Response Assessment of Meningioma: 1D, 2D and Volumetric Criteria for Treatment Response and Tumor Progression

Raymond Y. Huang[1], Prashin Unadkat[1], Wenya Linda Bi[2], Elizabeth George[1], Matthias Preusser[3], D. Jay McCracken[4], Joseph R. Keen[5], William L. Read[4], Jeffrey J. Olson[4], Katharina Seystahl[6], Emilie Le Rhun[7], Ulrich Roelcke[8], Susanne Koeppen[9], Julia Furtner[10], Michael Weller[6], Jeffrey J. Raizer[11], David Schiff[12], Patrick Y. Wen[13]

1 Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115, USA.

2 Center for Skull Base and Pituitary Surgery, Department of Neurosurgery, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts, 02115, USA

3 Clinical Division of Oncology, Department of Medicine I, Comprehensive Cancer Centre, Medical University Vienna - General Hospital, Vienna, Austria

4 Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia 30322 USA

5 Department of Neurosurgery, Ochsner Medical Center, New Orleans, LA USA

6 Department of Neurology, Clinical Neuroscience Center, University Hospital Zurich and University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland

7 Univ. Lille, U-1192, F-59000 Lille, France; Inserm, U-1192, F-59000 Lille, France; CHU Lille, General and Stereotaxic Neurosurgery service, F-59000 Lille, France; Oscar Lambret Center, Neurology, Medical Oncology Department, F-59000 Lille, France;

8 Department of Neurology and Brain Tumor Center Cantonal Hospital Aarau Tellstrasse 1 5001 Aarau Switzerland

9 Department of Neurology Clinic, Essen Medical Center, Essen, Germany

10 Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria

11 Medical Neuro-Oncology, Northwestern Medicine, 710 N. Lake Shore Dr.; Abbott Hall-Room 1123, Chicago, IL 60611, USA

12 Departments of Neurology, Neurological Surgery, and Medicine, University of Virginia, Box 800432 ,Charlottesville, VA 22908 USA

13 Center For Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, 450 Brookline Avenue, Boston, MA, 02215, USA.

Corresponding Author: Raymond Y. Huang MD. PhD

Address: Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115

Telephone: 617-732-7260

E-mail: ryhuang@bwh.harvard.edu

Conflict of Interest statement(s): All authors declare no conflict of interest relevant to this study.

Funding Sources: R.H is supported by the ARRS/ASNR Scholar award.

Abstract

Background

Meningiomas are the most common primary brain tumors in adults. Due to their variable growth rates and irregular tumor shapes, response assessment in clinical trials remains challenging and no standard criteria has been defined. We evaluated 1D, 2D, and volume imaging criteria to assess whether a volumetric approach might be a superior surrogate for overall survival (OS).

Methods

In this retrospective multicenter study, we evaluated the clinical and imaging data of 93 patients with recurrent meningiomas treated with pharmacotherapy. 1D, 2D, and volumetric measurements of enhancing tumor on pre- and post-treatment MRI were compared at 6 and 12 months after treatment initiation. Cox proportional hazards models were used to examine the relationship between each imaging criterion and OS.

Results

The median age of the patient cohort is 51 years old (range 12-88), with 14 WHO grade 1, 53 WHO grade 2, and 26 WHO grade 3 meningiomas. Volumetric increase of 40% and unidimensional increase by 10 mm showed the highest hazard ratios versus OS at both 6 months (HR= 2.58, 95%CI: [1.31-5.07], p=0.006) and 12 months (HR= 3.24, 95%CI: [1.49-7.0], p=0.002) after treatment initiation. Volume threshold above 40% did not show improved survival association. The inter-observer agreement of 1D, 2D and volume criteria is only moderate (kappa=0.49, 0.46, 0.52 respectively). None of the criteria based on tumor size reduction were associated with OS (p>0.09).

Conclusion

Compared to 1D (RECIST 1.1) and 2D (RANO) approaches, volumetric criteria for tumor progression has a stronger association with overall survival, although the differences were only modest. The inter-observer variability is moderate for all three methods. Further validation of these findings in an independent patient cohort is needed.

