Radiological assessment schedule for high-grade glioma patients during the surveillance period using parametric modeling

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Abstract

Background. An optimal radiological surveillance plan is crucial for high-grade glioma (HGG) patients, which is determined arbitrarily in daily clinical practice. We propose the radiological assessment schedule using a parametric model of standardized progression-free survival (PFS) curves.

Methods. A total of 277 HGG patients (178 glioblastoma [GBM] and 99 anaplastic astrocytoma [AA]) from a single institute who completed the standard treatment protocol were enrolled in this cohort study and retrospectively analyzed. The patients were stratified into each layered risk group by genetic signatures and residual mass or through recursive partitioning analysis. PFS curves were estimated using the piecewise exponential survival model. The criterion of a 10% progression rate among the remaining patients at each observation period was used to determine the optimal radiological assessment time point.

Results. The optimal follow-up intervals for MRI evaluations of isocitrate dehydrogenase (IDH) wild-type GBM was every 7.4 weeks until 120 weeks after the end of standard treatment, followed by a 22-week inflection period and every 27.6 weeks thereafter. For the IDH mutated GBM, scans every 13.2 weeks until 151 weeks are recommended. The optimal follow-up intervals were every 22.8 weeks for IDH wild-type AA, and 41.2 weeks for IDH mutated AA until 241 weeks. Tailored radiological assessment schedules were suggested for each layered risk group of the GBM and the AA patients.

Conclusions. The optimal schedule of radiological assessments for each layered risk group of patients with HGG could be determined from the parametric model of PFS.

Key Point

1. Parametric modeling in this cohort study of the data from 277 HGG patients proposed the optimal follow-up intervals for MRI evaluations according to the layered risk groups.

Importance of the Study

Objective evidence and rationale are indispensable to establishing an appropriate follow-up plan. Guidance on scheduling radiological assessments for HGG patients after standard treatment was provided on an

objective basis using parametric modeling of PFS curves. These results can be used for guidance and as a reference by health policymakers as well as in daily clinical practice.

The clinical outcomes of high-grade glioma (HGG) have improved to a certain extent with the establishment of standard treatment over the last decades.¹⁻⁴ Thanks to the current standard treatment protocol of surgical resection followed by concomitant chemoradiotherapy (CCRT) with adjuvant temozolomide (TMZ) for glioblastoma (GBM), the 2-year and 5-year survival rates of patients with GBM have increased from 10.9% to 27.2% and 1.9% to 9.8%, respectively.^{5,6} Patients with World Health Organization (WHO) grade III glioma without 1p/19q codeletions—namely, anaplastic astrocytoma (AA)—were treated with adjuvant radiation therapy (RT) with or without chemotherapy after surgery, which had been the widely accepted treatment protocol in most countries, with a median life expectancy of 32.4 months.⁷ Aside from WHO grade and 1p/19q codeletion, the other well-known prognostic factors in HGG include age, extent of resection, performance status, O⁶-methylguanine-DNA methyltransferase promoter (*MGMT*) methylation, and isocitrate dehydrogenase (*IDH*) 1 or 2 mutation status.⁸⁻¹⁰

Despite the current best standard treatment protocol, disease progression is still inevitable in the majority of patients with HGG. Therefore, an optimal surveillance plan after standard treatment is crucial to providing well-timed intervention.¹¹⁻¹³ Radiologic assessments using MRI are a pivotal part of HGG surveillance to evaluate treatment response and detect disease progression.¹⁴ However, there has been no consensus on the radiological assessment schedule for HGG, although there are crude recommendations from academic societies.^{15,16} The scheduling of radiological assessments is determined even more arbitrarily after the completion of a standard treatment protocol in daily clinical practice. In addition, it is difficult to find evidence appropriate for establishing an optimal radiological assessment schedule that integrates various prognostic factors at the time of treatment completion.

