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ORIGINAL ARTICLE - TUMOR - GLIOMA

Radiology reporting of low-grade glioma growth underestimates tumor expansion

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Abstract

Background An important aspect in the management of patients with diffuse low-grade gliomas (LGGs) involves monitoring the lesions via serial magnetic resonance imaging (MRI). However, radiological interpretations of LGG interval scans are often qualitative and thus difficult to use clinically.

Methods To contextualize these assessments, we retrospectively compared radiological interpretations of LGG growth or stability to volume change measured by manual segmentation. Tumor diameter was also measured in one, two, and three dimensions to evaluate reported methods for assessment of glioma progression, including RECIST criteria, Macdonald/RANO criteria, and mean tumor diameter/ellipsoid method.

Results Tumors evaluated as stable by radiologists grew a median volume of 5.1 mL (11.1%) relative to the comparison scan, and those evaluated as having grown had a median volume increase of 13.3 mL (23.7%). Diameter-based measurements corresponded well but tended to overestimate gold standard segmented volumes. In addition, agreement with segmented volume measurements improved from 17.6 ± 8.0 to 4.5 ± 5.8 to 3.9 ± 3.6 mm for diameter and from 104.0 ± 96.6 to 25.3 ± 36.8 to 15.9 ± 21.3 mL for volume with radiological measurements in one, two, and three dimensions, respectively. Measurement overestimation increased with tumor size.

Conclusions Given accumulating evidence that LGG volume and growth are prognostic factors, there is a need for objective lesion measurement. Current radiological reporting workflows fail to appreciate and communicate the true expansion of LGGs. While volumetric analysis remains the gold standard for assessment of growth, careful diametric measurements in three dimensions may be an acceptable alternative.

Keywords Low-grade glioma · Neuro-oncology · MRI · Longitudinal growth quantification

Introduction

There is consistent evidence that diffuse low-grade gliomas (LGGs) grow slowly but persistently before eventually evolving into aggressive high-grade tumors [1–5]. Serial imaging with MRI is one of the primary methods of monitoring LGG growth, treatment efficacy, and disease recurrence. Because LGGs exhibit gradual expansion and irregular morphology, growth can be difficult to visually determine between consecutive scans. However, changes in lesion volume on imaging are typically assessed qualitatively by radiologists who may report tumor stability without direct measurement or comparison to scans beyond the most recent.

LGG growth, as measured by diameter and volume, has been shown through a number of retrospective studies to predict patient prognosis. Tumors with faster growth have shorter overall survival (OS) and progression-free survival (PFS) [2,

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6–9]. Initial tumor volume has been found to correspond to clinical outcomes, with larger lesions being more likely to transform sooner [2, 5, 6, 10]. Despite the prognostic significance of these features, they are not commonly used in clinical practice. The majority of studies on the growth dynamics of LGGs use diametric growth, or velocity of diametric expansion (VDE), which only requires measuring the largest diameter in three orthogonal planes rather than measurement of the entire tumor volume.

Criteria for evaluating and reporting glioma size changes include the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which were designed for general solid tumors [11], the Macdonald criteria [12], and the Response Assessment in Neuro-oncology (RANO) criteria [13]. The Macdonald criteria were originally developed to evaluate volume changes in contrast-enhancing high-grade gliomas (HGGs) in clinical trials. The criteria define "progressive disease" as a 25% increase in the product of perpendicular diameters of the lesion, equivalent to a 40% volume increase. The RANO group and guidelines were established to improve upon the limitations of the Macdonald criteria [13, 14]. It similarly requires a 25% increase in the product of perpendicular diameters for a lesion to be considered "progressive." Both the Macdonald and RANO criteria have been adapted for assessing LGGs [14–16].

Despite established guidelines for tumor evaluation in clinical trials, LGG measurement is not commonly performed in clinical practice. Rather, qualitative assessments by radiologists remain the primary method of evaluating tumor change. To highlight the limitations of visual inspection, we present a comparison between 103 radiological interpretations of LGG change and the actual tumor volume change as measured by manual segmentation on MRI. We also include a case to illustrate the discrepancy between the language commonly used in radiology reports and the actual progression of the tumor (Fig. 1).

