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3D volume growth rate evaluation in the EORTC-BTG-1320 clinical trial for recurrent WHO grade 2 and 3 meningiomas

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Abstract

Background. We previously reported that tumor 3D volume growth rate (3DVGR) classification could help in the assessment of drug activity in patients with meningioma using 3 main classes and a total of 5 subclasses: class 1: decrease; 2: stabilization or severe slowdown; 3: progression. The EORTC-BTG-1320 clinical trial was a randomized phase II trial evaluating the efficacy of trabectedin for recurrent WHO 2 or 3 meningioma. Our objective was to evaluate the discriminative value of 3DVGR classification in the EORTC-BTG-1320.

Methods. All patients with at least 1 available MRI before trial inclusion were included. 3D volume was evaluated on consecutive MRI until progression. 2D imaging response was centrally assessed by MRI modified Macdonald criteria. Clinical benefit was defined as neurological or functional status improvement or steroid decrease or discontinuation.

Results. Sixteen patients with a median age of 58.5 years were included. Best 3DVGR classes were: 1, 2A, 3A, and 3B in 2 (16.7%), 4 (33.3%), 2 (16.7%), and 4 (33.3%) patients, respectively. All patients with progression-free survival longer than 6 months had best 3DVGR class 1 or 2. 3DVGR classes 1 and 2 (combined) had a median overall survival of 34.7 months *versus* 7.2 months for class 3 ($P = .061$). All class 1 patients (2/2), 75% of class 2 patients (3/4), and only 10% of class 3 patients (1/10) had clinical benefit.

Conclusions. Tumor 3DVGR classification may be helpful to identify early signals of treatment activity in meningioma clinical trials.

Key Points

- 3D volume growth rate (VGR) of meningioma may be predictive of 6-month progression-free survival.
- 3DVGR classification is more discriminative than the revised Macdonald criteria.
- 3DVGR classification is predictive of patient clinical benefit.

Meningioma is the most common intracranial tumor in adults. Most meningiomas are benign and correspond to CNS WHO grade 1.[1] However, approximately 20%–25% of cases show brain invasiveness, cellular atypia, or increased mitotic activity, leading to an increased risk for recurrence. These tumors are thus classified as CNS WHO grade 2 or grade 3 meningiomas.[1] These aggressive meningiomas frequently progress after local treatments like surgery and radiotherapy and constitute a therapeutic challenge and an unmet medical need in neuro-oncology. Despite multiple clinical trials of various drugs in the past years, limited evidence of activity and clinical benefit for meningioma patients are available for most of them.[2,3] In the last few years, knowledge on the mutational landscape, intracellular signaling pathways activation, and microenvironment in meningioma

Importance of the Study

In this study, our objective was to evaluate the discriminative value of the 3D volume growth rate (3DVGR) of meningioma in the phase II EORTC-BTG-1320 dedicated to WHO grade 2 and 3 meningioma patients. We observed that this 3DVGR classification was predictive of 6-month progression-free survival and patient overall survival. Moreover, it was more discriminative than the previous response criteria and was predictive of patient clinical benefit. In summary, 3DVGR classification may be helpful to identify early signals of treatment activity in meningioma clinical trials.

has increased considerably.[4,5] However, most of these mutations are observed in benign slow-growing skull base meningiomas with limited clinical therapeutic impact. Assessment of drug activity is particularly challenging in meningiomas because of tumor kinetic heterogeneity and lack of drug response. Notably, tumor volume stabilization or tumor growth slowdown should be considered as beneficial for the patient.[6] Recently, we reported that 3D volume growth rates (3DVGR) can be used to assess drug activity based on data issued from the CEVOREM meningioma clinical trial.[7] 3DVGR seemed to be more discriminative than classical PFS6 for signal of activity.[8] This classification segregates meningioma response into 3 main classes and a total of 5 subclasses based on 3DVGR before and under treatment (Figure 1A). The EORTC-1320-BTG randomized phase II trial evaluated the activity of trabectedin in recurrent aggressive meningiomas.[9] Trabectedin is a tetrahydroisoquinoline alkaloid derived from the Caribbean Sea squirt Ecteinascidia turbinata. Trabectedin forms DNA adducts, affects several transcription factors and DNA repair mechanisms, and has immunomodulatory and antiangiogenic properties.[10–12] Trabectedin has shown clinically meaningful efficacy and good tolerability in advanced soft tissue sarcoma and ovarian cancer and is currently approved in these indications. Yet, the use of trabectedin did not significantly improve patient progression-free survival (PFS) and overall survival (OS) with recurrent WHO grade 2 or 3 meningioma.[9]

