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Hypothetical generalized framework for a new imaging endpoint of therapeutic activity in early phase clinical trials in brain tumors

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Abstract

Imaging response assessment is a cornerstone of patient care and drug development in oncology. Clinicians/clinical researchers rely on tumor imaging to estimate the impact of new treatments and guide decision making for patients and candidate therapies. This is important in brain cancer, where associations between tumor size/growth and emerging neurological deficits are strong. Accurately measuring the impact of a new therapy on tumor growth early in clinical development, where patient numbers are small, would be valuable for decision making regarding late-stage development activation. Current attempts to measure the impact of a new therapy have limited influence on clinical development, as determination of progression, stability or response does not currently account for individual tumor growth kinetics prior to the initiation of experimental therapies. Therefore, we posit that imaging-based response assessment, often used as a tool for estimating clinical effect, is incomplete as it does not adequately account for growth trajectories or biological characteristics of tumors prior to the introduction of an investigational agent. Here, we propose modifications to the existing framework for evaluating imaging assessment

in primary brain tumors that will provide a more reliable understanding of treatment effects. Measuring tumor growth trajectories prior to a given intervention may allow us to more confidently conclude whether there is an anti-tumor effect. This updated approach to imaging-based tumor response assessment is intended to improve our ability to select candidate therapies for later-stage development, including those that may not meet currently sought thresholds for "response" and ultimately lead to identification of effective treatments.

Keywords

response assessment | brain tumors | clinical trials | growth rates

The failure rate of late-stage clinical trials in primary brain tumors is high[1–3] and malignant gliomas remain aggressive and incurable neoplasms with limited available therapies.[4–7] Although there are several tumor intrinsic, micro-environmental, and organ-based factors that make glioblastoma (GBM) and related primary brain tumors challenging to treat,[8,9] advances in discovery science and translational science provide a number of strong leads where new therapies are being developed, including concerted efforts to achieve adequate drug delivery across the blood-brain barrier. While tumor shrinkage is an ideal goal for any novel therapies, the mechanism of action of many new therapies, with a cytostatic rather than cytocidal/cytotoxic goal, would suggest tumor stability as an expected (and favorable) effect of treatment. Additionally, the impact of many cytocidal or cytotoxic therapies in brain tumor is growth arrest or cytostasis, further emphasizing the importance of measuring tumor stability as treatment effect independent of the mechanism of action. Similar to other systemic cancers, image-based stabilization or shrinkage in progressing brain cancer can provide attribution to the contemporaneous therapy. However, a progressing tumor in the brain can be particularly devastating with regard to the accumulation of neurological deficits, loss of independence, and eventual death associated with unchecked tumor growth. So much so that even a growth of 5%–10 % in or, adjacent to, a critical brain structure can cause neurological devastation. Additionally, patients and their families are emotionally impacted each time they learn that the therapeutic intervention is not controlling their tumors.Therefore, shrinking tumor or forestalling progression, which may include stabilization, in brain cancer has clear value in patient care and clinical development. Accurately measuring the impact of therapies early on, regardless of mechanism and expected clinical impact, would help guide later stages of development for brain cancer therapy.

As early preclinical science and early phase clinical trials provide leads for late-phase development, our field requires a clear decision-making process to confidently identify therapies that are worthy of further investment in treasure, time, and trial participants. Early clinical trials that define tolerability have always been a critical part of the decision-making process. Additionally, our field has supported tissue-based pharmacokinetic and pharmacodynamic investigations through window of opportunity studies in these early phase trials. Together these early evaluations elucidate issues related to toxicity, exposure, potency, selectivity, target engagement, and downstream effects of target engagement. While critical for limiting or discontinuing early clinical development, this information does not necessarily provide insight into the likelihood of clinical effect or success in late-stage trials. Instead, we often rely on image-based outcome data from patients who enrolled into the phase I, dose expansion, or small phase II studies.

One of the most dependable signals of clinical effect in early oncology trials is imaging-based tumor reduction, especially when the extent of reduction is large, beyond the level of noise or normal biologic/measurement variability, and durability is sufficiently long. Therapy-induced reduction in tumor size of well-defined magnitude and duration, identified through proper image acquisition and measured using specifically defined response criteria, would presumably forestall the accumulation of neurologic deficits and prolong survival, providing confidence for success of later-stage confirmatory trials. So much emphasis has been placed on the concept of durable tumor reduction as a representative surrogate for eventual survival benefit in later-stage trials that there exists the opportunity for accelerated or full approval by regulatory agencies for single agent or novel combinations. However, as stated previously, for the impact of most therapies do not lend themselves to radiographic response in brain tumor patients. Here, instead, slowed growth or durable tumor stabilization of tumor size may be more achievable and likewise beneficial.

