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Contrast-Enhancing Tumor Growth Dynamics of Preoperative, Treatment-Naive Human Glioblastoma

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BACKGROUND: Little is known about the natural growth characteristics of untreated glioblastoma before surgical or therapeutic intervention, because patients are rapidly treated after preliminary radiographic diagnosis. Understanding the growth characteristics of uninhibited human glioblastoma may be useful for characterizing changes in response to therapy. Thus, the objective of the current study was to explore tumor growth dynamics in a cohort of patients with untreated glioblastoma before surgical or therapeutic intervention. **METHODS:** Ninety-five patients with glioblastoma who had measurable enhancing disease on >2 magnetic resonance imaging scans before surgery were identified. Tumor growth rates were quantified in 4 different ways (the percentage change per day, the absolute rate of change per day, the estimated volumetric doubling time, and the radial expansion rate) using 3 different approaches (bidirectional product, enhancing disease, and total lesion volume). **RESULTS:** The median volumetric doubling time was 21.1 days, the percentage change in tumor volume was 2.1% per day, and the rate of change in total lesion volume was 0.18 cc per day. The length of follow-up between magnetic resonance imaging examinations should be >28 days to detect progressive disease with high specificity. Small initial tumor sizes (<3 cm in greatest dimension) are biased toward a large percentage change at follow-up. **CONCLUSIONS:** Presurgical, treatment-naive glioblastoma growth dynamics can be estimated in a variety of ways with similar results. The percentage changes in tumor size and volume depend on baseline tumor size and the time interval between scans. *Cancer* 2016;000:000-000. © 2016 American Cancer Society.

KEYWORDS: glioblastoma, growth rates, T1 subtraction, volumetry.

INTRODUCTION

Glioblastoma is the most common and aggressive form of primary brain tumor in adults. The current standard therapy for patients with glioblastoma consists of maximal surgical resection followed by concurrent radiation therapy and temozolomide chemotherapy, followed by adjuvant temozolomide, for which the median survival is only approximately 14.6 months.¹⁻³ Because glioblastomas are very aggressive and highly infiltrative, patients rapidly undergo surgery after a preliminary radiographic diagnosis. Because of this immediate need for therapy, very little is known about the natural growth characteristics of untreated glioblastoma before patients undergo surgical or therapeutic interventions, and only recently has there been documentation in a large cohort of patients with untreated glioblastoma.⁴

Because measurements in untreated tumors represent the best context in which to study uninhibited human glioblastoma growth in vivo before alteration in growth characteristics resulting from therapy or intervention, we hypothesized that this information may be useful for understanding both the maximum growth rates observable in these tumors as well as the minimum requirements for accurate assessment of “progressive disease,” because all tumors in this scenario should be continually growing and thus progressing. To accomplish this, first, we calculated growth rates using bidirectional product (commonly used for response evaluation in clinical trials), disease volume (enhancing voxels only), and total

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lesion volume (enhancement plus central necrosis). Then, we compared “spherical equivalent volumes,” which were measured using standard bidirectional measurements of tumor size, with true tumor volumes to determine the association between the measurements commonly used in radiographic response assessment and volumetry. We examined the dependence on the time interval between radiographic assessments to determine the optimal follow-up time between scans to truly detect “progressive disease” using standard response-assessment thresholds. Finally, we explored the dependence of percentage change and absolute change in tumor size with respect to the initial tumor size to better characterize any bias that may be associated with specific measures of tumor growth.

MATERIALS AND METHODS

Patients

In total, we identified 159 patients with histologically confirmed, newly diagnosed, treatment-naïve glioblastoma who had at least 2 magnetic resonance imaging (MRI) scans obtained before surgery, radiation therapy, or chemotherapy, separated by at least 7 days, among more than 2400 patients with glioblastoma in our neuro-oncology database. All participants gave informed written consent to have their imaging, molecular, and clinical information included in our database. All procedures complied with the principles of the Declaration of Helsinki and were approved by our Institutional Review Board. During the period of evaluation, which was often before treatment at our institution, the use of steroids was not well documented. However, a subset of patients (approximately 34%) did have documented steroid use available for interpretation. Patient demographics and the data available for analyses are provided in Table 1.

MRI

Structural MRI studies were obtained on either a 1.5-Tesla (GE Signa Excite HDx or Lx; GE Medical Systems, Waukesha, Wis; Siemens Avanto or Sonata; Siemens Healthcare, Erlangen, Germany) or a 3-Tesla (Siemens Trio, Allegra, or Verio; Siemens Healthcare, Erlangen, Germany) magnetic resonance system. Standard anatomic MRI studies consisted of precontrast and postcontrast (gadolinium-diethylenetriamine pentaacetic acid at a dose of 0.1 mmol/kg body weight), axial, T1-weighted images along with precontrast, axial, T2-weighted, and fluid-attenuated inversion recovery sequences with standard sequence parameters. Contrast-enhanced, T1-weighted digital subtraction maps were calculated to highlight areas

TABLE 1. Patient Demographics and Available Data for Analysis

Patient Demographics	No. of Patients
Total no. with imaging available	159
No. with > 2 scans who had measurable disease	95
Age: Mean \pm SD (range), y	60.2 \pm 13.9 (21-94)
Sex	
Men	58
Women	37
No. with positive growth rates	
Total lesion	89
Enhancement only	57
No. who had steroid dose available	31