Our aim with the present work was to validate the 3DVGR classification in the EORTC-BTG-1320 clinical trial to evaluate the predictive value of 3DVGR classification for response and clinical benefit prediction in an independent clinical trial dedicated to aggressive meningiomas.

Methods

Study Design

This study is a post hoc analysis of the EORTC-1320-BTG trial (NCT02234050). Briefly, the EORTC-1320-BTG was an open-label, prospective, multicenter, randomized phase II trial performed across Europe to assess the efficacy and toxicity of trabectedin versus local standard of care (LOC) treatment in patients with WHO grade 2 or grade 3 meningioma. Eligible patients were adults (≥18 years old) with a local histological diagnosis of WHO grade 2 (atypical, chordoid, clear cell) or grade 3 (papillary, rhabdoid, anaplastic/malignant) meningioma according to the WHO 2016 classification, radiologically documented progression of any existing tumor (estimated planar growth >25% in the last year, as documented by the local investigator) or appearance of new lesions (including intra- and extracranial sites). Other eligibility criteria included patients with no more options for local therapy (resection or radiotherapy), no prior systemic antineoplastic therapy for meningioma, measurable disease (10 mm × 10 mm) on cranial magnetic resonance imaging (MRI) at ≤2 weeks prior to randomization (baseline MRI), a WHO performance status of 0–2, and normal cardiac function and adequate liver, renal, and hematological functions. All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The trial was approved by the ethics committee of all participating sites. Signed informed consents were obtained from all study participants before registration. Patients were randomly assigned on a 2:1 basis by the minimization method to receive either trabectedin (24-h intravenous infusion every 3 weeks at a starting dose of 1.5 mg/m^2) or LOC treatment.

To be included in this subanalysis, a pre-inclusion MRI performed within the 12 months before inclusion (pre-inclusion MRI, distinct from baseline MRI) had to be available at the time of analysis (Supplementary Figure 1).

Assessments and Outcomes

Pre-inclusion MRI consisted of MRI performed within the 12 months before inclusion and at least 3 weeks before baseline MRI (Supplementary Figure 1). Baseline MRI was performed no more than 2 weeks prior to randomization. Baseline assessments included also physical examination. Then MRI were performed every 9 weeks, or if clinically indicated. The EORTC-1320 imaging protocol comprised a 2D FLAIR, a 2D diffusion-weighted imaging MR sequence, a T2-weighted-TSE MR sequence, and a 3D T1-weighted MR sequence with and without the intravenous application of a gadolinium-based contrast agent. The sequence parameters for the 3D gadolinium-enhanced MRI sequence were as follows: minimum TE, TI, TR, and flip angle according to manufacturer-specific/field-strength-specific recommendations for optimum image quality, SENSE/SMASH/GRAPPA/ASSET allowed, slice/3D slab orientation: sagittal or transverse, FOV:256 mm × 256 mm, matrix: 256 × 256, slice thickness: ≤1.5 mm, full brain coverage, and 0.1 mmol/kg body weight of a gadolinium-based contrast agent. Formalin-fixed, paraffin-embedded (FFPE) blocks of tumor samples were collected for translational research. Methylation analysis and copy number analysis were performed using 850k EPIC (Illumina, San Diego, CA) arrays as described previously.[13,14] Meningioma methylation classes (MC; MC-benign, MC-intermediate, MC-malignant) were determined by a previously reported

random-forest classifier.[14] Panel sequencing for genes altered in meningioma, namely *NF2, TRAF7, KLF4, SMO, AKT1, TERT* promoter, *ARID1A, SUFU*, *SMARCE1*, and *PIK3CA*, was performed using previously published methods.[15]

Response was evaluated according to modified Macdonald response criteria and graded as complete response, partial response (PR), stable disease (SD), or progressive disease.[16] PFS was measured from the date of randomization until the date of next progression per local assessment or the date of patient's death (whichever occurred first), whereas OS was calculated from the date of randomization until patient death from any cause.

