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Proposed response assessment and endpoints for meningioma clinical trials: report from the Response Assessment in Neuro-Oncology Working Group

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Abstract

No standard criteria exist for assessing response and progression in clinical trials involving patients with meningioma, and there is no consensus on the optimal endpoints for trials currently under way. As a result, there is substantial variation in the design and response criteria of meningioma trials, making comparison between trials difficult. In addition, future trials should be designed with accepted standardized endpoints. The Response Assessment in Neuro-Oncology Meningioma Working Group is an international effort to develop standardized radiologic criteria for treatment response for meningioma clinical trials. In this proposal, we present the recommendations for response criteria and endpoints for clinical trials involving patients with meningiomas.

Keywords

endpoint | MRI | meningioma | RANO | response

Meningiomas are the most common type of primary brain tumors in adults, accounting for approximately 36% of the total, with an annual incidence of approximately 7.6 per 100 000.[1] These tumors are classified by the World Health Organization (WHO) into 3 histologic grades. Using modern WHO criteria, ~70–75% of surgically resected meningiomas are grade I (benign), 20–30% are grade II (atypical), and 1–3% are grade III (anaplastic or malignant).[2–6]

Small asymptomatic tumors that are not associated with surrounding edema or concerning radiologic features

raising the specter of a higher-grade lesion can be safely observed with scheduled follow-up imaging. Large, growing, or symptomatic meningiomas require treatment, most frequently with surgery with or without radiation therapy. Occasionally, meningiomas refractory to surgery and radiation (stereotactic radiosurgery [SRS], stereotactic or nonstereotactic fractioned radiotherapy) prompt medical therapies, although the results of these medical treatments to date have been disappointing.[7–10]

Currently, there are no standardized response criteria or clinical trial endpoints in studies involving meningiomas. Many trials use a variation of the Macdonald criteria, which was developed for high-grade gliomas for determination of response and progression,[7,9,11] while others use Response Evaluation Criteria In Solid Tumors (RECIST), developed for systemic tumors.[12] These differences in response criteria make it difficult to compare one study to another. Moreover, no consistent definition exists for measurable disease, target lesions, or how to handle "pseudoprogression" related to treatments such as SRS and immunotherapy. There is a need for standardized response criteria in clinical trials involving meningiomas.

Similarly, there are currently no generally accepted endpoints for clinical trials of meningioma. Some trials use response rates based on reduction of lesion size, but this only occurs in a minority of patients even with effective therapy, especially for grade I meningiomas.[9,13] Many trials of recurrent meningiomas use 6-month or 12-month progression-free survival (PFS).[9] Recently, the Response Assessment in Neuro-Oncology (RANO) Working Group evaluated the historical data from clinical trials involving medical therapies for meningioma.[9]The weighted 6-month PFS (PFS6) for WHO grade I meningioma was 29% (95% CI: 20.3%–37.7%). For WHO grades II/III meningioma, the weighted average PFS6 was 26% (95% CI: 19.3%–32.7%).

The RANO Working Group established a Meningioma Subcommittee to evaluate the available data regarding response criteria and endpoints in clinical trials of meningioma. This committee consists of neuro-oncologists, neurosurgeons, radiation oncologists, neuroradiologists, and biostatisticians. Here, we propose consensus criteria for determining response in clinical trials involving meningiomas and discuss the most appropriate endpoints and trial designs. When appropriate, there is similarity in language to RANO criteria proposed for low- and high-grade gliomas and brain metastases to ensure as much consistency as possible in response criteria across different brain tumor types.[14–16]

Scope and Application

Integral to the practical utility of response assessment criteria for both everyday practice and the clinical trial setting is that numerical cutoffs incorporated to define response categories reflect changes that are felt to be clinically meaningful following therapeutic intervention. Historically, a 25% increase in bidimensional product to define progression and a 50% decrease to define partial response (PR) have been incorporated in response assessment criteria for high-grade glioma and low-grade glioma because these numerical cutoffs are agreed upon to likely be clinically meaningful. Similar cutoffs are proposed herein and are felt to be appropriate for patients with meningiomas that demonstrate faster growth because these cutoffs are also felt to reflect a clinically meaningful change for such tumors.