Authorship statement:

1. Study Design and Conception: Raymond Y. Huang, Patrick Y. Wen
2. Data Collection: Raymond Y. Huang, Matthias Preusser, D. Jay McCracken, Joseph R. Keen, William L. Read, Jeffrey J. Olson, Katharina Seystahl, Emilie Le Rhun, Ulrich Roelcke, Susanne Koeppen, Julia Furtner, Michael Weller, Jeffrey J. Raizer, David Schiff, Patrick Y. Wen
3. Data Analysis: Raymond Y. Huang, Prashin Unadkat, Wenya Linda Bi, Elizabeth George, Patrick Y. Wen
4. Manuscript writing and editing: Raymond Y. Huang, Prashin Unadkat, Wenya Linda Bi, Elizabeth George, Matthias Preusser, D. Jay McCracken, Joseph R. Keen, William L. Read, Jeffrey J. Olson, Katharina Seystahl, Emilie Le Rhun, Ulrich Roelcke, Susanne Koeppen, Julia Furtner, Michael Weller, Jeffrey J. Raizer, David Schiff, Patrick Y. Wen

Running title: Imaging Response Assessment of Meningioma

Keywords: Meningioma, Volume, Response, MRI, Survival

Key points

1. Volumetric progression criteria for meningioma is strongly associated with OS.
2. Measurement variability is similarly moderate for 1D, 2D and volumetric criteria.

Importance of Study

Meningiomas are the most common primary brain tumors in adults, with a subset requiring multiple surgeries and radiation over time. Due to their variable growth rates and irregular tumor shapes, consistent measurement for response assessment in clinical trials for recurrent meningiomas remains challenging and no standard criteria has been defined for the evaluation of response. Volumetric approach provides more accurate estimate of tumor burden but is also relatively more time-consuming and technical challenging. Using a multi-center data set of patients with recurrent meningiomas, we conducted a retrospective evaluation of 1D, 2D, and volume imaging criteria to assess whether a volumetric approach might be a superior surrogate for overall survival (OS). Our analyses showed that, compared to 1D and 2D approaches, volumetric criteria for tumor progression has a stronger association with OS and a lower inter-observer variability. While the observed improvement is only modest, our results prompt the need for further validation of volumetric criteria in future trials.

Introduction

Meningiomas are the most common primary brain tumors in adults, accounting for over 35% of all brain tumors.[1] Each year, more than 25,000 meningiomas are diagnosed in the United States. The World Health Organization (WHO) categorizes meningiomas into three grades using histopathologic criteria[2]. While most WHO grade I meningiomas can be cured with surgical resection, total resection may not be achievable for some patients due to location of the meningioma. WHO grades II and III meningiomas have a propensity to recur and are frequently treated with adjuvant radiation[3]. Nonetheless, a subset of patients treated with radiation therapy eventually progress and require further therapy[4]. Patients with recurrent meningiomas may

require multiple surgeries, radiation, brachytherapy, and attempts at pharmacotherapy. While clinical trials of systemic therapies for meningiomas to date have not shown significant benefit until now,[5] recent advances in our understanding of meningioma biology have led to clinical trials of targeted therapies and immunotherapies.[6]

Defining a threshold of progression that requires a pharmacotherapeutic approach as well as defining the optimal endpoint for clinical trials in meningioma is problematic. While the growth rates of meningiomas are variable, overall survival (OS) is often very long, and even progression-free survival (PFS) requires long-term follow-up. In addition, the radiographic response rates were low for historical medical therapy trials of all meningioma grades.[7] Thus, the same criteria used to evaluate other tumor types including high-grade glioma[8] or metastases[9] may not be sensitive to meningioma size change. Volumetric analysis of MRI data has been proposed as a better method for detecting change in slowly evolving brain tumors[10].

It is unclear whether volumetric approach offers significant advantage over 1D and 2D methods that are commonly used for brain tumor measurements. In contrast to intra-parenchymal tumors, meningioma growth often conforms to the contour of extra-axial structures such as the calvarium, skull base, and dural invaginations. This raises the question as to whether one or two-dimensional diameter measurements, unlike volumetric approach, can be consistently obtained or even represent the full tumor size.

In this study, we evaluated longitudinal MRI imaging data from a retrospective multicenter cohort of patients with recurrent meningioma who were treated with systemic agents for clinical management or as part of clinical trials [11,12,13,14,15,16]. Response criteria based on volumetric measurements were compared to those based on 1D and 2D measurements to determine which imaging criteria has the strongest correlation with overall survival and the greatest reproducibility.