Abbreviation: SD, standard deviation.

of subtle enhancement (Fig. 1C) using techniques outlined in a previous report.⁷

Tumor Measurements and Simple Growth Rate Calculations

Contrast-enhanced, T1-weighted subtraction maps were used to measure 3 separate surrogates of tumor size: 1) the bidirectional product of enhancing tumor from the slice with the largest 2-dimensional (2D) lesion extent, consistent with Response Assessment in Neuro-Oncology (RANO) recommendations⁸; 2) 3D enhancing disease volume; and 3) total 3D lesion volume, which included enhancing disease volume and areas of central necrosis. The absolute change and the percentage change in tumor size were calculated with respect to the first MRI assessment. Spherical approximations for bidirectional measurements were applied for estimations of volumetric doubling time and direct comparisons to enhancing disease and total lesion volume estimates by:

$$V_{est} = \frac{4}{3} \pi \left(\frac{\sqrt{a \cdot b}}{2} \right)^3 \quad (1)$$

where a and b are the 2 greatest perpendicular dimensions of the tumor in the axial plane. In patients who had a measured increase in volume observed, simple estimations of volume doubling time, in days, were estimated as:

$$VDt = \frac{dt \cdot \ln(2)}{\ln(V_2/V_1)} \quad (2)$$

where dt is the time interval between the MRI examinations, V_1 is the total lesion volume estimate on the first day, and V_2 is the total lesion volume estimate on the second day.⁹

Hypothesis Testing and Statistics

The average and median growth rates were quantified 4 different ways (percentage change per day, absolute rate of

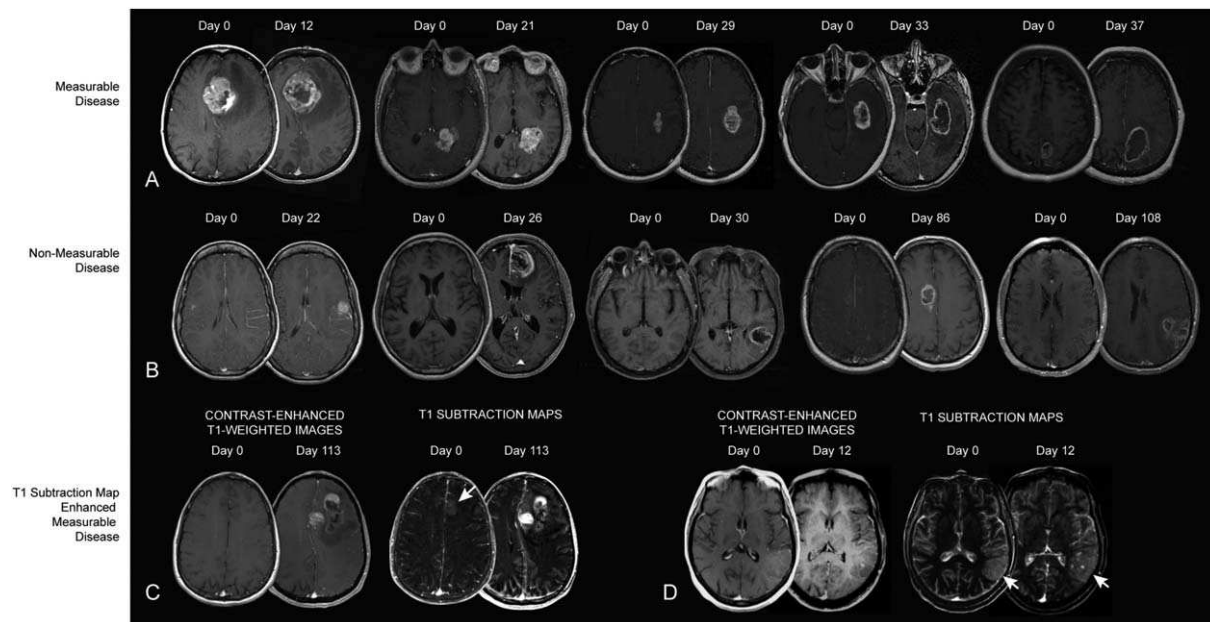


Figure 1. Representative images reveal the presurgical growth kinetics of treatment-naive glioblastoma. (A) These are 5 representative images from the 95 of 159 patients in the current study who had measurable, contrast-enhancing disease at >2 time points before surgery and received therapeutic intervention. The images reveal significant tumor growth between the 2 time points, ranging from 12 to 37 days between scans. (B) These are 5 representative images from patients who had no measurable, enhancing disease during the first magnetic resonance imaging scan followed by a finding of significant enhancing disease burden on the subsequent scan. These patients were not used in the current study, because growth kinetics could not be estimated from their first scans without measurable enhancing disease. These examples reflect both the challenges associated with measuring basal disease characteristics as well as the rapid growth rates observed in this disease. (C) This patient had nonmeasurable disease on postcontrast, T1-weighted images alone, but measurable disease was observed when using T1-subtraction maps to highlight areas of subtle, occult, enhancing tumor. (D) This patient had diffuse enhancement patterns that were easily identified using T1-subtraction maps to highlight subtle enhancing lesions.

change per day, estimated volumetric doubling time, and radial expansion rate) and were estimated using 3 different techniques (bidirectional product and spherical approximations; enhancing disease only; and total lesion extent, including enhancement and central necrosis). A Kruskal-Wallis test was used to determine whether there were significant changes in the measures with respect to the 3 different techniques explored. The correlation between bidirectional spherical estimates of tumor volume and actual total lesion volumes were explored using Pearson correlation coefficients (R^2). Receiver-operator characteristic (ROC) curves were used to determine the optimal number of days between subsequent MRI scans that would result in calling progressive disease (PD) with high specificity.

