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The value of quantitative pentavalent 99mTc-dimercaptosuccinic acid scan in predicting progression-free survival and overall survival in patients with glioblastoma multiforme

Ehab Saad, Ahmed Badawy, Mahasen Abougabal and Ahmed Kandeel

Department of Clinical Oncology, Cairo University, Kasr Alaini, Cairo, Egypt

Original Article

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Author for correspondence:
Ehab Saad, Department of Clinical Oncology, Cairo University, Kasr Alaini, Cairo, Egypt.
E-mail: ehab.saad239@gmail.com

Abstract

Aim: Glioblastoma multiforme (GBM) is the commonest and the most aggressive primary brain tumour. Pentavalent 99mTc-dimercaptosuccinic acid (99mTc (V)-DMSA) has been found to be a tumour-seeking agent. Pre-radiotherapy 99mTc (V)-DMSA positive scan was found to be significantly correlated with poor progression-free survival (PFS) and overall survival (OS). This study aims at evaluating the impact of quantitative 99mTc (V)-DMSA tumour uptake before and after radiotherapy on PFS and OS in patients with GBM.

Methods: A prospective study included 40 patients with GBM. Single-photon emission computed tomography studies were done before and after adjuvant radiotherapy and were qualitatively and quantitatively evaluated. The retention index (RI) of the viable tumour was correlated with PFS and OS.

Results: The qualitative enhancement of 99mTc (V)-DMSA uptake either positive or negative was significantly correlated with PFS at both early and late images (p-values 0·04 and 0·026, respectively) and OS only in the late image (p-value 0·036). The calculated ion/non-lesion ratios at late images were statistically correlated with PFS and OS (p-values 0·021 and 0·025, respectively). The baseline RI had significant correlation with PFS only (p-value 0·01).

Conclusion: The degree of 99mTc (V)-DMSA scan positivity is a poor prognostic factor for PFS and OS in GBM patients.

Introduction

Malignant brain tumours represent about 2% of all malignancies and they carry a poor prognosis with high morbidity and mortality.[1]

Gliomas are the most common central nervous system tumours, representing 40–50% of cases. They originate from glial cells, such as astrocytes, ependymal cells and oligodendrocytes. In World Health Organization (WHO) classification, gliomas are divided into low-grade gliomas (grades I and II), including oligodendrogliomas and astrocytomas, and high-grade gliomas (grades III and IV), including anaplastic astrocytomas and glioblastoma multiforme (GBM). GBM (grade IV) is the most common type and representing about 50% of primary gliomas and also the most resistant to treatment.[2,3]

The median survival for astrocytoma grade III is about 18 months and 12 months for GBM.[4,5]

Accurate diagnosis of brain tumours is done by anatomical imaging modalities, such as magnetic resonance imaging (MRI) and computed tomography; however, the MRI is considered as the main standard modality of anatomical imaging.[6]

It was proved that pentavalent 99mTc-dimercaptosuccinic acid (99mTc (V)-DMSA) created from labelling of meso-2,3-dimercaptosuccinic acid (DMSA) with technetium (99mTc) in alkaline form is a tumour-seeking substance.[7,8]

It has been reported that it can be used in detecting many types of cancers like brain tumours and it is particularly of value for detection of metastatic and high-grade tumour.[9]

After surgical management of GBM, pre-radiotherapy 99mTc (V)-DMSA positive scan was confirmed to be significantly correlated with poor progression-free survival (PFS) and overall survival (OS).[10]

We assumed that the degree of positivity of 99mTc (V)-DMSA scan may be correlated with PFS and OS and thus it is creating a new prognostic factor for patients with GBM.

The aim of this study is to evaluate the impact of quantitative 99mTc (V)-DMSA uptake by the viable tumour tissue on patients with pathologically proven GBM of the brain using brain single-photon emission computed tomography (SPECT) (lesion to non-lesion ratio) before and after the end of therapy and correlating the SPECT results (visual interpretation, lesion/non-lesion ratio and retention index (RI)) with the PFS and OS of these patients.

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Patients and Methods

Study design

This was a prospective follow-up study including 40 patients with pathologically proven GBM of the brain. They were referred to the Department of Clinical Oncology and Nuclear Medicine, Cairo University, for post-operative therapy in a period between June 2014 and June 2016. The age of selected patients was between 18 and 70 years and had a performance status (PS 0–2).

