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Health-related quality of life of glioblastoma patients receiving post-operative concomitant chemoradiotherapy plus adjuvant chemotherapy: A longitudinal study

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ABSTRACT

Background: Glioblastoma (GBM) is an aggressive primary malignant brain tumour with a dismal prognosis, despite the improvement from the new establishment of post-operative treatment protocol of concomitant chemoradiotherapy (CCRT) plus adjuvant chemotherapy. This study aimed to evaluate the health-related quality of life (HRQoL) in post-operative GBM patients treated with CCRT plus adjuvant chemotherapy with subjective standardised questionnaires at various time points.

Methods: Patients with newly diagnosed GBM who were treated at our centre with post-operative CCRT plus adjuvant chemotherapy were included. Their HRQoL scales were measured with the European Organisation for Research and Treatment of Cancer (EORTC) CLC30 and BN20 questionnaires. Assessments were made before the beginning of post-operative CCRT, and at 0 (within 2 weeks), 3 and 6 months after the end of CCRT. A mixed-level linear model was used to analyse the change in each HRQoL scale over time.

Results: 21 patients were recruited with a median overall survival of 27 months (range:4–55 months). There was no significant change in the global health status over time. An improvement in insomnia and an aggravation in communication deficit were found with statistical significance and clinical meaningfulness. Greater improvement in insomnia was associated with methylated MGMT gene promoter in the tumour while worse aggravation in communication deficit was associated with older age (≥65).

Conclusions: The global health status did not worsen during post-operative CCRT plus adjuvant chemotherapy, while the severity of insomnia lessened and communication deficit worsened. This may provide insight for clinicians to formulate treatment plan for patients with GBM.

1. Introduction

Glioblastoma (GBM) is an aggressive primary malignant brain tumour, with an annual incidence rate of less than 1 per 100,000 population in Hong Kong as the most common subtype of glioma [1]. An imperative improvement in the care for patients with GBM was the establishment of the treatment protocol known as the Stupp regimen: post-operative concomitant chemoradiotherapy (CCRT) plus adjuvant chemotherapy, with temozolomide (TMZ) as the chemotherapeutic agent [2]. Yet, the prognosis is dismal with a short median survival time of 14.6 months among European, Canadian and Australian populations [2], compared to 12.7 months in Hong Kong [3]. The effectiveness of TMZ is variable in every patient where a greater effect is associated with the methylation of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter [4].

With a very limited length of survival, the health-related quality of

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life (HRQoL) becomes important and the goals of care include both improving length of survival and reducing morbidity. However, these goals could be very challenging as the tumour itself could lead to, for example, deficits in cognitive and emotional functioning while these deficits may appear as side effects of treatment [5]. There are a limited number of longitudinal studies on the change in the HRQoL of patients with GBM over the time course of post-operative CCRT and they reported different changes in different aspects of patients' HRQoL [6–10].

This study aimed to evaluate the HRQoL in post-operative GBM patients treated with CCRT plus adjuvant chemotherapy with subjective standardised questionnaires at various time points.

2. Material and Methods

2.1. Patient selection and treatment

Patients were eligible for this observational study if they were diagnosed with histologically confirmed supratentorial GBM between July 2015 and October 2019, underwent surgical resection of the tumour, and planned to receive post-operative CCRT plus adjuvant chemotherapy. This prospective study was carried out in a university teaching hospital in Hong Kong. Those who were diagnosed with infratentorial GBM, did not complete the course of the CCRT plus adjuvant chemotherapy, or submitted only one questionnaire were excluded from this study. This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. All patients gave informed consent.

According to the Stupp regimen, the CCRT administered over 6 weeks comprised radiotherapy of a total dosage of 60 Gy in 30 fractions (given on weekdays in the 6 weeks in our centre) and concurrent chemotherapy of TMZ of 75 mg/m^2/day whenever radiotherapy was given, and the subsequent adjuvant chemotherapy consisted of 6 or more cycles of maintenance TMZ at a dosage of 150–200 mg/m^2/day for 5 consecutive days every 28 days. No other chemotherapeutic agents were prescribed.

