportion of patients; overall, 90 and 180 days before death) including outpatient care, therapeutic care, diagnostics, inpatient care, medical care and place of death; overall survival (OS) and compliance.

Adverse events were not assessed in this non-AMG/non-MPG clinical trial, since glioblastoma patients' death and worsening in general conditions was expected during the trial. Given the disease course, most glioblastoma patients were expected to die during the study period and it was an explicit aim of the study to examine the outcome development during and after the EIPC intervention compared to the control group until death. Safety was addressed by analyzing a study specific "distress score" every six months which was monitored by an internal trial steering committee (details published elsewhere[16]).

Statistical analysis

In the sample size calculation, an effect size (Cohen's *d*) of 0·5 was assumed for the comparison of the experimental treatment vs. control as previously found by Temel and colleagues.[4] This medium effect size corresponds to a clinically relevant difference of ten points in TOI and about four points for the sum of the FACT-G/Br subscales physical and function.[16] The two-sample *t*-test required 64 patients per treatment group to yield 80% power at two-sided significance level 5% (Stata 14.1, StataCorp, College Station, TX, USA; power twomeans). Thus, cautiously, 128 evaluable patients were needed to complete the trial. Accounting for up to 40% drop-out, 214 patients were needed to be randomized.

The primary analysis set was derived from the modified intention-to-treat (mITT) principle, i.e., including all patients randomized with a valid FACT-Br baseline assessment and at least one further valid FACT-Br assessment. Only these patients could contribute to fitting the outcome model. The primary outcome "change in TOI from baseline to month six" was evaluated by a mixed model for repeated measures (MMRM) with fixed effects 'baseline', 'study site', 'time point of PC intervention' (initial/recurrent diagnosis), 'caregiver availability', 'group', 'time' (visits), and the interaction 'group*time' (ARH1-structured covariance matrix over time) with corresponding marginal means and contrast tests ("pre-specified analysis"). Robustness of results to the missing at random (MAR) assumption was explored by imputation approaches. Specifically, further exploratory (post-hoc) analyses investigated (1) the influence of missing values due to death by stratification according to time of death (3-month-periods, "analysis adjusted for time of death") and (2) the outcomes restricted to patients alive 24 months after study inclusion ("survivors only analysis").[26] The sensitivity to ratings obtained from proxy-, joint- or self-assessments was evaluated. Secondary outcomes (i.e., further time points and measures) were

analyzed along the same lines. Time-to-event (e.g., death or censoring) distributions were summarized by the Kaplan-Meier method and compared by the (stratified) log-rank test and Cox proportional hazards regression. The impact of isocitrate dehydrogenase 1 or 2 (IDH) mutation, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, number of comorbidities, age (years) and surgery (resection/biopsy/no surgery) on survival and the primary outcome (TOI; here, also including tumor localization) was explored.

Analysis of the set of patients essentially observed and treated per protocol (PP) was secondary. This PP-set included all mITT patients with timely six-month (±7 days) FACT-Br assessments. Moreover, patients in the experimental group were required to have completed all scheduled PC appointments. In the following, only mITT will be presented (see supplemental material for PP data). Subgroup analyses were conducted by study site, time point of PC intervention, caregiver availability and gender. Calculations were done with the software SPSS Statistics 28 (IBM Corp., Armonk, NY, USA).

A data monitoring committee was not applicable in this non-AMG/non-MPG clinical trial. However, an internal trial steering committee was monitoring the progress and all procedures of the trial. Upcoming questions were answered by reaching a majority decision.

The study was registered at the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS); Registration number: DRKS00016066.

Results

Participants were enrolled between May 01st, 2019 (first patient in) and April 30th, 2021 (last patient in). The follow-up period was completed on April 30th, 2023 (last patient out). In total, 556 patients were screened for eligibility (Figure 1). Due to a slightly higher drop-out rate than expected (42% instead of 40%) a protocol amendment in February 2021 allowed for enrolling 234 instead of 214 patients. At the end, 231 patients and 197 caregivers were enrolled in the study. 325 patients were ineligible; 143 patients (44%) gave no informed consent, 182 patients (56%) finally did not fulfil all inclusion criteria and therefore could not participate in the trial. Of the 231 enrolled patients, 109 were randomized to the intervention and 108 to the control group. In the mITT population, 98 (intervention group) and 89 (control group) patients were included. The baseline characteristics of the patients as well as caregivers in the two groups were well balanced at baseline (mITT: Tables 2 A & B, PP: Tables S1 & S2).

The hazard ratio for death in the intervention compared to the control group was 1.56 (univariable Cox regression, 95% CI: 1·07 to 2·27, p=0·018), indicating a 56% increase in the hazard of death for patients in the intervention group (within the study period; mITT: Figure 2, PP: Figure S1). The median survival was 14 months in the intervention and 21 months in the control group. The survival benefit of the control group was visible in both, first (p=0·035) and recurrent diagnosis (p=0·28), but statistically significant only in the overall and the initial diagnosis group. Of note, statistically controlling for ‘MGMT and IDH status’ did not alter the effect of the randomized treatment, nor did the addition of ‘study site’, ‘time point of PC intervention’, ‘caregiver availability’, ‘number of comorbidities’, ‘age’ and ‘surgery’.

