Original article

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Posttherapy technetium-99m pentavalent dimercaptosuccinic acid brain single-photon emission computed tomography/computed tomography: diagnostic and prognostic values in patients with glioma

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Purpose **To assess the value of posttherapy ^{99m}Tc-pentavalent dimercaptosuccinic acid (DMSA-V) brain SPECT/CT in patients with brain glioma.**

Methods **Patients with pathologically or radiologically proven glioma were prospectively enrolled in this study. ^{99m}Tc-DMSA-V brain SPECT/CT images were acquired at 120–180 min after i.v. injection of 555–740 MBq of ^{99m}Tc-DMSA-V. Three nuclear medicine physicians blindly interpreted the scans visually as positive or negative for residual/recurrent disease. Agreement between two or more readers was considered a consensus. The composite reference standard was considered based on subsequent clinical/neuroimaging follow-up or histopathology whenever available. Overall survival (OS) was calculated from the date of initial diagnosis till the death or the date of last follow-up.**

Results **Thirty-four patients (18 males and 16 females; mean age 37.7 ± 16 years) were enrolled in this study. Interreader agreement between the readers ranged from 0.71 to 0.82. Based on the composite reference standard, residual/recurrent disease was confirmed in 16 patients, whereas 18 patients were negative for disease. Consensus reading of ^{99m}Tc-DMSA-V SPECT/CT accurately diagnosed 13 true positive (sensitivity 81%) and 17 true negative scans (specificity 94%). After a median follow-up of 22.9 months, 7/14 patients with positive ^{99m}Tc-DMSA-V SPECT/CT brain readings died compared to 4/20 with negative readings. The median survival was 24.1 months for the positive group and was not reached for the negative group.**

Conclusion **Posttherapy brain SPECT/CT scanning with ^{99m}Tc-DMSA-V is a noninvasive, reliable, and specific tool for evaluation of patients with brain glioma after definitive therapy. Scan positivity was associated with poor OS. *Nucl Med Commun* XXX: 000–000** **Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: **^{99m}Tc-DMSA-V, gliomas, radiation necrosis, SPECT/CT**

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Introduction

Gliomas account for approximately 30% of all brain and CNS tumors and 80% of malignant brain tumors [1]. Multimodality therapy consisting of maximum surgical excision followed by radiotherapy with or without chemotherapy is the standard treatment for high-grade gliomas. Despite advancements in surgery, radiation therapy, and chemotherapy, gliomas still carry dismal prognosis due to the high recurrence rate [2]. Radiation necrosis (RN), a delayed radiotherapy-related reaction represents a particular challenge for managing brain neoplasms. Several features could confound the discrimination between RN and tumor recurrence; first, RN may be silent or present with manifestations of increased intracranial tension or focal neurological symptoms, which are overlapping with glioma recurrence; thus, the clinical picture alone cannot be used for discrimination of the two conditions. Second, necrosis usually ensues within 6–24 months after irradiation; the time during which recurrence is common. RN has been reported as early as 3 months and up to 19 years following CNS irradiation [3]. Finally, cross-sectional imaging modalities (CT/MRI) are frequently unreliable for differentiation [4,5]. Conventional MRI cannot differentiate tumor recurrence from delayed radiation effects, whereas MR spectroscopy may have false-positive readings of tumor recurrence [6]. It is clinically crucial to distinguish those two conditions since the treatment approaches and prognosis are entirely different.

Various molecular imaging modalities have been investigated to discriminate RN from glioma residue/recurrence, including single-photon emission computed tomography (SPECT), and PET.

The most commonly used PET tracer is 18F-fluorodeoxyglucose (^{18}F-FDG); its uptake correlates with the amount of glucose consumed and the local

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metabolic rate within the glioma lesion. In high-grade glioma, ^{18}F-FDG uptake is typically similar to or less than that of normal gray matter; in low-grade glioma, uptake is similar to that of white matter [7].

SPECT could be a useful alternative in these situations being widely available, and relatively easier to interpret. Thallium-201 SPECT has been used with a sensitivity ranged from 0.43 to 1.00, and a specificity from 0.25 to 1.00 [8].