All patients received an MRI scan after surgical resection, within 24 h usually and no later than 48 h, for the assessment of the extent of surgical resection and any residual tumour, where these MRI images would serve as the baseline for future comparisons to identify any recurrence. "Total resection" was defined as the absence of any residual contrast enhancement seen on MRI T1-weighted sequence while anything less than total resection would be defined as "subtotal resection".

Patients were assessed with clinical assessments, HRQoL questionnaires and MRI scans at 4 time points, namely before the commencement of CCRT (T1) and at 0 (within 2 weeks), 3 and 6 months after the completion of CCRT (T2, T3 and T4 respectively). At T4, the post-CCRT adjuvant chemotherapy would be completed as well. Other details of treatment and clinical assessments in our institution were described by our group previously [11].

3. Assessment of HRQoL

The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 version 3.0 (QLQ-C30) questionnaire [12] and the additional module for brain cancer (QLQ-BN20) questionnaire [13] were adopted for the assessment of the HRQoL of patients. Both questionnaires are well established with robust psychometric properties for the measurement of the HRQoL in cancer patients [14]. Official translated versions of these questionnaires in traditional Chinese were used.

The EORTC QLQ-C30 is the core questionnaire and contains 30 questions which correspond to several domains of HRQoL: 5 functional scales (physical, role, emotional, cognitive and social functioning), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties), and the global health status. The QLQ-BN20 is a disease-specific questionnaire designed to supplement the core questionnaire. It has 20 questions that represent 11 symptom scales (future uncertainty, visual disorder, motor dysfunction, communication deficit, headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs and bladder control). We followed the instructions provided by the EORTC on converting the raw scores of questions into linear scales ranging from 0 to 100 points, where a higher score refers to the better level of a functioning scale (e.g. cognitive functioning) or the worse severity of a symptom scale (e.g. dyspnoea). A difference of 10 points or more on the scale was recognised as a clinically meaningful change in an aspect of the HRQoL [15].

3.1. Statistical analysis

All analyses were performed using SPSS (version 24) (IBM, New York, the United States). A mixed-effect linear model was conducted for all scales of EORIC QLQ-C30 and BNQLQ BN20. For each run of the model, an HRQoL scale was used as the dependent variable while independent variables included time (T1-T6), age (below 65 years vs 65 years and above), gender, MGMT gene promoter methylation status and use of corticosteroids, as well as the interactions of each with time, with a scaled identity covariance structure for random effects on time and on intercept. Statistical significance was defined as a p-value of less than 0.05. For an HRQoL scale to have significant change over time, both its F-statistics p-value of time and t-statistics p-value of time had to be less than 0.05. If so, the t-statistics of the interaction terms would then be looked into.

4. Results

During the period between July 2015 and October 2019, 21 patients were newly diagnosed with GBM and were admitted to our Department (Table 1). The median overall survival is 27 months (range: 4–55 months). At the time of analysis (July 2020), 11 patients were still alive who had a median overall survival of 39 months (range: 9–55 months) while another 10 patients had passed away with a median overall survival of 14 months (range: 4–31 months).

Compliance rates with HRQoL measurements (the percentage of the number of patients who completed the HRQoL questionnaires over the number of surviving patients) over the post-operative time course (T1-T4) were respectively 85.7% (18/21), 81.0% (17/21), 95% (19/20) and 83.3% (15/18).

Table 2 shows the variations of HRQoL scales over time. The global health status did not show any clinically meaningful change and its change over time lacked statistical significance. Insomnia and communication deficit were the only HRQoL scales with statistical significance

Table 1
Patient characteristics.

Characteristics	N (%, unless otherwise specified)
Total patient number	21
Men	8 (38.1)
Women	13 (61.9)
Age (years) (median[interquartile range])	51 [36.5–61.5]
less than65	17 (81.0)
≥65	4 (19.0)
Tumour location	
Right	14 (66.7)
Left	7 (33.3)
Surgery	
Gross total resection	8 (38.1)
Subtotal resection	13 (61.9)
MGMT gene promoter methylation status (n = 19)	
Unmethylated	10 (52.6)
Methylated	9 (47.4)
Use of corticosteroids	
Yes	9 (42.9)
No	12 (57.1)

Table 2
Mean values (SD) of HRQoL scales over time.