However, a substantial subset of meningioma tumors exhibit indolent and insidious growth. For these slow-growing tumors, numerical cutoffs of change in tumor size, particularly if increasing, are, by themselves, of limited value in the assessment of a therapeutic intervention, unless they also incorporate the variable of time. Therefore, the scope of the criteria detailed herein is intended to apply to patients with fast-growing meningiomas. Although arbitrary, a fast-growing meningioma can be defined as one that has demonstrated a ≥15% increase in bidimensional enhancing product in the past 6 months. Meningioma patients with slow-growing tumors, defined as <15% increase in bidimensional product over the preceding 6 months, will require modification of the proposed guidelines discussed below, including longer periods of evaluation. These criteria will need to incorporate numerical cutoffs of change in tumor size over time (ie, tumor growth rate) in order to effectively assess the value of specific therapeutic interventions for such tumors.

Specifications of Methods of Measurement

Method of Assessment

Standardized imaging acquisition technique and radiographic assessment methods should be used to characterize each lesion at baseline and during follow-up. It is important to use imaging techniques that are consistent across all imaging timepoints to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters.

Imaging Modality

Gadolinium-enhanced MRI is the most sensitive and reproducible method currently available to measure CNS lesions selected for response assessment. Although MRI is strongly encouraged as the default standard imaging technique, CT with and without contrast could be considered in select circumstances (eg, lack of availability or contraindication for MRI). MRI scanners of 1.5 or 3T are recommended, and ideally patients should be imaged on the same MRI or at least on MRIs with the same field strengths throughout the period of assessment. Use of thin-section imaging is recommended, ideally with ≤1.5 mm pixel resolution, especially for evaluating lesions <10 mm in maximal diameter and/or small changes in lesion size. One option is to adapt the proposed standardized Brain Tumor Imaging Protocol (BTIP) developed for gliomas also for meningioma trials.[17] In some cases, metabolic imaging (ie, PET) could be proposed to meningioma patients, although the evidence supporting the use of this imaging modality is limited and restricted to diagnosis (ie, grading) or tumor delineation (ie, planning

of radiation therapy).[18] There are also parallel efforts by the PET RANO workgroup to develop response criteria based on radiolabeled somatostatin receptor PET techniques that are currently evaluated in meningioma trials.

Imaging Definitions

Definition of Measurable Disease

Measurable disease is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI, with 2 perpendicular diameters of at least 10 mm, visible on 2 or more axial slices that are preferably, at most, 5 mm interslice thickness with no more than 1 mm interslice gap. As with the RANO criteria for high-grade glioma and RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be 2 times the slice thickness.[12,14] In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.[14] Measurement of tumor around a cyst or surgical cavity represents a particular challenge. In general, such lesions should be considered nonmeasurable unless there is a nodular component measuring more than 10 mm in each of 2 dimensions. The cystic or surgical cavity should not be measured in determining response.

For previously treated lesions, we recommend documenting how each lesion was previously treated (ie, surgical resection, SRS, fractionated radiation therapy, brachytherapy, etc). Lesions with prior local treatment can be considered measurable if there has been demonstrated progression since the time of local treatment. However, careful consideration should be given particularly to lesions previously treated with SRS given the possibility of treatment effect (discussed further below in the special consideration section). Whether such lesions can be considered measurable as a target lesion should be specified prospectively in the clinical protocol. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions.

Definition of Nonmeasurable Disease

Nonmeasurable disease is defined as lesions with maximal perpendicular diameter measures less than 10 mm or measurable in one dimension only, or masses with ill-defined margins. Patients without measurable disease, such as those with nonmeasurable disease only or those who undergo a complete resection, cannot be evaluated using response based on lesion size reduction and can only achieve stable disease as their best radiographic outcome. A potential caveat are small, less than measurable, but well-circumscribed lesions that disappear completely with treatment, in which case complete response (CR) would probably be the correct tumor biological assessment. Yet, for consistency within the RANO framework, only disappearance of measurable lesions should be labeled CR. Accordingly, if response rate is the primary endpoint of the study, patients with measurable disease are generally required for study eligibility. If duration of tumor control or survival is the primary endpoint, then patients with both measurable and nonmeasurable disease would be eligible for assessment because the determination of disease progression would be the primary interest.