Clinical benefit was defined per protocol by an improvement of neurological symptoms, and/or an improvement of general status (WHO performance status), and/or by a decrease or a discontinuation of steroids.

3DVGR Assessment

Isotropic (mm^3) 3D gadolinium-enhanced MRI sequences were required for volume measurement. Baseline and pre-baseline brain MRIs were required to assess pretreatment 3DVGR. All tumors were manually segmented by an experienced board-certified neuroradiologist (J.F.) on T1-weighted contrast-enhanced MR images using the open-source software ITK-SNAP. Tumor volumes were expressed in cubic millimeters (mm^3). If multiple tumor areas were seen, they were all segmented and included together for volume assessment.

3DVGR was expressed in %/6 months and was calculated as follows: GR = (V1 – V0)/V0 × 100/months (n) × 6.[8] 3DVGR classification was determined as previously reported[8] (Figure 1A).

Statistical Analyses

Categorical variables are presented as numbers and percentages, and the quantitative results as a median with minimum and maximum range or a mean with standard error as an index of dispersion. Comparisons were made with Student's *t*-test, Chi^2, or Fisher tests for qualitative data and *t*-test or Mann–Whitney for quantitative data, as appropriate. The survival rate was estimated using the Kaplan–Meier method. Association of 3DVGR classification with patient survival was analyzed using the Log-Rank test on OS from the first MRI evaluation to death, censored at the date of last contact. Six-month PFS (PFS6) rate was used for classification correlation. All tests were 2-sided, and a P value of <.05 was considered statistically significant. Analyses were performed with SPSS software v22.

Results

Subanalysis Cohort and Patient Characteristics (Table 1 and Supplementary Figure 2)

Among the 90 patients enrolled in the study, images qualifying for this post hoc analysis were available for 16 patients. At inclusion, the median age of 58.5 years (range, 38–73), the WHO performance status at inclusion was 0 for 2 patients, 1 for 8 patients, and 2 for 3 patients. Five patients had steroid treatment at inclusion. Treatments during the study were trabectedin (n = 9), bevacizumab (n = 2), hydroxyurea (n = 2), or palliative care (n = 3).

3D Tumor Volume Growth Rate Assessment

The mean time interval between pre-baseline MRI and baseline MRI was 3 months (±0.5). Mean pretreatment 3DVGR was 29.8 mm^3/month (±8.3). Pretreatment 3DVGR did not differ between MC (P = .44), *NF2* (P = 1.0) or *CDKN2A/B* (P = .287) molecular alterations.

Tumor volume evolutions under treatment are reported in Figure 1B. Under treatment, 3DVGR decreased in 4/9 patients in the trabectedin group, in 2/2 patients in the bevacizumab group (Figure 1C), and in 1/2 patients in the hydroxyurea group.

The first follow-up MRI was obtained 9 weeks after the baseline MRI. At this time point, 3DVGR classes were 1 (n = 1, 8.3%), 2A (n = 2, 16.7%), 2B (n = 1, 8.3%), 3A (n = 3, 25%), and 3B (n = 5, 41.7%). Best 3DVGR classes were 1, 2A, 3A, and 3B in 2 (16.7%), 4 (33.3%), 2 (16.7%), and 4 (33.3%), respectively (Figure 2 and Supplementary Figure 3). Four patients were not evaluable due to early progression, before the first MRI evaluation (Supplementary Figure 2). Regarding the 3 patients treated with palliative care only, 2 was not evaluable due to early progression, and the 2 others were evaluated in class 3 as best 3DVGR response.

3DVGR classes according to patient PFS are reported in Figure 3. Four patients were still under treatment at the end of study. 3DVGR was correlated to 6-month PFS (PFS6; P = .008, *Fisher exact test*). All patients with PFS longer than 6 months had best 3DVGR class 1 or 2. In contrast, all patients with PFS shorter than 6 months had best 3DVGR class 3 or not evaluable due to early progression.