A piecewise exponential model and its variations have been actively used in many medical fields for analyzing time-dependent survival data for the prediction of incidences and hazard rates.¹⁷⁻²¹ The piecewise exponential model adjusts for covariates by prescribing the log hazard ratio to be linear in the covariates and specifies constant baseline hazards in predefined time intervals allowing a complete specification of the estimation of hazard ratios.²² Piecewise exponential distribution has been recognized as a simple and flexible tool in survival analysis and has proven to be valuable in various situations in cancer research.²³

In this study, we converted the progression-free survival (PFS) curve of HGG, starting from the completion of the standard protocol, to a standardized curve using

piecewise exponential survival modeling to fit an even distribution of expected time points with the predetermined regular values of progression rate among the remaining patients at each time point. Additionally, patient groups were subclassified by the existence of a residual tumor and genetic markers to refine the radiological assessment schedule. By doing so, we could propose guidelines for the radiological assessment schedule of HGG patients in different risk groups after standard treatment based on a parametric model of standardized PFS.

Materials and Methods

Study Cohort

A total of 277 HGG patients from a single institute (Seoul National University Hospital) who completed the standard treatment protocol were enrolled in this cohort study. This study was approved by the institutional review board (no. H-2001-126-1096) of Seoul National University Hospital, and data were collected accordingly in a retrospective manner. The study population comprised dichotomic cohorts of GBM ($n = 178$) and AA ($n = 99$). Among 334 patients with newly diagnosed GBM treated with a standard protocol (CCRT with TMZ followed by 6 cycles of TMZ) after surgery between 2008 and 2016, excluded from the analysis were 156 patients (46.7%), because they were not able to complete the standard protocol due to disease progression or loss to follow-up ([Supplementary Figure 1A](#)). On the other hand, among 371 patients with newly diagnosed AA treated with the widely accepted protocol (RT or RT with chemotherapy) after surgery between 1990 and 2016, excluded were 272 patients (73.3%) due to unavailability of the appropriate data, including loss to follow-up, absence of genetic data, (1p/19q codeletion, and *IDH* mutation) or progression during the course of the initial standard treatment protocol ([Supplementary Figure 1B](#)).

The baseline clinical characteristics of the study population are summarized in [Table 1](#). The histological diagnoses were reviewed and confirmed according to the WHO 2016 classification. All the cases were confirmed with essential genetic signature of *IDH* mutation status and no evidence of 1p/19q codeletion for the diagnosis.

Radiological Assessment

The baseline scan of MRI in this study was performed in a month after the completion of standard or standard treatment protocol for GBM and AA. Residual tumor was

Table 1. Baseline clinical characteristics of study population (*n* = 277)

Characteristics	Glioblastoma (<i>n</i> = 178)	Anaplastic Astrocytoma (<i>n</i> = 99)
Age, y		
Median (range)	53 (16–81)	40 (19–72)
Sex, <i>n</i>		
Male	106 (59.6%)	62 (62.6%)
Female	72 (40.4%)	37 (37.4%)
Time of diagnosis to study enrollment, mo		
Median (range)	74 (33–138)	75 (37–184)
Extent of resection, <i>n</i>		
Total	116 (65.2%)	55 (55.6%)
Subtotal/partial	48 (26.9%)	25 (25.2%)
Biopsy	14 (7.9%)	19 (19.2%)
Standard treatment protocol, <i>n</i>		
CCRT/TMZ-TMZ	178 (100%)	0
Radiation therapy only	0	77 (77.8%)
Radiation therapy–chemotherapy	0	22 (22.2%)
Residual tumor after standard treatment, <i>n</i>		
No residual tumor	99 (55.6%)	35 (35.4%)
Residual tumor	79 (44.4%)	64 (64.6%)
MGMT promoter status, <i>n</i>		
Unmethylated	62 (34.8%)	48 (48.5%)
Methylated	114 (64.1%)	47 (47.5%)
Not available	2 (1.1%)	4 (4%)
IDH mutation status, <i>n</i>		
Mutation	27 (15.2%)	66 (66.7%)
Wild type	151 (84.8%)	33 (33.3%)
Karnofsky performance scale*		
100	75 (42.1%)	51 (51.5%)
90	49 (27.5%)	39 (39.4%)
80	14 (7.9%)	4 (4.1%)
70	23 (12.9%)	2 (2.0%)
60	9 (5.1%)	1 (1.0%)
50 or less	2 (1.1%)	0
NA	6 (3.4%)	2 (2.0%)
Follow-up duration,* mo		
Median (range)	10 (1–95)	34 (1–160)
Number of MRI taken*		
Median (range)	6 (2–23)	7 (2–26)
Overall survival state		
Death, <i>n</i>	97 (54.5%)	42 (45.4%)
Median survival,** mo (range)	28 (12–106)	46(8–175)