In the setting of recurrent GBM, investigators postulated treatment-induced periods of disease *stability,* as evidenced by durable progression-free survival (PFS) lasting at least 6 months, ought to forestall the accumulation of neurologic deficits maintaining stability of function and likely be associated with prolonged survival. While there is certainly merit in this endpoint, investigators and regulators have concerns about the normal variability and/or basal rate of growth in some tumors that might make PFS6 achievable by prognostic factors, or not directly related to the therapeutic intervention being studied. Moreover, thresholds for stability in the current Response Assessment in Neuro-Oncology (RANO) criteria are set arbitrarily at less than 25% increase or 50% decrease in tumor size based on cross-sectional diameters on MRI,[10] which similarly do not account for the growth rate prior to initiation of the experimental agent. Therefore, we hypothesize that additional

confidence can be gained by clearly understanding the natural history and growth trajectory of an individual tumor prior to initiating a therapy. In this way, the change in growth rate after initiation of therapy is more easily and directly attributable to the therapy under examination.

The concept of using tumor growth dynamics to determine prognostic impact and treatment effects in cancer is not a new idea. Previous studies have demonstrated a clear correlation with tumor size,[11–20] growth rate,[11,21–23] and survival in GBM. Decades of excellent research on tumor growth modeling have been outlined in numerous review articles and book chapters,[24–36] many of which emphasize the use of sophisticated biophysical models (eg, continuum-based,[37] hybrid discrete and continuous,[38] nonlinear,[39] and Bayesian[40]), interacting microenvironmental characteristics (eg, tumor-immune cell interactions,[41,42] avascular tumor growth,[43] and cellular lifespan estimates[44]), and often involve imaging information[45–48] with a significant amount of biological, phenotypical, and technical assumptions. While an exhaustive review of this rich literature is beyond the scope of the current narrative, these data clearly support the notion that changes in tumor size and behavior over time should be seriously considered when trying to gain insight into therapeutic efficacy in early phase studies.

While there is ample evidence that complex modeling or tumor growth characteristics reflects important aspects of tumor biology and therapeutic effects, the use of growth rates as a regulatory tool in early phase neuro-oncology clinical trials needs to be straightforward, intuitive, clinically meaningful, available to all clinicians, and build on the expansive experience of endpoints used for early phase trials. Adequate use of growth rates as a measure of therapeutic effect in early phase trials, therefore, can only be achieved through optimizing both the experimental conditions and imaging methodology used to evaluate therapies in this context, while continuing to focus on individual patient changes before and after treatment to increase control over the normal variability that exists within the patient population. In the current position paper, we describe a generalized framework and approach to develop and evaluate a new imaging endpoint aimed to better define potential for "clinical effect" in early phase brain tumor clinical trials. The goal is to provide a roadmap for achieving scientific evidence useful for guiding brain tumor drug development from early to later stages of development.

Definition of "Clinical Effect" as a New Endpoint for Early Phase Trials

Current RANO criteria[10] sets a single size requirement (ie, "measurable disease," defined bidimensional as 10 mm × 10 mm) and relies on changes in tumor size, based on discrete thresholds, after treatment to determine therapeutic effect (Figure 1A), for which we are only able to make three determinations:

(1) Increasing tumor size relative to baseline → Drug *is not* working.
(2) No change in tumor size relative to baseline → Drug *may* be working.
(3) Decrease in tumor size relative to baseline → Drug *is* working.

This fundamentally assumes that the growth rate before initiating experimental therapy is sufficiently rapid to be observably reduced, and that the pace is affected by the experimental therapy. However, the growth rate before initiating experimental therapy is not captured. Using a similar approach to those presented by Ferté et al.[49] and Dromain et al.,[50] if we were to measure the rate of tumor growth *prior* to and quantify the growth trajectory *after* initiating these new therapies, there are more nuanced determinations that can be made about the therapeutic effect for an individual patient's tumor (Figure 1B), including:

(1) Growth rate on treatment is *equal to or greater* compared to pre-treatment growth rate → Drug *is not* working.
(2) Growth rate on treatment is *slower* compared to pre-treatment growth rate → Drug *may* be working.
(3) Growth rate on treatment is *zero* and pre-treatment growth rate is sufficiently high → Drug *is* working.