In the whole cohort, median PFS and OS were 2.4 months (95% CI: 2.2–2.6) and 12.4 months (95% CI: 1.0–23.8), respectively. First 3DVGR classes 1 and 2 (combined) had a median overall survival of 34.7 months (95% CI: not estimated due to limited event number) versus 7.2 months (95% CI: 2.9–11.5) for class 3. Overall survival from the first MRI evaluation tended to be longer in the classes 1 and 2 versus 3 (P = .061, Supplementary Figure 4).

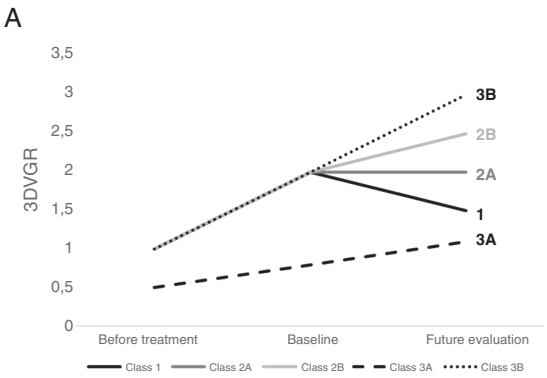
3DVGR Versus Modified Macdonald Response Criteria

The best objective responses according to centrally assessed modified Macdonald response criteria were SD, progression, or undetermined in 7, 6, and 3 patients, respectively. Regarding the 7 stable patients, they were divided into classes 1 (2 patients), 2 (4 patients), or 3 (1 patient) by the 3DGVR classification (Figure 4).

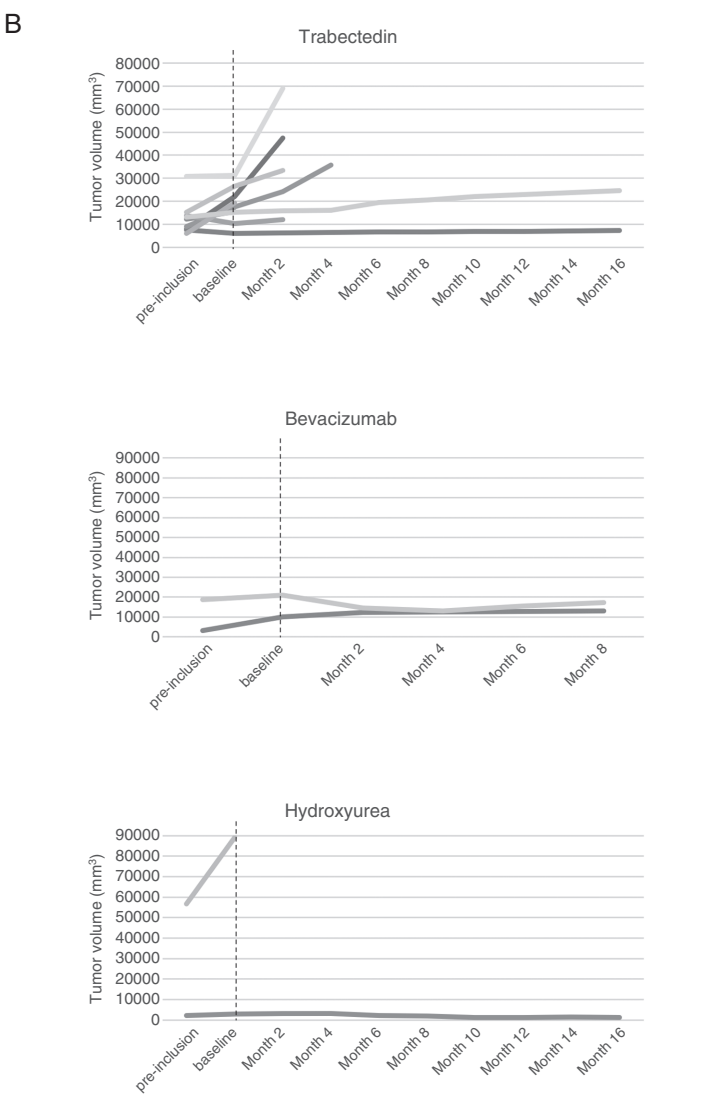
3DVGR Clinical Benefit

Six patients presented with clinical benefit. All class 1 patients (2/2), 75% of class 2 patients (3/4), and only 10% of class 3 patients (1/10) experienced with clinical benefit.