Method

Patients

This multi-center retrospective study was approved by institutional review boards of local institutions of participating sites, and the requirement for informed consent was waived at all sites. Patients were identified using the following inclusion criteria: 1. Patients with histologically proven meningiomas who were treated with first- or second-line systemic therapy; 2. At least one baseline MRI exam within three months before initiation of therapy was available. 3. Post-therapy MRI until progression or last follow-up date with frequency of imaging as determined by clinical or trial-specified protocol of each contributing site; 4. MRI exams consisting of a gadolinium-enhanced T1-weighted sequences with no more than 7 mm slice thickness. Clinical variables including age, histological grade, number of prior surgical resections, radiation treatments, stereotactic surgery (SRS), and systemic therapies were also collected. For a subset of patients, the clinical and imaging data have been collected as part of previously published clinical trials [11,12,13,14,15,16] or retrospective clinical studies.

One dimensional, 2-dimensional and volumetric measurements of contrast enhancing tumor

Semi-automatic volumetric segmentation of tumor on gadolinium-enhanced T1-weighted imaging was performed. Tumor segmentations were done using 3D Slicer Software (version 4.4, Boston, MA)[17]. Robust Statistics Segmentation (RSS) tool[18] were used to provide initial contour of enhancing abnormalities. The resultant segmented volume contours were then overlaid with source images and edited by a radiologist to manually add pixels for tumor regions not included in the preliminary contour or remove pixels for non-tumor regions such as surgical

scars or areas of radiation necrosis that were included in the preliminary contour. The tumor volumes (in cubic centimeters) were calculated by multiplying the total pixel counts with pixel volume. In addition, one-dimensional diameter measurements as well as 2-dimensional diameter product were recorded (supplemental figures 1 and 2). For patients with multifocal measurable tumors, each parameter was calculated by summing the measurements from up to 5 target lesions. To determine inter-observer variability of volumetric measurement, two independent sets of volume measurements were performed, one by a second radiologist using the same software and the third set by a neurosurgeon using BrainLab Elements (BrainLab Munich, Germany). For each patient, tumor location (convexity vs skull base), tumor shape (nodular vs en plaque), and maximum MRI slice thickness were also determined at time of imaging evaluation. Volume growth rates (in cubic centimeter per 6 months) were calculated by linear fitting of tumor volume measured on at least two MRI studies.

Following calculation of tumor volume, we examined several threshold values for 1D, 2D and volumetric measurements in defining progression and response. Since currently there is no standard imaging criteria for meningioma trials, we evaluated several traditional cut-off values based on 1D (RECIST 1.1)[19] and 2D criteria (RANO) criteria[20] that are intended for solid tumors and high-grade gliomas, respectively. For volumetric measurements, we calculated equivalent threshold values based on spherical assumption, so that a 25% change in 2D area is equivalent with a 40% change in volume, and a 50% decrease in area is analogous to a 65% decrease in volume. Since these thresholds were chosen arbitrarily, we compared several additional thresholds for each measurement type. The following imaging endpoints for progression were determined by comparing to the baseline scan or to the nadir scan: greater than 20%, 30%, 40%, 50% and 60% increase in tumor volume; greater than 15% and 25% in 2-dimensional diameter product; greater than 10% and 20 % increase in 1-dimensional diameter; greater than 5 mm and 10 mm increase in 1-dimensional diameter. For response, the following endpoints

were determined comparing to the baseline scan: greater than 65%, 40% and 20% reduction in tumor volume; greater than 50% and 25% reduction in 2-dimensional diameter product; greater than 10% and 20 % reduction in 1-dimensional diameter; greater than 5 mm and 10 mm reduction in 1-dimensional diameter.

Statistical Analysis

All statistical analyses were conducted using MATLAB statistical toolbox (version 2015a Natick, MA). Spearman statistics was applied to summarize the effect of tumor location, tumor shape, and scan resolution on the correlation between pairs of 1D, 2D and volume measurements. A p-value of less than 0.05 was considered significant. The optimal cut-off value of volumetric criteria for each time point was determined by increasing the threshold until the maximal hazard ratio among the criteria that achieved statistical significance is reached, as confirmed by plotting the hazard ratios with respect to cut-off values (supplemental figure 3). For each imaging criteria, inter-observer agreement was determined by the number of identical pairs of 6-month progression status based on measurements generated by the two radiologists divided by the total number of patients. A k statistic was used to summarize the concordance between the readers. A k value of 0 indicates lack of concordance and a value of 1 indicates perfect concordance. The degree of inter-rater concordance is classified as the following: 0-0.2: poor; 0.2-0.4: fair; 0.4-0.6: moderate; 0.6-0.8: good; and 0.8-1: very good. Correlations between tumor size based on 1D, 2D and volume measurements by different readers were summarized with the Spearman statistic. A p-value of less than 0.05 was considered significant.