Overall, 14·6% of the study visits were done by an unblinded assessment researcher. Specifically, for the primary endpoint n=20 assessments (25·6%) in the intervention

and n=7 assessments (10·1%) in the control group were unblinded. We found that unblinded assessment significantly reduced the TOI by 13·2 points (95%CI -20·8 to -5·7, p<0·001) independent of the visits. The treatment difference (intervention vs. control) after six months was 17.3 (95%CI -7.5 to 42.2, p=0.17; unblinded) and 3.8 (95%CI -5.2 to 12.7, p=0.40; blinded).

The rate of proxy-assessments of the FACT-Br ranged between 2·7% - 13·6% for all visits. The rate of joint-assessments was 4·9% - 11·8%. In 87% of assessed outcomes the type of assessment significantly explained variability in the outcome (MMRM, p≤0·05, see Table S3). Moreover, these analyses suggest that QoL, as measured by the TOI, was rated significantly lower when caregivers contributed to the assessment. While this is a noteworthy finding in its own right, our study aims to focus on the patient's perspective. In the following, therefore, only data resulting from self-assessment are presented. Data including proxy- and joint-assessments are presented in the supplemental material (mITT and PP: Tables S5-101, Figures S7-28).

Primary outcome – TOI (mITT)

In all three analyses (pre-specified, adjusted for time of death, survivors only) the change of TOI from baseline to six months (primary endpoint) or any further time point was better (i.e., higher QoL) for the intervention than the control group (Figure 3).

In the pre-specified analysis, these differences were, however, not statistically significant (primary endpoint: estimated marginal mean (EMM) difference 4·1, 95%CI -4·4 to 12·6, p=0·34, Table S4), whereas there was a significant 'group' effect (p=0·041) in the exploratory analysis adjusted for time of death with a significantly higher change of TOI in the intervention group throughout the study (primary endpoint: EMM difference 6·3, 95%CI -2·5 to 15·1, p=0·16). Although QoL also increased

stronger relative to baseline in the analysis including survivors only in the intervention than in the control group, there were no significant group differences (primary endpoint: EMM difference 5·7, 95%CI -7·7 to 19·2, p=0·40).

For the primary outcome (TOI), descriptive (mean, SD, n) and inferential statistics (EMMs, 95% CI, p-value for interaction) for important subgroups are illustrated in Forest plots (Figure 4). In total, an average improvement in QoL in the TOI of 4·1 points (6·3, or 5·8, respectively) favoring EIPC was observed. The change in favor of the intervention was significant in patients with ≥3 comorbidities (p=0·029) and particularly pronounced for women and participants without caregivers, however these changes were not statistically significant.

There was no evidence for any interaction of MGMT- or IDH-status, age, surgery or tumor location with treatment and the direction of the treatment effect remained consistently unchanged in favor of the experimental treatment (not statistically significant).

Secondary outcomes (mITT)

Analyzing the subscores of the FACT-Br scale, the change from baseline in EWB was in favor of the intervention for the pre-specified analysis ('group' effect: p=0·0093) and in the analysis adjusted for time of death ('group' effect: p=0·011). In addition to these within group effects, differences between groups were significant after 15 and 24 months (Figure S2). Patients in the intervention group showed a higher SWB in the analysis including survivors only ('group' effect: p=0·038) as well as improved BRCS for the analysis adjusted for time of death ('group' effect: p=0·018). For the BRCS, the group difference was significant in the analysis adjusted for time of death at the time points 12 and 18 months and after 12 months in the survivors only analysis. There was

no significant group difference between the intervention and the control group in FWB, PWB, FACT-G and FACT-Br. Patients in the intervention group, however, showed a significantly better change from baseline in PWB after three months in the pre-specified analysis and in the analysis adjusted for time of death. FACT-G was significantly higher in the intervention group after three months in the pre-specified analysis and the analysis adjusted for time of death and after 15 months in the survivors only analysis.

PC needs (IPOS-total) decreased significantly in the intervention compared to the control group (meaning fewer palliative symptoms and burden) in all three analyses ('group' effects, pre-specified: p=0·0024; adjusted for time of death: p=0·0009; survivors only: p=0·0014) (Figure S3). In addition to within group effects, IPOS-total scores were significantly lower in the intervention than in the control group after months 6, 9, 18, and 24. The subscores IPOS-GS and IPOS-KS showed no within group effects, whereas there was a significant difference between groups in the IPOS-PP subscore ('group' effects, pre-specified: p≤0·0001; adjusted for time of death: p≤0·0001; survivors only: p≤0·0001). PP issues were significantly less pronounced in the intervention compared to the control group after months 6, 9, 15, 18, and 21 months.

The intervention group showed a stronger decrease from baseline in each HADS score (meaning less psychological symptoms) compared to the control group throughout the study in all three analyses (Figure S4). The HADS-total score showed a significant 'group' effect in the analysis adjusted for time of death (p=0·0051) and in the survivors only analysis (p=0·031), with significantly higher changes from baseline (i.e., lower scores) in the intervention group at month 15 and 24. Anxiety (HADS-A) was also significantly lower in the intervention than in the control group in all three analyses ('group' effects, pre-specified: p=0·045; adjusted for time of death: p=0·012; survivors

only: p=0·045). Patients in the intervention group showed fewer depressive symptoms (HADS-D) than in the control group in the analysis adjusted for time of death (p=0·019). Apart from the within group effects there were significant differences between groups in favor of the intervention group at the time points 15 and 24 months for HADS-A and after 12, 15, and 24 months for HADS-D.