Regarding the 2 patients under bevacizumab, none of them had steroids at baseline. One patient presented with



Classes	3DVGR
1	Volume decrease ≥ 25%
2A	Tumor stabilization [0%/6 months ≤ 3DVGR ≤ 10%/6 months]
2B	3DVGR severe slowdown [10%/6 months < 3DVGR ≤ 30%/6 months if preinclusion 3DVGR > 30%/6 months]
3A	persistent low progression [3DVGR ≤ 30%/6 months]
3B	Quick progression [3DVGR > 30%/6 months]



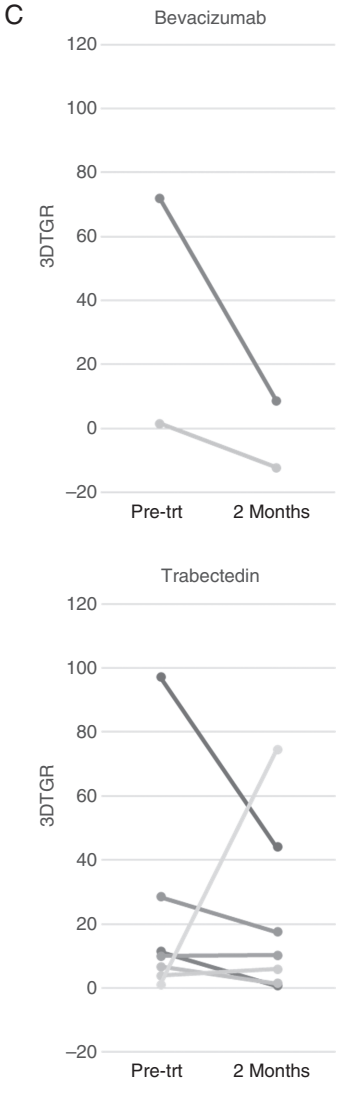


Figure 1. (A) Schematic representation of 3D volume growth rate classification (left). Definition of 3DVGR classes (right). (B) Tumor volume evolution before and under treatment. (C) 3D volume growth rate evolution before and 2 months after treatment initiation.

Table 1. Patient characteristics

Characteristics	*N* = 16	%
Age (median, range)	58.5 (38–73)	
Grades		
2	13	81
3	3	19
WHO status		
0	5	31
1	8	50
2	3	19
Neurological symptoms	4	25
Sex (female/male)	6/10	37/63
Steroids	5	31
Treatments		
Trabectedin	9	57
Bevacizumab	2	12
Hydroxyurea	2	12
Palliative care	3	19
Molecular alterations		
NF2 mutations	8/ 13	61
pTERT mutation	0/ 13	0
CDKN2A/B deletion	3/ 13	23
Methylation subgroups		
Benign	2/ 13	16
Intermediate	5/ 13	38
Malignant	6/ 13	46

clinical benefit under bevacizumab, based on neurological examination and WHO performance status improvement.

Discussion

Our study helps to validate the clinical value of the 3DVGR assessment for meningioma clinical trials. We showed that this classification allows a more accurate patient stratification than classical modified Macdonald criteria and is a relevant surrogate marker of PFS at 6 months. Moreover, this classification correlated to clinical benefit for patients, highlighting its potential role in early drug evaluation.

Assessment of drug activity in meningioma clinical trials remains challenging but crucial in a disease where effective systemic treatments are limited. Therapy benefit assessment faces different challenges[17]: low prevalence rendering phase 3 clinical trial challenging, highly variable growth rate, low response rate (less than 5%), and prolonged overall survival.

SD patients often present with highly variable evolutions, including very quick progression and more prolonged stabilization, underlining the heterogeneity of this subgroup.[6] There is an urgent medical need to refine response criteria in meningioma clinical trial to allow early detection of drug activity.