Evaluation of Small Lesions

We recognize that many patients with meningiomas present with small, subcentimeter lesions and that some centers routinely perform MR imaging with 3 mm slice thickness or less. There was debate within the group whether the lower size limit of a measurable lesion could be reduced to 2 perpendicular diameters of at least 5 mm or even less. However, the consensus was to maintain consistency with RECIST 1.1 and the RANO criteria for gliomas and brain metastases given concerns about reproducibility and interpretation in changes of small lesions.[12,14] Patients with nonmeasurable disease can still be included on trials where response is not the primary endpoint (for example, on trials with PFS, overall survival [OS], or other primary endpoints). For studies in which objective response is the primary endpoint, diameters greater than 10 mm in 2 dimensions should be used to define measurable disease.

Complete response and unequivocal progressive disease (PD) can likely be interpreted even with lesions as small as 5 mm. However, small changes may be difficult to interpret and can be subject to imaging measurement inaccuracies. A minimum change of 25% increase in the product of the maximal perpendicular diameters to determine PD or a minimum change of 50% decrease in area to determine PR from a 5 × 5 mm tumor is within the margin of error of measurement and may not be reproducible when 2D assessment of MRI data is performed. In addition, because of the intrinsic uncertainty of measurements of small lesions, any lesion <10 mm in diameter should be regarded as unchanged from baseline unless there is at least a 3 mm change in the measurement. For investigators who choose to lower the minimum size limit of measurable disease to 5 mm, we strongly recommend MR imaging with 1.5 mm slice thickness or less.

The decision to include patients with multiple lesions whose summed area is ≥100 mm^2 but whose largest lesion measures <100 mm^2, but >25 mm^2, should be taken with caution when objective response rate is the primary endpoint. If such patients are included, response should be assessed using the sum of the products of the maximal diameters of the lesions, and the response criteria should be clearly delineated in the protocol. Thin section MRI with ≤1.5 mm slice thickness would be required in this setting.

Number of Lesions

If there are multiple contrast-enhancing lesions, a minimum of 2, and maximum of 5, of the largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined, similar to the criteria proposed for gliomas.[14] In general, the largest progressive lesions should be selected. However, emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, if the largest lesions do not lend themselves to reproducible

measurement, the next largest lesions that can be reproducibly measured should be selected. For patients with recurrent meningiomas who have multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. Such changes should qualify as progression.

Definition of Progression to Allow Clinical Trials Enrollment

Currently, patients with any worsening of their imaging studies are eligible for entry onto clinical trials for recurrent meningioma, even if the change is minimal. Ideally, patients should be required to have tumor growth that exceeds a quantifiable and reliable threshold. For high-grade gliomas, it is recommended that patients become eligible for clinical trials only if there is a 25% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions, while on stable or increasing doses of corticosteroids. However, empirically meningioma patients are frequently determined to have developed progression based on smaller increases in tumor size. For trials where landmarks (eg, PFS6) are the primary endpoints, it will be important to obtain scans over the same time period before therapy (ie, 6 months for PFS6) to ensure that prior to enrollment in the clinical trial the tumor growth is sufficiently rapid that the tumor will not be considered stable while on study simply based on its baseline rate of growth. We therefore recommend that patients be considered eligible for clinical trials if there is 15% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions within the prior 6 months, while on stable or increasing doses of corticosteroids, or if a new lesion develops. Slow-growing meningiomas not meeting the criteria should not be included in clinical trials with PFS endpoints; more sensitive measures of response such as a change in rate of growth might be more suitable for such meningiomas.

Evaluation of Tumor Response and Progression

General Principles

Since meningiomas are almost always enhancing, evaluation of tumor size will be based only on the product of the maximal cross-sectional enhancing diameters. There will be no evaluation of non-enhancing disease.

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. Table 1 lists the criteria for radiographic changes after therapy.

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. In studies for which objective response is not the primary endpoint, the protocol must specify prospectively whether entry is restricted to those with measurable disease or if patients with nonmeasurable disease are also eligible.

In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely—for example, at 8- to 12 -week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan when criteria for progression were first met.