The survival data were estimated based on the Kaplan-Meier method. For each patient, overall survival (OS) was calculated from the date of systemic therapy initiation to death. Progression

free survival (PFS) was calculated from the date of therapy initiation to progression or death. Patients who did not die or died of non-meningioma related causes were censored according to the last contact date per the clinical data provided by the contributing sites. At 6-month and 12-month landmark time points, progression and response status were determined using 1D, 2D and volumetric imaging criteria with different threshold values, and a Cox proportional hazards model was used to examine the relationship between each imaging criterion at the different pre-specified time-points and remaining OS. The remaining OS was defined as time from specified landmark time to death or last follow-up. All patients who had died prior to the specified landmark time were excluded from the analysis. To account for multiple comparisons among 3 different methods (1D, 2D and volume), a stricter p-value of less than 0.01 was considered significant.

To determine whether the growth rate changes remain constant over time following treatment initiation, we evaluated serial imaging of the patients who have at least 2 MRI within 6 months from treatment initiation and at least 2 MRI after 6 months. Paired student's t-test was performed to compare the mean rates of volumetric growth before and after 6 months. A p-value of less than 0.05 was considered significant. For patients who were alive 6 months after treatment initiation, survival analysis was also performed using volumetric growth rate during the first 6 months as predictor and Cox proportional hazards models were constructed using continuous rate variables. p-value of less than 0.05 was considered significant.

Results

Patients

A total of 93 patients met the inclusion criteria for this study. Patient characteristics are summarized in Table 1. The median age was 51 years old (range 12-88), and the cohort consisted of 14 WHO Grade I, 53 WHO grade II, and 26 WHO grade III tumors. 32 patients had undergone more than 2 prior surgical resections. 52 patients had at least one prior fractionated radiation treatment. 14 patients received at least one prior stereotactic radiosurgery. 8 patients received one prior medical therapy. The most common pharmacotherapeutic agents used in this retrospective study was bevacizumab monotherapy (N=29). For the 85 patients who received treatment as first-line therapy, the median time under treatment was 167 days. Eight patients were treated as second-line therapy, and the median time under treatment was 195 days.

Sixty-one patients had progressed and 42 patients had died at the last follow-up. The median PFS was 315 days and the median OS was 976 days. The median follow-up time for all patients was 792 days; it was 760 days for patients alive at the last follow-up. The median time interval between MRI scans was 75 days, ranging from 21 days to 200 days. The median imaging slice thickness was 2 mm, ranging from 0.7 mm to 7 mm.

Response to treatment

Using 1-D, 2-D and volumetric criteria, progression status was determined at 6- and 12-month time points (Table 2). 88 patients were alive at the 6-month landmark, and 81 patients were alive at the 12-month landmark. As expected, imaging criteria with lower threshold values identified more patients who progressed at each time point. Cox proportional hazards analysis of these imaging criteria showed that many of the criteria show significant correlation with OS with the 40% threshold volumetric criteria demonstrating highest hazard ratio of 2.58 at 6

months (p=0.006) and 3.24 at 12 months (p=0.002). 1-D criteria with a 10-mm threshold also shows similarly strong association with OS for both landmarks points (HR=2.42, p=0.008 at 6 months and HR=2.25, p= 0.009 at 12 months). After adjustment for age, WHO tumor grade, baseline tumor volume, number of prior surgeries, radiation and radiosurgery treatments, and prior systemic treatment events, a strong association between OS and the progression status at 6 and 12 months using 40% threshold volumetric criteria (HR= 2.77, p=0.006) and 12 (HR=4.02, p=0.002) remained. There is also very strong association between the 40% volume progression criteria and PFS for patients alive at 6 months after adjusting for the same clinical variables (HR=29.9, p< 0.0001).

Radiographic response based on different threshold of 1-D (20%, 10%, 10 mm, 5 mm), 2-D (50%, 25%) and volumetric (65%, 40%, 20%) measurements were also examined at both 6- and 12-month time points (Table 3). The percentage of patients who showed response ranged from 3% to 19% at 6 month, and 4% to 20% at 12 months. None of the response criteria correlated with OS survival (p-values ranges from 0.09 to 0.87). There is a greater percentage of patients who showed treatment response using 25% volume threshold criteria in the bevacizumab (monotherapy and combined therapy) treated group compared to non-bevacizumab regimens (18% vs 9%), although the difference was not significant (p=0.22).