Both groups showed a mild cognitive clinically relevant decline (max. 2 points) throughout the study according to the MoCA without a significant group effect (Figure S5). In the analysis adjusted for time of death, change in cognition was, however, significantly better in the control compared to the intervention group at month 12.

For the caregiver burden (ZBI), both groups showed a slight increase in burden throughout the study with no significant differences between groups (Figure S6).

Whereas ‘baseline’ and ‘time of death’ were always significant in the fixed effects analyses, we found differential effects for ‘time point of PC intervention’, ‘caregiver availability’, ‘study site’, ‘time’, ‘group*time’, and ‘time*time of death’ depending on the outcomes and analysis sets (please see Tables S5-101).

Health care use

In terms of overall health care utilization there were no significant differences between the two groups, except for the mean number of visits to a PC outpatient clinic (PC intervention visits not included), which was significantly higher in the intervention group (p=0·013) (Table S102). The proportion of patients attending a PC outpatient clinic was also significantly higher in the intervention group (p=0·0012), as was the use of physiotherapy services outside the clinic (p=0·0087) (Table S105). In addition, the proportion of patients receiving inpatient PC was significantly higher in the intervention group (p=0·023). Also, a significantly higher proportion of patients in the intervention

group were admitted to a PC unit (p=0·022). In total, 32·65% of the patients in intervention and 26·97% of the patients in the control group received specialized PC independent of the proactive specialized PC service in the intervention group (p=0·40, Table S105). Furthermore, patients in the intervention group had regular proactive specialized PC intervention visits, which were attended in 95·5% of the cases.

To assess whether health care use differed near death, we analyzed total health care use and proportional health care use 180 and 90 days before death. Total health care use was not significantly different between groups (Tables S103-104). However, 180 days and 90 days before death, a significantly higher proportion of patients in the intervention group were admitted to a PC unit (p=0·018, p=0·020; respectively) (Tables S106-107); 90 days before death, a significantly higher proportion of patients in the intervention group attended a PC outpatient clinic (p=0·026) and a significantly lower proportion of patients in the intervention group attended a radiotherapy outpatient clinic (p=0·031) (Table S107).

The place of death was as follows (intervention vs. control group): at hospital n=10 (14·9%) / n=10 (20·8%), home n=20 (29·9%) / n=13 (27·1%), nursing home n=2 (3·0%) / n= 0 (0·0%), inpatient hospice n=16 (23·9%) / n=13 (27·1%), and other/unknown n=19 (28·3%) / n=12 (25·0%). This frequency distribution did not differ by treatment group (p=0·718).

As mentioned above, adverse events were not assessed. Regular analysis of the distress score throughout the intervention period did not indicate a need for early study discontinuation.

Discussion

This is the first RCT to investigate the impact of early specialized PC on glioblastoma patients and their caregivers. Although patients in the intervention group did not benefit in terms of survival time and QoL (TOI) after six months in the pre-specified analysis, EIPC had a multidimensional positive impact on patients with newly diagnosed and recurrent glioblastoma, even beyond the PC intervention period, while caregivers did not benefit in terms of their burden. The clearest effects were seen in relation to emotional, social, psychological and practical/communicative aspects, but also functional, physical and brain-specific factors were positively influenced by EIPC, at least in an analysis adjusted for time of death. Though this was not a pre-specified analysis it was necessary to remove the confounding effect of death as survival was shorter in the intervention group and this type of analysis has been applied before.[27,28]

In contrast to EIPC studies in systemic solid malignant tumors,[4,12,13] there was no evidence of longer or equal life expectancy in the intervention compared to the control group, but it was shorter. One limitation, which may have influenced OS, is that the study was not controlled for more detailed tumor characteristics known to be related to survival (e.g., tumor size and location, extent of resection). Moreover, patients in the control group showing higher OS than expected may have also benefited from the optimized standard care approach in this study in terms of survival, with PC “on demand”. A reason for shorter OS in the intervention group might be that these patients received significantly more PC in addition to the EIPC intervention and were thus likely to be better informed and able to balance potential medical interventions against their remaining life expectancy. Therefore, they may have opted out of therapies such as - according to our data - radiation in the last phase of life. This may consequently lead to shorter survival. One reason for such decisions may be that, given the high value of

autonomy in general, a disease such as glioblastoma with an unavoidable decline of autonomy may lead to the realization that life should not be prolonged as an end in itself. Drawing up a living will and appointing a health care proxy can strengthen these decisive aspects of autonomy, which are an integral part of specialized PC and were one focus of the EIPC intervention. In accordance to our data the retrospective analysis of Pando and colleagues found that PC patients refusing recommended treatment in forms of radiation, surgical intervention or chemotherapy show decreased survival.[29] It should be noted that patients' survival is not the outstanding and only valid goal of PC in any cancer patient, and especially not in highly malignant primary brain tumors with overall short survival and extremely high morbidity including severe neurological disease burden. Rather, the 'how' of survival, which may conflict with existing, culture-dependent hospital strategies of 'doing everything possible', provides an essential alternative perspective for evaluation. The evidence from discrete choice experiments that elicited preferences for PC underscores the vital role of pain control and QoL in PC, showing that patients and proxy respondents prioritized holistic symptom management over additional survival time.[30] Therefore, recent RCTs on PC do not focus on survival any longer.[26] This is a striking difference from other medical specialties, where survival is usually seen as the most important factor and death as a failure, which may be inappropriate.[29] The results of our study emphasize the need to empower patients or their legal representatives to understand the trade-offs between their care options and thus set the stage for selecting options that are consistent with their values and preferences to receive treatment that is beneficial to them.