Minor Response Criteria

Given the relatively low rate of response expected, especially for grade I meningioma, we propose addition of minor response, characterized by a 25% or greater but less than 50% reduction in the product of the maximal perpendicular diameters, similar to the RANO criteria for low-grade gliomas.[15]

Baseline Documentation of Target and Nontarget Lesions

All baseline evaluations should be performed as close as possible to the treatment start and not more than 4 weeks before the beginning of treatment. A sum of the products of the maximal perpendicular diameters for all target lesions will be calculated and reported as the baseline area. Target lesions should be measurable. As discussed previously, if there are multiple lesions, at least 2 and up to 5 lesions may be selected. All other lesions should be identified as nontarget lesions and should also be recorded at baseline. Measurements of nontarget lesions are not required and these should be followed as "present," "absent," or "unequivocal progression."

Definition of Best Overall Response

Best overall response represents a composite of target and nontarget response (see definitions above), as well as corticosteroid use and clinical status (Table 1). In nonrandomized trials where response is the primary endpoint, confirmation of PR, minor response (MR), or CR at a minimum of 8 weeks, or until the next planned scan per protocol if that is longer, is required to deem either one the best overall response.

At each protocol-specified timepoint, a response assessment should occur. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

Evaluation of Target Lesions (Table 1)

Complete response (CR)

Disappearance of all CNS target lesions; sustained for at least 8 weeks, or until the next planned scan

Table 1 Summary of the proposed RANO response criteria for meningiomas

Criterion	CR	PR	MR	SD	PD
Target lesions	None	≥50% decrease in area relative to baseline	≥25% and <50% decrease in area relative to baseline	<25% decrease relative to baseline but <25% increase in area relative to nadir	≥25% increase in area relative to nadir*
Nontarget lesions	None	Stable or improved	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Stable or decreased	NA[+]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	All	Any[+]

NA, not applicable.
*Progression occurs when this criterion is met.
**New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression (see "Guidance in the case of new lesion(s) while on immunotherapy").
[+]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

per protocol if that is longer; no new lesions; no or only replacement doses of corticosteroids; stable or improved clinically.

Partial response (PR)

At least a ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 8 weeks, or until the next planned scan per protocol if that is longer; no new lesions; stable to decreased corticosteroid dose compared with dose at time of baseline scan; stable or improved clinically.

Minor response (MR)

At least a ≥25%, but less than 50%, decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 8 weeks, or until the next planned scan per protocol if that is longer; no new lesions; stable to decreased corticosteroid dose compared with dose at time of baseline scan; stable or improved clinically.

Progressive disease (PD)

Increase by ≥25% in sum of the products of perpendicular diameters of target lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response; any new lesion; clear progression of nontarget; clear clinical deterioration not attributable to other causes apart from the tumor (ie, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; or failure to return for evaluation as a result of death or deteriorating condition.

Stable disease (SD)

Does not qualify for complete response, partial response, minor response, or progression. As with CR, PR, and MR, stable disease should be sustained for at least 8 weeks, or until the next planned scan per protocol if that is longer. If the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Evaluation of Nontarget Lesions

Nontarget lesions should be assessed qualitatively at each of the timepoints specified in the protocol and should be sustained for at least 8 weeks similar to the criteria for target lesion evaluation.

CR

Disappearance of all enhancing CNS nontarget lesions and no new lesions.

Non-CR/Non-PD

Persistence of one or more nontarget lesions.

PD

Any of the following: unequivocal progression of existing enhancing nontarget lesions, new lesion(s) (except while on immunotherapy-based treatment). In the case of immunotherapy-based treatment, new lesions alone may not

constitute PD (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

Specific Considerations

Assessment of Target and Nontarget CNS Lesions

a. **Target lesions that become too small to measure:** While on study, all CNS target lesions should have their actual measurement recorded, even when very small (eg, 4 × 4 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the investigator does not feel comfortable assigning an exact measure, a minimum of 1 mm can be used for either one of the bidimensional measurements.

b. **Lesions that coalesce on treatment:** As lesions coalesce due to tumor growth, a plane between them may be maintained that would aid in obtaining maximum area of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal perpendicular diameters of the "coalesced" lesion should be measured and compared with the sum of the areas of the preexisting lesions.

