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# Volumetric analysis: Rethinking brain metastases response assessment

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## Abstract

**Background**. The Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria are the gold standard for assessing brain metastases (BMs) treatment response. However, they are limited by their reliance on 1D, despite the routine use of high-resolutionT1-weighted MRI scans for BMs, which allows for 3D measurements. Our study aimed to investigate whether volumetric measurements could improve the response assessment in patients with BMs.

**Methods**. We retrospectively evaluated a dataset comprising 783 BMs and analyzed the response of 185 of them from 132 patients who underwent stereotactic radiotherapy between 2007 and 2021 at 5 hospitals. We used T1-weighted MRIs to compute the volume of the lesions. For the volumetric criteria, progressive disease was defined as at least a 30% increase in volume, and partial response was characterized by a 20% volume reduction.

**Results**. Our study showed that the proposed volumetric criteria outperformed the RANO-BM criteria in several aspects: (1) Evaluating every lesion, while RANO-BM failed to evaluate 9.2% of them. (2) Classifying response effectively in 140 lesions, compared to only 72 lesions classified by RANO-BM. (3) Identifying BM recurrences a median of 3.3 months earlier than RANO-BM criteria.

**Conclusions**. Our study demonstrates the superiority of volumetric criteria in improving the response assessment of BMs compared to the RANO-BM criteria. Our proposed criteria allow for evaluation of every lesion, regardless of its size or shape, better classification, and enable earlier identification of progressive disease. Volumetric criteria provide a standardized, reliable, and objective tool for assessing treatment response.

## Key Points

- Volumetric criteria demonstrated better performance in brain metastases (BMs) response classification.
- Volumetric measurements provide a comprehensive evaluation of every lesion.
- Volumetric criteria identified recurrences earlier than 1D criteria in BM.

Brain metastases are the most common intracranial tumors in adults. Around 20% of patients with cancer develop brain metastases (BMs), with special incidence in lung cancer, breast cancer, and melanoma.[1] The occurrence of BM is growing because of improvements in patient survival due to the use of novel therapies effective against primary tumors.[2]

## Importance of the Study

Consensus criteria for the assessment of posttreatment response in brain metastases (BMs) are essential to standardize therapeutic decisions and allow comparison between clinical trials. Here, we compared the well-established Response Assessment in Neuro-Oncology (RANO) criteria for BMs with novel volumetric criteria. Volumetric measurements allowed for the evaluation of every BM, even those not measurable, due either to their size or shape, by the RANO-BM criteria. Furthermore, the RANO-BM criteria were shown to label stable diseases in most of the BMs studied and required at least 3 more months of follow-up than volumetric criteria to identify progressive disease. In accordance with the above, volumetric criteria may be preferable to RANO-BM in assessing response.

The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria[3] is an international, multidisciplinary effort to develop standardized response and progressive disease criteria for use in clinical trials of treatments targeting brain metastases. According to RANO-BM, the response of the overall disease in the brain is accurately represented by the sum of the longest diameter of a limited number of metastases. However, that assumption has a number of limitations.[4] For instance, ring-enhancing lesions or those with the longest diameter in contrast-enhanced (CE) area of less than 1 cm are considered nonmeasurable and should be assessed qualitatively.[3]

Technological developments in MRI have improved the quality of medical images. T1-weighted MR images are performed routinely at high resolution (3D images) in BM studies, which allows for the volumetric assessment of lesions. However, the 1D RANO-BM criteria are still the gold standard for progressive disease and response definition in clinical trials.

In various tumor types, including Ewing sarcoma and non–small cell lung cancer, volumetric assessments have been shown to be superior predictors of treatment response and prognosis compared to traditional 1D measurements.[5–7] Additionally, previous studies have emphasized the importance of employing volumetric methods for accurate assessment.[8,9] Particularly in the context of BMs, some authors of the RANO-BM criteria in a subsequent study acknowledged the importance of investigating the disparities in lesion assessment when utilizing 1D versus volumetric criteria.[10]

The purpose of this study was to compare the accuracy of the assessment of brain metastasis (BM) response to treatment using volumetric criteria and RANO-BM. We hypothesized that volumetric criteria based on the total volume (CE plus necrotic volume) would provide a more accurate evaluation while being able to assess every BM regardless of size, shape, or enhancement type.

## Materials and Methods

### Patients

Patients included were all participants in a retrospective, multicenter, nonrandomized study approved by ethics boards at 5 hospitals. All patients were diagnosed with BM in the period 2007–2021 and followed up with MRI according to standard clinical practice. Inclusion criteria were: (i) Having received stereotactic radiotherapy (SRT), that is either fractionated stereotactic radiotherapy or single-session stereotactic radiosurgery, at any time over the evolution of the disease, (ii) the longest diameter of at least 10 mm before SRT, since lesions under 10 mm are considered nonmeasurable by RANO-BM and criteria cannot be compared and (iii) the availability of volumetric gadolinium contrast-enhanced MR images over the entire follow-up (slice thickness < 2 mm). Our goal in this study was to compare how different criteria perform in identifying the events of either progressive disease or response, thus radiation necrosis lesions were excluded from the study.