Clinical evaluation

All patients were clinically assessed at the clinical oncology outpatient clinic to determine the performance status and general conditions of the patient to decide the treatment protocol. The performance status was determined using Eastern Cooperative Oncology Group scoring system.[11]

All patients were first surgically managed either by complete resection, partial resection or biopsy. After surgery, all patients received wide field radiotherapy with a total radiation dose of 60Gy/30F/6weeks, using 6 MV photon concomitantly with temozolamide, and then after a 4-week break, patients received up to six cycles of adjuvant oral temozolomide (150–200 mg/m^2) for 5 days for every 28 days.

Follow-up brain SPECT studies were acquired before and least 4 weeks after the end of radiotherapy and also early images were acquired around 30 and late around 120 minutes after I.V. injection of 555–740 MBq of 99mTc (V)-(DMSAV) using the same acquisition protocol as in the baseline study.

The baseline and follow-up studies were qualitatively interpreted by visual assessment and also quantitatively assessed by drawing a region of interest around the area of abnormally enhanced tracer uptake in the SPECT images and a mirror image area on the background then calculating the counts per pixel in both regions. After that, we calculate the lesion/non-lesion ratio by dividing the count per pixel in the lesion area on the count per pixel in the non-lesion area.

The RI of the viable tumour was also calculated by subtraction of the lesion/non-lesion ratio in the early images from that of the late images and dividing the subtraction result by the lesion/non-lesion ratio in the early images and expressing it into %. According to the RI, the tumour behaviour was classified into retention, washout or no change.

The response of tumour after therapy was classified by visual assessment of the studies as follows:

1. Progression: increase in the size or tumour uptake intensity in the follow-up study compared to the baseline study.
2. Regression: reduction in the size or tumour uptake intensity in the follow-up study compared to the baseline study.
3. Stationary: almost no changes between the baseline and follow-up study.
4. Resolution: complete disappearance of the viable tumour in the follow-up study.

Residual or recurrent disease after the end of the primary treatment was based on tumour board decision to individually select the best management either by re-surgery, re-irradiation or chemotherapy, according to the previous treatment, PFS and performance status.

Follow-up of the patients

The patients were followed up over 2 years to estimate the PFS and OS.

The OS was calculated from the date of diagnosis (in the current study, we considered it as the date of surgery) till the end of follow-up period or death.

The PFS was calculated from the date of diagnosis (date of surgery) to the date of documented disease progression (clinical deterioration of the patients or radiological evidence of disease progression) or the date of death from any cause.

Statistical analysis

Microsoft Excel 2010 was used for data entry, and the statistical package for social science (SPSS version 21) was used for data analysis. Simple descriptive statistics (arithmetic mean and standard deviation) were used for summary of quantitative data, and frequencies were used for qualitative data.

Bivariate relationship was displayed in cross-tabulations, and comparison of proportions was performed using the Chi-square test. Mann–Whitney and Kruskal–Wallis tests were used to compare non-normally distributed quantitative data. Non-parametric Spearman's correlation was used to compare non-normally distributed quantitative data.

Results

The study included 16 females (40%) and 24 males (60%). Their age ranged from 18 to 73 years with a mean age of 47·83 ± 12·934. The majority of our patients (17 patients; 42·5%) had a performance status 1. All patients (100%) had a pathologically proven grade IV glioma of the brain. Twenty-five per cent of the patients had tumour site in the temporo-parietal region of the brain and 50% of the patients had tumour on the right side of the brain. Twenty-six patients (65%) underwent partial surgical resection, 14 patients (35%) underwent biopsy only, and no complete resection was done. The extent of surgical resection had no statistical significant correlation with the PFS or OS.

The patients were followed up over time to estimate the PFS and OS and correlating them with the patient characteristics.

No significant correlation was found between the two studied parameters and patient characteristics ($p > 0{\cdot}05$) (Table 1).

Correlation was performed between the PFS and OS with the baseline SPECT results eliciting that qualitative assessment of enhanced 99mTc-DMSA (V) uptake either positive or negative was significantly correlated with PFS at both early and late images (p-values 0·04 and 0·026, respectively) as well as with the OS only in the late image (p-value 0·036) (Table 2).