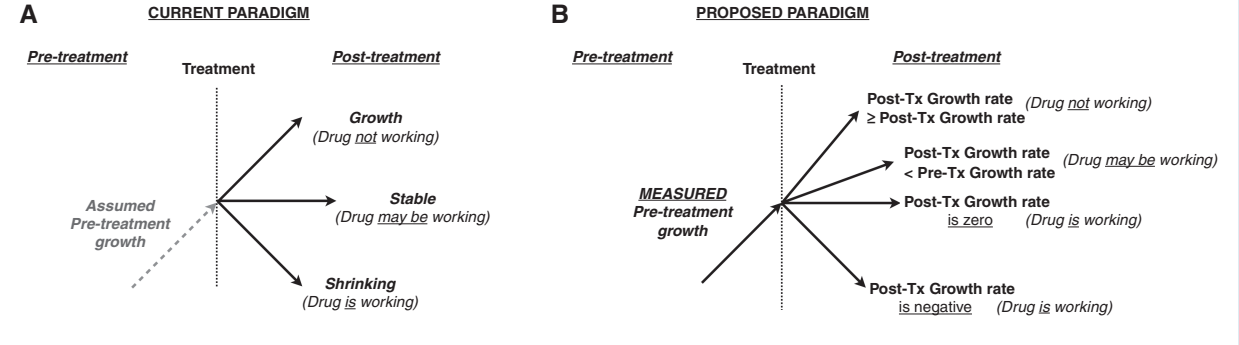


Fig. 1 Current and proposed paradigm for using image-based measurements for determining experimental drug effects. (A) The current paradigm assumes tumors are growing prior to starting study drug, for which we can only determine whether drug is working based on tumor shrinkage. (B) In the proposed paradigm, pre-treatment growth rates are measured for individual patients and *change* in growth rate after treatment can be used to delineate more nuanced therapeutic effects including tumor stability or inhibited growth rates.

(4) Growth rate on treatment is *negative* and pretreatment growth rate is sufficiently high → Drug *is* working.

In addition to the change in growth rate on therapy indicating clinical effect, we also need to consider the durability, or duration this of change in growth rate, into the calculus of clinical effect. For this, we propose considering benchmark PFS as the minimum period of time an altered growth rate needs to be sustained at the growth rate estimated. In this way, we capitalize on the extensive work previously performed in our field to determine the duration that constitutes an acceptable progression-free period. For example, in recurrent GBM patients, we can use PFS6, or a duration of 6 months from the start of therapy, as a meaningful interval of progression-free time. In other settings, where prior consensus does not exist, investigation would be needed to determine an acceptable durability of control. The issue remains, what progression-free interval or proportion free from progression at a certain interval translates into overall survival benefit or other measures of patient benefit. Our proposal is also consistent with common patient concerns of whether the treatment is changing the course of their disease at all and whether treatment is slowing or stopping their cancer.

Based on these conditions, we postulate that:

> A therapeutic effect can be determined in the setting of any brain cancer where 1) growing tumor prior to the treatment of interest can be shown to either stabilize or shrink over some meaningful period, and 2) the alteration in tumor growth can be primarily attributable to the specific intervention and not natural history or prior therapeutic interventions (e.g. adequate washout from prior therapies, change in corticosteroid dose, etc.).

Outside of the regulatory environment, these additional distinctions made possible by examining both pre-treatment and post-treatment growth behavior may provide guidance for clinical development during early phase trials by providing higher confidence around the impact of the therapy on the tumor (Figure 2). Knowing there is at least a minimal therapeutic effect might lead drug developers to investigate alternate dosing schedules to improve drug exposure, the use of combination to translate a subclinical effect into a clinical effect, identifying responding biomarker subtypes, and/or abandoning further development altogether. Within the regulatory environment, if this new framework is sufficiently validated, it could provide regulatory authorities with more convincing evidence of treatment effect and encourage closer attention.

Improved Methodology to Accurately Capture Clinical Effect in Early Phase Trials

To develop a new framework in the setting of early phase trials, several procedures and methods need to be refined. These include standardizing image acquisition parameters to ensure repeatable measurements over time, clearly defining the process in which central evaluation of image measurement and interpretation is implemented, defining a minimum pretreatment growth rate, and requiring a *hyperacute* baseline immediately prior to treatment initiation to precisely estimate growth rates after treatment.

Standardization of MRI Acquisition and Post-Processing

Image acquisition is an important starting point for imaging endpoint development. In 2015, our team published consensus recommendations for a standardized Brain Tumor Imaging Protocol (BTIP),[51] detailing the specific minimum requirements for MRI sequences in brain tumor clinical trials that would provide the best uniformity within and across centers for central review and endpoint development. At this time, we made an important request to integrate these minimum recommendations into the standard of care imaging protocols at academic centers and clinical sites, as this information would lead to better fidelity of historical imaging data if it was used to estimate pretreatment tumor growth behavior. In addition, differences in head orientation altering the tilt and skew of images during longitudinal evaluations can make image interpretation very challenging, particularly if only using bidirectional (planar) measurements of the tumor. Best efforts for obtaining scans using the same head orientation are critical, and most contemporary MRI scanners have tools to aid in this process (eg, Siemens "*AutoAlign*" function to align images along the AC-PC line); however, post hoc alignment tools for registration of images over time are freely available and routinely used in neuroimaging research and clinical care.

Radiographic Read Paradigm

Like image acquisition and post-processing, the approach whereby central evaluation of image interpretation is performed is critical to reduce bias and increase reproducibility. Our team has recently published a position paper on recommended image radiographic read paradigms for use in brain tumors, including selection of the proper response criteria, display procedures, reading queue, data locking procedures, and measurement adjudication design considerations.[52] Additional visualization tools such as "digital flipbooks", using aligned images over time to create a dynamic "movie" may provide a better gestalt of changes than side by side comparisons and can also provide confirmation of central image interpretation.