We used a dataset of 783 lesions treated with SRT, of which only 220 were at least 10 mm in longest diameter, and of these, 35 developed radiation necrosis. Thus, a total of 185 lesions in 132 patients were studied, accounting for 682 segmentations/time points. Therefore, the average number of follow-ups for each BM was 3.7. More data relative to the patients and BMs included in the study are available in Table 1.

### MR Imaging

The volumetric contrast-enhanced T1-weighted MRI sequence used to delineate the BMs and compute their volumes was gradient echo, using 3D spoiled gradient-recalled echo or 3D fast-field echo, after i.v., administration of a single dose of gadolinium-based contrast agents with a 6–8-min delay. MRI studies were performed in the axial or sagittal plane with a 1.0 T ($n = 7$), 1.5 T ($n = 528$) or 3.0 T ($n = 147$) MR imaging unit. Imaging parameters were slicing thickness of 0.5–2.0 mm (median 1.3 mm) and 0.4–1.0 mm (median 0.5 mm) pixel spacing.

### Volume Measurement

T1-weighted images were retrospectively analyzed by the same image expert and reviewed by both an image expert with more than 6 years of experience in tumor segmentation and a senior radiologist with 27 years of experience.

To determine the tumor volume, each BM lesion was automatically delineated using a gray-level threshold chosen to identify the CE tumor volume. Segmentations were then corrected manually, slice by slice, as described in a previous work.[11] Total tumor volume was computed as the volume within the surface delimiting CE areas, thus including both the CE volume and the necrotic central regions with little or no contrast enhancement.

**Table 1.** Summary of Patients in the Study (Data is Given for Each BM)

| | *n* (%) |
|---|---|
| Sex | |
| Male | 89 (48.1) |
| Female | 96 (51.9) |
| Age | |
| <55 | 55 (29.7) |
| ≥55 to <65 | 82 (44.3) |
| ≥65 | 48 (26.0) |
| Primary tumor histology | |
| NSCLC | 114 (61.6) |
| Breast | 32 (17.3) |
| SCLC | 14 (7.6) |
| Melanoma | 5 (2.7) |
| Others | 20 (10.8) |
| Radiation therapy | |
| Single-session stereotactic radiosurgery | 99 (53.5) |
| Dose (Gy) [median (range)] | 20 (16–24) |
| Fractionated stereotactic radiotherapy | 86 (46.5) |
| Number of fractions [median (range)] | 5 (3–14) |
| Dose per fraction (Gy) [median (range)] | 5.5 (2.5–20) |
| Upfront whole brain radiotherapy | 30 (16.2) |
| Lesions' volume at diagnosis | |
| <1 $cm^3$ | 44 (23.8) |
| 1–4 $cm^3$ | 74 (40.0) |
| >4 $cm^3$ | 67 (36.2) |
| Lesions' maximum diameter at diagnosis | |
| 1–2 cm | 94 (50.8) |
| 2–3 cm | 49 (26.5) |
| >3 cm | 42 (22.7) |
| Number of metastases at diagnosis | |
| 1 | 72 (38.9) |
| 2 | 58 (31.4) |
| 3 | 28 (15.1) |
| ≥4 | 27 (14.6) |

## Radiation Therapy and Study Endpoints

All BMs in the study were treated with SRT, with the first scan corresponding to the pretreatment case and subsequent scans being conducted after SRT. Thirty of them had previously received whole brain radiotherapy (WBRT) for the BMs. The median time between the end of WBRT and SRT was 6.5 months (1.3–15.2).

Patients were followed up with a volumetric MRI scan and clinical follow-up appointment every 3.35 months (median, interquartile range: 2.33–4). Lesions measurements were performed for the postcontrast T1-weighted sequences on every available MRI scan from pre-SRT to either second irradiation, surgical intervention, or a maximum of 2 years after SRT.

## BM Response Assessment

Two distinct criteria were compared when assessing BM response to SRT. Firstly, the RANO-BM criteria, which rely on 1D measurements. According to these criteria, a BM is deemed measurable if it exhibits contrast enhancement, has a minimum size of 10 mm in at least 1D, and is visible across 2 or more axial slices. Additionally, the perpendicular distance to the longest dimension within the measurement plane should be at least 5 mm for the lesion to be considered measurable. In our study, we applied constraints individually to each BM, focusing solely on lesions with the longest diameter exceeding 10 mm. We will use the term "RANO diameter" to denote the longest diameter within the CE area in accordance with the RANO-BM criteria to differentiate it from the maximum diameter of the lesion, which is calculated based on its volumetric reconstruction. Secondly, we implemented ad hoc volumetric criteria based on a fixed percentage variation in volume.

Changes in distant lesions, corticosteroid use, or clinical status were not considered in the definition of our response criteria.