Methods

A cohort of LGG patients ($n = 10$) with imaging over many years was previously described [10]. These patients were managed by watchful observation for an extended period of time without oncological treatment. Tumors on serial T_2-weighted MRIs during this pre-treatment management phase were manually segmented using ITK-SNAP (version 3.6.0) [17] to obtain volume measurements, which were described previously [10]. Interrater and intrarater error were quantified by mean Dice coefficient and reported previously for the MRIs of this cohort (intrarater, C.G. 0.867; interrater, C.G. and S.E.K. 0.914) [10]. These measurements of the tumor's volume over time were used for further analysis in this study.

Linear measurements were made for each scan as follows. RECIST measurements were taken as the longest diameter on an axial plane. RANO measurements were the product of the longest diameter on an axial and its longest perpendicular diameter on the same slice. The mean tumor diameter/ellipsoid method was calculated as the mean of the three longest diameters in the axial, sagittal, and coronal views. The ellipsoid tumor volume was determined assuming the lesion was ellipsoid in shape: $Volume = \frac{4}{3}\pi abc$, where a, b, and c are the maximal radii in three orthogonal dimensions. We evaluated standard radiological measurements for diameter and volume against manual segmentation and assessed for a relationship using adjusted coefficient of determination (R^2) and agreement using Bland-Altman plots [18].

Volumetric information (current tumor volume, tumor volume on comparison scan) was acquired for a total of 103 radiology interpretations. The actual growth between two scans compared by a radiologist was calculated as the difference between the segmented volumes of the scans. Changes in both absolute volume and percent volume were calculated. The patient with the tumor growing at the median rate of the cohort was chosen for the case illustrated in Fig. 1.

All analyses were performed in R (version 3.5.1), and the Mann-Whitney U test was used to compare the volumes of tumors that were categorized as stable to those categorized as having grown.

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This work was approved as a retrospective chart review by Western University's Research Ethics Board.

Results

Radiology assessments of tumor volume change were assigned to categories of "no change" ($n = 67$) or "change" ($n = 36$). Key phrases for this categorization are summarized in Table 1. When a report expressed comparisons with more than one previous scan, each comparison was treated as an individual interpretation.

Among tumors that were evaluated as no change by radiologists, volumetric measurements revealed a median volume growth of 5.1 mL (11.1%) compared to previous imaging. Among tumors that were interpreted as having grown (change), a median growth of 13.3 mL (23.7%) was measured. The measured absolute and percent volume growth in tumors reported as having grown (change) were significantly greater than the volume increases of tumors that were classified as stable (no change) ($P < 0.001$) (Fig. 2). Scans radiologists used for comparisons were acquired at a median time period of 200.5 days prior to the scan of interest (range, 27–1289 days).