c. **Definition of new lesion(s):** The finding of a new lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with ≤1.5 mm slice thickness, then the new lesion should also be visible in axial, coronal, and sagittal reconstructions of ≤1.5 mm projections. If a new lesion is equivocal, for example because of its small size (eg, ≤5 × 5 mm), continued therapy may be considered, and follow-up evaluation will clarify if it truly represents new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

d. **Guidance for special shape or location-related challenges in tumor measurement:** For meningiomas with dural tails that can be distinguished from the main tumor bulk by signal intensity, measurements should be applied to the main tumor bulk and not to the dural tail. If dural tails cannot readily be discerned from the main tumor, as often is the case in en plaque meningiomas, the lesion is best regarded as nonmeasurable by 2D criteria but still can be measured by volumetric criteria as outlined below. Similarly, for tumors that have ill-defined brain or bone invasion or are distorted in shape by bony hyperostosis, making 2D measurement unreliable, the lesion should be regarded as nonmeasurable. For skull base tumors, lesions can be considered measurable only when the tumor margins can be well visualized from extra-osseous structures such as fat or enhancing muscle. In these situations, fat-suppression technique is necessary to improve visibility of tumor margin. We also recognize the difficulty in making consistent 2D measurements in certain anatomical locations where the selection of image slice and tumor axis for measurement can be variable. To minimize inconsistency, we advise the measurements be made on equivalent image slice and tumor axis within the same patient, preferably by the same reader.

e. **Definition of unequivocal progression of nontarget lesion(s):**
   1. ***When the patient also has measurable disease***, to achieve "unequivocal progression" on the basis of nontarget disease alone, there must be an overall level of substantial worsening in nontarget disease such that, even in the presence of SD or PR in target disease, the overall tumor burden of all nontarget disease has increased sufficiently to merit discontinuation of therapy.
   2. ***When the patient has only nonmeasurable disease***, there must be an overall level of substantial worsening so that the tumor is now measurable to merit discontinuation of therapy.

f. **Guidance in the case of uncertain attribution of radiographic findings and/or equivocal cases:** In the case of patients receiving intensity modulated radiotherapy (IMRT), SRS, brachytherapy, immunotherapies, or other targeted approaches that may cause a local inflammatory response, there may be radiographic evidence of enlargement of target and nontarget lesions which may not necessarily represent tumor progression. Although the incidence of the phenomenon is not well known and requires further study, transient tumor growth following radiosurgery occurred in 7 patients (8.1%) in a study of 865 meningioma patients treated with radiosurgery.[19] Transient increases in the volume of enhancement have also been observed in 3 of 13 (23%) patients with recurrent WHO grade III meningioma treated with boron neutron capture.[20] Furthermore, in cases of invasive meningiomas where enhancing tumor often involves brain parenchyma, it is our experience that SRS-induced inflammation/necrosis can be difficult to distinguish from true invasive tumor. If there is evidence of radiographic progression in these treatment settings, additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. The methods used to distinguish between the 2 entities should be specified prospectively in the clinical protocol. Patients may be continued on protocol therapy pending further investigation with one or more of the following options: (1) Repeat the scan at the next protocol scheduled evaluation or sooner. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study, especially if there is also clinical progression. If the lesion is stable or decreased in size, then this may be consistent with treatment effect and the patient may remain on study. For patients with equivocal results even on the next restaging scan, the scan may be repeated at a subsequent protocol scheduled evaluation or sooner, although surgery and/or use of an advanced imaging modality (in the case of SRS) should be considered. (2) Surgical pathology obtained via biopsy or resection. (3) For SRS treated lesions, an advanced imaging modality such as perfusion MR

imaging, MR spectroscopy, or PET may be considered to provide additional evidence of tumor progression or treatment response.[21] Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

g. **Guidance in the case of new lesion(s) while on immunotherapy:** For patients receiving immunotherapies, an initial increase in the size of meningiomas may potentially be followed by radiographic stabilization or regression, a similar phenomenon that has been seen with other tumors.[22] This may be related to the mechanism of action for immunotherapy, including immune infiltrates, as well as the time required for development of an effective immune response. The RANO group has developed Immunotherapy Responses Assessment in Neuro-Oncology (iRANO) criteria to address this issue.[23] Patients who have received immunotherapies within the past 6 months and develop worsening of radiologic findings that would otherwise qualify for PD may stay on study if they are clinically stable. They should be closely followed clinically and with neuroimaging studies. If the subsequent evaluation confirms that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected. Since inflammatory changes may not resolve over 1 month, close observation over a period of 3 months may be allowed. As "pseudoprogression" from immunotherapies is unlikely to occur later than 6 months after treatment, any radiologic progression after this time will be considered true progression.

