Model Conceptualization for IDH-Mutant Diffuse Glioma: A Case Study Exploring Two Alternative Structures

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Background

Health economic models of interventions for early-stage cancers are associated with several interconnected challenges that influence their conceptualization. Considering the case of IDH-mutant diffuse glioma, there are several challenges in developing a model aimed at establishing the cost effectiveness of a treatment introduced at an earlier stage of the disease, before chemo-radiation therapy (Rt/Ct):

- **Data maturity:** Data collected in a pivotal clinical trial are unlikely to capture downstream consequences, such as the use of subsequent interventions (e.g., surgery), which may then influence future costs and outcomes.
- **Surrogacy:** The relationship between short-term benefits (e.g., delayed progression) and long-term outcomes (e.g., extending survival) may be difficult to establish, where there is no clearly established surrogacy relationship.
- **Heterogeneity:** In early-stage cancers, people may follow markedly different journeys through a treatment pathway depending on treatment decisions made (e.g., people may choose to 'opt out' of further cytotoxic chemotherapy).
- **Model structure:** Conventional modelling structures (e.g., a three-state partitioned-survival analysis model) may not adequately capture all important aspects of the disease and its treatment.

Using a case study in IDH-mutant diffuse glioma, we explored two candidate modelling approaches.

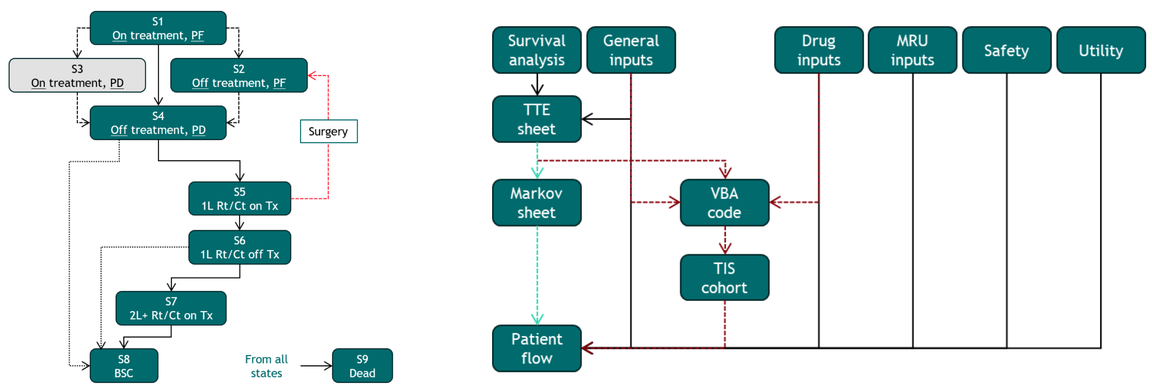
Methods

Following a model conceptualization process, Two candidate modelling approaches were developed:

- **STM:** A cohort-level state-transition model using Markov methodology.
- **PLS:** A patient-level simulation model using microsimulation methodology.

Both models included nine health states, spanning three treatment lines and best supportive care (BSC), informed using the same input data. Critically, the PLS allowed for time-varying transitions between latter health states, whereas the Markov model required time-invariant transition probabilities except for those transitions which could be based on time since model entry (i.e., initial transitions plus background mortality linked to age). An overview of the model structure is presented in **Figure 1**.

Figure 1: Model schematic and use of information per model structure (solid arrows represent available transitions in model base case)



Notes: Left: Solid lines represent the base-case structure. Long-dashed lines are available in scenario analysis. Short dashed lines represent those patients that choose no further treatment; Right: Each model structure treats the same set of inputs differently. The red lines represent the PLS, whilst the cyan lines represent the STM. See **Table 1**.

Abbreviations: BSC, best supportive care; Ct, chemotherapy; MRU, medical resource use; PD, progressed disease; PF, progression-free; PLS, patient-level simulation; Rt, radiotherapy; STM, state-transition model; TTE, time to event; TID, time in state; Tx, treatment; VBA, Visual Basic for Applications.