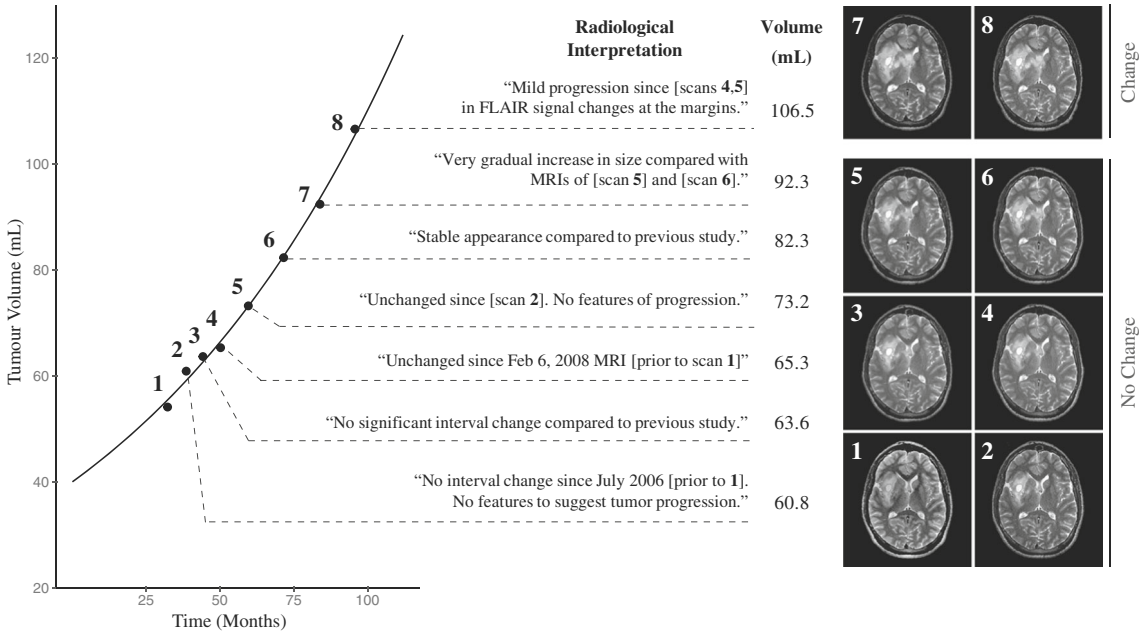

Fig. 1 Tumor growth trajectory on MRI and corresponding radiological interpretations of a 39-year-old male who presented with a right-sided frontal-temporal (insular) oligodendroglioma. On scans 1–6, the tumor was evaluated as stable. On scans 7 and 8, the tumor was evaluated as having grown

Of the 103 interpretations, 20 (19.4%) included tumor measurements by the radiologist. Of these, 14 included measurements along 3 axes (70%), 2 contained measurements of 2 axes (10%), and 4 contained measurement along a single axis (20%). No significant difference was found in the growth between tumors that were measured and not measured (volume, $P = 0.223$; percent volume, $P = 0.084$).

Concordance was assessed between the tumor diameter calculated from segmented volume ("segmented tumor diameter") and each of maximal one-dimensional diameter, the mean of the two perpendicular (two-dimensional) diameters used in Macdonald/RANO criteria, and the mean of the maximal diameters in three dimensions. Association with segmented tumor diameter improved with further measurement, from a R^2 of 0.875 for maximal diameter and mean of RANO diameters to 0.951 for the mean of three maximal diameters (Fig. 3b). Mean difference from segmented tumor diameter improved from 17.6 ± 8.0 mm (95% CI 1.9 to 33.3 mm) for measurements in one dimension to 4.5 mm ± 5.8 (95% CI − 6.8 to 15.8 mm) for two dimensions to 3.9 mm ± 3.6 (95% CI − 3.2 to 10.9 mm) for three dimensions (Fig. 4). Volumes estimated from RECIST, Macdonald/RANO, and three-dimensional diameter, assuming an ellipsoid shape, were evaluated for concordance with segmented tumor volume. Agreement with segmented tumor volume similarly improved with additional measurements from a mean difference of 104.0 ± 96.6 mL (95% CI − 85.3 to 293.3 mL) for measurements in one dimension (RECIST) to 25.3 ± 36.8 mL (95% CI − 46.9 to 97.6) for two dimensions (RANO) to 15.9 ± 21.3 mL (95% CI − 25.8 to 57.7 mL) for three dimensions. The Bland-Altman plots additionally highlight that systematic biases worsened with increasing tumor size for all measurement methods (Fig. 4).

Table 1 Keywords in radiological interpretation categories

No change	Change
Stable	Slightly increased
No interval change	Subtle increase
Size of mass appears similar	Slight progression
Minimal change	Marginal increase
Unchanged	Gradual increase
	Increased bulk
	Progressive change

Discussion

LGGs and other brain tumors are often monitored by serial MRI, but radiological assessment of the imaging is generally qualitative. Our analysis revealed a median tumor growth of 5.1 mL (11.1%) when reports described no change and a median growth of 13.3 mL (23.7%) when reports described change. We also compared the ellipsoid method of volume calculation, where volume is derived from the largest diameters in three planes to segmented tumor volume, and found it to be a reasonable alternative, with a coefficient of determination of 0.945 ($P < 0.001$) (Fig. 3). Estimates of tumor diameter improved from a