PFS6 is today the most consensual criterion to evaluate recurrent high-grade meningioma in clinical trials and allows comparison between historical clinical trials.[6,18,19] However, PFS6 also presents many limitations, especially in the case of slow-growing tumors. Other classical neuro-imaging primary efficacy endpoints are response rate by Macdonald, RECIST, RANO criteria, or volumetric estimation.[20] Symptom evaluation has also been used as

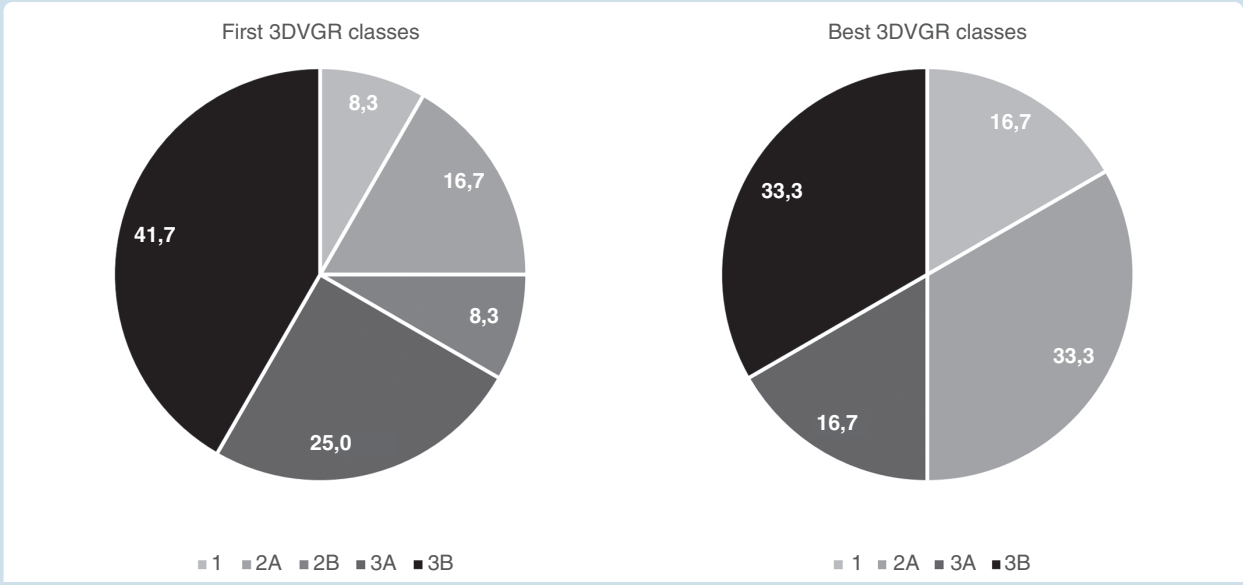


Figure 2. First (left) and best (right) 3D volume growth rate classification.