Correlation of 1-D, 2-D and Volume measurements

There is stronger correlation between 1-D vs 2-D (rho=0.91, 95% C.I 0.89 - 0.91) comparing to 1-D vs volume (rho=0.67, 95%CI 0.60 - 0.72) and 2-D vs volume (rho=0.72, 95%CI 0.66 - 0.77). For both en plaque tumor shape and skull base locations, the correlation between 2-D and volumetric measurements and between 1-D and volumetric measurements became similar

(Table 4). Compared to slice thickness greater than 2 mm, slice thickness of less than 2 mm did not result in a substantial improvement in the degree of correlation among the imaging criteria. Tumor size greater or smaller than 2 c.c. also did not affect the degree of the correlation between the imaging criteria.

Volumetric Growth Rates during and after the first 6 months Following Treatment initiation

The median volumetric growth rate during the first 6 month is 3.10 cc/6 months (CI -23.80 to 101.12). When measured separately within each tumor grade, the median volumetric growth rate was 1.58 cc/6 months (95%CI= -17.41 to 59.41) for grade 1 tumors, and 3.31 cc/6 months (95%CI= -27.14 to 79.03) for grade 2 tumors, and 4.31 cc/6 months (95%CI= -17.40 to167.77) for grade 3 tumors. There was no significant difference comparing the rates between different grades (p=0.059 between grade 2 and 3, p=0.17 between grade 1 and 3, and p=0.93 between grade 1 and 2). For patients who remained alive at 6 months, the volume growth rates during the first 6 month following treatment were associated with overall survival (HR= 1.0014, p=0.034). For patients who had at least 2 MRI scans after the first 6 month following treatment initiation, the median rate of tumor growth after 6 months is 1.57 (-7.50- 34.5) cc/6 months. There was no significant difference in the mean growth rates before and after 6 months from time of treatment initiation (p=0.52).

Inter-observer variability of volumetric measurement

The progression criteria based on volume measurements performed by three readers (two radiologists and one neurosurgeon) demonstrate moderate agreement, with Cohen's kappa of 0.52 (95% CI 0.45- 0.59) for the 40% threshold volume criteria, 0.48 (95% CI 0.41- 0.54) for the 30% threshold criteria, and 0.44 (95% CI 0.37- 0.51) for the 20% threshold criteria. For 2D measurements, Cohen's kappa is 0.46 (95% CI 0.38- 0.54) for the 25% threshold criteria and 0.38 (95% CI 0.29- 0.47) for the 15% threshold criteria. For 1D measurements, the kappa is 0.49 (95% CI 0.42- 0.56) for the 20% threshold criteria, 0.42 (95% CI 0.34- 0.50) for the 10% threshold criteria, 0.65 for the 10 mm criteria, 0.48 (95% CI 0.41- 0.55) for the 5 mm criteria.

Discussion

In this retrospective multicenter evaluation of patients with recurrent meningioma undergoing systemic therapy, we compared several progression and response MRI imaging criteria based on 1D, 2D and volumetric measurements of contrast-enhancing tumor. We demonstrated that the progression status at 6- and 12-months criteria following initiation of treatment defined by many of the imaging examined in this study showed an association with overall survival. As expected, a 20% volume increment threshold identified more patients with tumor progression at 6 and 12 months, as compared to the 30% and 40% volume thresholds, although there is a weaker association with overall survival with the lower percentage, or more sensitive, threshold. It is possible that volume measurement variability can result in false identification of progression at lower threshold values, as suggested by a lower inter-rater agreement at the 20% threshold compared to higher threshold values. It is important to know that subsequent interventions, if any, are unknown for most patients and may have an impact on their survival outcome. In addition, since clinical outcomes other than death were not evaluated in this study, it remains

unclear whether the lower threshold criteria can allow earlier prediction of subsequent clinical deterioration.

Progression determined by the 10 mm 1D criteria also resulted in a strong association with survival but identified fewer patients as progressors compared to a 40% volume progression. Other 1D and 2D imaging criteria appear to be inferior surrogates of overall survival compared to using volume. The difference could be due to more accurate estimation of tumor burden using volumetric approach comparing to 1D or 2D methods. In an example case of a patient with a grade 2 meningioma, 1D and 2D measured at the site of maximal tumor cross-sectional diameters did not reflect the growth pattern of the regions with more active tumor growth (supplemental figure 1). It is not infrequent for recurrent meningiomas to show components within the same tumor bulk that grow more rapidly than the remaining part of tumor, and volumetric measurement likely can account for this localized change better than 1D and 2D cross-sectional methods if the latter two were performed only on the slice of largest tumor area, which is commonly done in clinical trials.