Another SPECT agent technetium-99m (^{99m}Tc)-methoxy isobutyl isonitrile (^{99m}Tc-MIBI) showed favorable results and was associated with outcome. However, MIBI is excreted in the choroid plexus and could lead to false results [9,10]. Pentavalent dimercaptosuccinic acid (DMSA-V) has the advantage of easy preparation and better background clearance with no excretion in the ventricles [11]. It has been reported as a noninvasive biomarker of cancer proliferation [12]; however, there are scarce reports in glioma patients [13,14].

The aims of this study were to: (a) evaluate the reproducibility and diagnostic performance of posttherapy DMSA-V brain SPECT/CT in differentiating glioma recurrence/residual disease from postradiation changes and (b) assess the prognostic value of qualitative and quantitative DMSA-V brain SPECT/CT in terms of overall survival (OS).

Methods

Patients

Following approval by the Institutional Review Board for this prospective study, we obtained informed consent from all study participants. Thirty-four nonconsecutive patients with pathologically (n = 31) or radiologically (n = 3) proven gliomas were recruited for this study. Severely ill patients and patients with disturbed conscious levels who cannot lie down comfortably without movement were excluded (n = 2). Thirty-One patients underwent surgical excision of their primary tumor followed by concurrent radiochemotherapy. The patients were referred for ^{99m}Tc-DMSA-V SPECT/CT brain scanning within a mean interval of 70 days after completion of primary radiotherapy.

Scanning protocol

^{99m}Tc- DMSA-V was prepared as described by Hirano *et al*. [15], using a commercially available DMSA kit (Monrol, Istanbul, Turkey), which contains 1.4 mg DMSA and 0.5 mg stannous chloride dihydrate ($SnCl_2 \bullet 2H_2O$) as a reducing agent. Under aseptic conditions, 200 µl of 7% sodium bicarbonate solution ($NaHCO_3$) were added to the DMSA kit and reconstituted with 2 ml of ^{99m}Tc-pertechnetate solution [15].

SPECT/CT images of the brain were obtained approximately 30 min (early images) and at 2–3 h (delayed images) following intravenous administration of 555–740 MBq ^{99m}Tc-DMSA-V using a dual-head SPECT/CT gamma camera (Siemens Healthineers, Symbia T, Erlangen, Germany) fitted with a low energy high-resolution collimator, using 15% energy window set at 140 KeV. Patients were imaged in the supine position with their arms to the side, and their neck hyperextended. Precautions to avoid movement were considered, including a head strap and special positioning aids as appropriate.

A total of 64 frames were acquired, for 25 s each, in a noncircular 360° arc and a matrix size of 128 × 128. After SPECT acquisition, a low-dose CT was acquired for anatomical mapping and attenuation correction. The CT tube voltage was 130 kV, tube current 80 mA, automodulated using manufacturer dose-reduction algorithm (CARE Dose, Siemens Healthineers). The total study duration was approximately 30 min.

Data interpretation

Data were transferred to a workstation running OsiriX MD version 8.0 (Pixmeo, Bernex, Switzerland). Three independent nuclear medicine physicians blindly interpreted tracer accumulation in the brain. Readers 1, 2, and 3 had nuclear medicine reading experiences of 10, 15, and 22 years, respectively.

The methodology described by Henze *et al*. [16] was used for qualitative reporting, where focally increased tracer uptake, compared with the contralateral side, was considered abnormal.

Data were recorded visually for each reader as either positive or negative. A consensus decision was considered based on the agreement between any two, or all the three, readers.

Reader 1 repeated the visual interpretation at least 3 months after the initial reading, and the second reading was considered for the consensus reporting. The two readings were used to calculate intrareader agreement.

Lesion quantification was performed by one reader (Reader 1) employing a volume of interest (VOI) on the lesion (L) site. An isocontour was set to 40% and the isocontour mean was recorded. A mirror VOI was placed on the contralateral normal brain tissue (NL) and was adjusted to avoid areas of high uptake (e.g. the physiologic skull bone uptake). In the presence of midline lesion, the NL VOI was placed on the cerebellum. When the lesion showed no significant uptake, the VOI placement was guided by the CT portion of the study (i.e. site of prior intervention) and prior MR studies to determine the original lesion site.