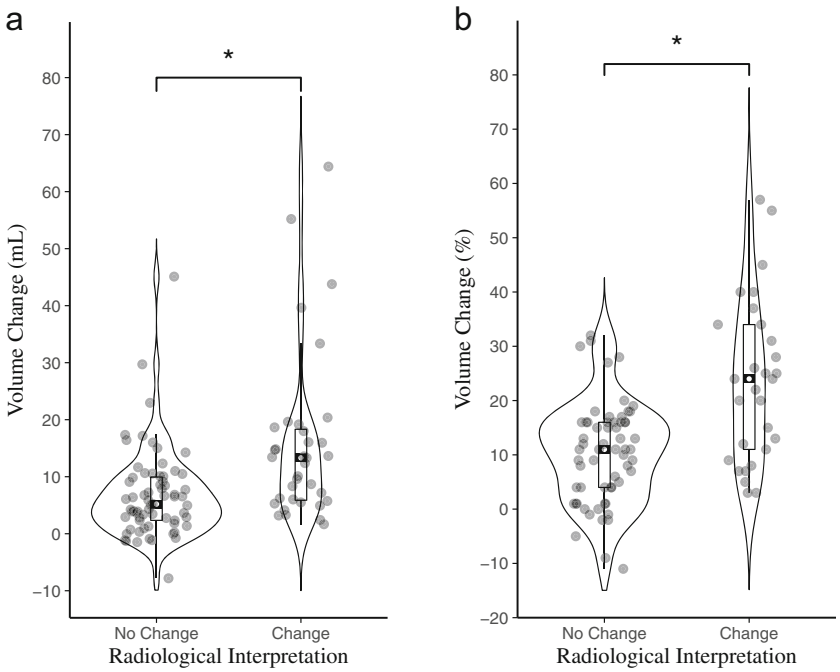

Fig. 2 Measurements of **a** absolute volume and **b** percent volume change in low-grade gliomas that were interpreted by radiologists as stable ("no change") or having grown ("change") compared to a previous scan. The amount of growth in tumors interpreted as having grown was significantly greater than that in tumors interpreted as stable (*$P < 0.001$)

mean difference of 17.6 to 4.5 to 3.9 mm for one-, two-, and three-dimensional measurements, a 4.5-fold improvement from one to three measurements. Similarly, estimates of tumor volume improved from a mean difference of 104 to 25.3 to 15.9 mL, a 6.5-fold improvement in agreement.