RESULTS

Measurable Disease, Nonmeasurable Lesions, and Added Benefits of T1 Subtraction

Of the 159 patients who had imaging data available, in total, 95 patients (approximately 60%) had measurable

disease on contrast enhancement at >2 time points (Fig. 1A), whereas the remaining 64 patients (approximately 40%) only had measurable enhancing disease at a single time point (Fig. 1B) and subsequently were not used in the analysis of growth rates. It is noteworthy that some patients without measurable disease at baseline had very rapid tumor growth during the evaluation period, with contrast-enhancing tumors growing to >20 cc in total volume as quickly as within 1 month (Fig. 1B). Also, the use of T1 subtraction maps allowed for measurement of occult, enhancing tumor even when they were not apparent on standard postcontrast T1-weighted images (Fig. 1C,D).

Linear Growth Rates Estimated by Bidirectional Product, Enhancing Disease Volume, and Total Lesion Volume

Figure 2 and Table 2 highlight the growth rates quantified 4 different ways (percentage change per day, absolute rate of change per day, estimated volume doubling time,⁹ and radial expansion rate) estimated with 3 different techniques (bidirectional product and spherical approximation;

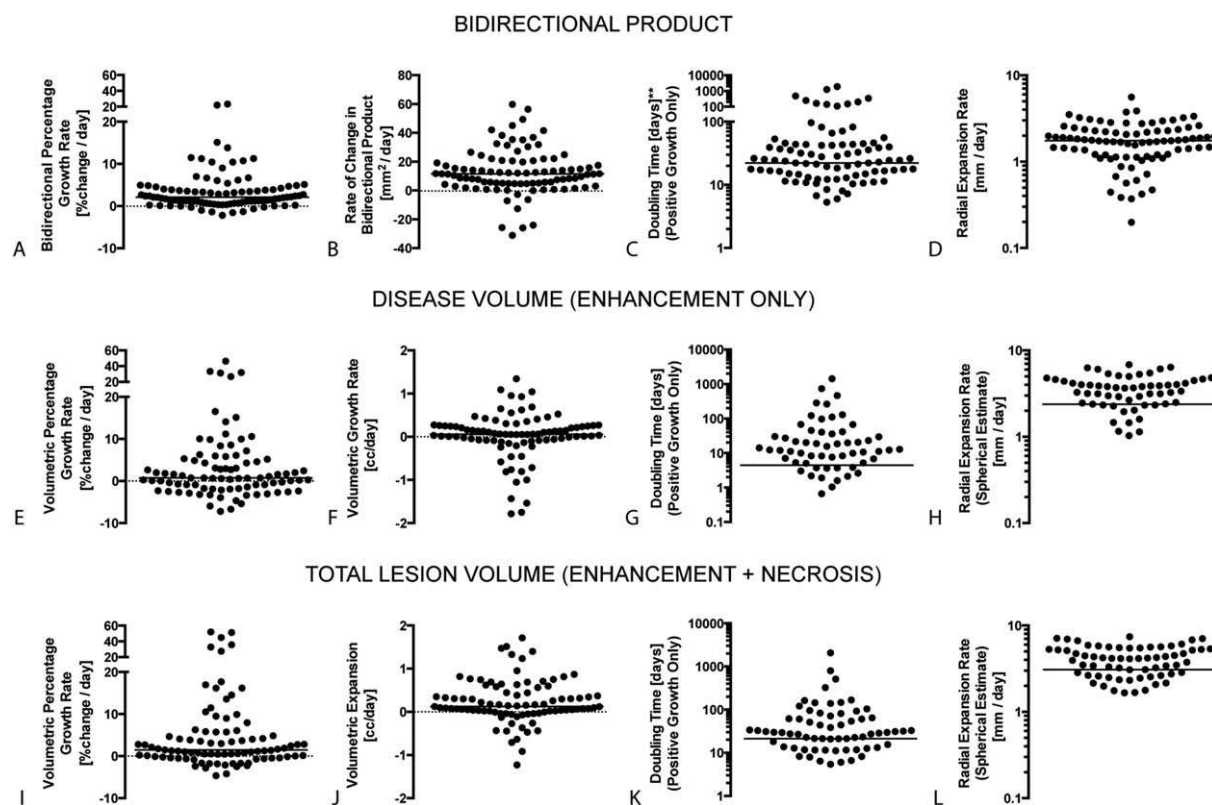


Figure 2. Treatment-naïve glioblastoma growth kinetics are illustrated. (A) Estimates of the percentage change in bidirectional lesion size per day are illustrated in units of percentage change per day. (B) The absolute rate of change in the bidirectional product was measured in square millimeters per day. (C) Volumetric doubling time was measured using a spherical volumetric approximation of bidirectional product measurements (in patients who had positive growth rates) in units of days. (D) The radial expansion rate was measured as the average lesion radius estimated from bidirectional product measurements. Radial expansion was measured in units of millimeters per day. (E) The volumetric percentage change was measured in enhancing tumor volume per day. (F) The volumetric growth rate of enhancing tumor was measured in cubic centimeters per day. (G) The volumetric doubling time of enhancing tumor burden is illustrated. (H) The radial expansion rate of enhancing disease in millimeters per day was estimated using a spherical estimation applied to enhancing volume measurements. (I) The volumetric percentage change in lesion volume (enhancement plus central necrosis) per day is illustrated. (J) The volumetric growth rate of total lesion size is illustrated in cubic centimeters per day. (K) The volumetric doubling time of total lesion size is illustrated in days. (L) The radial expansion rate of total lesion size was estimated using a spherical estimation applied to total lesion volume measurements.

TABLE 2. Average Linear Growth Rates in Untreated, Preoperative Glioblastoma Estimated by Bidirectional Product, Disease Volume (Enhancement), and Total Lesion Volume (Enhancement and Necrosis)

Measurement Type	Average \pm SEM (Median)			
	Percentage Growth Rate, % change/d	Growth Rate, cc/d	Doubling Time, d	Radial Expansion Rate, mm/d
Bidirectional	3.4 ± 0.46 (2.1)	12.7 ± 1.6 (11.4) mm ² /d	50.8 ± 30.9 (22.3)	1.8 ± 0.1 (1.7)
Disease volume	5.9 ± 2.0 (0.7)	-0.09 ± 0.10 (0.06)	38.9 ± 19.3 (4.4)	0.72 ± 0.46 (2.4)
Total lesion volume	6.6 ± 1.7 (1.5)	0.18 ± 0.07 (0.14)	41.0 ± 28.2 (21.1)	1.9 ± 0.4 (3.1)

Abbreviation: SEM, standard error of the mean.

enhancing disease only; total lesion extent, including enhancement and central necrosis). The percentage rate of change (\pm standard error of the mean) in the bidirectional product was approximately $3.4\% \pm 0.46\%$ change per day (median, 2.1% change per day), the percentage