CCRT, concomitant chemoradiotherapy; TMZ, temozolomide; MGMT, O6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; *after the completion of standard treatment protocol; **from the operation date.

defined by any measurable enhancing lesion in the baseline scan. In most patients, MRI was performed regularly every 2 to 4 months for 2 years after standard treatment, and the interval was extended to every 3–6 months in the subsequent period, depending on the patient's condition and compliance. All radiological data were reviewed and reassessed cross-sectionally based on recent Response Assessment in Neuro-Oncology (RANO) criteria to define the progression of disease.¹⁴ If progression was confirmed in serial MRI assessments, the time of progression was back-dated to the first date that the patient met the criteria for radiographic progression. In this study, PFS was defined as the period from the date of MRI assessment after the completion of standard treatment to the date on which radiological progression was confirmed. The data of patients without events such as disease progression was classified as censored observations at the time of the most recent follow-up. The tumor size was estimated from bidimensional measurements of the longest diameter and its longest perpendicular diameter in the axial plane of T1 enhanced images or T2 images in case of non-enhancing tumors. Clinical symptom during the surveillance period was defined as emergence of new neurologic signs or aggravation of preexisting symptoms described in the medical record.

Parametric Modeling

A piecewise exponential distribution was used to model the standardized PFS curve to determine the optimal intervals for a radiological assessment schedule. A standard exponential distribution assumes a constant hazard function, which means that the instantaneous rate of occurrence of the event does not change over time. If a schedule is determined based on the progression rate among the remaining patients, MRI assessments are implemented in equal time intervals. To establish a more flexible but still scientifically sound assessment schedule, a piecewise exponential distribution is a useful alternative. A piecewise exponential distribution assumes different hazards in predefined time intervals and can reflect changes in the recurrence rate of disease over time. That is, a piecewise exponential distribution is suitable for planning an assessment schedule that varies over time depending on the risk of disease progression. Let $S(t) = P(T > t)$ be the PFS curve, where T is the survival time of a patient, and let $h(t)$ be the hazard function defined as $h(t) = (P(T = t)/P(T > t))$. Then, the hazard function and the corresponding PFS curve of a given piecewise exponential distribution are given as follows. For given knots of survival time $0 = \tau_0 < \tau_1 < \dots < \tau_J = T$, the hazard function is given as

$$\lambda(t) = \lambda_j, \quad \text{if } t \in [\tau_{j-1}, \tau_j)$$

and the corresponding PFS curve is

$$\begin{aligned}
 S(t) &= \exp \left(- \int_0^t \lambda(x) dx \right) \\
 &= \exp \left(- \sum_{k=1}^{j-1} \lambda_k (\tau_k - \tau_{k-1}) - \lambda_j (t - \tau_{j-1}) \right), \\
 &\quad \text{if } t \in [\tau_{j-1}, \tau_j)
 \end{aligned}$$

where $\lambda_1, \dots, \lambda_J$ are constants that represent the hazard in each interval. Note that a piecewise exponential distribution has a constant hazard λ_i within each interval. If the criterion of a 10% progression rate among the remaining patients is used to determine the radiological assessment time point, the interval between 2 consecutive scheduled MRI assessments becomes $-\frac{1}{\lambda_i} \ln(1 - 0.1)$ within each interval. To estimate $\lambda = (\lambda_1, \dots, \lambda_J)$, the maximum likelihood method was used. To determine which decreases the Bayes information criterion (BIC) value the most, the number of knots (J) and the knot location $\tau = (\tau_0)$ were selected by BIC by iteratively adding candidate knots. The group of candidate knots are defined as knots that are obtained by equally dividing the time interval between 0 and the date of the last uncensored observation in each group. The estimated PFS curve has a constant hazard between 2 consecutive chosen knots but has different hazard values for different intervals to reflect that the risk of recurrence of the disease changes over time.