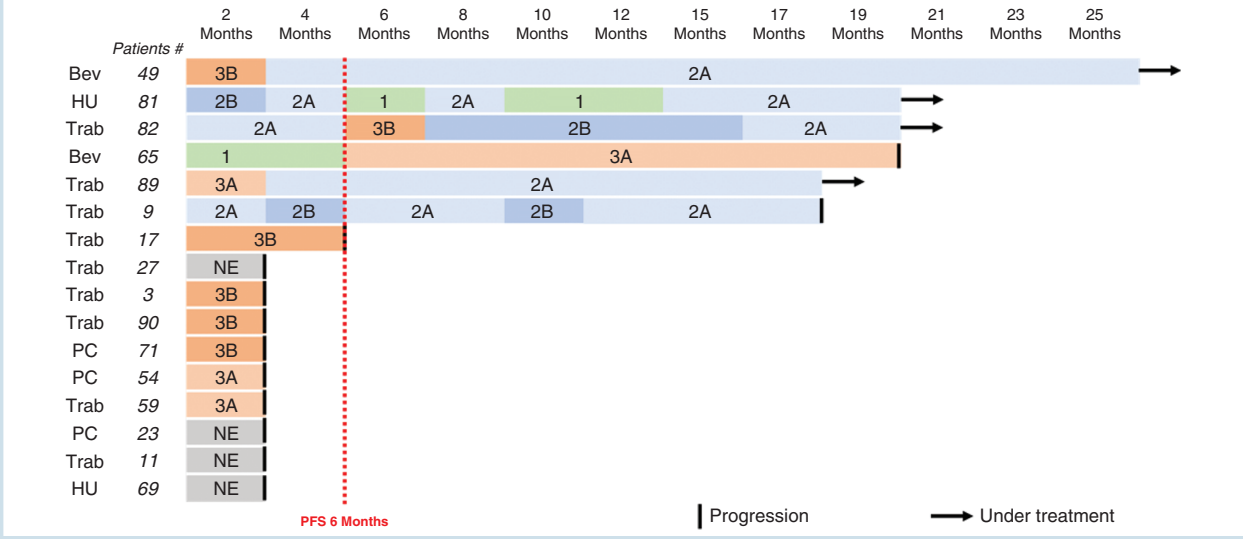


Figure 3. Progression-free survival (PFS) according to 3D volume growth rate classification. Bev: bevacizumab; HU: hydroxyurea; NE: not evaluable; PC: palliative care; Trab: trabectedin.

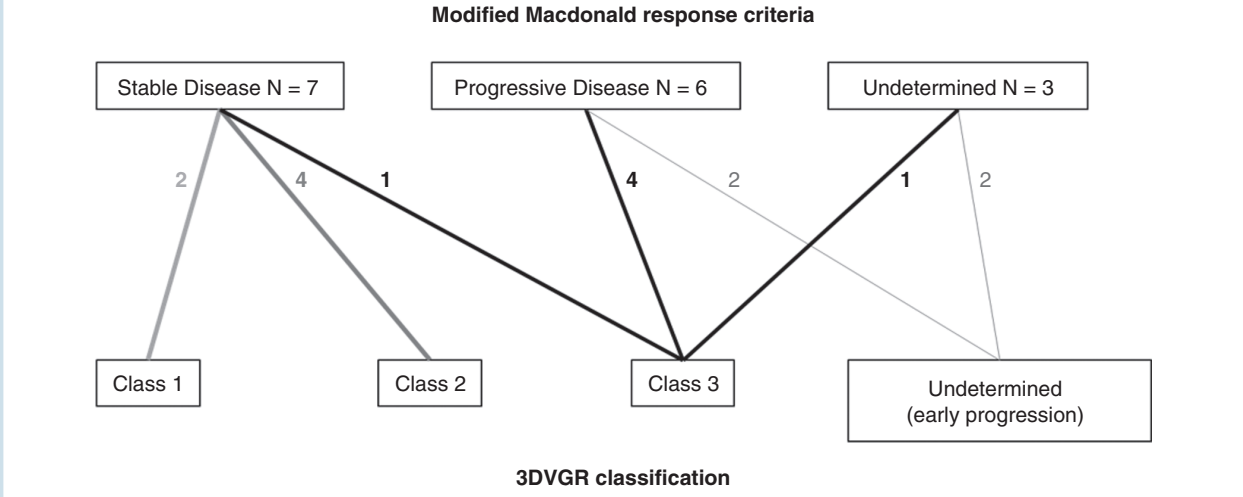


Figure 4. Comparison between patient repartition using modified Macdonald response criteria and 3D volume growth rate classification.

a secondary endpoints.[21,22] Finally, changes in apparent diffusion coefficient of meningioma treated with proton therapy has also been suggested to be predictive of treatment response.[23]

Recently, the RANO group revised meningioma assessment for clinical trials by defining the notion of minor response corresponding to a tumor area decrease of 25%. The authors also highlighted the interest of volume assessment and encouraged volumetric analysis inclusion as a secondary endpoint in clinical trials.[6] Previous studies highlighted the better accuracy of volume assessment versus larger diameter (1D) or 2 largest orthogonal diameters (2D).[24] As example, in the study of Huang and colleagues,[17] 40% threshold volumetric criteria had the highest predictive value for OS and the highest correlation with PFS for patients alive at 6 months versus 1D or 2D evaluation.[17] The volume estimation accuracy was superior probably due to the better estimation of meningioma tumor burden using the volumetric approach compared to the 1D or 2D methods. Hence, volume assessment improves the sensitivity threshold and the precision of tumor delineation due to the frequent asymmetrical meningioma configurations with various extensions and shapes, including the "en plaque" shape that is often difficult to estimate in 2D.[25–27]