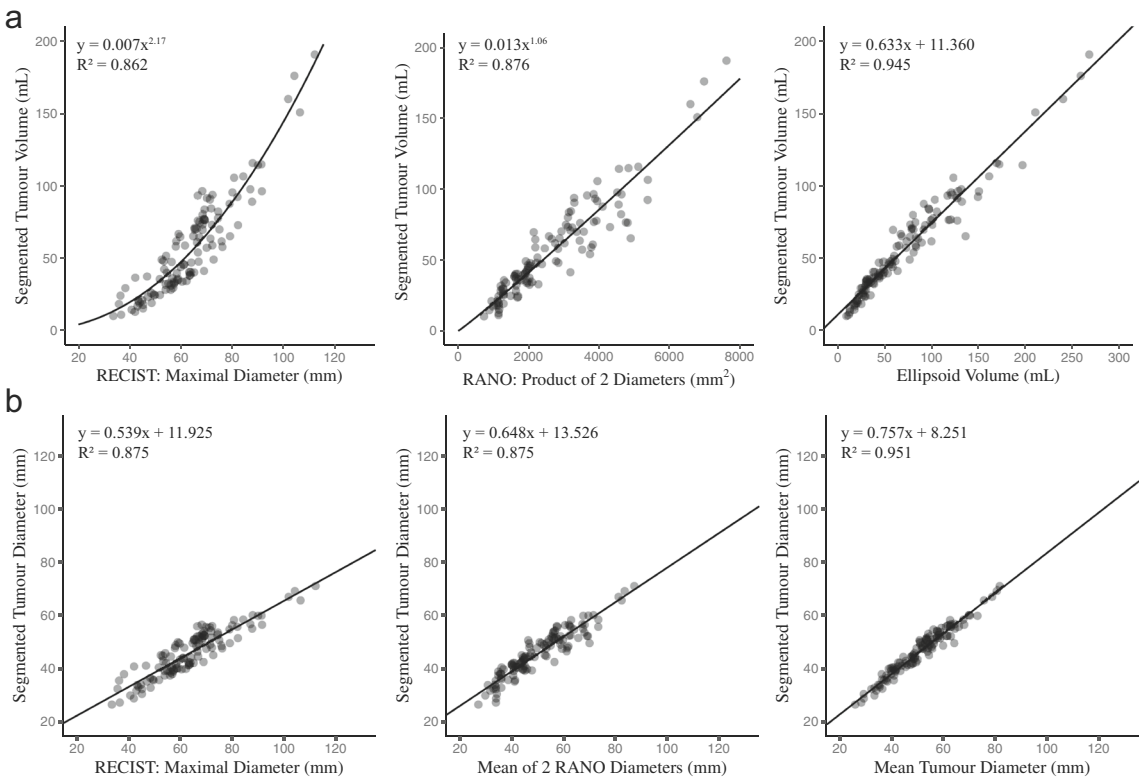

Fig. 3 Comparison of RECIST (maximal diameter in one dimension), Macdonald/RANO (product of longest diameter and longest perpendicular diameter), and ellipsoid tumor volume (calculated from three largest orthogonal diameters assuming ellipsoid shape) measuring methods to **a** segmented tumor volume and **b** diameter derived from segmented tumor volume