rate of change in enhancing tumor volume was $5.9\% \pm 2\%$ change per day (median, 0.7% change per day), and the percentage rate of change (\pm SEM) in total lesion volume (enhancement and necrosis) was $6.6\% \pm 1.7\%$ change per day (median, 1.5 % change per

day). Although these were fundamentally different measures, the percentage change in these parameters was not significantly different (Kruskal-Wallis test; $P = .063$)

The absolute rate of change in bidirectional product was $12.7 \pm 1.6 \text{ mm}^2$ per day (median, 11.4 mm^2 per day), the change in enhancing disease volume was $-0.09 \pm 0.10 \text{ cc}$ per day (median, 0.06 cc per day), and the change in total lesion volume was $0.18 \pm 0.07 \text{ cc}$ per day (median, 0.14 cc per day) in patients with treatment-naive glioblastoma. In patients who exhibited a positive tumor growth rate, the average volumetric doubling time (VDt) was 50.8 ± 30.9 days (median, 22.3 days) when the spherical approximation to the bidirectional product was used, the average volumetric doubling time for contrast-enhancing disease was 38.9 ± 19.3 days (median, 4.4 days), and the average volumetric doubling time for the total lesion was 41.0 ± 28.2 days (median, 21.1 days). No significant difference in doubling times was observed across the 3 approaches (Kruskal-Wallis test; $P = .12$; note that only data with positive growth rates were included).

Evaluation of the radial expansion rates, which were estimated by spherical approximation of the volumes for bidirectional product measurements, was $1.8 \pm 0.1 \text{ mm}$ per day (median, 1.7 mm per day), radial expansion rates estimated through spherical approximation of enhancing disease volume were $0.72 \pm 0.46 \text{ mm}$ per day (median, 2.4 mm per day), and radial expansion rates estimated through spherical approximation of total disease volume were $1.9 \pm 0.4 \text{ mm}$ per day (median, 3.1 mm per day). Significant differences in radial expansion rate estimates were observed between the 3 estimation techniques (Kruskal-Wallis test; $P = .002$), in which radial growth rates were significantly different when using the bidirectional product compared with the enhancing tumor volume (Dunn test; $P < .001$).

It is important to note that we observed a substantial number of patients (6 of 95 for total lesion and 38 of 95 for enhancing tumor only) who had either stable or slightly shrinking tumors at subsequent time points (Table 1). In the 6 patients who had stable or negative total lesion volumetric growth rates, we hypothesized that this may have been because of an increasing steroid dose between scans or measurement error because of technical factors, including differences in slice prescription, contrast agent concentration, and timing or differences in acquisition parameters. To test whether there was an association between changes in steroid dose and changes in tumor volume, we examined 31 of the 95 patients (33%) who had steroid dose and measurable tumor information avail-

able at both time points. We did not observe an association between the rate of change in tumor volume and the change in steroid dose for these patients ($R^2 = 0.015$; $P = .5149$) (Supporting Fig. 1; see online supporting information), suggesting that the slight decrease in tumor size observed may be a result of measurement error at short-interval follow-up times. In the 31 patients who had stable or decreasing enhanced tumor volumes, all but 6 had stable or increasing total lesion volumes, suggesting that the volume of macroscopic necrotic tissue within the tumor was the source of much of the growth over the observation period.