However, performing volumetric analyses in real time adds cost and complexity and is currently not available in all centers. Hence, currently, tumor size evaluation remains based on the product of the maximal cross-sectional enhancing diameters.[6]

We recently proposed to integrate volume assessment and more specifically 3DVGR calculation into meningioma clinical trials.[8] The double interest of our 3DVGR classification is to introduce the notion of positive impact of the slowdown of meningioma growth (class 2) with real patient benefit, as well as the use of the patients' own comparison, enabling personalized response assessment. In the CEVOREM study, evaluating the combination of everolimus and octreotide, only 10% of the treated tumors presented with a volume reduction that did also not reach the 25% decrease defining PR.[7] Nevertheless, patients experienced clinical benefit of this treatment with neurological improvement and prolonged PFS and OS. These results illustrated that 3DVGR slowdown under treatment might lead to patient benefit although no tumor size reduction was observed. 3DVGR appeared particularly relevant for slow-growing CNS WHO grade 1 meningiomas for which PFS6 rate is not applicable. In the present study, similarly, we observed that several patients with clinical benefit presented with no response according to modified Macdonald criteria; however, they were classified as 3DVGR class 1 or 2. Hence, 3DVGR class seems more sensitive than classical response criteria for discrimination of patient benefit.

The low number of patients for whom pre-baseline MRI were available is a limitation of our study. However, the results are in line with observations in the CEVOREM trial and reinforce the interest in longitudinal 3DVGR assessment in meningioma clinical trials.

In conclusion, meningioma 3DVGR classification allows a more accurate patient response stratification and is correlated to PFS6 and clinical benefit. This classification may be of interest for future meningioma clinical trials to early identify active and promising systemic therapy.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

meningioma | response criteria | volumetric assessment

Conflict of interest

E.T. has received honoraria for lectures or advisory board participation from Novocure, Servier, Léo Pharma and Gliocure. T.Gr. has received study drug support from Novartis. M.P. has received honoraria for lectures, consultation, or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dohme, Tocagen. The following for-profit companies have supported clinical trials and contracted research conducted by M.P. with payments made to his institution: Böhringer-Ingelheim, Bristol-Myers Squibb, Roche, Daiichi Sankyo, Merck Sharp & Dohme, Novocure, GlaxoSmithKline, AbbVie. J.F. has received honoraria for lectures and consultations from the following for-profit companies: Novartis, Seagen. M.W. has received research grants from Quercis and Versameb, and honoraria for lectures or advisory board participation or consulting from Bayer, Curevac, Medac, Neurosense, Novartis, Novocure, Orbus, Philogen, Roche and Servier. W.W. has received study drug support from Apogenix, Pfizer, and Roche and consulted for MSD and Roche with all financial reimbursement to the University Clinic. R.S. has received honoraria for lectures and advisory board participation from AbbVie, Merck, Tocagen, and AstraZeneca. E.L.R. has received honoraria for lectures or advisory board from AbbVie, Adastra, Daiichi Sankyo, LEO Pharma; Seagen, and Tocagen. M.B. reports personal fees from Boehringer Ingelheim, Guerbet, Springer, grants from DFG, European Union, and Hopp Foundation, all outside the submitted work. G.L. declares consulting or advisory role funding from ABBVIE, Bayer, Novartis, Orbus Therapeutics, BrainFarm, Celgene, CureTeq, Health4U, Braun, Janssen, BioRegio Stern, Servier, Novocure, and travel funding from Roche and Bayer. F.S. reports honoraria for lectures from Illumina, honoraria for advisory board from AbbVie, and for other consultancy from Bayer. A.S., JM.S., P.B., V.G. and T.Go.: no conflicts of interest reported.

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Authorship statement

The study was developed by E.T. and M.P. in collaboration with T.Gr. and J.F. as well as the EORTC headquarters (T.Go. and V.G.). Statistical analyses were performed by E.T. Translational research and molecular marker evaluation were coordinated and performed by F.S. The literature search was done by E.T., T.G. and M.P. Data were collected by all authors. The data were analyzed by E.T., J.F., T.Gr. and M.P. The manuscript drafts were written by E.T., T.Gr., M.W., E.L.R. and M.P. All authors approved the final version of the manuscript.

Data Availability

Statement declaring that the data will be made available upon reasonable request.

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