h. **Corticosteroid use:** Corticosteroids may be indicated in patients with meningioma based upon factors such as edema, which can occur in the absence of lesional progression. Thus an increase in corticosteroid dose alone, in the absence of clinical deterioration related directly to tumor progression, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression and should be classified as non-evaluable at that timepoint. If their corticosteroid dose can be reduced back to baseline, they will be considered as having SD; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression.

i. **Clinical deterioration:** While the definition of clinical deterioration is left to the discretion of the treating physician, it is recommended that a decline in the KPS of at least 20 points from baseline, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose. The RANO Working Group has recently proposed Neurologic Assessment in Neuro-Oncology (NANO) criteria to quantify clinical changes more objectively.[24] The criteria require validation but potentially provide a more comprehensive evaluation of neurologic function than KPS.

j. **Volumetric criteria:** The value of volumetric measurements has been compared to bidimensional measurements in the evaluation of response in brain tumors.[25–28] For some tumors, such as en plaque meningiomas, standard 2D measurements are very difficult and volumetric measurements would be preferable. At present, however, performing volumetric analyses in real time adds cost and complexity and is not available at all centers. At the same time, the RANO Meningioma group believes that evaluation and reporting of volumetric response in clinical trials (in addition to the bidimensional RANO Meningioma criteria) will add to the knowledge base and either ultimately justify or negate the value for volumetric measurements in future trials, and encourages its inclusion as a secondary endpoint when feasible.

The appropriate cutoff that should be chosen to define a PR when volumetric measurements are used is also a matter of debate. Assuming a perfect sphere, a bidimensional 25% reduction in area corresponds to approximately a 65% volumetric reduction, while a bidimensional 25% increase in area corresponds to approximately a 40% volumetric increase. There is evidence showing concordance of response assessments when using these cutoffs in other types of brain tumor patients.[27] At the same time, volumetric changes of at least 20% appear to be reproducible between readers[29,30] and in one study were shown to be associated with improvements in neurological signs and symptoms.[31] To provide preliminary support for the use of volumetric evaluation in clinical trials, the RANO Meningioma group initiated a multicenter retrospective study evaluating the MR imaging data of patients with recurrent meningioma enrolled in systemic therapy trials (article in press). The analysis revealed that a 40% increase in tumor volume during the first 6 and 12 months after treatment initiation accounts for approximately half of the study population and was associated with decreased OS. The use of a 20% volume threshold to define progression did not improve correlation with survival, although it remains unclear whether the lower thresholds may be associated with other measures of patient benefit such as quality of life, neurocognitive function, or OS. Criteria using 65%, 40%, and 20% thresholds of volume reduction identified a small percentage of responders, and no survival advantage was demonstrated among the responders regardless of criteria used.

The group believes that the use of the same criteria and cutoffs across trials will allow trial results to be placed into their proper context. It is also important to recognize that the correlative relationship between 2D and volume measurements may alter due to differences in 3D shape, and comparing trial results using different endpoints (2D vs volume) is currently not advised. Thus, for investigators

who choose to report volumetric response data, we propose the following (Table 2):

1. Progressive disease will be defined as ≥40% increase in the sum of tumor volume of CNS target lesions in addition to the corticosteroid and clinical status criteria as outlined previously.
2. Partial volumetric response will be defined as ≥65% decrease in the sum volume of CNS target lesions, in addition to the corticosteroid and clinical status criteria as outlined previously.
3. It may be possible to consider a lower threshold for volumetric response and we encourage digital archiving of trial images and accompanying linked clinical outcome data to allow for pooling of studies to determine whether different thresholds might be justified in the future.

