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Response assessment of meningioma: 1D, 2D, and volumetric criteria for treatment response and tumor progression

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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 have 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. One-dimensional (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 (range 12–88), with 14 World Health Organization (WHO) grade I, 53 WHO grade II, and 26 WHO grade III meningiomas. Volumetric increase of 40% and unidimensional increase by 10 mm at 6 months and 12 months provided the strongest association with overall survival (HR = 2.58 and 3.24 respectively, $p<0.01$). Setting a volume change threshold above 40% did not correlate with survival. The interobserver 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 with 1D (Response Evaluation Criteria In Solid Tumors 1.1) and 2D (Response Assessment in Neuro-Oncology) approaches, volumetric criteria for tumor progression has a stronger association with OS, although the differences were only modest. The interobserver variability is moderate for all 3 methods. Further validation of these findings in an independent patient cohort is needed.

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 the 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 have been defined for the evaluation of response. Volumetric approach provides more accurate estimate of tumor burden but is also relatively more time-consuming and technically challenging. Using a multicenter dataset 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 OS. Our analyses showed that, compared with 1D and 2D approaches, volumetric criteria for tumor progression has a stronger association with OS and a lower interobserver variability. While the observed improvement is only modest, our results prompt the need for further validation of volumetric criteria in future trials.

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 3 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 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 the volumetric approach offers significant advantage over one-dimensional (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 1D or 2D diameter measurements, unlike the volumetric approach, can be consistently obtained or even represent the full tumor size.

In this study, we evaluated longitudinal MRI 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.[11–16] Response criteria based on volumetric measurements were compared with those based on 1D and 2D measurements to determine which imaging criteria have the strongest correlation with OS and the greatest reproducibility.

Method

Patients

This multicenter 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: (i) patients with histologically proven meningiomas who were treated with first- or second-line systemic therapy, (ii) at least one baseline MRI exam within 3 months before initiation of therapy was available, (iii) posttherapy MRI until progression or last

follow-up date with frequency of imaging as determined by clinical or trial-specified protocol of each contributing site, and (iv) MRI exams consisting of gadolinium-enhanced T1-weighted sequences with no more than 7 mm slice thickness. Clinical variables including age, histologic grade, number of prior surgical resections, radiation treatments, stereotactic surgery, 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[11–16] 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 v4.4.[17] A Robust Statistics Segmentation tool[18] was 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 to remove pixels for nontumor 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, 1D diameter measurements as well as 2D diameter product were recorded (Supplementary 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 interobserver variability of volumetric measurement, 2 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. 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 centimeters per 6 months) were calculated by linear fitting of tumor volume measured on at least 2 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 cutoff values based on 1D (Response Evaluation Criteria In Solid Tumor [RECIST 1.1])[19] and 2D criteria (Response Assessment in Neuro-Oncology [RANO])[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 to 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 comparison with the baseline scan or with the nadir scan: greater than 20%, 30%, 40%, 50%, and 60% increase in tumor volume; greater than 15% and 25% in 2D diameter product; greater than 10% and 20% increase in 1D diameter; greater than 5 mm and 10 mm increase in 1D diameter. For response, the following endpoints were determined compared with the baseline scan: greater than 65%, 40%, and 20% reduction in tumor volume; greater than 50% and 25% reduction in 2D diameter product; greater than 10% and 20% reduction in 1D diameter; greater than 5 mm and 10 mm reduction in 1D diameter.

Statistical Analysis

All statistical analyses were conducted using MatLab statistical toolbox v2015a. Spearman statistics were 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 cutoff value of volumetric criteria for each timepoint was determined by increasing the threshold until the maximal hazard ratio (HR) among the criteria that achieved statistical significance was reached, as confirmed by plotting the HRs with respect to cutoff values (Supplementary Figure 3). For each imaging criterion, interobserver agreement was determined by the number of identical pairs of 6-month progression status based on measurements generated by the 2 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 interrater 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, OS was calculated from the date of systemic therapy initiation to death. 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 timepoints, progression and response statuses 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 prespecified timepoints 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 remained constant over time following treatment initiation, we evaluated serial imaging of the patients who had at least 2 MRIs within 6 months from treatment initiation and at least 2 MRIs 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 a 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 (range 12–88), and the cohort consisted of 14 WHO grade I, 53 WHO grade II, and 26 WHO grade III tumors. Thirty-two 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, and 8 patients received one prior medical therapy. The most common pharmacotherapeutic agent used in this retrospective study was bevacizumab monotherapy ($N = 29$). For the 85 patients who received first-line therapy, the median time under treatment was 167 days. Eight patients received second-line therapy, with median time under treatment of 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 (range 21–200 d). The median imaging slice thickness was 2 mm (range 0.7–7 mm).