Defining a Minimum Growth Rate or Percent Increase for Inclusion (Example of Recurrent GBM Trials)

If our goal is to define therapeutic effect as including stabilization of tumor over some meaningful period of time, we have to ensure that a minimal growth rate be considered as a part of inclusion criteria. Assuming a linear and constant tumor growth rate or trajectory, some minimum requirements can be estimated to ensure that unresponsive tumors do not reach the required landmark PFS benchmark simply due to prognostic factors. Using bidirectional

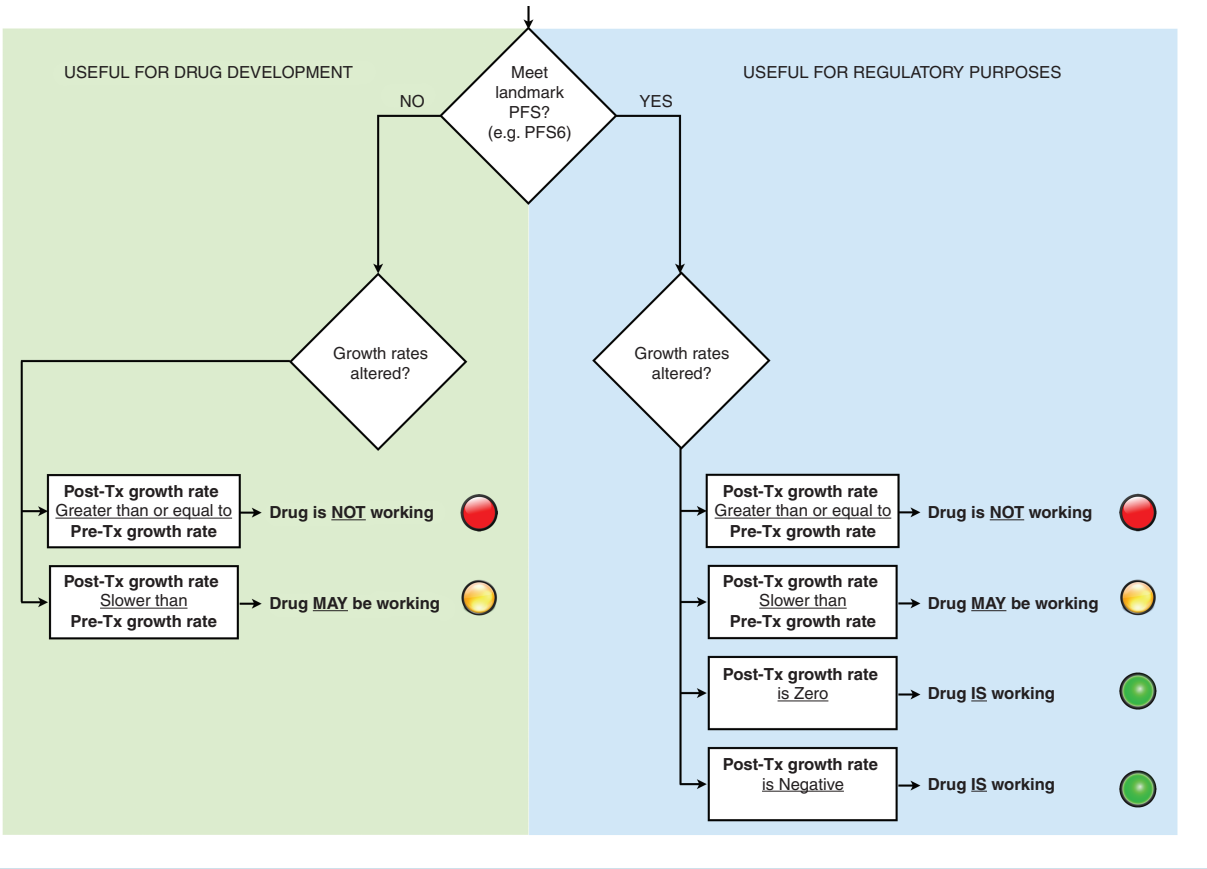


Fig. 2 Framework for determining therapeutic activity in early phase trials. To gain confidence that a drug has therapeutic activity that is likely to lead to clinical benefit using data from early phase trials, we propose using progression-free survival (PFS) benchmarks (eg, PFS6) combined with evidence of altered growth rate trajectory. In patients who reach the PFS benchmark, evidence of tumor shrinkage or stabilization could provide confidence the drug is effective, whereas if the growth rate has slowed there may be some limited evidence of activity. If patients do not reach landmark PFS, but there is evidence the tumor has slowed its growth rate trajectory, this may be evidence of some therapeutic activity and may require adjustments to dose and timing in order to increase clinical benefit.