Correlation of Bidirectional Spherical Estimates of Volume Versus Actual Lesion Volumes

Because bidirectional measurements of tumor extent are used for the current response assessment of glioblastoma, and because there are currently questions regarding the potential added value of volumetric analyses applied to response assessment, our objective was to test whether there was a strong association between spherical estimates of tumor volume calculated from bidirectional measurements and total lesion volume measured using direct segmentation. Spherical estimates of tumor volume calculated from bidirectional measurements appeared to be highly correlated with total tumor volume for both the first and second MRI scans obtained for each patient (Fig. 3A,B), in which the slope of the correlation was 0.93 ± 0.03 ($P < .0001$) and 1.12 ± 0.04 for days 1 and 2, respectively. When combining these data, the association was almost 1:1 (slope, 1.04 ± 0.03 ; $P < .0001$) (Fig. 3C). When examining the change in tumor volume between the 2 time points using both techniques, the association was still statistically significant, although growth rates appeared to be higher when using direct segmentation compared with estimates using bidirectional measurements (slope, 0.75 ± 0.08 ; $P < .0001$) (Fig. 3D).

Dependence of the Percentage Change in Bidirectional and Lesion Volumes on Follow-Up Times and Call of PD

Next, we explored the dependence of the percentage change in bidirectional measurements and total lesion volumes on the probability of calling PD at various times for the first follow-up examination, assuming that all tumors were considered PD because they were treatment-naive. This information may be useful for recommending the minimum time to the first follow-up MRI examination that may be required to call PD with high specificity. By using an increase of 25% for bidirectional measurements⁸