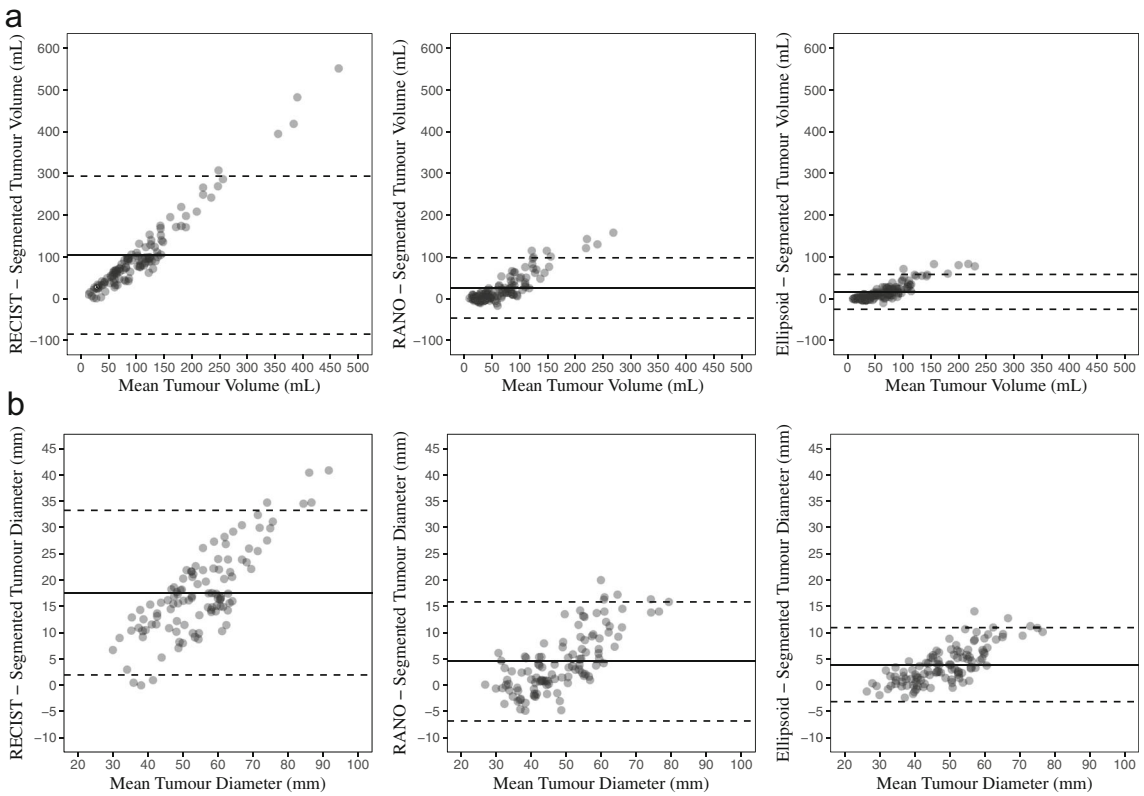

Fig. 4 **a** Bland-Altman plots assessing association between segmented tumor volume and each of volume calculated from one-dimensional diameter measurement (RECIST), two-dimensional diameter measurement (RANO), and three-dimensional diameter measurement. **b** Bland-Altman plots are used for assessing agreement between diameter derived from segmented tumor volume ("segmented tumor diameter") and each of one-dimensional diameter measurement (RECIST), mean of two-dimensional diameter measurement (RANO), and mean of three-dimensional diameter measurement. Measurements in fewer diameters overestimate both **a** tumor volume and **b** tumor diameter, with greater overestimation of larger tumors. Solid lines represent the mean difference between **a** volumes or **b** diameters obtained by the tested measurement method and segmented tumor **a** volume or **b** diameter. Dashed lines represent 95% confidence intervals. Variability also decreased with increasing measurements

To the best of our knowledge, there have been no previous analyses of clinical radiological assessments of LGG growth/stability. Jakola et al., however, published a report of a case that documented the disparity between radiological interpretations of "no sign of growth" 12 and 22 months after discovery of the lesion and retrospective volumetric measurements that revealed increases of 12% and 10% between consecutive scans [19]. These values are consistent with the 11.1% of growth we found among tumors evaluated as stable. Interestingly, though this tumor was much smaller than those in our cohort (2.74 mL vs. median 30.31 mL on index MRI), the percent tumor volume change seems consistent among scans that are evaluated as stable. In the case described, when growth was radiologically detectable at 32 months and three studies after lesion discovery, a 63% change in volume had occurred since the previous scan and a change of 101% since the index scan [19].

Despite the publication of RANO and other guidelines, we found that qualitative assessments ($n = 83/103$) vastly outnumbered interpretations that included linear measurements ($n = 20/103$) among the radiology reports we examined. Even among tumors measured, four of the measurements were in one dimension and two were in two dimensions. The one-dimensional measurements are in line with the RECIST criteria for systemic tumors [11]. Importantly, these criteria specify that progression constitutes a 20% increase in diameter. This corresponds to a volume increase of 73% [20], deviating greatly from the Macdonald and RANO criteria, which require only 40% change in volume (25% change in the product of two diameters) for disease progression, and include additional recommendations for glioma assessment that RECIST do not. RECIST has furthermore not been validated among LGGs specifically and, among the methods we assessed, was most prone to overestimating tumor volume and mean diameter (Figs. 3 and 4). For these reasons, RECIST and one-dimensional measurements should generally not be used for glioma measurement. Our volume comparisons to radiology reports show that radiologists are able to visually appreciate change at a median of 23.7% volume growth and thus would likely notice the 40% volume required described by the Macdonald and RANO criteria. However, an expansion of this degree

between consecutive scans may not occur until late in the disease course. Small changes on consecutive scans that are interpreted as stable, which would typically already indicate a median of 11.1% change by our analysis, may add up to 40% over a few scans.

Different methods for measuring the progression of gliomas have been previously compared [15]. Linear measurements in one-dimensional (in accordance with the RECIST criteria), two-dimensional (in accordance with WHO, Macdonald, and RANO methods), and three-dimensional volumes were used to study the growth of 31 non-enhancing gliomas in a cohort a of 67 glioma patients [15]. Among scans of the non-enhancing tumors, fewer tumors were categorized as progressing when area and volume were measured ($n = 4$, $n = 3$) than when one-dimensional and two-dimensional measurements were made ($n = 13$, $n = 15$), suggesting that the latter measurements overestimate tumor expansion [15]. Criteria typically require measuring maximal diameter, and our analyses similarly showed that maximal linear diametric measurements overestimated tumor size compared to volumetric evaluation (Fig. 4). While agreement between standard radiological metrics and manual volumetry was identified, Bland-Altman plotting clearly demonstrates a disparity that notably increases with increasing lesion size. Correlation between one-dimensional and two-dimensional measurements among both enhancing and non-enhancing gliomas has been demonstrated, but such measurements were found to be prognostic for only HGGs and not LGGs [15]. Among LGGs, only three-dimensional diameter and volume measurements were predictive of clinical outcome, suggesting that non-enhancing gliomas may be more difficult to accurately measure using only linear measurements [15]. Other studies on the reliability of different measurements have primarily focused on HGGs, with mixed results. Some have shown that measurements by the Macdonald/RANO methods overestimate tumor size, are subject to high interrater variability, and may not be predictive of clinical outcomes [21–23]. However, at least two studies have shown that disease classification into complete response, partial response, progressive disease, and stable disease by RECIST, RANO, and three-dimensional linear measurements was predictive of HGG clinical outcomes [15, 24], though this effect was only detectable at 2 months and lost at 6 months in one of the studies [24].