Furthermore, to reflect the effects of the patients' clinical condition on the schedule, the proportional hazards model was used, where the baseline hazard function is a piecewise constant. That is, the hazard function $\lambda(t|z)$ of a patient with a covariate vector z , which includes significant variables for progression of diseases, is given as

$$\lambda(t|z) = \lambda_0(t) \exp(z^T \beta),$$

where $\lambda_0(t)$ is the baseline hazard function, which is assumed to be a piecewise constant.

Statistical Analysis

All statistical analyses were performed using R version 3.6.3 (<http://www.r-project.org>). Kaplan–Meier (K-M) survival analysis was used to estimate PFS. Recursive partitioning analysis (RPA) was performed to stratify the patients into each layered risk group for PFS using the rpart package of R. Variables selected for stratification were those that were significant in reference to previous studies, including the existence of a measurable residual tumor, MGMT, and IDH mutation.^{24–28}

Results

Parametric Model for MRI Schedule in GBM Patients

Among 178 GBM patients who were successfully treated with the standard treatment of CCRT with TMZ followed by 6 cycles of TMZ, 151 patients were IDH wild-type (IDH^{wt} GBM) and 27 patients were IDH mutation (IDH^{mut} GBM). The median number of MRI scans taken after the completion of standard treatment was 6 (range, 2–23) during a median follow-up period of 10 months (range, 1–95 mo).

In the IDH^{wt} GBM group, disease progression occurred in 112 patients (74.2%), with a median PFS from the completion of standard treatment to disease progression of 50 weeks (95% CI: 40–60). Parametric modeling

of the standardized PFS curve of the whole IDH^{wt} GBM group resulted in 2 phases (close and regular follow-up periods) with even distributions of MRI evaluations and an intervening inflection period when the cutoff value of a 10% progression rate among the remaining patients at each observation period was applied. The optimal follow-up interval for MRI evaluations for the entire IDH^{wt} GBM group was every 7.4 weeks until 118 weeks after the end of standard treatment, followed by a 22-week inflection period and every 27.6 weeks thereafter (Figure 1A). An estimated 14% of patients would be progression free after 19 scans and 201 weeks of follow-up, and an open follow-up plan can then be recommended. The MRI evaluation schedule could be refined by stratifying the risk groups using RPA (Supplementary Figure 2A). The IDH^{wt} GBM patients could be classified into 3 risk groups: (i) patients with no residual tumor after standard treatment, (ii) patients with a residual tumor and methylated MGMT promoter, and (iii) patients with a residual tumor and unmethylated MGMT promoter. The same parametric modeling for each of these risk groups showed nice strata of PFS (Supplementary Figure 2B). Using the same cutoff value of a 10% progression rate among the remaining patients at each observation period, the optimal follow-up interval for MRI assessments in patients without residual tumors after standard treatment was every 8.9 weeks until 116 weeks (13 scans) after standard treatment, followed by a 20-week inflection period, and every 31.5 weeks thereafter until 2 scans were acquired (Figure 1B). Patients with residual tumors and methylated MGMT promoters are recommended to undergo MRI assessments every 7 weeks from the end of standard treatment to 120 weeks (17 scans) and every 24.9 weeks until 2 scans are acquired after a 23-week inflection period (Figure 1C). On the other hand, patients with a residual tumor and unmethylated MGMT promoter are suggested to undergo MRIs in intervals of 4.4 weeks up to 118 weeks (27 scans), followed by a 9-week inflection period, and then every 15.4 weeks until 4 scans are acquired (Figure 1D). The expected percentages of progression-free patients after the evaluation period (close and regular follow-up periods), which is 201 weeks after the completion of standard treatment, are 18%, 12%, and 3% for each of the 3 risk groups, respectively. The differences in the time points between the K-M curves and the standard curve at each 10% interval in progression rate among the remaining patients are shown (Supplementary Figure 3).