	T1 (n = 18)	T2 (n = 17)	T3 (n = 19)	T4 (n = 15)	p-value of F-statistics of time	p-value of t-statistics of time
EORTC QLQ-C30 global health status and function scales*						
Global health status	57.9 (22.8)	64.7 (18.0)	66.2 (21.2)	66.7 (21.1)	0.511	0.047
Physical functioning	70.7 (28.7)	75.7 (23.6)	75.4 (24.9)	76.4 (24.0)	0.077	0.347
Role functioning	63.9 (33.9)	70.6 (26.7)	74.6 (26.3)	76.7 (25.8)	0.520	0.535
Emotional functioning	78.7 (15.7)	85.8 (14.4)	83.8 (13.7)	76.7 (21.6)	0.453	0.937
Cognitive functioning	75.9 (20.8)	77.5 (18.6)	71.1 (22.1)	71.1 (24.8)	0.230	0.981
Social functioning	67.6 (18.5)	75.5 (20.5)	74.6 (23.8)	81.1 (22.6)	0.474	0.986
EORTC QLQ-C30 symptom scales**						
Fatigue	37.0 (21.9)	20.3 (18.9)	33.9 (25.5)	31.9 (26.2)	0.215	0.601
Nausea and vomiting	11.1 (18.1)	9.8 (19.6)	7.0 (12.8)	5.6 (13.6)	0.586	0.725
Pain	17.6 (21.7)	17.6 (22.4)	20.2 (21.9)	15.6 (16.0)	0.863	0.970
Dyspnoea	13.0 (23.3)	2.9 (11.1)	10.5 (15.9)	13.3 (21.1)	0.601	0.535
Insomnia	33.3 (30.2)	13.7 (20.6)	22.8 (27.3)	24.4 (26.6)	0.027	0.007
Appetite loss	13.0 (23.3)	11.8 (23.4)	19.3 (23.1)	15.6 (21.3)	0.725	0.204
Constipation	20.4 (30.5)	9.8 (15.7)	15.8 (20.4)	22.2 (27.2)	0.318	0.489
Diarrhoea	7.4 (14.3)	5.9 (13.1)	12.3 (16.5)	13.3 (16.9)	0.968	0.177
Financial difficulties	22.2 (22.9)	25.5 (30.1)	33.3 (36.9)	20.0 (27.6)	0.369	0.050
EORTC QLQ-BN20 symptom scales**						
Future uncertainty	16.9 (14.4)	17.6 (15.6)	21.1 (11.2)	18.9 (13.9)	0.720	0.946
Visual disorder	15.4 (20.2)	7.8 (10.9.)	8.8 (11.5)	14.8 (14.3)	0.848	0.554
Motor dysfunction	17.9 (20.9)	10.5 (20.2)	15.8 (25.5)	17.0 (20.1)	0.049	0.056
Communication deficit	11.1 (15.7)	7.8 (12.9)	14.6 (19.6)	23.0 (21.2)	0.001	0.025
Headaches	20.4 (20.3)	21.6 (20.2)	22.8 (25.0)	17.8 (21.3)	0.341	0.585
Seizures	11.1 (28.0)	2.0 (8.1)	3.5 (10.5)	0.0 (0.0)	0.302	0.675
Drowsiness	16.7 (20.6)	19.6 (29.0)	24.6 (26.9)	35.6 (26.6)	0.030	0.828
Itchy skin	22.2 (30.2)	31.4 (32.2)	12.3 (16.5)	13.3 (16.9)	0.731	0.793
Hair loss	18.5 (23.5)	31.4 (32.2)	17.5 (23.2)	17.8 (21.3)	0.312	0.347
Weakness of legs	18.5 (28.5)	19.6 (23.7)	22.8 (29.5)	26.7 (28.7)	0.086	0.349
Bladder control	13.0 (20.3)	3.9 (11.1)	8.8 (26.9)	6.7 (18.7)	0.328	0.216

T1 = before CCRT (baseline); T2 = less than 2 weeks after CCRT; T3 = 3 months after CCRT; T4 = 6 months after CCRT.
*A higher score means the better the global health status or a type of functioning is
**A higher score means the worse a symptom is

in the F-statistics ($p = 0.027$ for insomnia, $p = 0.001$ for communication deficit) and t-statistics ($p = 0.007$ for insomnia and $p = 0.025$ for communication deficit) in the mixed-effect linear model. Insomnia showed a declining trend while communication deficit showed an increasing trend.