While, calculated lesion/non-lesion ratios at late images showed a statistical significant correlation with PFS and OS (p-values 0·021 and 0·025, respectively) (Figures 1 and 2); moreover, the baseline RI has a significant correlation with PFS only (p-value 0·01) as seen in Table 2 and Figure 3.

The other studied parameters had no non-significant correlation with PFS and OS ($p > 0{\cdot}05$) (Table 3).

Till the last follow-up, 27 patients died with a significant correlation with PFS (p-value 0·033) (Table 3).

Most patients with residual or recurrent disease after the primary treatment were treated with palliative chemotherapy (CCNU-Oncovin), with average 3–6 cycles, or by best supportive care for patients with poor performance status.

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Table 1. Relation between progression-free survival and overall survival with patient's characteristics

Variable	Progression-free survival (weeks)		Overall survival (weeks)	
	n	*p*-Value	n	*p*-Value
Age	40	0·068	40	0·05
Sex				
Male	24	0·259	24	0·719
Female	16		16	
Maximum tumour dimension	27	0·362	27	0·790
Tumour side				
Right	20	0·277	20	0·931
Left	19		19	
Intra-axial	1		1	
Performance status				
Score 1	17	0·061	17	0·224
Score 2	9		9	
Score 3	14		14	

Table 2. Correlation between progression-free survival and overall survival with the baseline SPECT results

Variable	Progression-free survival			Overall survival		
	n	Chi-square	*p*-Value	n	Chi-square	*p*-Value
Baseline SPECT early image						
Negative	8	6·011	**0·04**	8	5·095	0·078
Positive	32			32		
Baseline SPECT late image						
Negative	8	4·927	**0·026**	8	4·403	0·036
Positive	32			32		
Baseline dual-phase SPECT imaging						
Retention	19	7·795	0·099	19	7·846	0·097
Washout	9			9		
No change	2			2		
Negative	7			7		
Not available	3			3		
Baseline L/N in early image	38		0·075	38		0·083
Baseline L/N in late image	39		**0·021**	39		**0·025**
Baseline retention index	38		**0·01**	38		0·199

Note: Two cases were missed in calculation of L/N in early image and one case lost to follow-up. Boldface in *p*-value indicates that these values are significant.

Discussion

GBM is considered as the commonest and deadliest primary brain neoplasm. The only generally accepted independent prognostic factors are patient age and performance. A large single institution study involved 492 patients who underwent craniotomy for newly diagnosed glioblastoma WHO grade IV, in that 274 patients were male and 218 were female. The median age of patients was 62 years. The study confirmed that the following parameters were significantly correlated with survival in univariate analysis: age, performance, primary tumours, multifocal GBM, neurological affection, neuropsychological deficits, convulsions, incidental discovery, total or subtotal resection, radiotherapy, chemotherapy, combined radio-/chemotherapy with temozolomide, re-craniotomy and second tumour in patient history, and the following parameters were significantly correlated with survival in multivariate analysis: age, performance, multifocal tumour, total or subtotal resection, radiotherapy, chemotherapy and combined radio-/chemotherapy with temozolomide.[12]