In the IDH^{mut} GBM group, disease progression occurred in 16 patients (59.3%), with a median PFS from the completion of standard treatment to disease progression of 59 weeks (95% CI: 35–74). Parametric modeling of the standardized PFS curve of the whole IDH^{mut} GBM group resulted in a single phase with even distributions of MRI evaluations. Using the same cutoff value of a 10% progression rate among the remaining patients at each observation period, the optimal follow-up interval for MRI evaluations for the entire IDH^{mut} GBM group was every 13.2 weeks until 151 weeks after the end of standard treatment (Figure 2A). An estimated 30% of patients would be progression free after 11 scans and 151 weeks of follow-up, and an open follow-up plan can then be recommended. If

Fig. 1 (A) Schedule of radiological assessments for all *IDH^{wt}* GBM patients after standard treatment obtained by using a parametric model, with an expected 10% disease progression rate among the remaining patients at each observation period. (B) Radiological assessment schedule model for the *IDH^{wt}* GBM risk group with no residual mass. (C) Radiological assessment schedule model for the *IDH^{wt}* GBM risk group with a residual mass/methylated MGMT promoter. (D) Radiological assessment schedule model for the *IDH^{wt}* GBM risk group with a residual mass/unmethylated MGMT promoter.

we classify the patients into subgroups with or without residual mass, the optimal follow-up interval for MRI assessments in patients without residual tumors after standard treatment was every 13.5 weeks until 81 weeks (6 scans), followed by a 30.2-week inflection period (1 scan), and every 61.4 weeks thereafter until 151 weeks (Figure 2B). Patients with residual tumors are recommended to undergo MRI assessments every 8.2 weeks from the end of standard treatment to 90 weeks (11 scans) and every 37.1 weeks until 151 weeks (Figure 2C). The expected percentages of progression-free patients in the *IDH^{wt}* GBM group by 151 weeks after the completion of standard treatment are 26% and 45% with or without residual tumor, respectively. The differences in the time points between the K-M curves and the standard curve at each 10% interval in progression rate among the remaining patients are shown in Supplementary Figure 4.

To identify a specific subgroup of rapid tumor growth at progression which requires special attention during the surveillance period, we look into the prognostic differences of tumor size and emergence of clinical symptom at progression as surrogate markers for tumor growth rate. We could observe that there were significant differences in OS from the progression time point between groups classified by size and clinical symptom in the *IDH^{wt}* GBM group (Supplementary Figure 5). Among the 112 *IDH^{wt}* GBM patients, patients with tumor size ≥ 3 cm at progression showed significantly worse prognosis in survival compared with patients with tumor size < 3 cm at progression ($P = 0.0011$). Similarly, there was significant difference in OS between patients who had clinical symptoms at progression and who were asymptomatic ($P < 0.0001$). This implies that special attention is needed when there is evidence of rapid growth of tumor such as clinical symptom,

Fig. 2 (A) Schedule of radiological assessments for all *IDH^{mut}* GBM patients after standard treatment obtained by using a parametric model, with an expected 10% disease progression rate among the remaining patients at each observation period. (B) Radiological assessment schedule model for the *IDH^{mut}* GBM risk group with no residual mass. (C) Radiological assessment schedule model for the *IDH^{mut}* GBM risk group with a residual mass.

and modulation in MRI scan schedule should be taken into consideration.

Parametric Model of the MRI Schedule in AA Patients

In 99 AA patients who completed RT with or without chemotherapy, the median number of MRI scans taken was 7 (range, 2–26) during a median follow-up period of 34 months (range, 1–160 mo). A total of 66 patients had mutated *IDH* (*IDH^{mut}* AA group), while 33 patients had wild-type *IDH* (*IDH^{wt}* AA group).