The biggest increase in the mean score from baseline was found in drowsiness with a difference of + 18.9 points at T4, but this scale lacks statistical significance. The biggest decrease was found in insomnia with a difference of − 19.6 points at T2. In the insomnia scale, clinically meaningful differences compared to T1 were found at T2 and T3. In the communication deficit scale, that happened at T4. Although clinically meaningful differences from T1 could be found in the mean scores of other scales at various time points, they also lacked statistical significance.

As shown in Table 3, insomnia showed a trend of declining severity (Fig. 1A) while communication deficit showed a trend of increasing severity over time (Fig. 1B).

Patients with methylated MGMT gene promoter in the tumour, compared to those with unmethylated MGMT gene promoter, tended to have greater improvement (greater decrease in score) in insomnia across these time points ($p = 0.010$) (Fig. 2A). For communication deficit, older patients (≥65 years), compared to younger patients (less than65 years), tended to have worse aggravation (greater increase in score) ($p = 0.012$) (Fig. 2B).

5. Discussion

5.1. Comparison with other studies

Our study has shown that there is no statistically significant change in patients' global health status over time but there are statistically significant and clinically meaningful improvement in insomnia and aggravation in communication deficit. Our results are different from other similar studies.

Pollom et al. (2017), with the most similar findings to ours, also reported worsening communication deficit from before CCRT to 12 months after the beginning of CCRT with both statistical significance and clinical meaningfulness among the 30 post-operative patients in the United States [7].

Reddy et al. (2013), conducting a clinical trial on 24 post-operative patients in the United States, revealed that clinically meaningful improvement was observed in insomnia, future uncertainty, motor dysfunction and drowsiness, and clinically meaningful worsening was seen in cognitive functioning, social functioning, appetite loss and communication deficit, but no analysis on statistical significance was carried out (their article defined "significant" as our definition of "clinically meaningful") [8].

Lombardi et al. (2018) conducted a prospective study on 111 post-operative patients in Italy and none of the EORTC HRQoL scales studied, which did not include insomnia, was found to have both statistically significant and clinically meaningful change over time, while emotional functioning improved and the symptoms of itchy skin and hair loss worsened with statistical significance but without a clinically meaningful change in points [6].

Minniti et al. (2013) included 65 elderly patients in their study in Italy, who were treated according to a modified Stupp regimen with a lower dose of radiation, and they reported statistically significant improvement in global health status (by 9.6 points to 6 months after CCRT), social functioning (by 10.4 points to 6 months after CCRT) and cognitive functioning (by 9.5 points to 6 months after CCRT), as well as statistically significant worsening of fatigue (by 5.6 points to 4 months after CCRT), but no significant or meaningful change was found regarding insomnia or communication deficit [9].

Daigle et al. (2013) did not use EORTC questionnaires and concluded that quality of life generally decreased in patients who underwent surgical biopsy but remained stable in patients who underwent craniotomy during the period from before surgery to 3 months after surgery (about 1 month after CCRT) [10].

Table 3
HRQoL scales with statistically significant change over time.

	T1 (n = 18)	T2 (n = 17)	T3 (n = 19)	T4 (n = 15)	p-value of F-statistics of time	t-statistics of time		t-statistics of the interaction of time and gender		t-statistics of the interaction of time and age group		t-statistics of the interaction of time and MGMT promoter methylation status		t-statistics of the interaction of time and use of corticosteroids	
						Estimate (95% confidence interval)	p-value	Estimate (95% confidence interval)	p-value	Estimate (95% confidence interval)	p-value	Estimate (95% confidence interval)	p-value	Estimate (95% confidence interval)	p-value
Insomnia	33.3 (30.2)	13.7 (20.6)	22.8 (27.3)	24.4 (26.6)	0.027	−21.3 (−36.4, −6.1)	0.007	−5.0 (−15.2, 5.2)	0.328	−10.0 (−22.0, 2.1)	0.103	−11.6 (−20.3, −2.9)	0.010	−2.7 (−12.1, 6.6)	0.560
Communication deficit	11.1 (15.7)	7.8 (12.9)	14.6 (19.6)	23.0 (21.2)	0.001	11.8 (1.6, 22.0)	0.025	−1.1 (−7.9, 5.7)	0.751	10.5 (2.4, 18.6)	0.012	1.5 (−7.3, 4.3)	0.609	1.6 (−4.6, 7.9)	0.602

T1 = before CCRT (baseline); T2 = less than 2 weeks after CCRT; T3 = 3 months after CCRT; T4 = 6 months after CCRT.