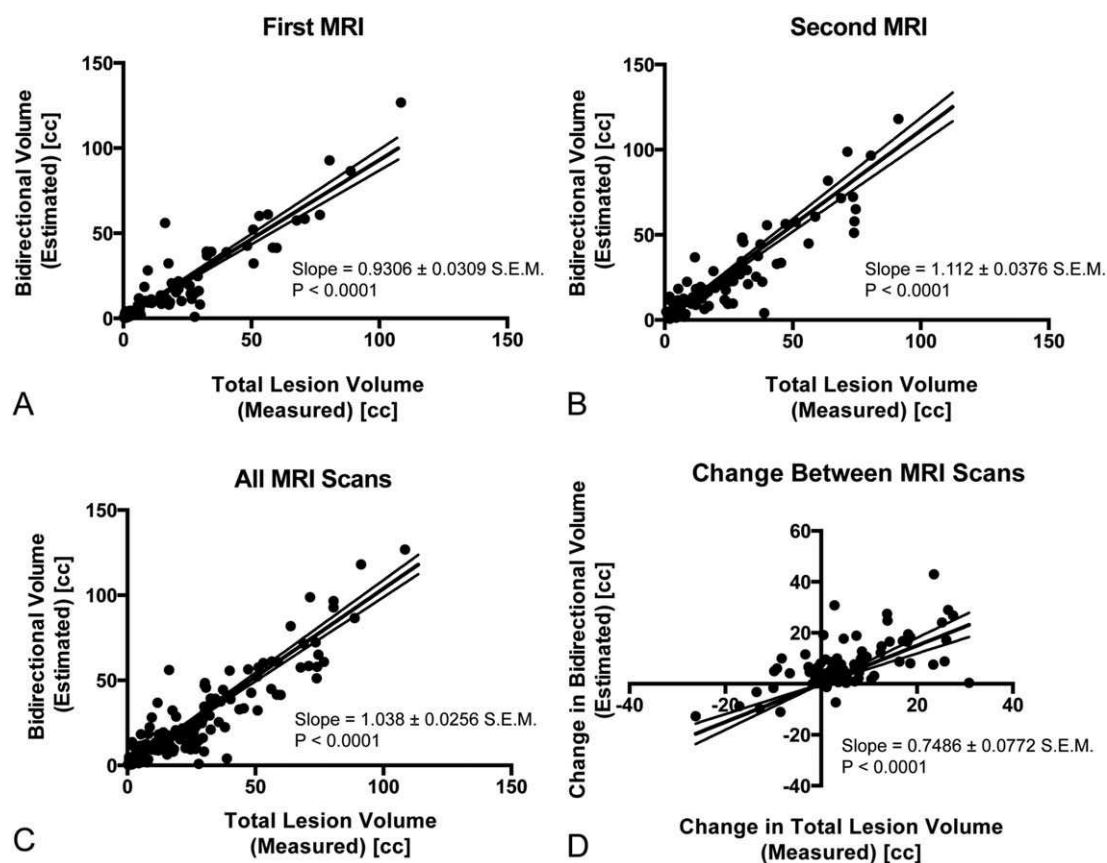


Figure 3. Correlations between bidirectional measurements and total lesion volumetry are illustrated in patients who had treatment-naïve, presurgical glioblastoma. (A) The correlation between bidirectional estimates of tumor volume (using spherical approximation) and total lesion volume ($P < .0001$) during the first magnetic resonance imaging (MRI) examination is illustrated. Note that the slope is approximately unity, suggesting good correspondence between these measurements. (B) The correlation between bidirectional estimates of tumor volume (using spherical approximation) and total lesion volume ($P < .0001$) during the second MRI examination is illustrated. Note that the slope is approximately unity, suggesting good correspondence between these measurements. (C) The correlation between bidirectional estimates of tumor volume (using spherical approximation) and total lesion volume ($P < .0001$) is illustrated when pooling both MRI examinations. Note that the slope is approximately unity, suggesting good correspondence between these measurements. (D) The correlation between change in bidirectional estimates of tumor volume (using spherical approximation) and change in total lesion volume ($P < .0001$) during the 2 MRI examinations is illustrated. Note that the slope is approximately 0.75, suggesting that the change in total lesion volume was greater than the change in volume estimated using the bidirectional product.

to define PD (Fig. 4A-C), the results suggest that a follow-up time > 28 days (1 month) will result in 38% sensitivity and 84% specificity for calling PD, whereas a slightly longer follow-up time of 42 days would result in approximately a 94% specificity for identifying PD (Table 3). When using a 40% increase in total lesion volume¹³ to define volumetric PD (Fig. 4D-F), the results similarly indicated 45% sensitivity and 85% specificity for identifying PD ($> 40\%$ change) when evaluated > 28 days between scans and 92% specificity for identifying PD for follow-up times > 42 days. These results suggest that > 28 days should be required between follow-up MRI examinations in patients with glioblastoma to identify those who have PD with high specificity.

Dependence of the Percentage Change in Bidirectional and Lesion Volumes on Baseline Lesion Size

Next, the relation between a change in tumor size and baseline tumor size was examined (Fig. 5). The results clearly indicated that the percentage change at follow-up is highly biased toward smaller lesions (< 3 cm in greatest dimension or approximately 10 cc total lesion volume) (Fig. 5A,D; Supporting Fig. 2; see online supporting information). When tumors are small at baseline, small changes in tumor size result in high percentage changes. In lesions that measure > 3 cm in greatest dimension, the average change in bidirectional product was approximately 16.5%. We observed no significant correlation