measurements, if we assume first that a tumor must be "measurable" at baseline (1 cm^2 or 10 mm × 10 mm in a single plane), then a tumor will reach the benchmark PFS6 if it does not grow larger than 1.25 cm^2 over 6 months from the start of treatment. This results in a minimum growth rate of approximately 4 mm^2 per month to ensure the tumor will progress without any treatment prior to the 6-month benchmark (Supplemental Figure S1). Similarly, using volumes and an assuming a baseline volume of 1 mL and 40% threshold for disease progression, the minimum growth rate to ensure the tumor will progress without any intervention prior to 6 months would be approximately 67 μL per month. Similar parameters can be developed for different tumor types in different lines of therapy in different clinical scenarios.[53–55] Other brain tumors types have variable growth rates and, therefore, may have different criteria for the minimum growth rates required for such evaluations. For example, the RANO meningioma group suggests a 15% increase in volume over 6 months as requirement for study entry.[56] Additionally, recent evaluations in isocitrate dehydrogenase (IDH) mutant lower grade gliomas suggest growth rates prior to initiating therapy around 26.6% over 6 months, and growth rates differed between IDH mutant astrocytoma versus oligodendroglioma.[53] Although each tumor type and clinical setting (eg, first line vs. relapsed) may exhibit different growth rates, the approach for determining minimal growth rates should be similar.

Establishing Appropriate Baseline Prior to Treatment Initiation

Current clinical trial recommendations often allow recurrent GBM patients to use scans obtained within 14–21 days of study treatment initiation as a "baseline" for radiographic response assessment; however, given the average doubling time of treatment naïve GBM is approximately 21 days,[57] a delay of 14–21 days can result in a significant distortion in our ability to accurately determine therapeutic effects. Obtaining a scan closer to the start of treatment can mitigate these issues and provide more insight into the true growth rate of the tumor. To demonstrate the magnitude of this issue, we recently evaluated this effect in an investigator-initiated trial in recurrent GBM where we obtained a pre-treatment baseline on 12 patients within 1–2 days before initiating therapy (Figure 3). Consistent with most recommendations, the median time between the progression

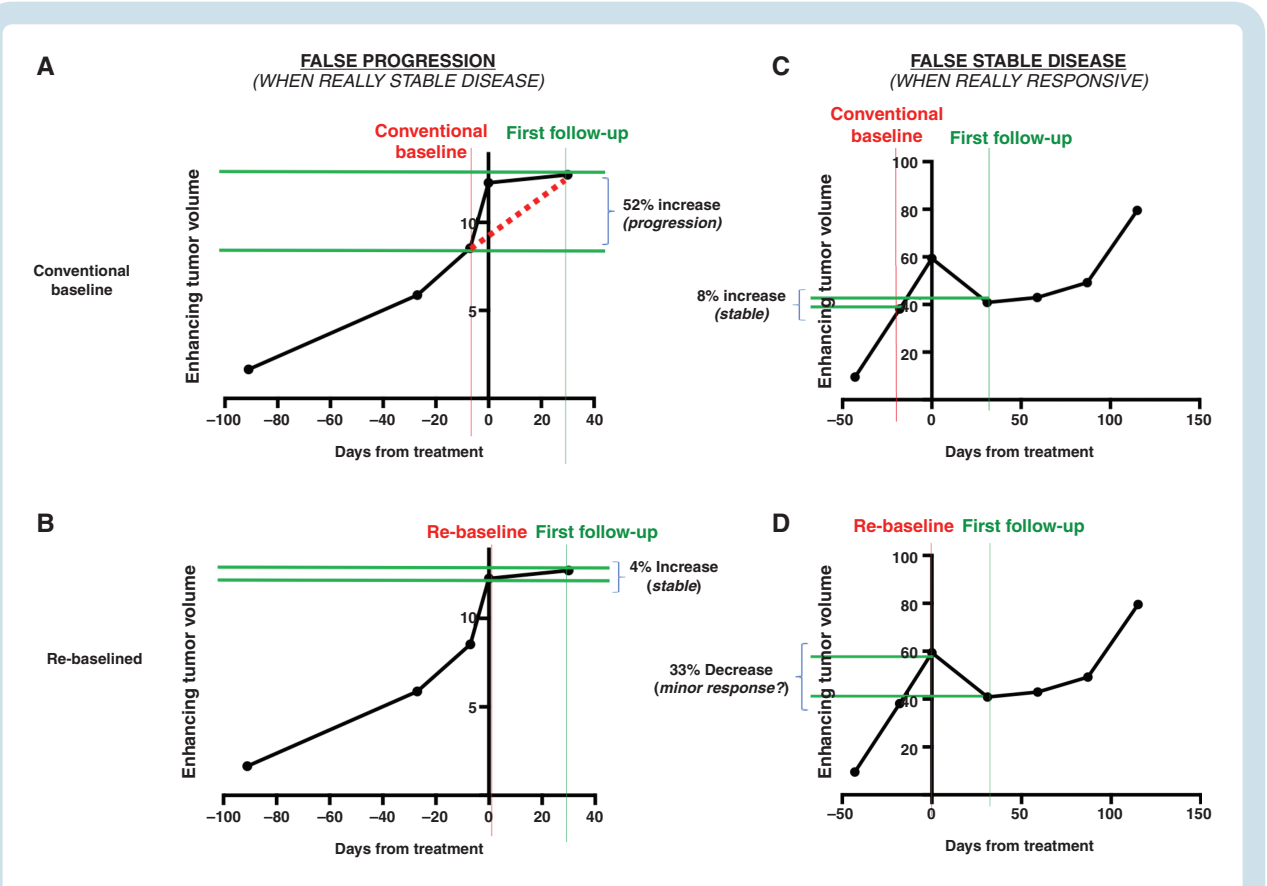
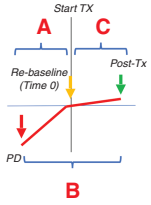