VOIs were recorded for both early and delayed images to calculate the early (L/NL1) and delayed (L/NL2) ratios, respectively. The retention index (RI) was calculated as the ratio of delayed and early L/NL ratios according to

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this equation: [(L/NL2) – (L/NL1)] ÷ L/NL1. To ensure the reliability of the quantification methodology, five patients were randomly repeated by the same reader (Reader 1) after an interval of 3 months, and VOIs were redrawn. The difference in the quantification endpoints (i.e. L/NL ratio) was less than 5%.

Reference standard

Pathology was considered the gold standard whenever resurgery/rebiopsy was performed as part of the patient's standard of care. In the absence of histopathological evaluation, subsequent neuroimaging follow-up was used as the reference test. A lesion was considered positive if subsequent follow-up neuroimaging documented progression or partial regression after therapy. A lesion was considered RN if the initial neuroimaging studies were negative with continued negativity in the follow-up period (at 3, 6, and 12 months) unaccompanied by clinical worsening.

Statistical analysis

True positive and true negative were categorized according to subsequent histopathological/imaging validation. Diagnostic performance indices (sensitivity, specificity, accuracy, positive predictive value, and negative predictive value) were accordingly calculated. Inter- and intraobserver agreements were measured using Cohen's Kappa test for any given two readings. Fleiss' Kappa was used to calculate the agreement between the three readers [17].

The area under the receiver operating characteristic curve (AUC) analysis was used to evaluate the L/NL ratios as continuous parameters with respect to the final tumor status and to identify the best discriminative cutoff point. All patients continued to have follow-up for a minimum of 1 year. OS was calculated from the date of the initial diagnosis till the date of death or the date of the last follow-up for censored participants. Survival analysis was performed using the Kaplan–Meier method, and the log-rank test was used to compare the difference between categorical groups.

Qualitative data were summarized and expressed as frequencies and percentages, whereas quantitative data were summarized and expressed as mean ± SD or median (range). In all analyses, a P-value < 0.05 was considered statistically significant. Data analysis was conducted using SPSS version 21.0 (IBM Corp, Armonk, New York, USA).

Results

Patients

Thirty-four patients (18 males and 16 females; mean age 37.7 ± 16 years) were enrolled in this study; four patients were less than 18 years (7, 11, 14, and 17 years). Most tumors were anatomically located in the parietal lobe (14 out of 34), seven in the frontoparietal region, four in the temporoparietal region, four in the temporal lobes, three in the frontal, one in the occipitoparietal, and one in the posterior fossa. Karnofsky performance score (KPS) ranged from 20 to 100 (median = 90).

Thirty-one patients underwent surgical excision of their primary tumor. The mean tumor size, as measured by MRI, was 4.8 ± 1.4 cm, and the mean resected tumor bulk was 3.2 ± 1.4 cm. Half of the study populations were pathologically graded IV, eight were grade III, four were grade II, and two were grade I. The typical imaging features were consistent with grade IV glioma in the three patients who did not undergo surgical resection [18].

Eight patients underwent resurgery: seven were proved to have recurrent tumor and one was having gliosis. The rest of the patients had one or more MRI neuroimaging studies as the reference standard. Accordingly, residual/recurrent disease was confirmed in 16 patients, whereas 18 patients remained disease-free.

Agreement analysis

The three nuclear medicine physicians agreed on the classification of 28 out of 34 (80%) of the ^{99m}Tc-DMSA-V SPECT/CT studies. Pairwise interreader agreement ranged from 0.71 to 0.82. The overall agreement between the three readers was 0.76, reflecting excellent concordance. Intraobserver agreement for Reader 1 was 0.76 (95% CI, 0.50–0.94).

Diagnostic performance

Consensus reading successfully identified 13 out of 16 true positive (Fig. 1) and 17 out of 18 true negative (Fig. 2) lesions. The overall accuracy was 88% (95% CI, 72–96%). Table 1 summarizes the diagnostic performance indices.