One special and unique feature of this study was a 12-month long intervention period with an equally long follow-up observation period. It is striking that the observed effects were particularly evident after the intervention had ended, suggesting a long-term

impact. Our patient population benefited most from the EIPC intervention in terms of social, emotional, psychological and practical/communicative issues that are essential for patients with advanced disease and towards the end of life. When adjusting for time of death even physical, functional and brain-specific factors measured by the TOI improved in the intervention compared to the control group. Without this adjustment, dying would presumably be reflected in a reduced QoL, albeit not necessarily so.[31] In retrospect, the question remains whether the TOI focusing on physical and functioning aspects was the appropriate primary outcome for this patient group. For future studies in PC, at least in neurological patients, the primary outcome should rather focus on emotional, social, psychological and practical/communicative aspects. Eligible patient reported outcome measures that could be used here should measure palliative burden, including psychological, emotional, communicative, and practical issues (IPOS, HADS and FACT-Br with its subscores focusing on emotional well-being (EWB) and social well-being (SWB)) which could form an “alternative TOI” focusing on other than functional aspects. QoL measures also ask about some of these aspects, but often prioritize physical functioning, which is usually declining due to the incurable illness.[14] At the same time, it was important for us to invite comparisons with the study by Temel and colleagues.[4] In our study, some of the effects were smaller than in Temel's study. Here, one decisive factor might be the rater-blinded assessments (i.e., 85.4% of assessments) in our study. We found that, in case of unblinding, the difference between study groups in QoL was higher than when the blinding was maintained. Moreover, we have to take into account that in the more than ten years since this study, PC structures and awareness of this approach have grown, and that patients in the control group also had access to PC. In addition, the regular assessment of QoL during neurosurgery/neurooncology visits may have prompted the primary neurosurgeon/neurooncologist to seek additional care if they felt the need. Moreover,

this study was conducted during the COVID19-pandemic, which may have impacted our results and limited the comparability to studies before 2020. While glioblastoma patients´ survival did not seem to differ pre- and post-COVID,[32] QoL as well as other social and emotional factors might have been biased by isolation and lockdowns.[33] Patients in the control group may have benefited more socially from the personal outcome assessments (following a strict hygiene concept) than those in the intervention group who had social contacts despite the COVID-19 pandemic due to the intensive care provided by the EIPC team. This may have led to a less pronounced EIPC effect between groups than expected. Moreover, comparability to international studies is limited due to different health care systems in other countries. PC structures world-wide have evolved during the last years and have also reached an advanced integration in the health care system in Germany. This might have led – in addition to our optimized standard care approach - to less pronounced effects in the intervention group.

A major strength of this RCT was the high enrollment rate and long follow-up period. The latter could be reached through outcome assessments at patients´ whereabouts during the first year. This might have also led to an unexpected high number of self-assessments. A much higher expected number of missing values was the reason for allowing joint- and proxy-assessment in advance. However, although the percentage of joint- and proxy-assessment was low (i.e., <20%), it had a significant impact on results, probably reflecting the high burden on caregivers themselves. Such bias through proxy-assessment underestimating patients´ QoL by caregivers has also been described previously.[34] A finding that should give pause for thought is that caregivers, who accompanied study patients in about 90%, did not appear to benefit from the EIPC intervention –at least according to the ZBI which is in line with previous findings in cancer[35] and neurological patients.[36–38] This seems to contrast with the PC approach

claiming to help both the patient and the caregivers ('unit of care') and/or rather points to the enormous strain of caregivers who may need more specific palliative intervention themselves. In everyday PC, support that is offered by professionals as 'advocates' for patients may not be what caregivers would prefer for patients and themselves from their perspective. This is a dilemma that can aggravate distress. Future research should aim on how to reach caregivers with the PC approach in an appropriate way. Caregivers appear to bear much of the burden of patients, as indicated by the fact that patients without caregivers benefited more from PC as well as women, who were less likely than men to be cared for by a close relative. This last aspect suggests that, in addition to caregivers, gender-specific aspects need to be investigated in more depth. Taken together, our data show that PC offered to glioblastoma patients at an early stage of the disease leads to sustainable and long-lasting positive effects on emotional, social, psychological and practical/communicative aspects during the course of the disease and till the end of life. However, patients with EIPC had a lower survival rate than those in the control group, regardless of factors such as MGMT/IDH, number of comorbidities, age or surgery. The control group had a higher survival rate for both initial and recurrent diagnoses, but this was only statistically significant for the overall and initial diagnosis groups, suggesting that patients with recurrent diagnoses benefit from EIPC without it having a greater impact on survival. However, due to the smaller sample size of patients with recurrent diagnoses, we could not confirm this with absolute certainty. So, when is the best time to integrate specialized PC? This depends on what is most important to the patient: prolonging life or enhancing emotional, social, psychological, practical and communicative well-being. Patients and clinicians must consider these factors when discussing treatment.