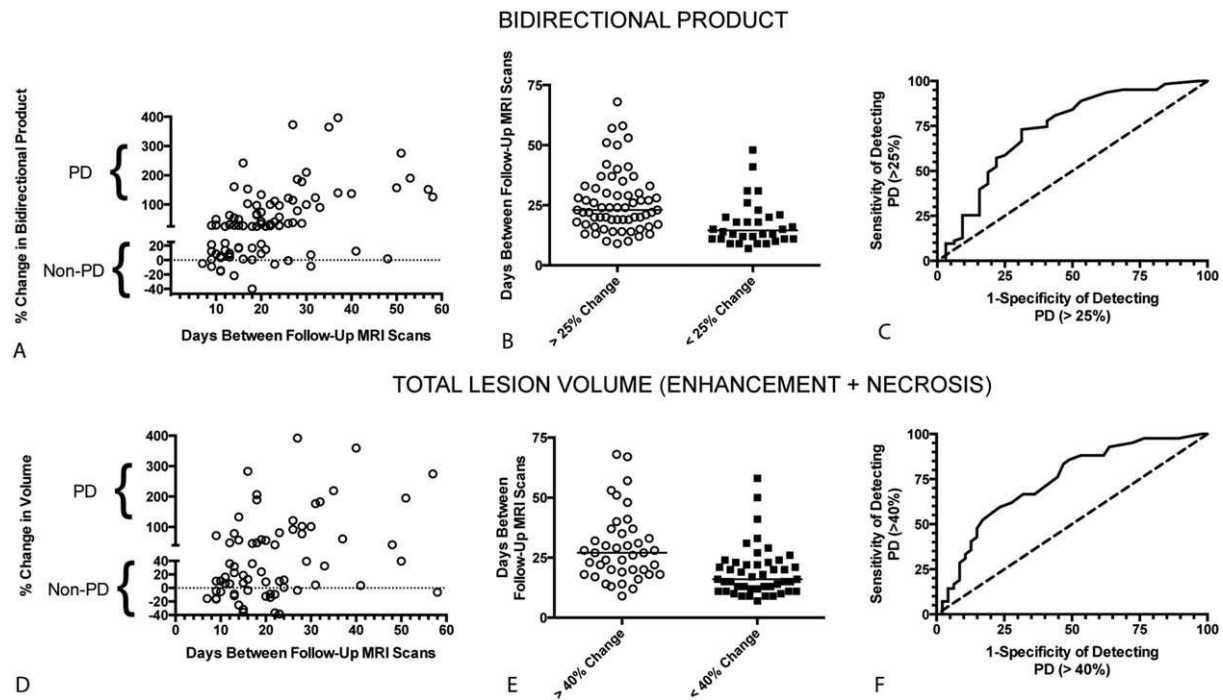


Figure 4. Correlations between the percentage change in tumor size (bidirectional product or total lesion volume) are illustrated as a function of days between follow-up magnetic resonance imaging scans. (A) The percentage change in the bidirectional product estimated from 2 sequential scans is illustrated as a function of the follow-up time between scans. Also included are the corridors for defining progressive disease (PD) as a change $>25\%$ in the bidirectional product. (B) Grouping of patients is illustrated according to whether they would be categorized in the PD group ($>25\%$ change) or the non-PD group ($<25\%$ change). (C) Receiver-operator characteristic (ROC) curves are illustrated for identifying the sensitivity and specificity to detect PD using bidirectional measurements for various follow-up times. (D) The percentage change in total lesion volume from 2 sequential scans is illustrated as a function of the follow-up time between scans. Also included are the corridors for defining PD as a change $>40\%$ in tumor volume. (E) Grouping of patients is illustrated according to whether they would be categorized in the PD group ($>40\%$ change) or the non-PD group ($<40\%$ change) using volumetric criteria. (F) ROC curves for identifying the sensitivity and specificity to detect PD are illustrated using total lesion volume for various follow-up times.

between an absolute change in either bidirectional measurements or absolute total lesion volume measurements and baseline tumor size or the time interval between MRI examinations.

DISCUSSION

Because of the need for rapid surgical intervention upon radiographic detection, very few studies have been published exploring the intrinsic growth kinetics of treatment-naive glioblastoma before surgical or therapeutic interference. Results from the current study are consistent with the study by Stensjoen et al⁴ as well as other previous reports. The median volumetric doubling rate reported in the current study for all glioblastomas was approximately 21.1 days, which is similar to 29.8 days, the median reported in the study by Stensjoen et al.⁴ The median rate of percentage change in tumor volume for our study was approximately 2.1% per day, whereas Stensjoen et al⁴ reported a median rate of 1.4% per day. Our

TABLE 3. Sensitivity and Specificity for Radiographically Identifying Progressive Disease in Treatment-Naive Glioblastoma for Various Follow-Up Examination Times

Follow-Up, d	Bidirectional, %		Total Lesion Volume, %	
	Sensitivity	Specificity	Sensitivity	Specificity
>14	86	49	90	37
>28	38	84	45	85
>42	11	94	18	92
>56	4	97	8	96

results appear to be in the same relative range as the small pilot study by Yamashita and Kuwabara,¹⁴ who reported a mean doubling time of 19.3 days in 6 patients who had relapsed high-grade gliomas. Our results for doubling time, however, were slightly lower than those reported by Blankenberg et al,¹⁵ who documented a median doubling time of approximately 78 days for 9 patients who were