Parametric modeling of the standardized PFS curve for the whole *IDH^{wt}* AA group resulted in a single phase of regular follow-up, with the cutoff value of a 10% progression rate among the remaining patients. The optimal follow-up interval for MRI evaluations of the entire *IDH^{wt}* AA group was every 22.8 weeks until 241 weeks after the end of standard treatment (Figure 3A). An estimated 33% of patients would be progression free after 10 scans and 241 weeks of follow-up, and an open follow-up plan can then be recommended. MRI evaluation schedule could be refined by stratifying the patients into risk groups according to the existence of residual tumor. The optimal follow-up intervals for MRI assessments in the *IDH^{wt}* AA group with residual tumor is every 16.9 weeks until 241 weeks (14 scans) after the standard treatment (Figure 3B). Patients in the *IDH^{wt}* AA group without residual tumor are recommended to undergo MRI assessments every 51.9 weeks from the end of standard treatment to 241 weeks until 4 scans are acquired (Figure 3C).

The entire *IDH^{mut}* AA group suggested performing 5 MRI scans during the surveillance period of 241 weeks in intervals of 41.2 weeks (Figure 3D). An estimated 54% of patients would be progression free after 241 weeks of follow-up, and an open follow-up plan can then be recommended. The *IDH^{mut}* AA group with residual tumor are suggested to

undergo 8 scans of MRIs in intervals of 29.2 weeks up to 241 weeks (Figure 3E). And the *IDH^{mut}* AA group without residual tumor are suggested to undergo only 2 scans of MRIs in intervals of 89.8 weeks up to 241 weeks (Figure 3F). The expected percentages of progression-free patients after the evaluation period (regular follow-up periods) were 42% in the *IDH^{mut}* AA group with residual tumor and 75% in the *IDH^{mut}* AA group without residual tumor at 241 weeks after the completion of standard treatment, respectively. The differences in the time points between the K-M curves and the standard curve at each 10% interval in progression rate among the remaining patients are shown in Supplementary Figure 6.

The parametric modeling results of the MRI evaluation schedule for GBM and AA are summarized in Figure 4A. For easy application in clinical practice, the results have been simplified to round numbers for a schedule and are provided in the form of a guideline chart (Figure 4B).

Discussion

Patients diagnosed with HGG remain at a high risk of disease progression even after a complete event-free course of standard treatment. Accordingly, there is an undeniable need for continuous radiological evaluations over the long term, but little evidence exists to support the optimal frequency and intervals of MRI assessments.^{11,29} There is a strong demand for evidence-based protocols for optimal radiological assessments after standard treatment for HGG patients. The ideal radiological assessment schedule should be able to detect disease progression in time without losing undetected patients while minimizing unnecessary tests for the sake of cost-effectiveness. Therefore, tools that can predict the frequency and timing of disease progression are pivotal in determining

Fig. 3 (A) Schedule of radiological assessments for all IDH^{wt} AA patients after standard treatment obtained by using a parametric model, with an expected 10% disease progression rate among the remaining patients at each observation period. (B) Radiological assessment schedule model for the IDH^{wt} AA risk group with residual mass. (C) Radiological assessment schedule model for the IDH^{wt} AA risk group with no residual mass. (D) Radiological assessment schedule model for all IDH^{mut} AA patients. (E) Radiological assessment schedule model for the IDH^{mut} AA risk group with residual mass. (F) Radiological assessment schedule model for the IDH^{mut} AA risk group with no residual mass.

A

Fig. 4 (A) Summary of the optimal radiological assessment schedule with an expected 10% disease progression rate among the remaining patients with HGG based on the parametric model. (B) Simplified guidance on the schedule of optimal radiological assessments for HGG patients according to risk group.

optimal radiological assessment schedules. The standardized PFS curve generated by parametric modeling can be an apt tool for such purposes. We set a criterion of a 10% progression rate among the remaining patients at each observation period to determine the optimal radiological assessment time points. This criterion may be

adjusted and applied to the same standardized PFS curve to accommodate diverse circumstances in medical practice. To place the schedule within the context of the various situations and any desired cutoff value, we opened the R script for the piecewise exponential survival model calculation ([Supplementary Material 2](#)) with a sample

Fig. 4 Continued

dataset of *IDH^{mut}* GBM group used in the present study (Supplementary Material 3).