Ethics

The trial was conducted in compliance with the study protocol, the Declaration of Helsinki and Good Clinical Practice and has been approved by each local ethics committee (Cologne, reference 19-1024_7). Written informed consent was provided by all participants (patients/caregivers).

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Conflict of interest

HG is co-speaker of the German Society of Neurology (DGN) commission for Neuropalliative Care. UH received speakers and/or advisory board honoraria from Servier, Medac and Bayer. LR is chair of the Board of Directors of the International Association for Hospice and Palliative Care (IAHPC). RR is co-speaker of the physicians´ section of the German Association of Palliative Medicine. RR has received honoraria for scientific counseling services from Grunenthal, Lilly & Company, Tilray Germany and speaker fees from Aristo Pharma, Avextra, Cannamedical, Grünenthal, Hormosan, Tilray Germany. All other authors declare no competing interests.

Authorship

HG, MH, ClB, GB, TB, HC, UH, DM, LR, RR, OS, HV, RV, and RG were responsible for study conceptualization. HG, CN, MH, ClB, GB, ChB, HC, UH, MJ, MN, LR, RR, MS, OS, NT, HV, and RG curated the data. HG, CN, MH, DC, MJ, DM, and WM performed the formal analysis. HG, MH, ClB, GB, TB, HC, UH, DM, LR, RR, MS, OS, NT, HV, RV, and RG were responsible for funding acquisition. HG, CN, IA, ClB, GB, ChB, HC, BH, DHH, UH, BJ, MJ, CHN, MN, LR, MarR, RR, MaxR, MS, OS, JS, NT, HV, LvB, and RG enrolled patients and collected data (investigation). HG, MH, ClB, GB, DC, HC, UH, DM, LR, RR, OS, HV, RV, and RG were responsible for study methodology. HG, CN, TB, BJ, MJ, and RG were responsible for project administration. HG, ClB, GB, HC, UH, DM, MN, LR, RR, MaxR, MS, OS, NT, HV, RV, and RG offered the resources. HG, ClB, GB, ChB, TB, HC, UH, DM, MN, LR, RR, MaxR, MS, OS, NT, HV, and RG supervised the study. HG, MH, ClB, GB, ChB, DC, HC, UH, DM, WM, MN, LR, RR, MaxR, MS, OS, NT, HV, RG validated the data. HG, CN, DC, DM, and WM were responsible for data visualization. HG, CN, MH, DC, DM, and WM wrote the original draft. All authors reviewed and approved the final version of the manuscript. HG, ClB and OS formed the internal steering committee. HG, MH, WM, CN and MJ have accessed and verified the data.

Data sharing

The study protocol is available via open access links. We will grant access to individual participant data (deidentified participant data) including a data dictionary with publication to all requestors, upon written reasonable request sent to heidrun.golla@med.uni-goettingen.de and after approval of a proposal, with a signed data access agreement.

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Figure Captions

Figure 1: Trial profile (mITT), primary endpoint (after 6 months). MoCA = Montreal Cognitive Assessment, OSTC = optimized standard care, control group, PC = palliative care, OSTC+PC= intervention group; miTT (modified intention-to-treat): all patients randomized with a valid FACT-Br assessment at baseline and at least one further valid FACT-Br assessment.

Figure 2: Kaplan-Meier estimates of cumulative overall survival according to treatment group (modified intention-to-treat (mITT) population). Blue = intervention group, grey = control group; HR = hazard ratio.

Figure 3: **Change in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy-Brain (FACT-Br) from baseline (EMM with 95% CI)**. Change = post value (month 3-24) minus baseline value. Higher scores indicating better QoL with respect to physical, functional and brain specific factors, range of TOI 0-148. Blue: intervention, grey: control, EMM = estimated marginal mean, CI = confidence interval.

Figure 4: Forest plot of subgroup results for the primary outcome measure 'Trial Outcome Index' (TOI) with interaction tests. CI = confidence interval; EMM = estimated marginal mean; SD = standard deviation

Table 1

	Patients	Caregivers
Inclusion criteria	• Patients with newly diagnosed glioblastoma (histologically confirmed by biopsy or resection) within 4 weeks of diagnosis **or** • Patients with recurrent glioblastoma within 4 weeks after diagnosis of recurrence (confirmed according to RANO criteria and/or radiological deterioration leading to a change in oncological treatment as indicated by the investigator)	• Caregiving persons (relatives or other closely related persons) of special importance for the patients, i.e., they live with them or have face to face contact with them at least twice a week **Note:** Patients can also be included if no such caregiver exists.
	and	
	• ECOG 0-2* • age ≥ 18 years • ability to understand, read and respond to the German language • ability to give informed consent	
Exclusion criteria	• unwillingness to abide by the protocol • being legally incapacitated • on-going drug abuse or alcohol abuse or a psychiatric condition that, in the opinion of the investigator makes the patient or caregiver unsuitable for study participation • any kind of dependency on the investigator or employed by the sponsor or investigator • held in an institution by legal or official order	

Table 1: Key in- and exclusion criteria.[13] *Eastern Cooperative Oncology Group [ECOG] performance status: Grade 0: fully active, able to carry on all pre-disease performance without restriction; Grade 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; Grade 3: capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; Grade 4: completely disabled; cannot carry on any selfcare; totally confined to bed or chair; Grade 5: dead. Please notice: At the time point of study planning and start of study the new WHO classification (2021) was not yet available, that's why IDH mutant patients could also be included in this study according to the old WHO classification (2017).