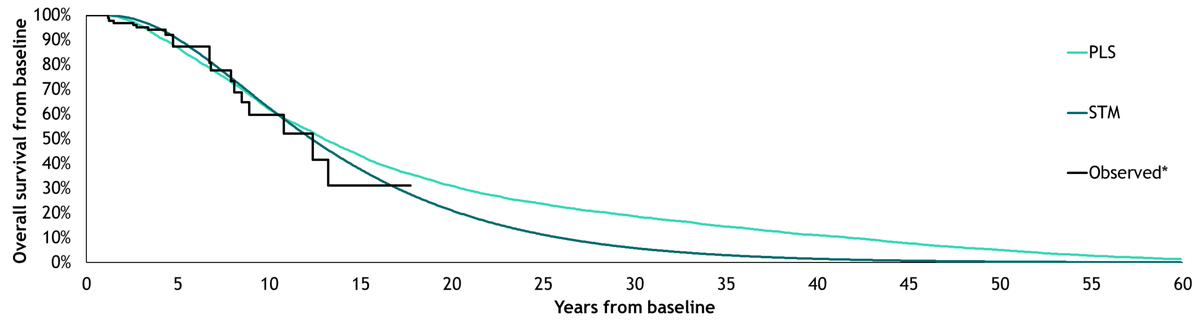
The goal of the exploration of the two model structures was to better understand how the models compared in terms of their ability to accurately represent model outcomes over a lifetime horizon. However, the model was designed to consider a hypothetical standard of care (W&W) for patients not in immediate need of Rt/Ct, rather than any new intervention. Therefore, the median and mean survival (expressed as total estimated life-years [LYs]) for a hypothetical standard were compared, and practical considerations for both models were noted.

Results

When using best-fitting extrapolations, median survival estimates were similar across both models (14.03 versus 13.95 years for the PLS versus STM, respectively). Mean LYs were lower for the PLS (16.03 years) versus the STM (17.38 years).

A scenario was added using exponential extrapolations for the constant transitions beyond S4 in the STM and removing excess mortality in S5-6. This reflects IDH-mutant diffuse glioma deaths predominantly occurring at the end of the pathway. As can be seen in Figure 2, PLS overall survival is lower in the first 10 and higher in later years.

Figure 2: Overall survival estimates for current standard of care by model structure



Notes: *Observed data refers to re-baselined Kaplan-Meier estimate of overall survival, taken from Bhatia *et al.*, (2024) [5], re-baselined using median progression-free survival from Fukuya *et al.*, (2019) [6].
Abbreviations: 1L, first-line; 2L+, second-line and beyond; BSC, best supportive care; Ct, chemotherapy; PD, progressed disease; PF, progression-free; Rt, radiotherapy; PLS, patient-level simulation; STM, state-transition model; KM, Kaplan-Meier.

This reflects the reducing hazards implied by the source material. Most extrapolations fit best with simple reducing hazards models like log-logistic or log-normal. The PLS estimates higher survival than the Markov model in this scenario (PLS and Markov medians: 12.80 vs 11.96, means: 17.75 vs 13.94). We consider this scenario to more accurately represent the evidence, and that the higher tail is a fair representation given modern treatments available and estimating general population mortality individually in the PLS [1].

The STM was faster in terms of both build and run time (particularly for sensitivity analysis), but the simplifying assumptions required for long-term survival (i.e., constant probabilities), and therefore may have omitted important aspects of the disease (such as accurately capturing disease progression). Structural decision making and limitations are summarized in **Table 1**. Overall, the Markov approach had to include several simplifications which limited accuracy of both the survival extrapolations and capturing of treatment costs.