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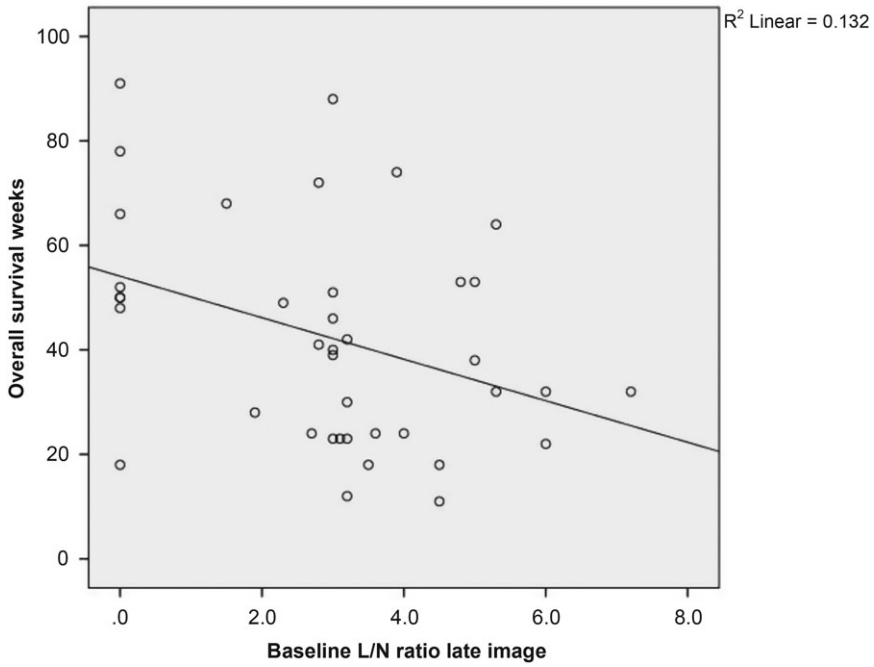

Figure 1. Correlation between baseline lesion/non-lesion ratio and overall survival.

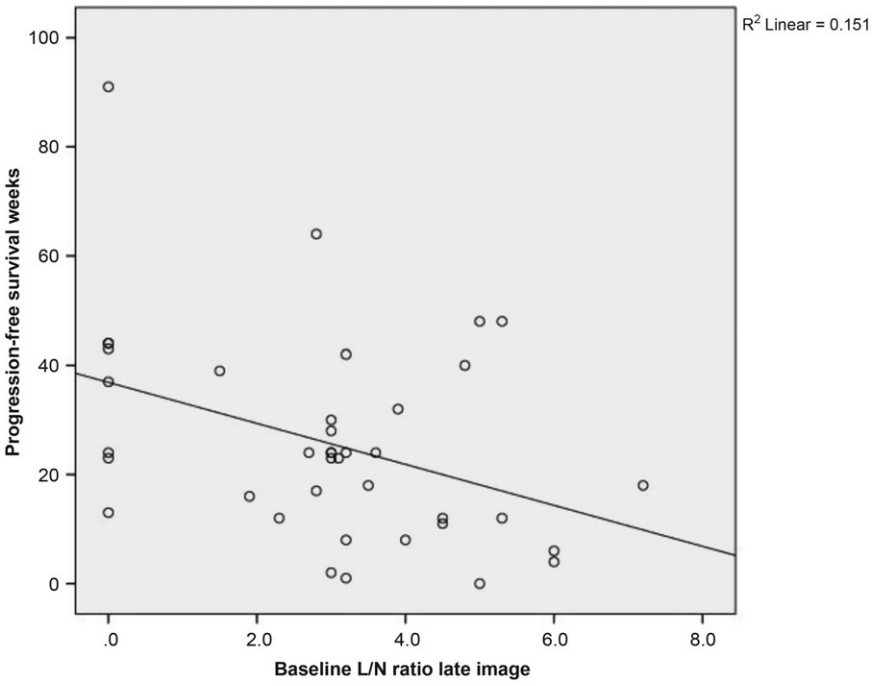

Figure 2. Correlation between baseline lesion/non-lesion ratio and progression-free survival.

Another study retrospectively evaluated the survival of 205 patients with GBM in China. After initial diagnosis, the survival rate at 6 months was found to be 82%, at 12 months was 52%, at 18 months was 27% and at 24 months was 17%. This study concluded that old age, baseline Karnofsky performance status score and site of the tumour were significant factors of prognosis, and among the options of treatment of GBM, radiotherapy was the most valuable predictive factor of prognosis followed by radical surgical resection and systemic chemotherapy.[13]

Compared to magnetic resonance spectroscopy (MRS), 99mTc (V)-DMSA SPECT has higher sensitivity as neuro-imaging tool to detect tumour recurrence in glioma patients with a high specificity (100%). 99mTc (V)-DMSA brain SPECT has higher accuracy in comparison to proton magnetic resonance spectroscopy ((1) H-MRS) for the detection of residual tumour or recurrence in GBM patients with previous radiation therapy. It can differentiate between residual tumour and irradiation necrosis.[14]