## Progressive Disease

The definition of progressive disease according to the criteria described above was given by:

- RANO-BM: An increase of 20% or more in the RANO diameter of target lesions. In addition, any lesion with the longest diameter smaller than 10 mm was regarded as unchanged from the baseline unless there was a minimum 3 mm change in the longest diameter measured.
- Total Volume Increase: defined as a minimum 30% increase in total volume, with an additional 0.2 $cm^3$ increase for lesions below 1 $cm^3$ in volume. The specific choice of the 30% threshold was established following a preliminary study evaluating potential thresholds ranging from 10% to 100% (Supplementary Figure 1). Our analysis determined that the 30% threshold was the most restrictive percentage at which all BMs labeled as a progressive disease by the RANO-BM criterion were also identified as a progressive disease by the total volume criterion.

The nadir of the lesions (including the baseline) was taken as the reference to determine the increase. Table 2 summarizes the different progressive disease criteria compared in this study.

## Response

Partial response criteria are summarized in Table 2 and were defined as follows for each criterion:

- RANO-BM: At least a 30% decrease in the RANO diameter of the target lesion sustained for at least 4 weeks, taking as reference the baseline RANO diameter.
- Total-Vol: At least a 20% decrease in the total volume, considered to be the lowest threshold that can be reliably detected.[3] The baseline volume was taken as a reference.

Complete response was defined in all cases as the disappearance of target lesions sustained for at least 4 weeks, in line with the RANO-BM criteria.

### Stable Disease

In both criteria, when neither the increase in size was sufficient to define progressive disease nor the reduction to qualify for a response, the BM was considered to be stable.

### Analysis and Statistics

The computation of times to progressive disease or response was performed by evaluating the differences in maximum tumor distances in the CE area and volumes for each BM using MATLAB R2022b, The MathWorks, Inc., United States. The Kaplan–Meier method was used to compare time-to-event outcomes per lesion between criteria. *P*-values smaller than .05 were considered statistically significant.

### Ethical Approval

We have complied with all relevant ethical regulations. Human data were obtained in the framework of the study MetMath (Metastasis and Mathematics), a retrospective, multicenter, nonrandomized study approved by the corresponding institutional review boards.

## Results

Out of the total 783 lesions examined, only 220 (28.1%) had the longest diameter exceeding 10 mm, making them measurable by the RANO-BM criteria. In this study, we evaluated 185 BMs, 17 of them (9.2%) were considered nonmeasurable by RANO-BM criteria, due to their restrictions. However, all lesions could be effectively assessed when using volumetric criteria.

An overview of the changes in total volume and RANO diameter for each BM within the study is depicted in Figure 1. The time point displayed for each lesion corresponds to

**Table 2.** Summary of Progressive Disease and Partial Response Criteria Compared in this Work. Measured Magnitude for Each Criterion. In the Case of Progressive Disease: Minimum Fractional Increase, Taking as a Reference the Nadir of the Lesion (Including the Baseline). For the definition of Response: Minimum Percentage of Volumetric and Reference for Each Criterion Studied

| | Measurement | Progressive disease | | | Partial response | |
|---|---|---|---|---|---|---|
| | | Increase (at least) | Reference | Small lesions | Decrease (at least) | Reference |
| **RANO-BM** | Longest distance (CE) | 20% | Nadir (baseline) | <10 mm (additional 3 mm increase) | 30% | Baseline |
| **Total volume** | Total volume | 30% | | <1 $cm^3$ (additional 0.2 $cm^3$ increase) | 20% | |

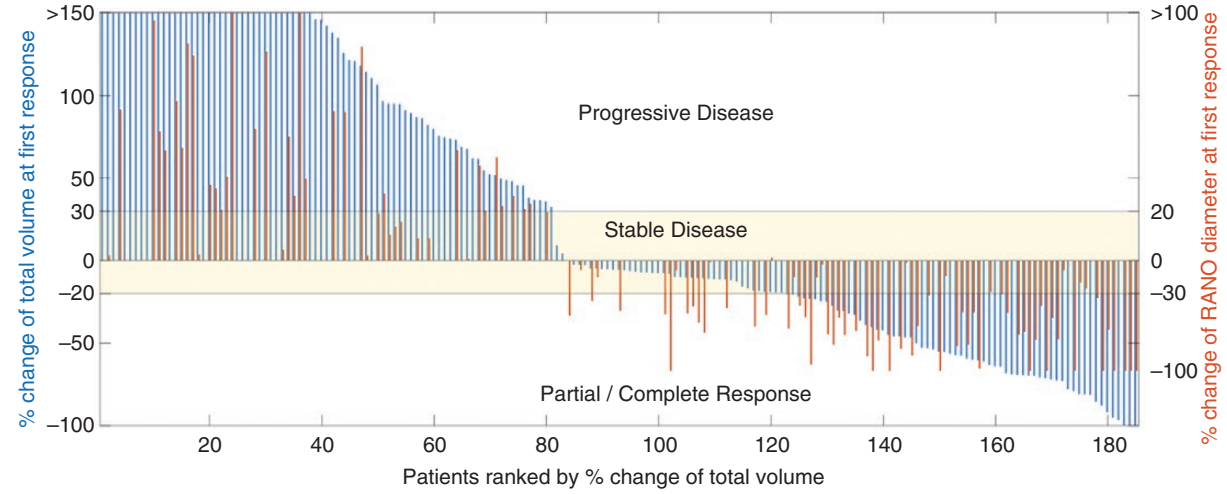


**Figure 1.** Percentage changes in total volume (blue) and RANO diameter (red) at the first instance of progressive disease or response as defined by any of the criteria. On the *x*-axis are all the lesions ordered by total volume change, from the one that increased the most (1) to the one that decreased the most (185). When no progressive disease or response was detected, the latest available time point was used. The RANO diameter axes have been adjusted to match the definitions of the volumetric criteria.