Fig. 3 Added value of a "hyperacute" baseline scan to more accurately determine response. (A) Using a conventional baseline of 14–21 days prior to treatment initiation, this particular patient would have exhibited disease progression (52% increase in volume) at the first follow-up time point. (B) However, when a hyperacute baseline is obtained 1–2 days prior to treatment, it becomes clear that the drug has stabilized growth rates and the tumor has only grown only 4% after starting study drug. (C) Similarly, using a conventional baseline, this patient shows stability on study drug (8% increase in volume). (D) After using a hyperacute baseline 1–2 days prior to treatment, this patient actually showed 33% *reduction* in tumor volume, suggesting the drug may have had a clinical effect.

scan typically used as the baseline for most trials and the start of therapy (or baseline "on study" scan) was 12.5 days (Range: 28 to 5 days). Of these 12 patients, seven had >40% growth in tumor volume over the period between the progressive disease scan typically used as a baseline and the new "hyperacute" baseline scan obtained just prior to treatment initiation. If the progression scan in this study was used as the baseline, 8/12 patients would have had >40% increase in volume by the first posttreatment follow-up exam. However, when the immediate pretreatment MRI is used as a baseline, only 2/12 patients had tumors with volumetric growth of over 40% at the first follow-up exam, suggesting that growth between the typical baseline time point and the start of treatment is large enough to significantly misinterpret growth stabilization as early treatment failure. Without obtaining a "hyperacute" baseline 1-2 days prior to the start of treatment, the majority of patients in this study would have exhibited radiographic progression after the first 28 days on treatment. It appears that a new baseline not only provides a more accurate understanding of growth rate coming into a study, increasing the number of scans over which to calculate pretreatment growth rates, but it also provides a better understanding of the true impact of study drug on tumor growth. Interestingly, many Phase I–III trials in recurrent GBM allow for a baseline scan to be obtained within 14–21 days of initiating therapy and the efficacy results show that most tumors progress at the time of the first imaging assessment. Although it is impossible know the impact of stopping a study drug at the time of first imaging assessment on patient survival, this information does raise questions on whether patients were taken off study drug before true progression (Figure 4). Therefore, we recommend evaluating the benefit of obtaining a new baseline MRI very close to the start of study drug, within 1–2 days for recurrent GBM and fast-growing tumors. If demonstrated beneficial for trial evaluation, it needs to be realized that obtaining a scan this close to starting study drug may be cost-prohibitive or logistically challenging. To test whether the hyperacute baseline scan and modified RANO provide value in determining clinical effect and predicting survival, we propose a validation study detailed below. Logic would follow that different patient populations and different tumor types may have different requirements for the appropriate timing of a baseline before initiating



		A	B	C	
Patient	Days btw PD and baseline	% Change PD to re-baseline	% Change w PD as baseline	% Change w re-baseline at time zero	Comments
1	20	76.6	111.6	19.8	PD would have been called at first scan
2	18	55.8	7.2	−31.2	
3	21	94.8	92.1	−1.4	PD would have been called at first scan
4	8	32.6	61.5	21.8	PD would have been called at first scan
5	12	443.5	747.4	55.9	PD would have been called at first scan
6	28	100.4	99.4	−0.5	PD would have been called at first scan
7	5	−3.8	25.2	30.1	
8	14	34.2	60.3	19.4	PD would have been called at first scan
9	5	4.8	32.7	26.6	
10	8	3.7	−12.1	−15.3	
11	7	43.6	48.9	3.7	PD would have been called at first scan
12	13	103.0	224.5	59.9	PD would have been called at first scan

A 7/12 (58%) patients had PD between the PD scan and the new baseline (most that weren't were scanned WITHIN 8 DAYS)

B 8/12 (67%) of patients would have had PD called at first scan if there was NO RE-BASELINE

C 2/12 (17%) of patients would have had PD called at first scan if there was RE-BASELINE

Fig. 4 Effects of hyperacute baseline in a prospective phase II trial. Of the 12 patients enrolled in this study, 7 patients (58%) exhibited growth between the traditional baseline scan and hyperacute baseline scan consistent with progressive disease. Two-thirds (8/12) patients would have had tumor progression at the time of the first post-therapy MRI scan if the conventional baseline was used. However, using a hyperacute baseline 1–2 days prior to treatment, only 17% (2/12) patients exhibited disease progression at the time of the first posttreatment MRI exam.

therapy. As such, similar approaches could be taken to separately evaluate these scenarios, where lower-growing tumors such as meningioma or lower grade gliomas may allow for a longer, but explicitly defined, timeframe for an appropriate baseline scan.