The global health status in EORTC CLC-Q30 questionnaire is measured by two individual questions respectively about overall health and overall quality of life. Some researchers have argued that the measurement of global health should instead be calculated as a summary score of other scales measured in the questionnaire, but some have suggested that if the intention is to capture the perception of patients about their overall health and quality of life, the global score is suitable [16].

In our study, no significant change in the perception of patients' own overall health and quality of life could be found over the post-operative treatment. None of the aforementioned studies similar to ours showed a statistically significant and clinically meaningful change in global health status, except that the improvement of global health status (by 9.6 points) found in Minniti et al. (2013) almost was considered as clinically meaningful [9].

6. Implications

There are few studies on the HRQoL in brain tumour patients, and even fewer on patients with GBM or non-European populations [17–19]. Our study is the first longitudinal analysis on the HRQoL of patients with GBM treated with surgery and in an Asian population. Our group previously found that the frequency of pseudo-progression in patients with GBM in the Chinese population of Hong Kong was lower than that reported in the literature [20]. This might imply that GBM may have different biological characteristics in different ethnicities.

There is no significant decline in the global health status, so this treatment regimen should be continued as clinical practice.

Insomnia in the forms of sleep disturbance and somnolence could be common in patients with brain tumour [21], particularly among those who have undergone radiotherapy [22]. However, the severity of insomnia decreased over time in our patients. This may be because of the therapeutic effect of TMZ on GBM. The fact that TMZ is more effective in GBM with methylated MGMT gene promoter might be the reason why insomnia was lessened in greater degree in patients with methylated MGMT gene promoter. It has been established that early palliative care starting at the diagnosis of cancer could improve the HRQoL of patients and even their survival [23]. So, the palliative treatment for insomnia in patients with GBM may include early intervention, instead of reducing the dose of TMZ unless it is supported by other factors such as patients' preference. However, there is still a lack of evidence on the benefit of pharmacological interventions in insomnia for brain tumour patients [21].

Communication deficit is a common cognitive symptom among patients with GBM with a prevalence of about 70% in newly diagnosed patients and with a worse severity in recurrent GBM [24]. The elderly patients included in our study showed a worse trend of aggravation of communication deficit than younger patients, as opposed to the aforementioned study conducted by Minniti et al. (2013) on elderly patients treated with a lower dose of radiation that showed no significant change in communication deficit [9]. Such observation may prompt a hypothesis of whether the radiation dose would affect the communication ability of elderly patients. Less communication deficit in the end-of-life phase was found to be an important factor of death with dignity in patients with high-grade brain tumours [25]. Future research may investigate if any adjustment in treatment is beneficial in the end-of-life care for patients with communication deficit.

7. Limitations

Our study has a few limitations. Firstly, this is a single-centre study with small sample size, so it is not possible to include many clinical variables in our statistical analysis, such as tumour location and extent of resection. Secondly, there might be selection bias as the compliance rate never reached 100%. Thirdly, due to the dismal survival of patients with GBM, the survival bias of data collected at later time points could