While a volumetric approach provides a more complete representation of tumor size compared to cross-sectional measurements, there can be considerable variability in determining tumor contours during volume measurements. In fact, the inter-rater agreement of volumetric progression criteria was only moderate, similar to 1D and 2D methods. Unlike a pre-operative newly diagnosed tumor, recurrent meningioma following multiple prior surgeries and radiation treatment often demonstrates complex post-treatment changes including surgical scarring, packing material in the surgical cavity such as fat, and radiation necrosis. It is therefore likely to result in some degree of variability among readers during manual or semi-automatic volume measurement. Furthermore, it is common for meningiomas to involve calvarium and skull base, making it difficult to determine tumor margins in the presence of fatty marrow without

special acquisition technique such as fat suppression. These are important considerations in designing future clinical trials.

Volumetric growth rates measured during the first 6 month after treatment initiation were associated with survival. As expected, median growth rates were higher among meningiomas of higher grades, although there is a broad range of rates for all grades. Growth rates beyond 6 months were not significantly different from the first 6 months, although the lack of an observed difference could be due to small sample size and also insufficient longer-term follow-up imaging data. In this study, there were also too few subjects with sufficient pre-treatment imaging data to allow calculation of growth rate change before and after treatment.

We also examined the effect of slice thickness, tumor shape, tumor size, and tumor location in affecting the correlation among 1-D, 2D and volume measurements. Among these factors, nodular tumor shape and skull base location have stronger correlations between volume and 1-D measurements and between volume and 2-D measurements. Tumor size and MR slice thickness did not have a significant impact on measurement correlations. 1D and 2D measurements correlate highly with each other.

Consistent with prior systemic therapy trials of meningioma, response events were identified in a small percentage of patients, ranging from 4% to 20% among various imaging criteria examined in this study. None of the imaging response criteria applied at 6- and 12- months landmark resulted in a significant association with overall survival. The imaging appearance of meningiomas among patients who received bevacizumab, an antiangiogenic therapy agent, showed markedly lower enhancement intensity similar to the “pseudoresponse” phenomenon observed in high-grade gliomas[20]. The effect on enhancement intensity may result in underestimation of tumor size and therefore lower the response rate. Although we observed a lower response rate in the bevacizumab-treated group comparing to other treatment similar to

the prior analysis[11], the difference was not significant. This warrants further evaluation in future trials where this class of treatment agent is used.

Our study is limited by its retrospective design and the relatively small number of patients. It will require validation in prospective clinical trials of larger sample size. This study also includes patients with all tumors grades and had very heterogeneous prior treatment history, therefore very aggressive meningiomas and indolent growing meningiomas are both included, making it difficult to determine if one imaging criteria is more favorable than the other for a specific tumor subtype. Finally, the imaging acquisition techniques were highly variable among the contributing sites and not necessarily optimized for volumetric measurement. Our attempts in investigating anatomical and technical factors that may impact meningioma size measurement provides a glimpse of the challenges in identifying an optimal approach; standardizing imaging protocol in clinical trials of meningioma is necessary to allow future refinement of imaging response criteria and ability to compare across trials.

Conclusion

In this study, we evaluated volumetric imaging criteria in determining progression and response in a multicenter data set. Compared to 1D (RECIST 1.1) and 2D (RANO) approaches, volumetric criteria for tumor progression has a stronger association with overall survival although the differences were modest at best. The inter-rater variability is similarly moderate for all three approaches. Given the time-consuming nature and technical challenges in implementing volumetric criteria during clinical work-flow, further validation is needed before widespread use. In contrast, a 10 mm change in maximal diameter is strongly associated with OS and further validation of this simple measurement approach is warranted.

References

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro-oncology*. 2017;19(suppl_5):v1-v88.

2. Louis D, Ohgaki H, Wiestler O, Cavenee W. *WHO Classification of Tumours of the Central Nervous System*. Vol 1. 4th ed. France: International Agency for Research on Cancer; 2016.

3. Aizer AA, Arvold ND, Catalano P, et al. Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma. *Neuro-oncology*. 2014;16(11):1547-1553.

4. Stafford SL, Pollock BE, Foote RL, et al. Meningioma radiosurgery: tumor control, outcomes, and complications among 190 consecutive patients. *Neurosurgery*. 2001;49(5):1029-1037; discussion 1037-1038.

5. Wen PY, Quant E, Drappatz J, Beroukhim R, Norden AD. Medical therapies for meningiomas. *J Neurooncol*. 2010;99(3):365-378.

6. Gupta, S, WL B, IF D. Medical management of meningioma in the era of precision medicine. *Neurosurgery Focus*. 2018:E3.

7. Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. *Neuro Oncol*. 2014;16(6):829-840.

8. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28(11):1963-1972.

9. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-278.

10. Pohl KM, Konukoglu E, Novellas S, et al. A new metric for detecting change in slowly evolving brain tumors: validation in meningioma patients. *Neurosurgery*. 2011;68(1 Suppl Operative):225-233.

11. Furtner J, Schöpf V, Seystahl K, et al. Kinetics of tumor size and peritumoral brain edema before, during, and after systemic therapy in recurrent WHO grade II or III meningioma. *Neuro-oncology*. 2016;18(3):401-407.

12. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol*. 2015;17(1):116-121.

13. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology*. 2015;84(3):280-286.

14. Raizer JJ, Grimm SA, Rademaker A, et al. A phase II trial of PTK787/ZK 222584 in recurrent or progressive radiation and surgery refractory meningiomas. *J Neurooncol*. 2014;117(1):93-101.

15. Seystahl K, Stoecklein V, Schüller U, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake. *Neuro Oncol*. 2016;18(11):1538-1547.

16. Grimm SA, Kumthekar P, Chamberlain MC, et al. Phase II trial of bevacizumab in patients with surgery and radiation refractory progressive meningioma. *JCO*. 2015;33(15_suppl):2055-2055.

17. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9):1323-1341.

18. Gao Y, Kikinis R, Bouix S, Shenton M, Tannenbaum A. A 3D interactive multi-object segmentation tool using local robust statistics driven active contours. *Med Image Anal*. 2012;16(6):1216-1227.

19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

20. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28(11):1963-1972.

Table 1 Patient Characteristics

	Total (N=93)	WHO grade I (N=14)	WHO grade II (N=53)	WHO grade III (N=26)
Age; median (range) year	51 (12-88)	39 (26-81)	52(29-88)	55(12-85)
Number of prior surgical resection(s); median (range)	2 (1-12)	1.5 (1-4)	2 (1-8)	1 (1-12)
Patients with >= 1 Prior fractionated radiation treatment	52	8	30	14
Patients with > =1 prior stereotactic radiosurgery	14	1	8	5
Patients with 1 prior medical therapy	8	0	6	2
Systemic Therapy received during imaging assessment				
Bevacizumab (monotherapy)	29	6	15	9
Bevacizumab (combination therapy) ǂ	3	0	2	1
Vatalanib	12	0	8	4
Pasireotide	10	2	5	3
Imatinib	7	0	5	2
Sunitinib	7	0	5	2
Doxorubicin	7	1	4	2
Other *	18	5	9	4
median PFS (days)	315	411	251	118
median OS (days)	976	1070	889	776
ǂ bevacizumab combination	etoposide (1), doxorubicin (2)			
***Other threatment**	90Y DOTATOC 177-Lu DOTATATE (1), Y-90-DOTATOC (3), Y-90-DOTATOC/Somato (1), 177-Lu DOTATATE (5), octreotid (3), lanreotide (2), temozolomide (1), Cyclophosphamide/Carboplatin/Etoposide/Vincristine (1), Mifepriston (1)			

Table 2. Progression status at 6-month and 12-month landmarks versus residual overall survival.

Criteria	Progression <= 6 month; N=88 alive at 6 months	Overall Survival		Progression <= 12 month; N=81 alive at 12 months	Overall Survival	
		Hazard Ratio (95% CI)	P value		Hazard Ratio (95% CI)	P value
60 % increase Volume	43%	2.37 (1.21 - 4.63)	0.011	48%	3.24 (1.49 - 7.01)	0.003
50 % increase Volume	46%	2.40 (1.23 - 4.69)	0.009	49%	3.23 (1.49 - 7.00)	0.003
40 % increase Volume	47%	2.58 (1.31 - 5.07)	0.006	49%	3.24 (1.49 - 7.00)	0.002
30% increase Volume	49%	2.32 (1.18 - 4.55)	0.014	51%	2.87 (1.33 - 6.20)	0.007
20% increase Volume	53%	1.80 (0.91 - 3.55)	0.091	56%	2.23 (0.81 - 3.67)	0.045
25% increase 2D	45%	1.69 (0.87 - 3.27)	0.12	49%	2.59 (1.20 - 5.60)	0.015
15% increase 2D	50%	1.28 (0.66 - 2.50)	0.45	54%	1.84 (0.85 - 3.96)	0.12
20 % increase 1D	45%	2.02 (1.04 - 3.92)	0.039	49%	2.01 (0.94 - 4.27)	0.06
10 % increase 1D	53%	1.75 (0.89 - 3.43)	0.10	54%	1.61 (0.75 - 3.49)	0.21
10 mm increase in 1D	43%	2.42 (1.25 - 4.71)	0.008	47%	2.25 (1.08 - 4.68)	0.009
5 mm increase in 1D	52%	1.76 (0.90 - 3.42)	0.095	52%	2.49 (1.15- 5.39)	0.02

Table 3. Response status according to imaging criteria versus residual overall survival at 6-month and 12-month landmarks.