**Table 3.** Classification Results for Response Obtained for Each BM ($n$ = 185) Under the Criteria Compared in this Study: RANO-BM vs. 30% increase in total volume

| | Progressive disease, *n* (%) | Stable disease, *n* (%) | Partial response, *n* (%) | Complete response, *n* (%) | Nonmeasurable, *n* (%) |
|---|---|---|---|---|---|
| RANO-BM | 42 (22.7) | 97 (52.4) | 19 (10.3) | 10 (5.4) | 17 (9.2) |
| Total volume | 80 (43.2) | 45 (24.3) | 50 (27.0) | 10 (5.4) | – |

the earliest instance at which any of the criteria classified the lesion as progressive disease or response. If neither of these events occurred, the analysis used the last available time point. The absence of a RANO diameter bar can indicate either no change in size or a nonmeasurable lesion by RANO-BM. Notably, changes in RANO diameter and total volume have a limited correlation, with a Spearman correlation coefficient of 0.53.

Table 3 provides a numerical summary of the results, revealing that over half of the examined BMs (97 out of 185) were classified as stable diseases according to the RANO-BM criteria. However, the application of volumetric criteria enhanced the classification of BMs, labeling them as either progressive disease or responsive in most of the cases, while simultaneously allowing the assessment of all BMs.

### Progressive Disease

Out of the total of 185 BMs studied, 80 (43.2%) exhibited progressive disease according to at least one of the criteria in the study. Both methods yielded the same interval of progression for 24 lesions (30% of all progressive lesions). However, 38 BMs were identified as progressive according to the volumetric criteria but not according to the RANO-BM criteria. Among the remaining 18 lesions, classified as a progressive disease by both criteria but with different times to progression, 14 were labeled as progressive by the volumetric criteria before by RANO-BM (Figure 2A).

Figure 2 provides 2 illustrative examples showing cases where the RANO-BM criteria either detected progressive disease significantly later, with a delay of 4.6 months (c) or failed to detect progressive disease at all as the lesions continued to grow (d). In addition, the Kaplan–Meier curve in Figure 2B shows that the use of volumetric criteria predicted time to progression with a median difference of 3.3 months compared to the RANO-BM criteria.

When examining different subgroups within the cohort, we observed a more substantial difference in median time for non–small cell lung cancer (NSCLC), which was 4.4 months. However, the groups for small cell lung cancer (SCLC) and breast cancer were relatively small (9 and 11 lesions, respectively), resulting in nonstatistically significant differences (Supplementary Figure 2). Regarding the type of radiotherapy, the median differences were 4.3 months for SRT alone and 2.2 months for the subgroup of patients treated with WBRT before SRT (Supplementary Figure 3).

To assess the impact of selecting a 30% increase in total volume, other percentages were also considered. Supplementary Figure 5A demonstrates that the use of 20%, 30%, or 40% results in nearly identical survival curves. Supplementary Table 1 further compares percentages ranging from 10% to 100%, evaluating the number of progressive diseases for each increase. Every 10% increase leads to the classification of 1 to 4 BMs less as progressive disease.

### Partial Response

Of the 185 BMs analyzed, 64 showed a response to SRT according to at least 1 of the 2 criteria. Interestingly, 22 (34.4%) lesions showed identical response times according to both criteria. However, it's noteworthy that while RANO-BM failed to classify 35 BMs as responsive, the volumetric criteria did not classify 4 of them when they were classified by RANO-BM. Furthermore, only 4 cases showed differences in response time between the 2 criteria (Supplementary Figure 3A).

The Kaplan–Meier curves in Figure 3B highlight that the RANO-BM criteria classified fewer lesions as responsive and did so later compared to the volumetric criteria. More specifically, the RANO-BM criterion delayed the identification of response by a median of 4.9 months compared to the volumetric criterion.

The study also evaluated the contrast-enhanced (CE) volume and the total volume calculated from a simplified method, which involved measuring the 3 longest orthogonal diameters of the tumor (see Supplementary Information). Both analyses yielded consistent results with those obtained from the precise calculations of the total volume (Supplementary Figure 4).

Other percentages were also taken into consideration to evaluate the effects of choosing a 20% reduction in overall volume. The application of –10%, –20%, or –30% yields comparable survival curves, as shown in Supplementary Figure 5b. Supplementary Table 2 assesses the number of responses for every fall in percentage, comparing further values between –10% and –100%. A median of 7 BMs less are classified as respondents with every 10% drop.