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Table 2

Patients	Intervention Group (n=98)	Control Group (n=89)
Sex		
Male	54 (55·1%)	50 (56·2%)
Female	44 (44·9%)	39 (43·8%)
Age (years)	61 (56-70)	59 (55-67)
Time of glioblastoma diagnosis		
First diagnosis	77 (78·6%)	71 (79·8%)
Recurrent	21 (21·4%)	18 (20·2%)
First recurrence	16 (76·2%)	16 (88·9%)
Second recurrence	3 (14·3%)	2 (11·1%)
Third recurrence	2 (9·5%)	0 (0%)
MGMT status		
methylated	46 (46·9%)	45 (50·6%)
unmethylated	47 (48·0%)	41 (46·1%)
n.d.	5 (5·1%)	3 (3·4%)
IDH status		
wild-type	91 (92·9%)	86 (96·6%)
mutant	7 (7·1%)	3 (3·4%)
Glioblastoma localization*		
Parietal	30 (30·6%)	19 (21·3%)
Frontal	33 (33·7%)	26 (29·2%)
Occipital	13 (13·3%)	8 (9·0%)
Temporal	42 (42·9%)	48 (53·9%)
Corpus callosum	4 (4·1%)	3 (3·4%)
Marital status		
Single	9 (9·2%)	6 (6·7%)
Married	76 (77·6%)	70 (78·7%)
Partnership	5 (5·1%)	2 (2·2%)
Separated	2 (2·0%)	2 (2·2%)
Divorced	2 (2·0%)	5 (5·6%)
Widowed	4 (4·1%)	4 (4·5%)
Children		
Yes	74 (75·5%)	72 (80·9%)
n=1	16 (21·6%)	18 (25%)
n=2	40 (54·1%)	39 (54·2%)
n=3	13 (17·6%)	11 (15·3%)
n=≥4	5 (6·8%)	4 (5·6%)
No	24 (24·5%)	17 (19·1%)
Living situation*		
Alone	13 (13·3%)	11 (12·4%)
With partner	81 (82·7%)	73 (82·0%)
With child/children	18 (18·4%)	28 (31·5%)
With parents	3 (3·1%)	1 (1·1%)
With other relatives/friends	0 (0%)	0 (0%)
Shared apartment	0 (0%)	0 (0%)
Nursing home	0 (0%)	0 (0%)
Other	1 (1%)	2 (2·2%)
Highest school-leaving certificate		

Advanced school-leaving certificate (*Abitur)*	31 (31·6%)	29 (32·6%)
Vocational technical diploma (*Fachabitur*)	9 (9·2%)	9 (10·1%)
Intermediate school-leaving certificate (*mittlere Reife*)	32 (32·7%)	26 (29·2%)
Secondary school-leaving certificate (*Hauptschulabschluss*)	19 (19·4%)	20 (22·5%)
Other	7 (7·1%)	2 (2·2%)
None	0 (0·0%)	3 (3·4%)
Advance directive		
Yes	59 (60·2%)	46 (51·7%)
No	39 (39·8%)	43 (48·3%)
Power of attorney		
Yes	58 (59·8%)	56 (62·9%)
No	39 (40·2%)	33 (37·1%)
Caregiver included in study		
Yes	91 (92·9%)	79 (88·8%)
No	7 (7·1%)	10 (11·2%)
Comorbidities*		
Cardiovascular diseases	38 (38·8%)	35 (39·93%)
Bronchopulmonary diseases	18 (18·4%)	12 (13·5%)
Metabolic diseases	30 (30·6%)	21 (23·6%)
Liver or kidney diseases	25 (25·5%)	20 (22·5%)
Infectious diseases	8 (8·2%)	3 (3·4%)
Neurological diseases other than GB	18 (18·4%)	19 (21·3%)
Diseases of the musculoskeletal system	21 (21·4%)	17 (19·1%)
Systemic malignant tumor diseases	13 (13·3%)	12 (13·5%)
Number of comorbidities		
n<3	71 (72·4%)	69 (77·5%)
n≥3	27 (27·6%)	20 (22·5%)

Table 2A: Baseline characteristics of the modified intention-to-treat (mITT) population (patients)

(*Data are n (%) and median (IQR). *Multiple answers possible. IDH= isocitrate dehydrogenase 1 or 2, MGMT= methylguanine DNA methyltransferase)*

Caregivers	Intervention Group (n=91)	Control Group (n=79)
Sex		
Male	38 (41·8%)	28 (35·4%)
Female	53 (58·2%)	51 (64·6%)
Age (years)	60 (54-67)	55 (47-63)
Patients´ relationship to the caregiver		
Partner	73 (80·2%)	59 (74·7%)
Child	4 (4·4%)	7 (8·9%)
Parent	8 (8·8%)	10 (12·7%)
Sibling	2 (2·2%)	1 (1·3%)
Friend	3 (3·3%)	1 (1·3%)
Other	1 (1·1%)	1 (1·3%)
Children		
Yes	76 (83·5%)	60 (75·9%)
No	15 (16·5%)	19 (24·1%)
Living situation*		
Alone	6 (6·6%)	7 (8·9%)
With partner	82 (90·1%)	66 (83·5%)
With child/children	23 (25·3%)	23 (29·1%)
With parents	1 (1·1%)	6 (7·6%)
With other relatives/friends	0 (0·0%)	0 (0·0%)
Shared apartment	0 (0·0%)	0 (0·0%)
Other	1 (1·1%)	1 (1·3%)