The optimal measurement of LGGs specifically has been less studied than HGGs. In our analysis, we found that the ellipsoid volume calculated from the three largest orthogonal diameters corresponded well with segmented tumor volume ($R^2 = 0.945$). An association was also noted between the diameter derived from the segmented volume and the mean of the largest diameters in three planes ($R^2 = 0.951$). Comparisons of the mean of the RANO two-dimensional measurements and the largest one-dimensional diameter according to RECIST to the diameter derived from segmented volume showed close correlation as well ($R^2 = 0.875$, 0.875). Measurements in more dimensions yield superior correlation. Notably, however, all three of these measurements overestimate the diameter and calculated volume compared to the segmented values. Bland-Altman plotting revealed that additional dimensional measurements improve the agreement while decreasing the variability, yet even still larger tumor sizes increased overestimation (Fig. 4). Another factor that favors measuring in three dimensions to obtain mean tumor diameter is that the majority of published work on growth rates of LGGs use this method [1–3, 8–10]. If used for prognostication, standardization of measuring methods to assess size and growth rate is needed. Methods that overestimate tumor size, especially as the lesions enlarge, as one- and two-dimensional diameter measurements do, would overestimate growth rate and underestimate PFS and OS.

One difficulty in assessing LGGs is their irregular morphology, which can lead to challenges in the reproducibility of linear diameter measurements; that is, the percent change in tumor size may vary depending on the axis chosen [22, 23]. In a study on measuring methods of glioblastoma multiforme, the use of two-dimensional rather than volume measurements changed the tumor progression classification in 6 of 23 patients (26%) [23]. Imaging parameters such as MRI slice thickness and head rotation further decrease the reliability of these measurements [25]. Some groups have thus advocated for volume measurement instead [3, 23, 25, 26]. Though the gold standard for measuring tumor volume on MRI is manual segmentation, the logistical and time requirements are currently barriers to its incorporation into routine practice. Linear measurements in three dimensions have been reproducibly prognostic of clinical outcomes and may be a viable alternative to volumetric analysis. As we and others have demonstrated, volume can be derived from the three diameters, assuming an ellipsoid shape, and vice versa. We found an acceptable correspondence between the calculated ellipsoid volume and the segmented volume ($R^2 = 0.945$) although agreement worsens with larger tumors (Fig. 4). In summary, until volumetric tools are easily accessible, we suggest measuring the three largest diameters to calculate and monitor mean diameter and total volume over time while being cognizant that linear measurements alone are not without bias.

Limitations of this study include the following. This cohort of LGGs consists of particularly slow-growing tumors of the IDH mutated, 1p19q co-deleted oligodendrogliomas. Thus, the reported median values for detectable and undetectable growth may not be generalizable to other LGGs. One advantage of this, however, is that our findings likely represent the sensitivity limits of visual assessment given the unusually slow growth of these ten patients' tumors. Other sources of error include interrater and intrarater variability in

segmentation, which have been quantified by the Dice similarity coefficient. Lastly, the analysis of radiological interpretations was performed on reports from a single institution, and interinstitutional differences in protocols for tumor measurement and radiological reporting may be sources of variability.

Conclusion

Tumor growth parameters are not commonly used in clinic although several studies have shown that growth and growth rates predict time to malignant transformation and overall survival. Radiology reports that describe tumor stability or growth in a qualitative manner currently tend to underestimate LGG expansion, which can be difficult to discern without volumetric analyses. Given the prognostic significance of tumor volume and linear growth rate, the management of LGGs should ideally evolve to include the consideration of these growth parameters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional research committee, Western University's Research Ethics Board, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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