## Discussion

This study demonstrates that volumetric criteria are more effective than RANO-BM criteria in evaluating the response to the treatment of BMs. Notably, the RANO-BM criteria were limited by size in 71.9% of our database. In addition, the RANO-BM criterion performed worse than the volumetric criteria in identifying the lesions, and when it provided the right classification, it did so later than the

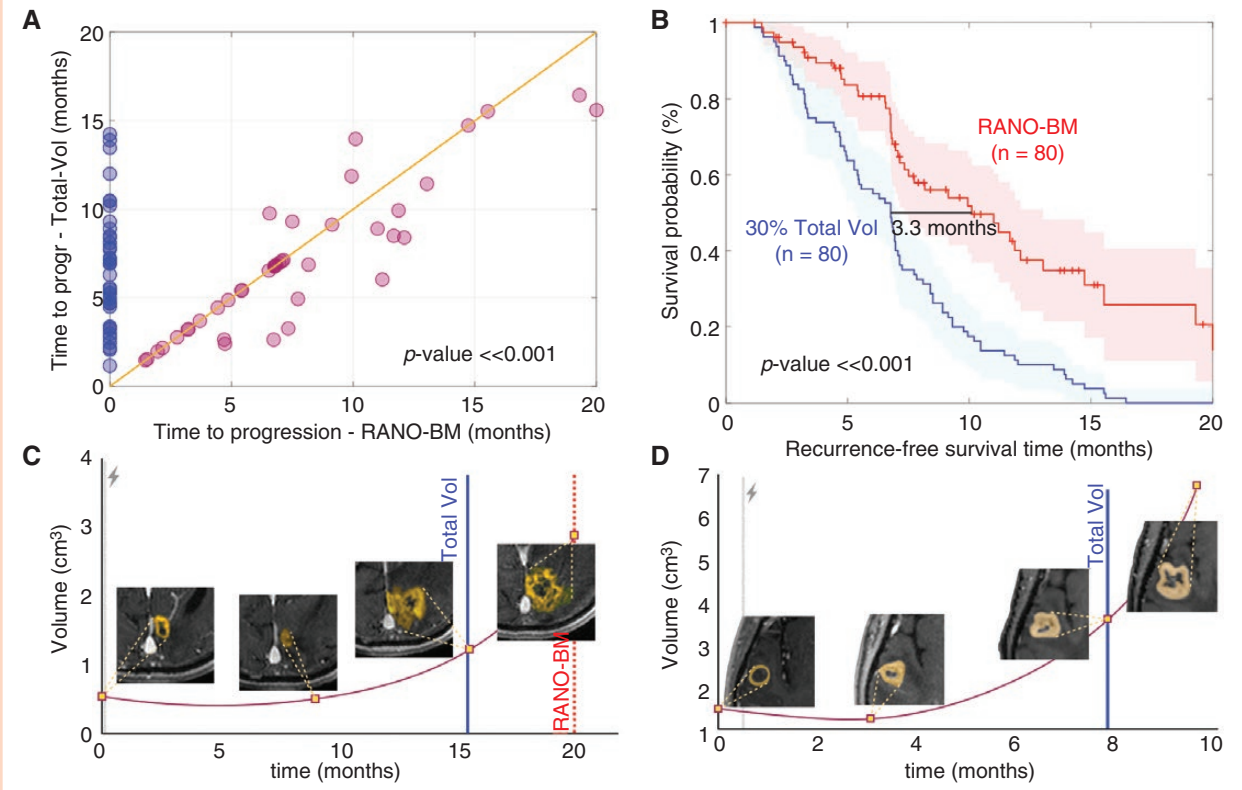


**Figure 2.** Comparison of criteria for progressive disease lesions. (**a**) Times to progression according to each criterion. Points over the line correspond to the lesions with the same time to progression and blue points on the vertical axis indicate BMs identified as progressive disease by total volume but not by RANO-BM. *P*-values correspond to the Wilcoxon signed-rank test for the points outside the axes. (**b**) Kaplan–Meier curves per lesion comparing time to progression for the 2 study criteria: total volume (30% increase) and RANO-BM criteria ($n = 80$ lesions). (**c**) Illustration of a progressive BM from a non–small cell lung cancer (NSCLC) where the RANO-BM criteria identified progressive disease 4.6 months later than the total volume criteria. (**d**) A progressive lesion from a small cell lung cancer (SCLC) was identified by the volumetric criteria but not by the RANO-BM criteria. Yellow squares represent measured volumes, dashed gray lines with flash symbols indicate the time of stereotactic radiotherapy treatment, and purple lines represent interpolated longitudinal volumetric data (provided for reference). Axial slices from contrast-enhanced (CE) T1-weighted MRI sequences are shown.

volumetric measures. More specifically, volumetric criteria detected nearly twice as many progressive lesions, on average, 3 months earlier and 2.67 more responsive BMs than the RANO-BM criterion.