In our study, we aimed to add another prognostic factor for patients with GBM, and this factor is quantification of tumour

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Table 3. Correlation between progression-free survival and overall survival with the follow-up SPECT results

	Progression-free survival			Overall survival		
Variable	n	Chi-square	*p*-Value	n	Chi-square	*p*-Value
Follow-up SPECT results						
Positive	21	9·643	0·008	21	5·313	0·07
Negative	6			6		
Not done	13			13		
Outcome after therapy						
Progression	12	3·071	0·546	12	2·970	0·563
Regression	6			6		
Stationary	4			4		
Resolution	3			3		
Not done	15			15		
Free patients from tumour by DMSA						
Yes	6	9·643	0·008	6	5·313	0·07
No	21			21		
Not done	13			13		
Follow-up L/N in early image	27		0·07	27		0·519
Follow-up L/N in late image	27		0·273	27		0·883
Follow-up retention index	27		0·648	27		0·643
Fate of the patients						
Death	27		0·033	27		0·064
Still alive	13			13		

Note: Twelve cases were missed in the follow-up due to death and one lost to follow-up.

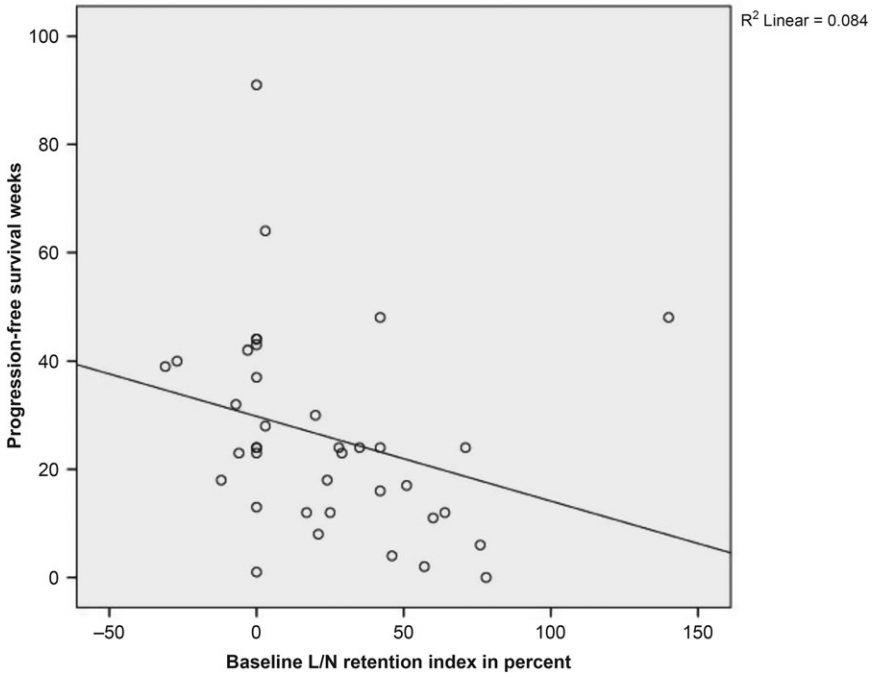

Figure 3. Correlation between baseline retention index and progression-free survival.

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uptake in brain SPECT study using 99mTc (V)-DMSA. After reviewing of literature, we found that some authors depend on DMSA (V) brain SPECT as prognostic factor in patients with GBM, but they depend on qualitative visual assessment of the study to detect positive and negative studies.[10]

Amr Amin et al. studied 40 adult patients (21 males and 19 females; mean age 48·6 ± 12·2 years; median 40 years and range 25–68 years) with a clear histopathological diagnosis of GBM. In this study, brain SPECT was done after primary surgical management (Baseline "BL"), 4–6 weeks after radiation and concomitant temozolomide therapy, at 6 months follow-up and when clinically justified. The end point of the study was 2 years clinical follow-up and/or death.

In this study, GBM lesions were classified according to the following criteria:

1. Negativity was considered when no viable tumour tissue was detected on BL study which was further affirmed by its continued negativity on follow-up that unaccompanied by clinical deterioration.
2. Positivity was considered if either:
   I. Viable tumour tissue was detected on BL study.
   II. Increase in the tumour size and L/N ratio was seen on follow-up neuro-imaging (FUNI) in comparison to BL study.
   III. Partial reduction of the tumour size and L/N ratio was detected on FUNI in comparison to BL study.
3. Negative and positive cases were considered as responders and non-responders, respectively.