Response to Treatment

Using 1D, 2D, and volumetric criteria, progression status was determined at 6- and 12-month timepoints (Table 2). Eighty-eight 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 timepoint. Cox proportional hazards analysis showed that many of these imaging criteria had significant correlation with OS, with the 40% threshold volumetric criteria demonstrating the highest HR of 2.58 at 6 months ($P = 0.006$) and 3.24 at 12 months ($P = 0.002$). One-dimensional criteria with a 10 mm threshold also showed 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, and prior systemic treatment events, OS remained strongly associated with radiographic progression, as defined by a 40% volumetric threshold, at 6 months (HR = 2.77, p = 0.006) and 12 months (HR = 4.02, p = 0.002). There is also a very strong association between the 40% volume progression criteria and PFS for patients alive at 6 months

Table 1 Patient characteristics

	Total (N=93)	WHO Grade I (N=14)	WHO Grade II (N=53)	WHO Grade III (N=26)
Age, y, median (range)	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 treatment:** 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).

after adjusting for the same clinical variables (HR = 29.9, $P < 0.0001$).

Radiographic response based on different thresholds of 1D (20%, 10%, 10 mm, 5 mm), 2D (50%, 25%), and volumetric (65%, 40%, 20%) measurements were also examined at both 6- and 12-month timepoints (Table 3). The percentage of patients who showed response ranged from 3% to 19% at 6 months, and 4% to 20% at 12 months. None of the response criteria correlated with OS survival (*P*-values range 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 with non-bevacizumab regimens (18% vs 9%), although the difference was not significant ($P = 0.22$).

Correlation of 1D, 2D, and Volume Measurements

There is stronger correlation between 1D versus 2D (rho = 0.91, 95% CI: 0.89–0.91) compared with 1D versus volume (rho = 0.67, 95% CI: 0.60–0.72) and 2D versus volume (rho = 0.72, 95% CI: 0.66–0.77). For both en plaque tumor shape and skull base locations, the correlation between 2D and volumetric measurements and between 1D and volumetric measurements became similar (Table 4). Compared with 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 cc 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 months was 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 I tumors; 3.31 cc/6 months

Table 2 Progression status at 6-month and 12-month landmarks versus residual OS

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 OS 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 1D, 2D, and volume measurement within subgroups separated by tumor shape (spherical vs nonspherical), MRI slice thickness (thicker or thinner than 2 mm), tumor location (convexity versus skullbase), and lesion size (smaller or greater than 2 cc)

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				**Skull base**			
	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 cc				**Lesion size >2 cc**			
	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				

(95% CI: −27.14 to 79.03) for grade II tumors; and 4.31 cc/6 months (95% CI: −17.40 to 167.77) for grade III tumors. There was no significant difference comparing the rates between different grades (P = 0.059 between grades II and III, P = 0.17 between grades I and III, and P = 0.93 between grades I and II). For patients who remained alive at 6 months, the volume growth rates during the first 6 months following treatment were associated with OS (HR = 1.0014, P = 0.034). For patients who had at least 2 MRI scans after the first 6 months following treatment initiation, the median rate of tumor growth after 6 months was 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).

Interobserver Variability of Volumetric Measurement

The progression criteria based on volume measurements performed by 3 readers (2 radiologists and 1 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-month criteria following initiation of treatment defined by many of the imaging examined in this study showed an association with OS. As expected, a 20% volume increment threshold identified more patients with tumor progression at 6 and 12 months compared with the 30% and 40% volume thresholds, although there is a weaker association with OS 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

interrater agreement at the 20% threshold compared with 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 with a 40% volume progression. Other 1D and 2D imaging criteria appear to be inferior surrogates of OS compared with using volume. The difference could be due to more accurate estimation of tumor burden using the volumetric approach compared with 1D or 2D methods. In an example case of a patient with a grade II 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 (Supplementary 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 2 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 with cross-sectional measurements, there can be considerable variability in determining tumor contours during volume measurements. In fact, the interrater agreement of volumetric progression criteria was only moderate, similar to 1D and 2D methods. Unlike a preoperative newly diagnosed tumor, recurrent meningioma following multiple prior surgeries and radiation treatment often demonstrates complex posttreatment 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 a special acquisition technique such as fat suppression. These are important considerations in designing future clinical trials.

Volumetric growth rates measured during the first 6 months 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 as well as insufficient longer-term follow-up imaging data. In this study, there were also too few subjects with sufficient pretreatment 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 1D, 2D, and volume measurements. Among these factors, nodular tumor shape and skull base location have stronger correlations between volume and 1D measurements and between volume and 2D 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- month landmarks resulted in a significant association with OS. The imaging appearance of meningiomas among patients who received bevacizumab, an anti-angiogenic 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 compared with 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 tumor 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 criterion 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 to investigate anatomical and technical factors that may impact meningioma size measurement provide 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 dataset. Compared with 1D (RECIST 1.1) and 2D (RANO) approaches, volumetric criteria for tumor progression have a stronger association with OS, although the differences are modest at best. The interrater variability is similarly moderate for all 3 approaches. Given the time-consuming nature and technical challenges in implementing volumetric criteria during clinical workflow, 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.

Supplementary Material

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

Keywords

meningioma | volume | response | MRI | survival

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