The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group, in subsequent work,[12] strongly recommended the adoption of volumetric measurements. Previous research affirmed the superiority of volumetric measurements claiming them to be more precise, with higher interobserver reproducibility[13] and lower rates of misclassification in tumor response.[8,9,13,14] However, they did not propose a volumetric criterion for progressive disease BMs. Other authors have already used volumetric assessment to investigate the temporal response of BMs to SRT.[15–17] Although the RANO-BM working group introduced criteria for volumetric assessment, they recommended using a 65% increase in volume to define progressive disease, a threshold that has been proven to be too high and does not classify as progressive disease for all the lesions that would be identified as such by the 1D criteria (Supplementary Figure 1). The response criterion of a 20% decrease in volume has been adopted.

Comparative studies have been conducted for primary brain tumors,[18–22] without consensus on the superiority of 1D, 2D, or volumetric criteria. In the context of BMs, some studies have compared 1D criteria[23,24] while others did so with the RANO-BM and volumetric criteria with varying results.[25,26] Oft et al.[25] focused on volumetric regression, demonstrating the superiority of volumetric over 1D criteria for responsive lesions but not addressing progressive BMs. Another study comparing RANO-BM and volumetric criteria found no significant differences between them.[26] However, the study assessed 55 lesions using the volumetric criteria of Follwell et al.,[27] which used a strict threshold of a 71% increase in volume, potentially limiting its ability to show improvements in evaluation.

Several 1D criteria are available for BM response assessment, such as RANO-BM[3] or RECIST (Response Evaluation Criteria in Solid Tumors).[28] Both criteria share similar definitions for nonmeasurable lesions, such as those having the longest diameter smaller than 10 mm. With the improvement in the resolution of MR imaging, lesions smaller than 10 mm can be confidently measured, and excluding them no longer makes sense. In this study we focused on lesions

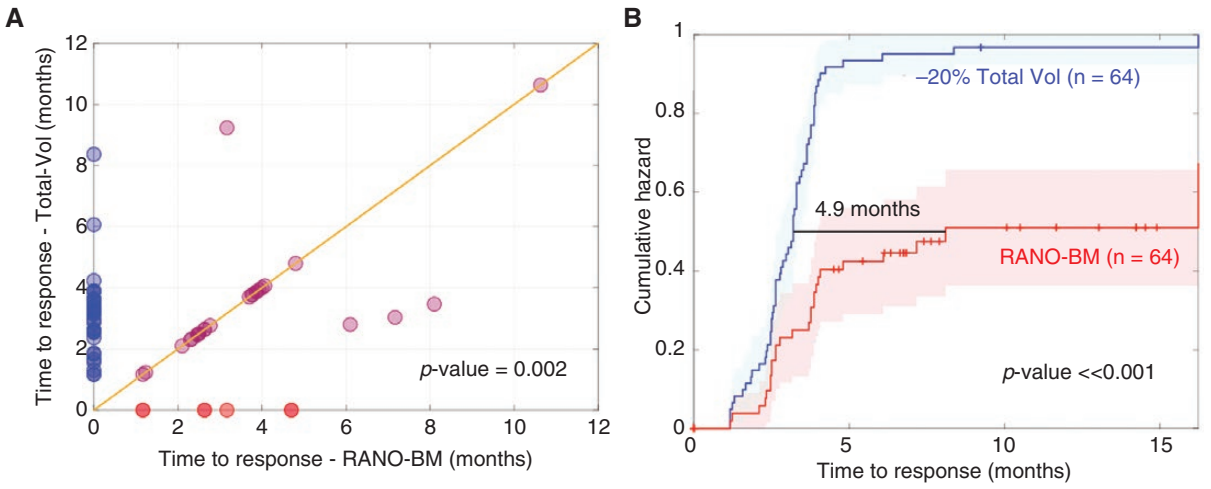


**Figure 3.** Comparison of criteria for responding lesions. (**a**) Times to progression according to each criterion. Points over the line correspond to the lesions with the same time to progression, blue points on the vertical axis indicate BMs identified as progression by total volume but not by RANO-BM, while red points on the horizontal axis signify response according to RANO-BM but not total volume. *P*-values correspond to the Wilcoxon signed-rank test for the points outside the axes. (**b**) Kaplan–Meier curves per lesion comparing time to response for the 2 criteria considered in this study: Total volume (20% decrease) and RANO-BM criteria for BMs labeled as responding by any of the criteria ($n$ = 64 lesions).

larger than 10 mm, aligning with the RANO-BM criteria to enable meaningful comparisons across different assessment criteria. However, a recent study has delved into sub-centimeter lesions, revealing that relying solely on the largest diameter of such lesions inadequately reflects their actual size,[29] as we also observed in larger tumors.

Concerns regarding the limitations of RANO-BM have also been addressed in a large study involving 408 BMs, where over a third were classified as stable lesions.[30] This agrees with our findings, indicating that RANO-BM criteria might be overly restrictive. Therefore, criteria such as the one proposed in this study, capable of accurately classifying lesions, hold the potential to enhance their management. Our dataset included only patients receiving SRS. However, this methodology could be applied to the assessment of other therapies.