Imaging Protocol Recommendations

To improve the reproducibility of imaging response assessment and to facilitate comparisons across clinical trials, a standardized imaging protocol is necessary. The BTIP published recently includes gadolinium enhanced 3D T1-weighted imaging with less than 1.5 mm slice thickness.[17] This protocol specifies parameters that can be readily implemented on modern scanners and should allow both diameter and volumetric measurement for most intracranial meningiomas. Additional sequences including T2-weighted imaging and diffusion weighted imaging specified in the BTIP may facilitate evaluation of advanced imaging analysis and identification of novel imaging biomarkers for future refinement of response assessment criteria. For meningiomas that involve the cranium, skull base, or extracranial spaces, we recommend applying fat-suppression techniques such as water excitation to the 3D T1-weighted sequence for better delineation of tumor margins from bone marrow. This also allows distinction of tumor from fat graft material commonly used during surgical resection of skull base meningiomas. We recognize that the option to apply fat suppression on some MR platforms is not available, and therefore alterations to the technique as specified in the BTIP may be necessary. In principle, the 3D T1-weighted sequence should have an isotropic resolution of less than 1.5 mm and should have the option to include a water excitation fat-suppression technique that has fewer artifacts related to field inhomogeneity. It is also necessary to include the full extent of tumor in the 3D sequence.

Summary

We propose response criteria for evaluation of therapies for meningioma in order to achieve consistency across clinical trials. These recommendations were generated as part of an international neuro-oncology effort toward consensus building. Implementation into future clinical trials will be critical to allow these criteria to be evaluated and validated. These criteria are a work in progress and we expect them to be iteratively updated as data and experience accrue.

Endpoints in Meningioma Clinical Trials

The determination of best clinical trial endpoints for meningioma has many of the same challenges encountered in other cancers trying to define a true OS advantage with therapy but having to rely on surrogate endpoints. Meningioma is complicated by the large spectrum of clinical symptoms that can occur depending on its size and location, and employing therapies at different timepoints can have very different results. Demonstrating an OS benefit represents the unequivocal gold standard of treatment

Table 2 Summary of the proposed RANO volumetric response criteria for meningiomas

Criterion	CR	PR	MR	SD	PD
Target lesions	None	≥65% decrease in volume relative to baseline	≥40% and <65% decrease in volume relative to baseline	<40% decrease relative to baseline but <40% increase in volume relative to nadir	≥40% increase in volume relative to nadir*
Nontarget lesions	None	Stable or improved	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	All	Any+

NA, not applicable.
*Progression occurs when this criterion is met.
**New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression (see "Guidance in the case of new lesion(s) while on immunotherapy").
+Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

efficacy. However, OS is also the most difficult to ascertain owing to the long time frame often needed to reach this endpoint, and the large amount of resources needed to perform such studies.

Therefore, similar to other cancers, meningioma trials have relied on surrogate endpoints to determine treatment efficacy. However, this must be done with caution as these surrogates, such as PFS, PFS6, and radiographic objective response rate (ORR), have not been shown to correlate with an OS advantage. With regard to brain tumors, even a PFS advantage may be meaningful in the absence of a true OS benefit owing to a potential reduction in neurologic morbidity. Here, we describe various clinical trial endpoints, and where in the disease course they may be most appropriate.

Objective Response Rate

The ORR is usually viewed as a strong indicator of a treatment's activity. However, ORRs following therapies for meningiomas have generally been very low. It is likely that this results from the use of ineffective therapies as well as factors related to inherent tumor biology. In a RANO review of the results of medical therapies for meningioma, 37 of 42 publications reported radiographic response data. Of the 555 patients included in those 37 reports, best radiographic responses were reported as 1 CR (0.2%), 10 PR (1.8%), 13 MR (2.3%), and 343 SD (62%). Therefore, the combined CR + PR + MR rate was 4.3%, suggesting that reduction in tumor size has been only rarely observed. However, once SD is included, the "potential clinical benefit rate" is much higher.

The inclusion of SD raises an interesting predicament. Meningiomas refractory to surgery and radiation therapy often grow quickly and have a weighted average PFS6 rate of 29% for the WHO grade I group and 26% for the WHO grades II and III group.[9] In such aggressive tumors, SD may be considered indicative of an active treatment. However, the poor PFS results despite the relatively high SD rates reported suggest either that these SD responses were in patients who were not progressing quickly enough to qualify for progressive disease on the first imaging timepoint or that the drug's effects were not durable. In either situation, simply attaining short duration SD as a best radiographic response is not a reliable surrogate endpoint for a drug's efficacy. However, since CR, PR, and MR are infrequent, it is perhaps more clinically relevant to include SD as a response but impose some time limit modifications to qualify as a response. For example, lack of PD, CR, PR, and MR on imaging over an interval of less than 6 months should not be considered clinically relevant SD.