The radiological assessment schedule based on the parametric model has some differences from the previously recommended guidelines. The National Comprehensive Cancer Network guidelines suggest that radiological assessments for HGG should begin 2–8 weeks post-RT, with brain MRI scans repeated every 2–4 months for 3 years, and subsequently decreasing to every 3–6 months for the survival period.³⁰ On the other hand, the European Society for Medical Oncology guidelines recommend a simple schedule of 3-month intervals for radiological assessments after standard treatment for most patients with HGG, whenever feasible.¹⁵ However, our study provides more sophisticated MRI assessment schedules for HGG according to the risk groups. The key feature of all the models in this study is the definition of a regular follow-up period. In general, the risk of disease progression and hazard of death were not constant over time in HGG but instead usually improved with time.^{2,31,32} For this reason, more frequent assessments are required in the early phase of the disease. The close follow-up periods after the completion of standard treatment in our study are approximately 118 weeks for *IDH^{wt}* GBM, 151 weeks for *IDH^{mut}* GBM, and 241 weeks for all AAs. These numbers roughly correspond to 3 or 4 years for GBM and 5 years for AA after the initial operation. For *IDH^{wt}* GBM, there were few differences in the recommended MRI schedules among risk groups except for *IDH^{wt}* GBM patients with a residual mass and unmethylated MGMT promoter, as these patients need more frequent scans than the other groups. If we compare the parametric model and K-M model of PFS for GBM, delays in the parametric model were observed in the late phase except for the *IDH^{wt}* GBM group with residual mass and unmethylated MGMT, which harbors delays in the middle of a close observation phase

(Supplementary Figure 3). Therefore, careful consideration is needed, especially for the phases with possible delayed exams, to see whether these discrepancies negatively impact the reliability of the current model. There are other limitations to this study. The number of patients in some risk groups may not be sufficient to draw stable results, which can give rise to under- or overestimations of the actual incidence of disease progression. Additionally, we cannot suggest a long-term follow-up plan for the open follow-up period. Indeed, there are patients with HGG who develop disease progression after a disease-free duration, but long-term follow-up is beyond the prediction range of the current model. The model resulting from the current study is based on a selective group of patients with favorable prognosis, since they were able to successfully complete standard or standard treatment protocols. Therefore, the recommendations cannot be generalized to all HGG patients and must be applied to the patients who fit the criteria during the surveillance period.

Conclusions

We successfully built a standardized parametric model for predicting the progression of HGG patients after standard treatment. Using these standardized PFS curves, optimal guidance was provided on scheduling radiological assessments for each layered risk group. Our results highlight the objective rationale for establishing optimal assessment schedules in HGG patients. These results can be used for guidance and as a reference by health policymakers as well as in daily clinical practice to secure the reasonable recommendations considering cost-effectiveness.

Supplementary Material

Supplementary data are available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