Criteria	Response <= 6 month; N=88 alive at 6 months	Overall Survival		Response <= 12 month; N=81 alive at 12 months	Overall Survival	
		Hazard Ratio (95% CI)	P value		Hazard Ratio (95% CI)	P value
65 % reduction in Volume	3%	0.48 (0.065 - 3.5)	0.47	4%	0.56 (0.076 - 4.14)	0.57
40% reduction in Volume	7%	0.55 (0.13 - 2.31)	0.42	9%	0.93 (0.28 - 3.07)	0.91
20% reduction in Volume	11%	0.66 (0.23 - 1.88)	0.44	12%	0.57 (0.17 - 1.89)	0.36
50% reduction in 2D	8%	1.98 (0.76 - 5.10)	0.16	7%	2.14 (0.74 - 6.16)	0.16
25% reduction in 2D	10%	1.06 (0.49 - 2.26)	0.87	14%	0.96 (0.42 - 2.19)	0.93
20 % reduction in 1D	11%	0.36 (0.11- 1.18)	0.09	10%	0.53 (0.18 - 1.55)	0.24
10 % reduction in 1D	19%	0.64 (0.29 - 1.42)	0.28	20%	0.56 (0.24 - 1.32)	0.69
10 mm reduction in 1D	10%	0.48 (0.17 - 1.38)	0.17	8%	0.69 (0.26 - 1.83)	0.46
5 mm reduction in in 1D	14%	0.63 (0.28 - 1.45)	0.28	12%	0.63 (0.25- 1.55)	0.31

Table 4. Correlation of 1-D, 2-D, and Volume measurement within subgroups separated by tumor shape (spherical vs non-spherical), MRI slice thickness (thicker or thinner than 2 mm), tumor location (convexity versus skullbase), and lesion size (smaller or greater than 2 c.c).

Nodular				En plaque			
	Volume	**2D**	**1D**		**Volume**	**2D**	**1D**
Volume	1.00	0.81 (0.76 - 0.86)	0.76 (0.70 - 0.82)	**Volume**	1.00	0.60 (0.46 - 0.71)	0.61 (0.41 - 0.71)
2D		1.00	0.90 (0.87 - 0.93)	**2D**		1.00	0.81 (0.89 - 0.94)
1D			1.00	**1D**			1.00
<= 2 mm resolution				**> 2 mm resolution**			
	Volume	**2D**	**1D**		**Volume**	**2D**	**1D**
Volume	1.00	0.76 (0.61 - 0.85)	0.51 (0.28 - 0.69)	**Volume**	1.00	0.71 (0.64 - 0.77)	0.66 (0.58 - 0.72)
2D		1.00	0.88 (0.80 - 0.92)	**2D**		1.00	0.90 (0.87 - 0.92)
1D			1.00	**1D**			1.00
Convexity				**Skullbase**			
	Volume	**2D**	**1D**		**Volume**	**2D**	**1D**
Volume	1.00	0.71 (0.63 - 0.71)	0.63 (0.53 - 0.71)	**Volume**	1.00	0.79 (0.69 - 0.85)	0.80 (0.71- 0.86)
2D		1.00	0.89 (0.86 - 0.92)	**2D**		1.00	0.94 (0.91 - 0.96)
1D			1.00	**1D**			1.00
Lesion size < 2 c.c				**Lesion size > 2 c.c**			
	Volume	**2D**	**1D**		**Volume**	**2D**	**1D**
Volume	1.00	0.60 (0.35 - 0.77)	0.58 (0.33 - 0.76)	**Volume**	1.00	0.69 (0.62 - 0.75)	0.64 (0.56 - 0.71)
2D		1.00	0.91 (0.84 - 0.95)	**2D**		1.00	0.89 (0.86 - 0.91)
1D			1.00	**1D**			1.00
All patients							
	Volume	**2D**	**1D**				
Volume	1.00	0.72 (0.66 - 0.77)	0.67 (0.60 - 0.72)				
2D		1.00	0.91 (0.89 - 0.91)				
1D			1.00				