It has been stated that reliable methods for response assessment, including standardized image acquisition with an MRI protocol are needed.[31] Such protocols recommend using volumetric measurements (0.5–1.4 mm slice thickness). In this study, semiautomatic segmentation was performed since it has been proven to be more efficient than manual delimitation[32] and to decrease interobserver variabilities.[33,34] Although semiautomatic segmentation could be time-consuming, it is expected that improvements in artificial intelligence (AI) programs will bring them closer to providing reliable automatic segmentation in the near future, which would speed up the process. We consider that the total volume is the best way to evaluate the whole lesion, besides, which is simpler to segmentation, however, similar results were found when evaluating only the CE volume.

A limitation of our study was that the study was conducted for each BM rather than for patients. In future work, per-patient evaluation could be considered, and volumetric quantification of the tumor could be combined either with other modalities of image assessment or patient data to allow a more precise evaluation of response to treatment, including, for instance, radiation necrosis. Another limitation is that the use of corticosteroids was not taken into account in defining the volumetric criteria, a well-acknowledged limitation even in RANO-BM criteria.[3] Notwithstanding, according to RANO-BM they are not applicable to establish progressive disease.[3]

The main strength of this study lies in its ability to obtain comparable results to those achieved through precise volume measurements when evaluating both the CE volume and employing a 3-distance approach (35), highlighting the superiority of any form of volumetric measurements over 1D assessments in evaluating BMs. Furthermore, the inclusion of data from multiple institutions enhances the robustness and generalizability of the findings. However, this will need to be further validated.

Integrating our analysis into the RANO framework would not require significant effort, but would provide benefits in terms of improved patient classification. First, if volumetric measurements of lesion size were available, incorporating the criteria discussed here would be straightforward. Volumetric measurements are not routine in many medical centers, but we have validated here that using the 3 longest tumor diameters provides a good approximation of lesion volumes for response assessment. Thus, volumetric measurements may be recommended and the preferred method as technological advances and AI methods are integrated into PACS systems, but until that time, orthogonal diameter measurements would be an acceptable substitute.

In conclusion, we have proposed a volumetric criterion for the response of BMs to treatment. An increase of 30% in volume (total or CE) defines progressive disease and a 20% volume decrease identifies partial responses. Such volumetric assessment has been shown to be superior

to 1D criteria by allowing for the evaluation of every BM, avoiding misclassification, and anticipating the response by more than 3 months when compared with the RANO-BM criteria. This superiority holds irrespective of tumor size, observer, or treatment and can be assessed by simply measuring 3 distances, offering a practical and efficient method for clinical assessment.

## Supplementary material

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


## Keywords

brain metastases | MRI | progressive disease | stereotactic radiosurgery | volumetric analysis

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## Conflict of interest statement

Authors have no conflicts of interest to disclose.

## Authorship statement

Conceptualization: B.O.-T., J.P.-B., E.A., V.M.P.-G. Methodology: B.O.-T., J.A.R.-R., E.A., J.P.-B., V.M.P.-G. Investigation: B.O.-T., J.P.-B., J.A.R.-R., D.A., A.O.-M., B.A., V.M.P.-G., E.A. Software: B.O.-T. Data curation: B.O.-T., J.P.-B., V.M.P.-G. Writing—Original draft: B.O.-T. Writing—Review and editing: B.O.-T., V.M.P.-G., J.P.-B. Supervision: J.P.-B., E.A., V.M.P.-G. Project administration: V.M.P.-G. Funding acquisition: V.M.P.-G.

## Data availability

Data generated or analyzed during the study are available from the corresponding author by request.