Progression-Free Survival

PFS is defined as the time from the initiation of the treatment under study until the time of documented disease progression or death, whichever occurs first. The advantage of PFS is that it represents the effect of the treatment under study, thus eliminating the effect of postprogression therapies which can complicate the interpretation of OS as an endpoint.

In the RANO review of published clinical trials of medical therapies in meningiomas, PFS6 was the only outcome reported with sufficient frequency to provide historical comparisons for clinical trials.[9] Additionally, given the concern over the high SD rates yet the poor PFS6 rates, it is likely that the 6-month timepoint eliminates most patients who are called SD but really are just progressing too slowly to reach the 25% growth threshold required for PD determination in most of these studies.

For trials where PFS or landmark endpoints (eg, PFS6) are the primary endpoints, it will be important to obtain scans over the previous 6–12 months to ensure that the rate of growth prior to enrollment in the clinical trial is sufficiently rapid that the tumor will not be considered stable while on study simply based on its slow baseline rate of growth.

From the historical data indicating that PFS6 for negative trials of WHO grade I meningioma is 29%, an increase of the PFS6 to 50% would probably be of interest. For WHO grades II and III meningioma where the historical PFS6 is 26%, an increase of PFS6 to 40% would probably be of interest in single arm studies.[9]

Ideally, trials using a PFS endpoint would be randomized, since it can be difficult to ensure that the patients enrolled in the trial match the historical controls. However, given the small number of meningioma patients available for accrual into clinical trials and paucity of testable/established therapies, most meningioma studies will likely include only a single arm. In these studies, it will be important to ensure as much as possible that the patients match the historical controls that they are being compared with, particularly with regard to relevant demographic factors, histopathologic grade, degree of prior treatment, and extent of surgery.

Irradiation (especially SRS) and immunotherapies may result in "pseudoprogression" complicating the interpretation of PFS as an endpoint, although this issue is probably less common than with gliomas.

Given the limitations of both ORR and PFS as endpoints, some trials, such as the Alliance trial evaluating targeted agents for recurrent meningioma (NCT02523014), use a coprimary endpoint of ORR and PFS6, in which therapeutic success of the trial will be defined by either endpoint criterion being satisfied.

Overall Survival

OS remains the unequivocal measure of a treatment's effectiveness. However, in trying to evaluate the effectiveness of newer therapies, OS is hindered by a real lack of historical comparative data as the reporting of OS data was quite minimal in the previous RANO reviews.[7,9] Without reliable historical comparison, OS is only useful in randomized studies. Moreover, the very long timelines, the influence of postprogression therapies, and the extensive resources required for large randomized studies make this endpoint unrealistic for most meningioma trials.

Other Endpoints

Given the limitations of the currently available standard endpoints, there is interest in novel endpoints for meningioma trials. Since radiographic response is uncommon, one endpoint under evaluation is whether therapies under consideration can decrease the rate of tumor volume growth. A local control endpoint, which is inclusive of stability or response, has been commonly employed for trials following radiosurgery, external beam radiation therapy, and surgery with subtotal resection. Data from completed meningioma clinical trials are currently being analyzed and the utility of this approach will be reported separately. Other non-radiological endpoints, including but not limited to quality of life, seizure frequency, time to second-line treatment, or cognitive function, will not be discussed in this paper.

Meningioma Clinical Trial Endpoints Recommendations

In summary, as radiographic responses are rare in meningioma, inclusion of SD seems clinically appropriate, as cessation of growth of these tumors should be considered beneficial given the poor survival of these patients and the neurologic morbidity from tumor growth. Therefore, an appropriate endpoint for medical therapy trials in surgery- and radiation-refractory meningioma is either PFS6 rate or a combination of PFS6 and radiographic response.

Summary

To address the variability in response criteria and endpoints used in meningioma clinical trials, the RANO group has proposed updated criteria for assessing response and selecting endpoints in these trials. These criteria are a work in progress. These recommendations will need validation in future clinical trials and eventually may require updating.

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