Keywords

follow-up | glioblastoma | high-grade glioma | MRI schedule | parametric model

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References

- van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol*. 2006;24(18):2715–2722.
- Tykocki T, Eltayeb M. Ten-year survival in glioblastoma: a systematic review. *J Clin Neurosci*. 2018;54:7–13.
- Anderson E, Grant R, Lewis SC, Whittle IR. Randomized phase III controlled trials of therapy in malignant glioma: where are we after 40 years? *Br J Neurosurg*. 2008;22(3):339–349.
- Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet*. 2002;359(9311):1011–1018.
- Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
- Stupp R, Hegi ME, Mason WP, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459–466.
- Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol*. 2013;31(3):337–343.
- Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol*. 2006;7(5):392–401.
- Christians A, Adel-Horowski A, Banan R, et al. The prognostic role of IDH mutations in homogeneously treated patients with anaplastic astrocytomas and glioblastomas. *Acta Neuropathol Commun*. 2019;7(1):156.
- Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997–1003.
- Monroe CL, Travers S, Woldu HG, Litofsky NS. Does surveillance-detected disease progression yield superior patient outcomes in high-grade glioma? *World Neurosurg*. 2020;135:e410–e417.
- Birk HS, Han SJ, Butowski NA. Treatment options for recurrent high-grade gliomas. *CNS Oncol*. 2017;6(1):61–70.
- Azoulay M, Santos F, Shenouda G, et al. Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. *J Neurooncol*. 2017;132(3):419–426.
- Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. *J Clin Oncol*. 2010;28(11):1963–1972.
- Stupp R, Brada M, van den Bent MJ, Tonn JC, ESMO Guidelines Working Group. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(Suppl 3):iii93–101.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Tumors (Version 3.2020). 2020.
- Heser K, Fink A, Reinke C, Wagner M, Doblhammer G. The temporal association between incident late-life depression and incident dementia. *Acta psychiatrica Scandinavica*. 2020;142(5):402–412.
- Sun Z, Niman SM, Pagani O, et al; POSITIVE Steering Committee. Estimation of historical control rate for a single arm de-escalation study—application to the POSITIVE trial. *Breast*. 2020;53:1–7.
- Qin N, Wang Z, Liu Q, et al. Pathogenic germline mutations in DNA repair genes in combination with cancer treatment exposures and risk of subsequent neoplasms among long-term survivors of childhood cancer. *J Clin Oncol*. 2020;38(24):2728–2740.
- Dieffenbach BV, Li N, Madenci AL, et al. Incidence of and risk factors for late cholecystectomy in survivors of childhood cancer: a report from the childhood cancer survivor study. *Eur J Cancer*. 2020;133:4–13.
- Chemaitilly W, Liu Q, van Iersel L, et al. Leydig cell function in male survivors of childhood cancer: a report from the St Jude lifetime cohort study. *J Clin Oncol*. 2019;37(32):3018–3031.
- Graff-Radford J, Lesnick T, Rabinstein AA, et al. Cerebral microbleed incidence, relationship to amyloid burden: the Mayo Clinic study of aging. *Neurology*. 2020;94(2):e190–e199.
- Han G, Schell MJ, Kim J. Improved survival modeling in cancer research using a reduced piecewise exponential approach. *Stat Med*. 2014;33(1):59–73.

24. Simonetti G, Gaviani P, Botturi A, Innocenti A, Lamperti E, Silvani A. Clinical management of grade III oligodendroglioma. *Cancer Manag Res*. 2015;7:213–223.
25. Felsberg J, Rapp M, Loeser S, et al. Prognostic significance of molecular markers and extent of resection in primary glioblastoma patients. *Clin Cancer Res*. 2009;15(21):6683–6693.
26. Jiang H, Ren X, Cui X, et al. 1p/19q codeletion and IDH1/2 mutation identified a subtype of anaplastic oligoastrocytomas with prognosis as favorable as anaplastic oligodendrogliomas. *Neuro Oncol*. 2013;15(6):775–782.
27. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol*. 2010;120(6):707–718.
28. Shin JY, Diaz AZ. Anaplastic astrocytoma: prognostic factors and survival in 4807 patients with emphasis on receipt and impact of adjuvant therapy. *J Neurooncol*. 2016;129(3):557–565.
29. Thompson G, Lawrie TA, Kernohan A, Jenkinson MD. Interval brain imaging for adults with cerebral glioma. *Cochrane Database Syst Rev*. 2019;12(12):Cd013137.
30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Tumors (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed June 2, 2020.
31. Johnson DR, Ma DJ, Buckner JC, Hammack JE. Conditional probability of long-term survival in glioblastoma: a population-based analysis. *Cancer*. 2012;118(22):5608–5613.
32. Polley MY, Lamborn KR, Chang SM, Butowski N, Clarke JL, Prados M. Conditional probability of survival in patients with newly diagnosed glioblastoma. *J Clin Oncol*. 2011;29(31):4175–4180.