Quantitative evaluation

The three quantitative indices (L/NL1, L/NL2, and RI) were not associated with the pathologic grade of glioma documented at presentation (i.e. classified as four grades from I to IV); however, two of these indices (L/NL1 and L/NL2) were significantly higher in recurrent lesions compared to their nonmalignant counterparts and were highly predictive of the true status of these lesions with AUC of 0.88 (95% CI, 0.72–0.96) and 0.93 (95% CI, 0.79–0.99), respectively (Fig. 3). The best discriminative cutoff values of L/NL1 and L/NL2 were 1.8 and 2.0, respectively. Both values resulted in sensitivity of more than 80% and specificity of more than 90%. Table 2 summarizes these quantitative metrics.

Association with survival

The median follow-up duration for the study participants after their SPECT/CT study was 22.9 months (range:

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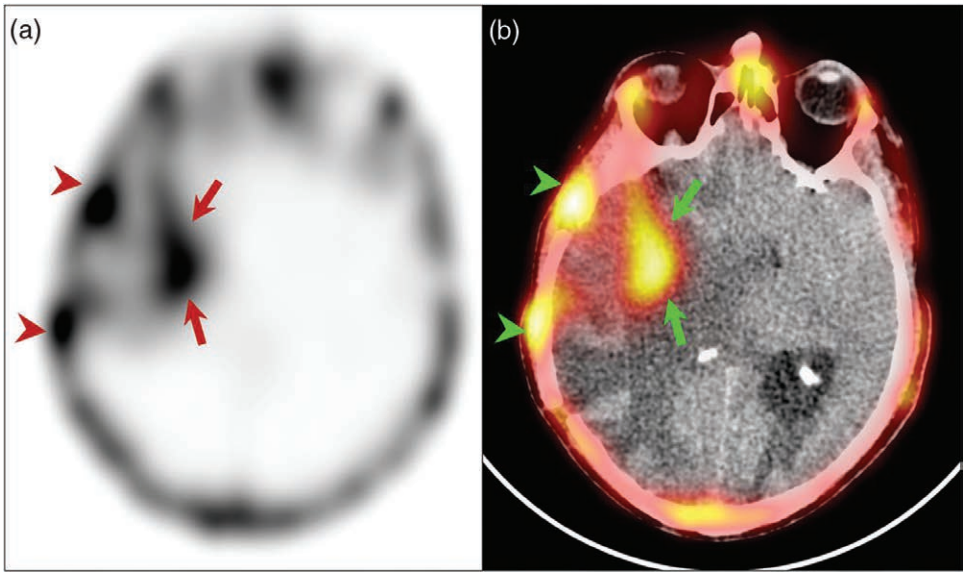
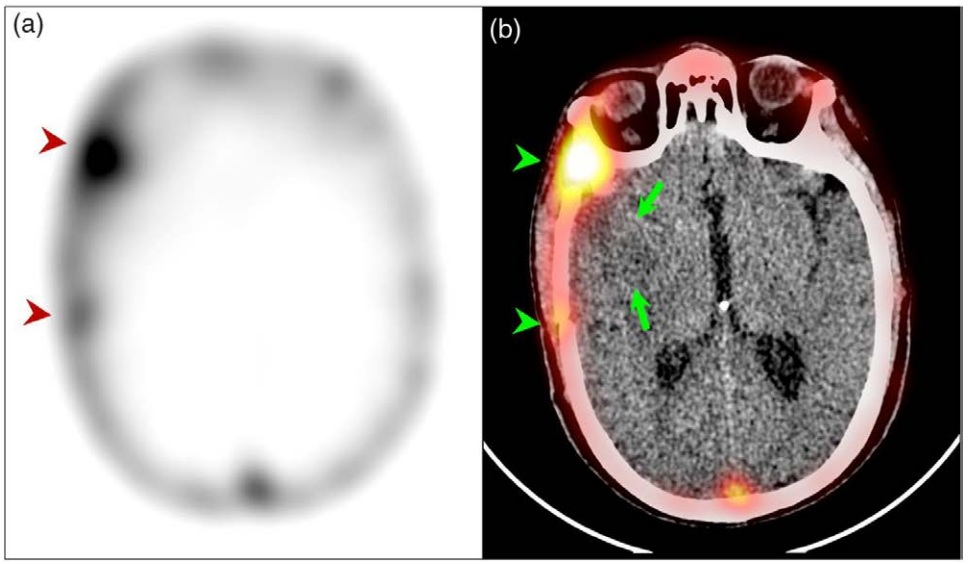
Fig. 1