Table 2B: Baseline characteristics of the modified intention-to-treat (mITT) population (caregivers)

*(Data are n (%) and median (IQR). *Multiple answers possible.)*

Table 2 clean

Patients	Intervention Group (n=98)	Control Group (n=89)
Sex		
Male	54 (55·1%)	50 (56·2%)
Female	44 (44·9%)	39 (43·8%)
Age (years)	61 (56-70)	59 (55-67)
Time of glioblastoma diagnosis		
First diagnosis	77 (78·6%)	71 (79·8%)
Recurrent	21 (21·4%)	18 (20·2%)
First recurrence	16 (76·2%)	16 (88·9%)
Second recurrence	3 (14·3%)	2 (11·1%)
Third recurrence	2 (9·5%)	0 (0%)
MGMT status		
methylated	46 (46·9%)	45 (50·6%)
unmethylated	47 (48·0%)	41 (46·1%)
n.d.	5 (5·1%)	3 (3·4%)
IDH status		
wild-type	91 (92·9%)	86 (96·6%)
mutant	7 (7·1%)	3 (3·4%)
Glioblastoma localization*		
Parietal	30 (30·6%)	19 (21·3%)
Frontal	33 (33·7%)	26 (29·2%)
Occipital	13 (13·3%)	8 (9·0%)
Temporal	42 (42·9%)	48 (53·9%)
Corpus callosum	4 (4·1%)	3 (3·4%)
Marital status		
Single	9 (9·2%)	6 (6·7%)
Married	76 (77·6%)	70 (78·7%)
Partnership	5 (5·1%)	2 (2·2%)
Separated	2 (2·0%)	2 (2·2%)
Divorced	2 (2·0%)	5 (5·6%)
Widowed	4 (4·1%)	4 (4·5%)
Children		
Yes	74 (75·5%)	72 (80·9%)
n=1	16 (21·6%)	18 (25%)
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Table 2A: Baseline characteristics of the modified intention-to-treat (mITT) population (patients)

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Friend	3 (3·3%)	1 (1·3%)
Other	1 (1·1%)	1 (1·3%)
Children		
Yes	76 (83·5%)	60 (75·9%)
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With parents	1 (1·1%)	6 (7·6%)
With other relatives/friends	0 (0·0%)	0 (0·0%)
Shared apartment	0 (0·0%)	0 (0·0%)
Other	1 (1·1%)	1 (1·3%)

Table 2B: Baseline characteristics of the modified intention-to-treat (mITT) population (caregivers)