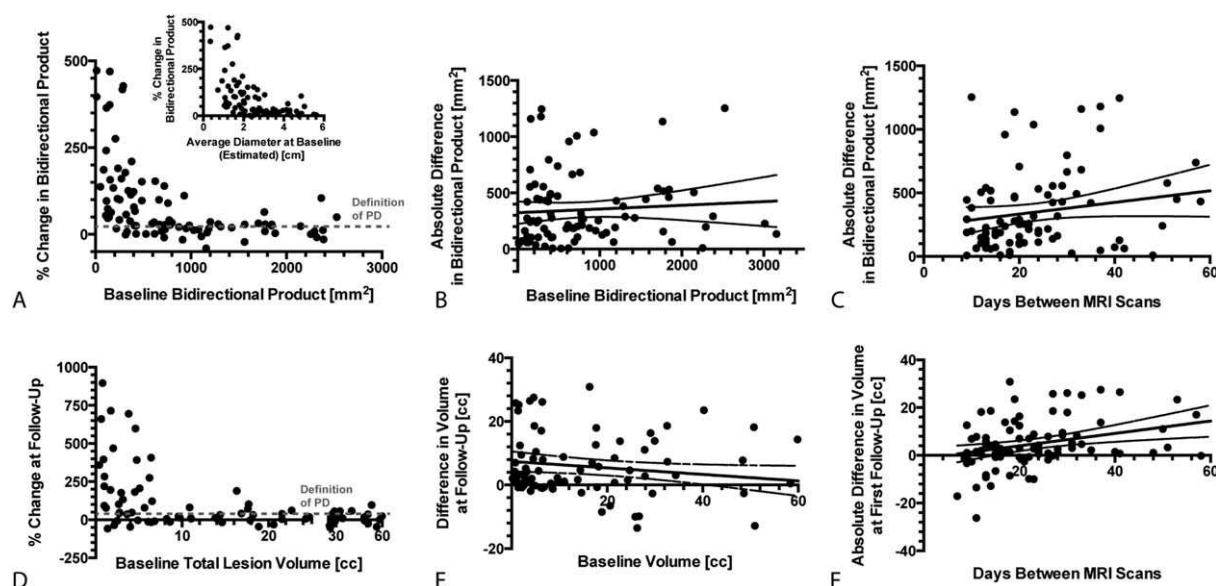


Figure 5. The change in tumor size is illustrated as a function of baseline tumor size. (A) The percentage change in the bidirectional product is illustrated as a function of baseline bidirectional tumor size. The *inset* was based on the same data along with the average greatest tumor dimension estimated from the bidirectional product. These data suggest that small tumors at baseline are likely to exhibit a large percentage change at the first follow-up. (B) The absolute difference in the bidirectional product (in square millimeters [mm^2]) is illustrated as a function of baseline bidirectional tumor size, indicating no real association between initial tumor size and absolute changes in size. (C) The absolute difference in bidirectional product (in mm^2) is illustrated as a function of follow-up time (in days between magnetic resonance imaging [MRI] scans). (D) The percentage change in total lesion volume (enhancement plus central necrosis) is illustrated as a function of baseline total lesion volume. Similar to bidirectional data, volumetric data indicate a bias toward a large percentage change in volume for tumors with small initial volumes. (E) The absolute difference in total lesion volume is illustrated as a function of baseline total lesion volume. Data indicate no real association between initial tumor volume and change in tumor volume. (F) The absolute change in total lesion volume is illustrated as a function of follow-up time between MRI scans.

treated for glioblastoma (World Health Organization grade 4). However, the range of doubling times for that study was from 22 to 181 days, depending on DNA ploidy, which is within the quartile range we observed—specifically, between 14 and 65 days.

In addition to providing a normative range of tumor growth rates for treatment-naïve glioblastoma, the current results suggest that the optimal follow-up between MRI examinations should be >28 days to reliably identify PD with high specificity. This is consistent with the current frequency of clinical monitoring, which typically ranges from 1 to 3 months, depending on the apparent tumor aggressiveness. Also, we observed a significant bias in small tumors (<3 cm in greatest dimension or a 10-cc volume) when using the percentage change in tumor size to characterize response. This observation has dramatic implications in terms of response assessment in clinical trials, in which response and progression are defined in terms of the percentage change from baseline.

It is important to note that the patients who were selected for the current study had slightly smaller total lesion volumes (median, 17cc) compared with the lesion

volumes among patients in previous studies from our institution^{5,6} involving the evaluation of presurgical enhancing tumor volumes (median, 33 cc⁵ and 48 cc⁶; Mann-Whitney test; $P < .0001$ compared with current study) but similar patient demographics (age range, mean Karnofsky performance status, sex, etc) and similar overall survival. This difference suggests that the patients who were able to have multiple scans before initial surgery had smaller tumors at detection and thus were able to have multiple scans before significant medical complications occurred that would require emergency surgical intervention. It remains to be empirically determined whether the growth rates estimated among patients with glioblastoma in the current study differ significantly from those among patients who had larger tumors at diagnosis. Data from the current study suggest that there is not a compelling association between initial tumor volume and the rate of change in tumor volume (Fig. 5), but future investigation is warranted.

Limitations

The ability to acquire serial scans in patients with glioblastoma before they receive any treatment is relatively

difficult because of the need for immediate surgical and therapeutic intervention. Therefore, an inherent limitation to the current study is the relatively low number of patients available for analysis. Also, it is important to mention that the focus of the current study were growth rates of contrast-enhancing and nonenhancing tumors, as assessed with T2 or fluid-attenuated inversion recovery, which were not included in the current study. In addition, we did not observe a significant association between steroid dose and changes in tumor volume; however, the majority of patients in the current study did not have steroid dose information available. This lack of steroid information is a potential limitation to the current study. Finally, it is important to recognize the potential for bias associated with reporting volumetric doubling times after the exclusion of patients who have negative growth rates, particularly when examining “enhancing only” tumors, in which 38 of 95 patients (40%) who had data available exhibited negative growth rates.

Conclusion

In summary, we observed that tumor volumes estimated using spherical approximation to bidirectional measurements of tumor size are highly correlated with total lesion size after segmentation. The results suggest that the optimal follow-up time between MRI examinations should be >28 days to reliably detect PD. The results also indicate that small initial tumor sizes are biased toward large percentage changes in tumor volumes at follow-up.

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CONFLICT OF INTEREST DISCLOSURES

Whitney B. Pope reports personal fees from Genentech/Roche outside the submitted work. Timothy F. Cloughesy reports personal fees from Roche/Genentech, Celgene, Tocagen, VBL Therapeutics, NewGen Therapeutics, Novartis, Upshire-Smith, Proximagen, Lpath, StemCycle, Amgen, CytRx Corporation, Agios, Celldex, Cortice, Novocure, AbbVie, Oxigene, Nektar, and Wellcome Trust outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Benjamin M. Ellingson: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition. Huytram N. Nguyen: Conceptualization, methodology, validation, and writing—review and editing. Albert Lai: Conceptualization, methodology, resources, data curation, and writing—review and editing. Ruben E. Nechifor: Conceptualization, methodology, validation, and writing—review and editing. Okkar Zaw: Conceptualization, methodology, validation, and writing—review and editing. Whitney B. Pope: Conceptualization, methodology, validation, and writing—review and editing. William H. Yong: Conceptualization, methodology, validation, and writing—review and editing. Phioanh L. Nghiemphu: Conceptualization, methodology, validation, and writing—review and editing. Linda M. Liau: Conceptualization, methodology, validation, and writing—review and editing. Timothy F. Cloughesy: Conceptualization, methodology, validation, and writing—review and editing.

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