Male patient, 34 years old, with right temporoparietal glioblastoma multiform and Karnofsky performance score of 50. (a) axial SPECT and (b) the corresponding fused SPECT/CT image demonstrating abnormal technetium-99m pentavalent dimercaptosuccinic acid uptake in the right temporoparietal region (arrows) indicating viable tumor tissue. The focal uptake in the skull bone (arrowheads) is likely related to the surgical intervention. The patient died 24 months after diagnosis. SPECT/CT, single-photon emission computed tomography/computed tomography.

Fig. 2



Male patient, 60 years old, with right temporoparietal glioblastoma multiform and Karnofsky performance score of 90. (a) axial SPECT and (b) the corresponding fused SPECT/CT image demonstrating no abnormal technetium-99m pentavalent dimercaptosuccinic acid uptake within the site of the primary lesion indicating no viable tumor tissue there. Twenty months after the primary diagnosis, the patient was still alive with no evidence of recurrence. SPECT/CT, single-photon emission computed tomography/computed tomography.

6.3–60.2 months). At the conclusion of this study, a total of 11 out of 34 patients died; among them, eight patients were having verified recurrent/residual tumors and three were negative.

Four out of 20 patients (20%) with negative DMSA-V findings died (median survival: not reached) compared with seven out of 14 with positive findings (median survival = 24.1 months, 95% CI, 22.7–25.4). The difference

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in OS probability between the patients with negative and positive DMSA-V findings was highly significant ($P = 0.004$).

As expected, patients with poor performance status (KPS < 80) or grade IV tumors had significantly shorter OS with median survival of 31.3 months (95% CI, 24.2–38.4 months). Table 3 summarizes the relationship of different study variables with OS.

It is worth noting that the visual findings of DMSA-V were marginally associated with KPS; 17 out of 24 patients (71%) with good performance status (KPS ≥ 80) were also having negative findings on consensus DMSA-V readings, compared with only three out of 10 patients with poor performance status that showed negativity on SPECT/CT ($P = 0.05$). Quantitatively, the early and delayed L/NL demonstrated statistically significant moderate negative correlation with KPS (respectively, rho = 0.64; 95% CI, 0.35–0.80 and 0.57; 95% CI, 0.31–0.75).

The subgroup of patients with both poor performance status (KPS < 80) and positive DMSA-V ($n = 7$) experienced the worst OS, with five out of the seven patients died (median survival: 23.5 months; 95% CI, 7.8–39.2) compared with those with high KPS and negative SPECT/CT findings ($n = 17$), where only two patients died (median survival: not reached). The hazard ratio for death was 15.4 (95% CI, 2.8–88.4; $P = 0.003$) for the group with positive DMSA-V and KPS < 80 (Fig. 4).

Table 1 **Diagnostic performance of the qualitative evaluation of technetium-99m pentavalent dimercaptosuccinic acid single-photon emission computed tomography/computed tomography for differentiating residual/recurrent glioma from postradiation necrosis**