## References


1. Achrol AS, Rennert RC, Anders C, et al. Brain metastases. *Nat Rev Dis Primers*. 2019;5(1):5.
2. Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. *Neuro Oncol*. 2016;18(8):1043–1065.
3. Lin NU, Lee EQ, Aoyama H, et al; Response Assessment in Neuro-Oncology (RANO) group. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270–e278.
4. Suh JH, Kotecha R, Chao ST, et al. Current approaches to the management of brain metastases. *Nat Rev Clin Oncol*. 2020;17(5):279–299.
5. Aghighi M, Boe J, Rosenberg J, et al. Three-dimensional radiologic assessment of chemotherapy response in ewing sarcoma can be used to predict clinical outcome. *Radiology*. 2016;280(3):905–915.
6. Xie H, Zhang X, Mo Y, et al. Tumor volume is better than diameter for predicting the prognosis of patients with early-stage non–small cell lung cancer. *Ann Surg Oncol*. 2019;26(8):2401–2408.
7. Jia B, Chen B, Long H, Rong T, Su X. Tumor volume is more reliable to predict nodal metastasis in non–small cell lung cancer of 30 cm or less in the greatest tumor diameter. *World J Surg Oncol*. 2020;18(1):168.
8. Sosna J. Is RECIST version 11 reliable for tumor response assessment in metastatic cancer? *Radiology*. 2019;290(2):357–358.
9. Kuhl CK, Alparslan Y, Schmoee J, et al. Validity of RECIST version 11 for response assessment in metastatic cancer: a prospective, multireader study. *Radiology*. 2019;290(3):349–356.
10. Wen PY, Chang SM, Van Den Bent MJ, et al. Response assessment in neuro-oncology clinical trials. *J Clin Oncol*. 2017;35(21):2439–2449.
11. Pérez-Beteta J, Molina-García D, Ortiz-Alhambra JA, et al. Tumor surface regularity at MR imaging predicts survival and response to surgery in patients with glioblastoma. *Radiology*. 2018;288(1):218–225.
12. Alexander B, Brown P, Ahluwalia M, et al. Clinical trial design for local therapies for brain metastases a guideline by the Response Assessment in Neuro-Oncology Brain Metastases Working Group. *Lancet Oncol*. 2018;19(1):e33–e42.
13. Bauknecht HC, Romano VC, Rogalla P, et al. Intra- and interobserver variability of linear and volumetric measurements of brain metastases using contrast-enhanced magnetic resonance imaging. *Invest Radiol*. 2010;45(1):49–56.
14. Kuhl CK. RECIST needs revision: a wake-up call for radiologists. *Radiology*. 2019;292(1):110–111.
15. Shepard MJ, Xu Z, Donahue J, et al. Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non–small cell lung cancer to the brain: a matched cohort study. *J Neurosurg*. 2020;133(3):685–692.
16. Goethe EA, Rao G, Harvey A, et al. Temporal change in tumor volume following stereotactic radiosurgery to a single brain metastasis. *World Neurosurg*. 2020;136(1):e328–e333.
17. Wijetunga AR, Jayamanne DT, Adams J, Back MF. Volumetric response of limited brain metastatic disease to focal hypofractionated radiation therapy. *Brain Sci*. 2021;11(11):1457.
18. Kanaly CW, Ding D, Mehta AI, et al. A novel method for volumetric MRI response assessment of enhancing brain tumors. *PLoS One*. 2011;6(1):e16031.
19. Pérez-Larraya JG, Lahutte M, Petrirena G, et al. Response assessment in recurrent glioblastoma treated with irinotecan-bevacizumab: comparative analysis of the Macdonald, RECIST, RANO, and RECIST F criteria. *Neuro Oncol*. 2012;14(5):667–673.

20. Shah GD, Kesari S, Xu R, et al. Comparison of linear and volumetric criteria in assessing tumor response in adult high-grade gliomas. *Neuro Oncol*. 2006;8(1):38–46.
21. Gahrmann R, van den Bent M, van der Holt B, et al. Comparison of 2D (RANO) and volumetric methods for assessment of recurrent glioblastoma treated with bevacizumab—a report from the BELOB trial. *Neuro Oncol*. 2017;19(6):853–861.
22. Heugenhauser J, Galijasevic M, Mangesius S, et al. MRI response assessment in glioblastoma patients treated with dendritic-cell-based immunotherapy. *Cancers (Basel)*. 2022;14(6):1579.
23. Qian JM, Mahajan A, Yu JB, et al. Comparing available criteria for measuring brain metastasis response to immunotherapy. *J Neurooncol*. 2017;132(3):479–485.
24. le Rhun E, Wolpert F, Fialek M, et al. Response assessment and outcome of combining immunotherapy and radiosurgery for brain metastasis from malignant melanoma. *ESMO Open*. 2020;5(4):e000763.
25. Oft D, Schmidt MA, Weissmann T, et al. Volumetric regression in brain metastases after stereotactic radiotherapy: time course, predictors, and significance. *Front Oncol*. 2021;10(1):590980.
26. Fischedick G, Haverkamp U, Fischedick A. Are three-dimensional volumetric measurements of brain metastasis the future for disease control? A comparative study. *Int J Radiat Oncol Biol Phys*. 2017;99(2):E659–E660.
27. Follwell MJ, Khu KJ, Cheng L, et al. Volume specific response criteria for brain metastases following salvage stereotactic radiosurgery and associated predictors of response. *Acta Oncol*. 2012;51(5):629–635.
28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 11). *Eur J Cancer*. 2009;45(2):228–247.
29. Ozkara BB, Federau C, Dagher SA, et al. Correlating volumetric and linear measurements of brain metastases on MRI scans using intelligent automation software: a preliminary study. *J Neurooncol*. 2023;162(2):363–371.
30. Mouraviev A, Detsky J, Sahgal A, et al. Use of radiomics for the prediction of local control of brain metastases after stereotactic radiosurgery. *Neuro Oncol*. 2020;22(6):797–805.
31. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. *Neuro Oncol*. 2020;22(6):757–772.
32. Odland A, Server A, Saxhaug C, et al. Volumetric glioma quantification: comparison of manual and semi-automatic tumor segmentation for the quantification of tumor growth. *Acta Radiol*. 2015;56(11):1396–1403.
33. Zhao B, Tan Y, Tsai WY, et al. Reproducibility of radiomics for deciphering tumor phenotype with imaging. *Sci Rep*. 2016;6(1):23428.
34. Balagurunathan Y, Kumar V, Gu Y, et al. Test–retest reproducibility analysis of lung CT image features. *J Digit Imaging*. 2014;27(6):805–823.