This study had concluded that at 2-year follow-up, patients with pre-radiotherapy negative 99mTc (V)-DMSA had longer median OS compared to the positive cases (16·67 versus 8·87 months, respectively; *p*-value 0·017) and that 99mTc (V)-DMSA brain SPECT might have an additional prognostic role in GBM patients. However, there is still some way to go before it can be routinely used and they suggested further prospective trials to reach a well-established benefit of this radiopharmaceutical in GBM patients.[10]

Our study included 40 patients with brain GBM (24 male and 16 female) with mean age 47·83 ± 12·934 years. The mean OS of these patients was 41·73 ± 21·023 weeks and the mean PFS was 25·53 ± 18·362 weeks. Baseline brain SPECT study was performed for all patients and the studies were classified by visual assessment into positive and negative. The results show statistical significance between the SPECT result (positive or negative) and the PFS and OS with *p*-values 0·026 and 0·036, respectively, and this matches with Amr Amin et al. study results.[10]

It showed statistical significance between the PFS and OS of these patients with the lesion/non-lesion ratios in the SPECT images with *p*-values 0·025 and 0·021, respectively. Also we found statistical significance between the RI of the tumour in the SPECT images and PFS of the patients with *p*-value 0·01.

As far as we know, this study is the first prospective study considering the possible prognostic utility of quantitative 99mTc (V) DMSA brain SPECT in GBM patients.

In GBM, less than 5% of patients survive more than 3 years after diagnosis in spite of recent advances in treatment.[15] Therefore, we need new prognostic tools for GBM.

Positron emission and SPECT are used as tools of metabolic imaging and are used to differentiate between GBM recurrence and radiation necrosis. However, SPECT is widely available and routinely used in contrast to PET, which remains relatively expensive.[15]

Thallium-201(Tl-201) is the most studied SPECT radiotracer, but it cannot be used as the sole non-invasive diagnostic or prognostic tool in brain tumour patients due to overlap between tumour uptake and histologic grades.[14]

99mTc-labelled compounds as (V) DMSA, MIBI and tetrofosmin have advantages compared to Tl-201 due to better image resolution and significantly less radiation exposure to patients.[16,17]

Deltuva et al. stated that "to the best of our knowledge, previous studies employed SPECT scans only once during the treatment period and currently there are no studies evaluating the association of repeated SPECT scans with the prognosis of malignant glioma patients. Changes in the bulk of malignant glioma tissue following surgery evaluated by SPECT may possibly serve as a novel prognostic ma rker of malignant glioma".[15] Hence, they evaluated MIBI uptake [pre- and post-operative] in predicting survival of malignant glioma patients and concluded that worse OS was associated with higher MIBI uptake. Their study included all grades of glioma, while in the present study GBM only was included where statistical analysis showed that (V) DMSA could have a prognostic role.

Alexiou et al. evaluated the prognostic value of 99mTc tetrofosmin in predicting OS of 18 GBM patients and found that its higher uptake was correlated with significantly worse survival.[18]

The present study could imply that 99mTc (V) DMSA brain SPECT may hold a promising prognostic role in GBM patients. However, we suggest further prospective trials to establish a prognostic benefit from this new neuro-imaging radiotracer in GBM patients.

Conclusion

99mTc (V)-DMSA has been found to be a tumour-seeking agent. It might have an additional prognostic role in GBM patients as our results show statistical significance between the SPECT result (positive or negative) and the PFS and OS with a significant *p*-value.

Another point in this study is the statistical significant correlation between the lesion to non-lesion ratio of the tumor and OS and PFS. We correlated the RI of the tumour with PFS, and we found a statistical significance between the RI and PFS. There is a statistical significance between the degree of tumour uptake in 99mTc (V)-DMSA brain SPECT and PFS and OS, so it may predict the prognosis of patients with GBM and can expect shorter PFS in tumours with increased RI.

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Conflicts of interest. The authors have no conflicts of interest.

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