Confounding Factors With Growth Rate Response Assessment

There are several confounding factors that may exist for *any* response assessment in brain cancer that should be addressed, including the impact of prior therapies, use of corticosteroids, and mechanisms of actions of therapy being evaluated. The impact of prior therapies usually has a time-limited effect; however, duration of the effect can vary given the type of tumor, the type of therapy, and the imaging parameter being measured. For instance, the time frame for contrast enhancement-related pseudoprogression from radiation and chemotherapy can differ for IDH wild-type GBM compared with IDH mutated tumors.[58] Additionally, T2 hyperintensity on T2 or fluid attenuated inversion recovery images can be related to post-surgical or post-radiation changes, and can wax for up to 2 years and can be mistaken for non-enhancing tumor growth[59] when determining eligibility or when on study. Changes in corticosteroid use can also lead to misinterpretation of imaging response. The use of corticosteroids in the setting of brain cancer is commonplace, especially in the setting of enlarging contrast-enhancing masses. An increase or decrease in the dosage of corticosteroids can have an impact on the measurement of contrast enhancement lesions, which in turn can affect both the determination of progression for study eligibility and response, stabilization, or progression while on the study. Finally, the mechanism of action of the agent under investigation could have a variable time course for recognizing imaging-based treatment effects, which might create challenges for accurately assessing growth rate. For instance, anti-vascular endothelial growth factor approaches might show rapid changes in contrast enhancement, indicating an imaging response. However, these approaches are rarely durable and do not often show true tumor control. Therefore, incorporation of durability into the growth rate assessment is critical for an accurate assessment of clinical effect. Therapies that induce inflammation, including immune base therapies, may be even more complex. These approaches might have an initial immune response that can be mistaken for tumor progression. Although the growth rate eligibility would still apply, this might require response approaches such as iRANO[60] or the modified RANO[61] criteria that allow for initial progression before determining or back-dating progression. However, any therapy that has a longer duration of progressive immune-related imaging changes might not be realistically evaluated for growth rates. This particular scenario might be best considered for an evaluation of overall survival rather than any response assessment. As with any response criteria evaluating treatment effect through imaging, parameters will need to be in place (likely specific to tumor type and line of therapy) to limit the confounding effects of prior therapies, corticosteroids, and other potential confounds. These parameters should be defined by data-driven evaluations or expert consensus until adequate data has been established.

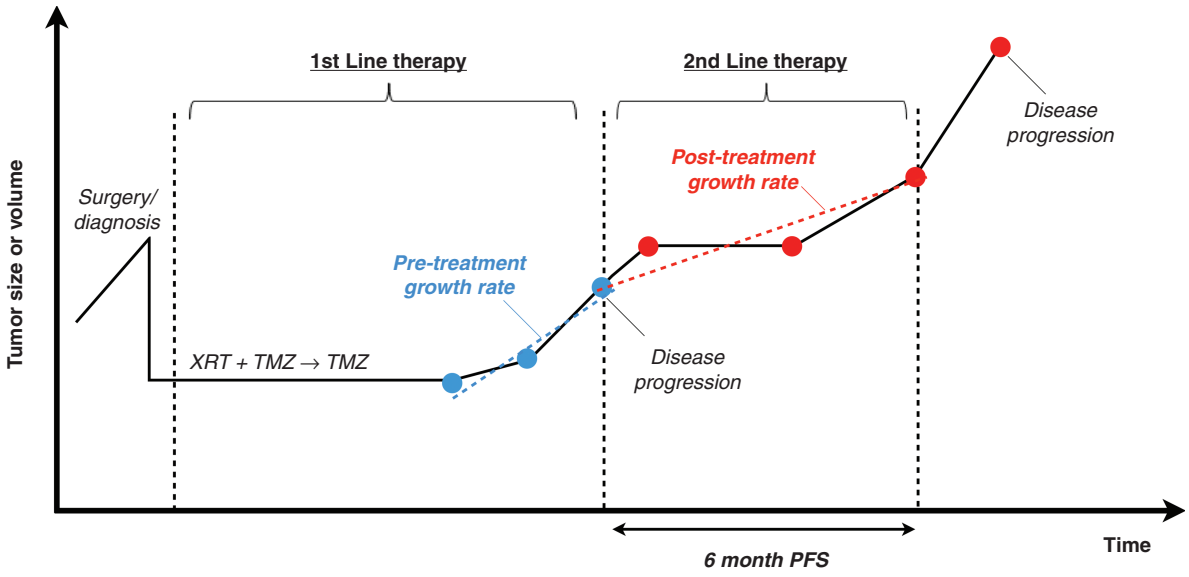


Fig. 5 Retrospective validation study in recurrent GBM. Using retrospective data from patients in a clinical trial, pretreatment growth rates can be estimated using 3 time points prior to and including disease progression. Then, using the conventional baseline or screening scan, posttreatment growth rates can be estimated over the duration of meaningful PFS duration (eg, PFS6).