Table 1: Features of and assumptions required for both model structures

Feature	Microsimulation	Markov
Accurately representing the evidence being to power the disease model	• VBA-based microsimulation with several large code elements to compute individual patients every 28-days until death. • Increased build time and model complexity despite microsimulation limited to state transitions and Rt/Ct usage. • Full patient history traceable per patient, removing the need for many complexities present in cohort approaches, especially with re-treatment rules and complex pathways. • Patients could skip states on their own accord (opting to move to BSC before a treatment line), which then applied overall survival from a different source. • All survival extrapolation distributions could be used, even for later states.	• Custom VBA function used to compute Markov trace with time-varying transitions in baseline states as well as time-varying general population mortality. • In only the model entry state, any survival extrapolation could be used. • Patients cannot "skip lines" as one-off transitions upon entry would complicate the approach. • In subsequent states, only exponential extrapolations could be used, which may provide a poor fit to data. • 100% transition out of 1L and 2L+ states required to correctly incorporate payoff approach to costs.
Accurately modelling treatment costs for the on-treatment health states	• Maximum treatment durations and stopping rules could be fully incorporated at any treatment line. • Grace periods between successive 2L+ treatment lines could be incorporated. • Rt in series with Ct could be modelled explicitly to account for contra-indication of CCNU with irradiation. • Re-treatment rules could be incorporated, precluding or allowing the use of a treatment multiple times for one patient (e.g., TMZ re-challenge). • Dosing could be handled on the patient-level and tracked accurately for every 28-day cycle.	• Baseline treatments could be tracked accurately as time from initiation is known. • Expected time on treatment (i.e., an estimate) used for all treatments at all subsequent lines. • Complex calculations required to correctly discount expected time on treatment in '2L+' stage, which consisted of up to four successive lines of Rt/Ct, taking grace periods between lines and expected time on treatment into account.
HRQoL	• Typical health-state utilities and AE adjustments on the cohort level.	• As the PLS, but requiring that utilities in S5/6 and S6/7 be equalised
General population mortality	• Tracked accurately on a per-patient basis, considering the non-linear association between age, sex, and mortality for the general population, per Lee *et al.*, (2024) [1].	• All patients assumed the same age at baseline and incremented one year in age per model year, in line with typical modelling precedent. This overestimates mortality at later years.
MRU costs	• Typical per-cycle costs, frequencies and one-off costs upon state entry, handled on the cohort level.	
AEs	• Typical per-cycle costs, utility decrements and one-off costs upon state entry.	

Abbreviations: 1L, first-line; 2L+, second-line and beyond; AE, adverse event; BSC, best supportive care; CCNU, lomustine; Ct, chemotherapy; HRQoL, health-related quality of life; MRU, medical resource use; Rt, radiotherapy; TMZ, temozolomide; VBA, Visual Basic for Applications.

An additional finding was that adding the Markov structure to the microsimulation model was not particularly burdensome, provided the microsimulation model is specified with a Markov adaptation in mind. There is expected to be additional utility of having two model structures available from both a structural uncertainty and uncertainty exploration perspective.

Discussion and Conclusions

While the STM may be preferred in terms of its relative simplicity, this would need to be weighed against the risk of 'incorrect' decision making based on inaccurate modelling of survival outcomes (which would need to be determined based on inspection of the input survival data). The Markov approach may oversimplify key elements of the model (e.g., the magnitude of overall survival benefit, feedback loops like resection surgeries, within-state time dependencies), whilst building the microsimulation was substantially more complicated and involved. Yet, given the right circumstances, both could be suitable for HTA.

Echoing sentiments raised in literature and published guidance, consideration of multiple model structures highlights fundamental structural uncertainties when addressing a decision problem [2-4]. Incorporating alternative structures better captures the cost-effectiveness of new interventions. Adding simpler model engines to a complex cost-effectiveness model is relatively straightforward and valuable, as it helps to identify errors, and ultimately determines the most accurate and useful approach for HTA decision-making.

Key References

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