*(Data are n (%) and median (IQR). *Multiple answers possible.)*

Fig 1_new

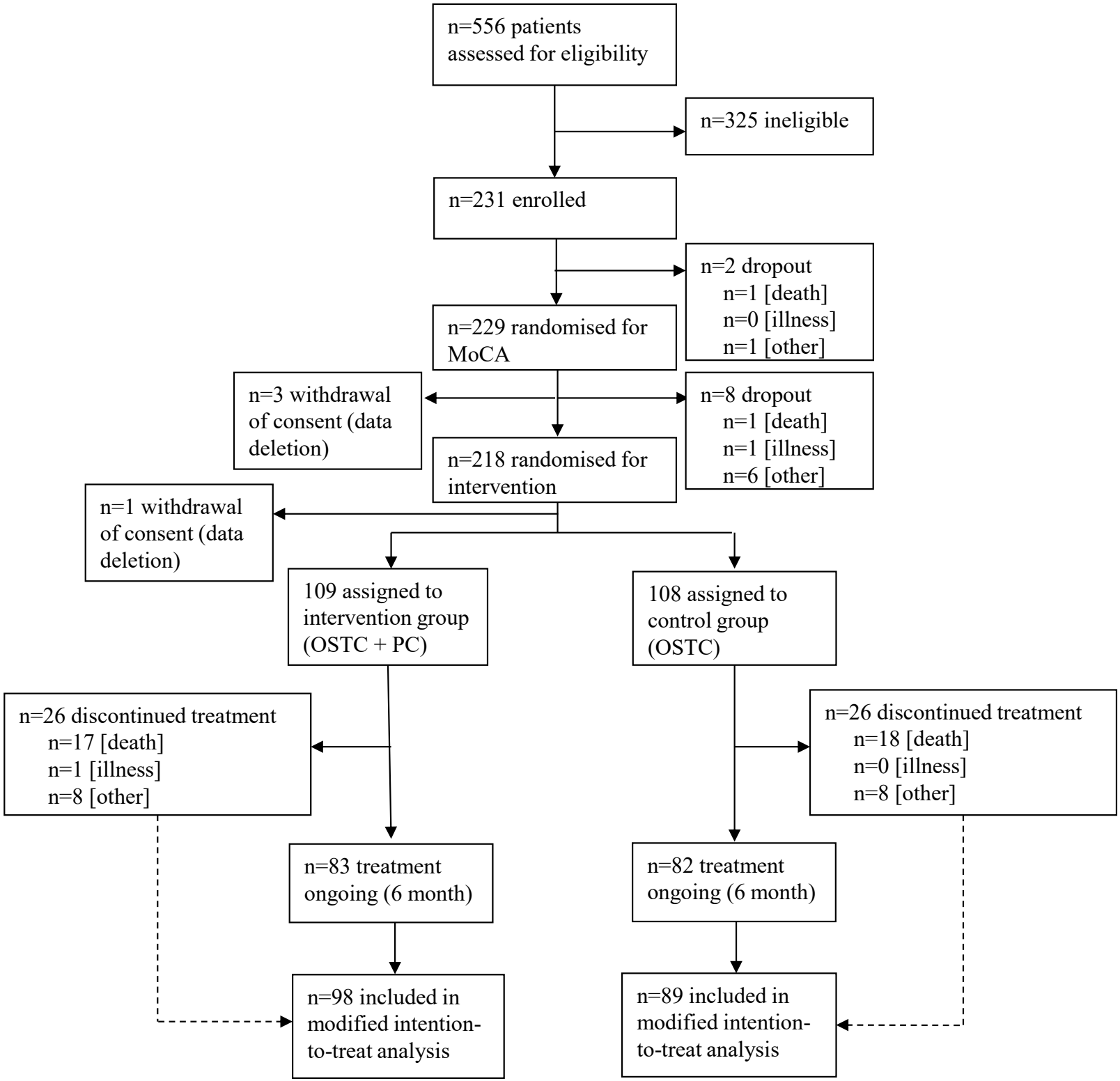
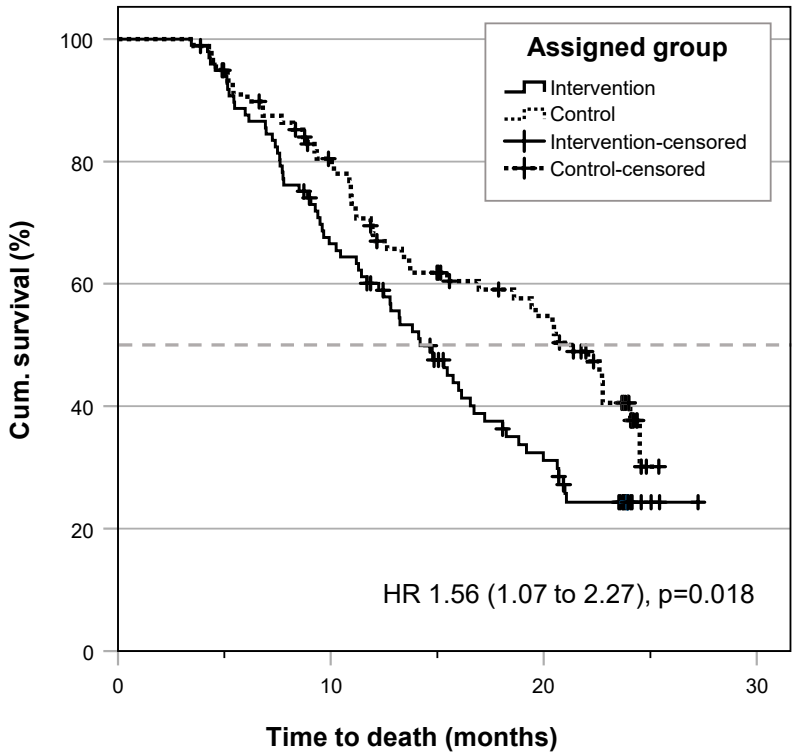


Fig 2_new



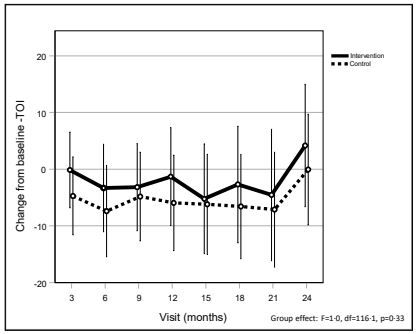
Numbers at risk (censored)

Intervention	98 (0)	91 (2)	62 (2)	40 (5)	24 (3)	3 (16)	0 (3)
Control	89 (0)	83 (1)	66 (6)	47 (5)	38 (4)	1 (27)	0 (1)

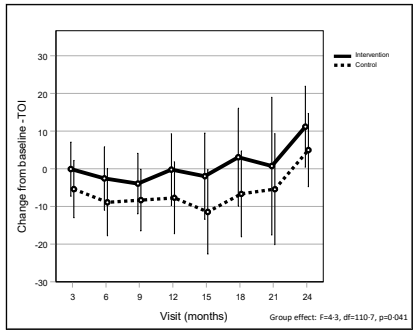
Fig 3_new

TOI

Pre-specified



Adj. for time of death



Survivors only

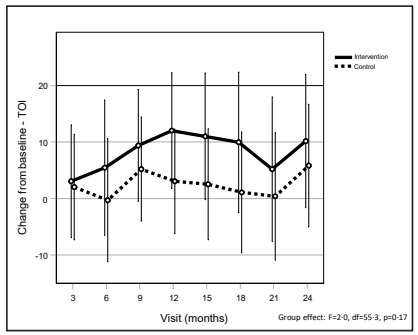


Fig 4_new