Plan for Validation and Testing of New Framework in Recurrent GBM

As with any new framework, details related to the response determination are critical and many questions must be addressed before growth rates can be used to guide decision-making and confidently attribute changes to therapy. To use the response rubric in Figure 2 as a surrogate for clinical benefit it needs to be linked with overall survival or other objective measures of patient benefit. To accomplish this, both retrospective and prospective investigations may be useful, although there are specific limitations to looking only at retrospective data. For example, Figure 5 outlines a "strawman" approach for utilizing retrospective data from individual institutions to establish clinical effect of a therapy based on growth rates before and after initiation of therapy. Using MRI scans at the time of first recurrence along with time points just prior to recurrence, an estimate of pre-treatment growth rate can be determined assuming the dosage of steroids was not changed. A caveat is that any change will have to be considered to have happened in the entire period between the scans. Similarly, the scan at the time of progression, combined with the second line on-drug time points through the time of second progression can be used to estimate both PFS and growth rate estimates over some benchmark PFS interval. Then, using log-rank or multivariable Cox regression accounting for other factors including age, tumor size, MGMT status, etc., the differences in OS between categories in Figure 2 can be compared. Additionally, continuous measures of tumor growth rate *change* before and after drug can be associated with overall survival.

As mentioned previously, the lack of a "hyperacute" baseline or scan immediately prior to recurrence can be a significant confound to estimates of growth rate and clinical effect (Figures 3 and 4). Thus, a prospective clinical trial with explicit inclusion criteria as outlined above is necessary to provide the cleanest data set with regard to evaluations of PFS and survival, including use of pre-treatment images and a "hyperacute" baseline scan just prior to treatment. This means that data from individual institutions that use BTIP in the standard of care for patients who are willing to be part of this prospective study would be the ideal setting to test this endpoint. Figure 6 shows the schema for a theoretical, prospective evaluation of this new endpoint for recurrent GBM. This study would require pre-treatment MRI scans to confirm progression and estimate pre-treatment growth rates, would require a "hyperacute" or re-baseline within 1–2 days of starting experimental therapy according to BTIP guidelines,[51] and require these scans all be collected and evaluated according to standardized guidelines. If the hyperacute scan better evaluates the impact of therapy and the time of progression, confirmation of progression might not be needed for future criteria.

Conclusions

We hypothesize that evaluating growth rates can provide insight into the clinical effect of a particular therapy in brain cancer. While survival is the gold standard endpoint for impact of therapy on patients, information about how a patient is doing while on a therapy using growth rates can provide insight into the trajectory of their disease.

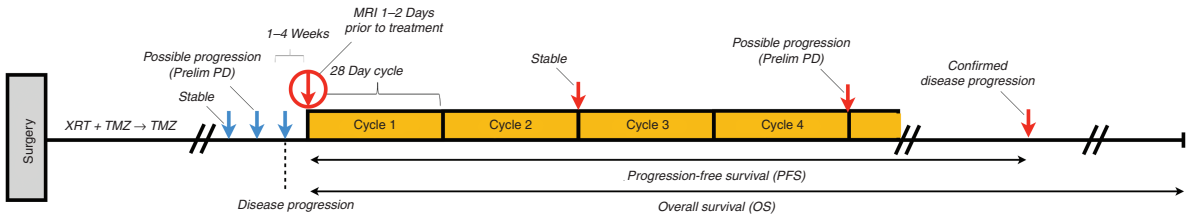


Fig. 6 Prospective validation study in recurrent GBM. Prospectively, we propose similarly collecting pre-treatment scans to estimate pre-treatment growth rates. However, unlike the retrospective validation study, we will obtain a hyperacute baseline MRI scan 1–2 days from the start of study drug to determine the impact of this time point on our ability to assess clinical effect in recurrent GBM.

The implications of establishing an imaging framework based on tumor growth rates could provide better decision making regarding, dose, schedule, and patient subgroups during early development as well as the decision to pursue later-stage clinical development. If this new framework is sufficiently validated, it could provide a reliable surrogate for clinical benefit and encourage regulatory attention. This approach could also help with important clinical decision-making at one of the most pivotal times in a brain cancer patient's treatment journey. Interestingly, the US FDA is currently evaluating tumor growth rates and the association with other outcomes like survival and PFS in other cancers.[62] The technologies, tools, and resources are available now to pursue retrospective and prospective evaluations of this new approach. Additionally, incorporating rules to mitigate the effect of pseudo-progression and pseudo-response developed by groups like RANO (eg, adequate washout from prior therapies, change in corticosteroid dose) need to be considered in the analysis of growth rates. Although the principles outlined here are predominantly applied to recurrent GBM, they can be easily adapted to any other brain tumor type or patient population[53–55,63–65] by incorporating the natural history of growth rates into the evaluation.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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