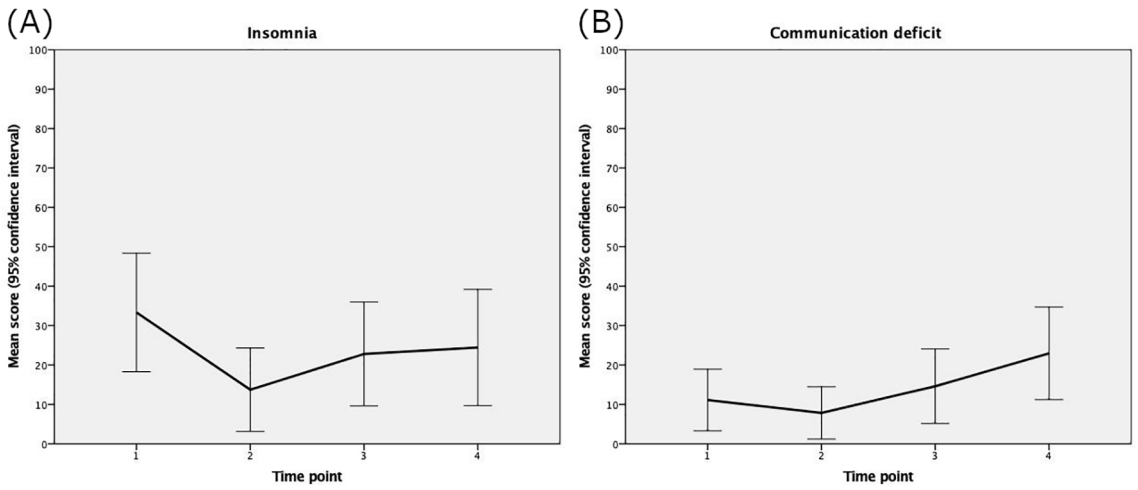

Fig. 1. Mean score of the insomnia scale (Fig. 1A) and that of the communication deficit scale (Fig. 1B) with the error bar representing the 95% confidence interval. T1 = before CCRT (baseline); T2 = less than 2 weeks after CCRT; T3 = 3 months after CCRT; T4 = 6 months after CCRT.

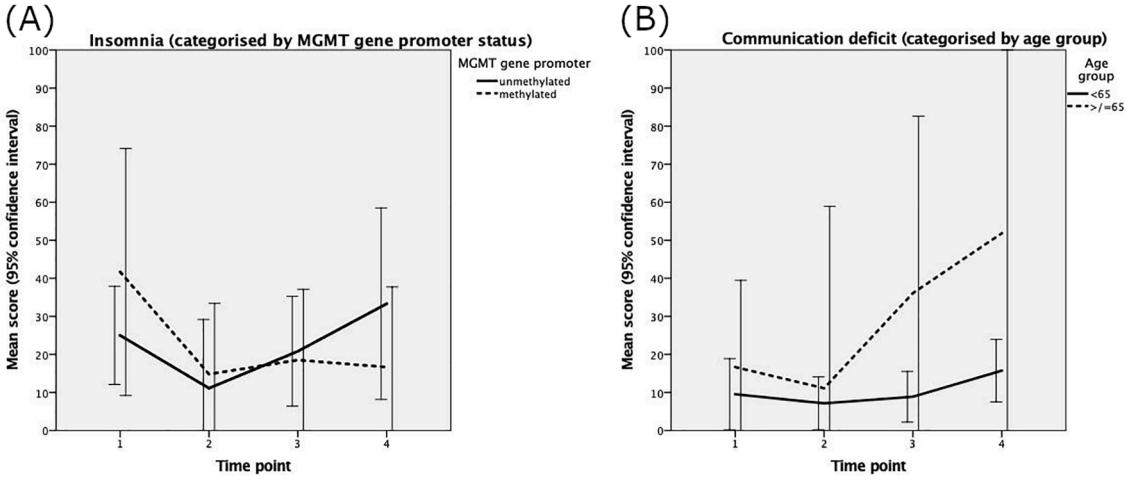

Fig. 2. Mean score of the insomnia scale stratified by the methylation status of the MGMT gene promoter (Fig. 2A) and that of the communication deficit scale stratified by age group of patients (Fig. 2B) with the error bar representing the 95% confidence interval. T1 = before CCRT (baseline); T2 = less than 2 weeks after CCRT; T3 = 3 months after CCRT; T4 = 6 months after CCRT.

be significant. Fourthly, our study did not have a control group, although forming a control group consisting of patients with GBM who are not fit enough to undergo CCRT would lead to selection bias with resultant misleading results.

8. Conclusion

Our study has found that there was no significant change in the global health status in post-operative patients with GBM in the time period from before CCRT to 6 months after CCRT while insomnia was alleviated and communication deficit worsened with statistical significance and clinical meaningfulness. Patients with methylated MGMT gene promoter in the tumour had greater improvement in insomnia over time while those with an age of $\geq$ 65 years had more severe worsening of communication deficit. This may provide insight for clinicians to formulate treatment plan for patients with GBM.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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