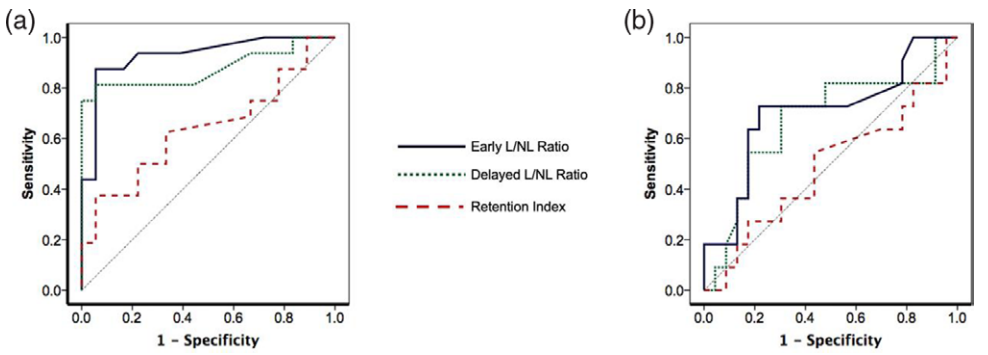
Diagnostic Parameter	Value (95% confidence interval)
Sensitivity	81% (54–96)
Specificity	94% (73–100)
Accuracy	88% (72–96)
Positive predictive value	93% (66–100)
Negative predictive value	85% (62–97)
Positive likelihood ratio	14.6 (2.2–100)
Negative likelihood ratio	0.2 (0.1–0.6)

Discussion

We prospectively studied 34 patients with brain glioma using ^{99m}Tc-DMSA-V SPECT/CT during their follow-up after radical therapy. The overall accuracy of qualitative readings was 88%, with highly reproducible results among three nuclear medicine physicians with different levels of experience.

The sensitivity and specificity of DMSA-V were 81 and 94%. These figures were in line with those reported by Amin *et al.* [13], who compared ^{99m}Tc-DMSA-V SPECT with ^{1}H-MRS in detecting recurrent glial tumors of the

Fig. 3



Receiver operating characteristics (ROC) analysis of the early and delayed lesion-to-nonlesion ratio (L/NL), and retention index, with respect to verified lesion nature (a) and overall survival (b).

Table 2 **Diagnostic performance of the quantitative metrics derived from technetium-99m pentavalent dimercaptosuccinic acid single-photon emission computed tomography/computed tomography with respect to the final true status of the brain lesion**

	Median (range)						
Metrics	Benign	Malignant	AUC (95% confidence interval)	Cutoff	Sensitivity	Specificity	*P*-value
Early L/NL	1.0 (0.5–2.3)	3.3 (0.7–7.1)	0.88 (0.72–0.96)	>1.8	81%	94%	<0.001
Delayed L/NL	1.0 (0.9–1.3)	3.8 (1.0–29)	0.93 (0.79–0.99)	>2.0	88%	94%	<0.001
Retention index	0 (–0.6 to 1.4)	0.2 (–0.3 to 6.3)	0.64 (0.46–0.80)	>1.0	38%	94%	0.2

L, lesion; NL, nonlesion; AUC, area under the curve.

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Table 3 Association of different patients' characteristics with overall survival in 34 patients with glioma

Characteristics	Events/total (%)	Median survival months (95% CI)	*P*-value
Age			
≤40 years	6/20 (30%)	Not reached	0.9
>40 years	5/14 (36%)	3 (2.3–3.7)	
Sex			
Male	4/18 (22%)	Not reached	0.13
Female	7/16 (44%)	3.0 (2.3–3.7)	
Karnofsky performance score			
KPS ≥ 80	4/24 (17%)	Not reached	0.003
KPS < 80	7/10 (70%)	26.3 (13.3–39.4)	
Pathology			
Grades I–III	2/14 (14%)	Not reached	0.04
Grade IV	9/17 (53%)	3 (2.4–3.6)	
SPECT/CT Reading			
Negative	4/20 (20%)	Not reached	0.004
Positive	7/14 (50%)	24.1 (22.7–25.4)	
Early lesion-to-nonlesion ratio			
≤1.8	3/20 (15%)	Not reached	0.003
>1.8	8/14 (57%)	26.3 (20.7–31.9)	
Delayed lesion-to-nonlesion ratio			
≤2.0	3/19 (16%)	Not reached	0.02
>2.0	8/15 (53%)	28.3 (22.4–34.2)	
Retention Index			
≤1.0	8/27 (30%)	3.0 (2.2–3.8)	0.6
>1.0	3/7 (43%)	3.0 (0.07–5.9)	

CI, confidence interval; KPS, computed tomography; SPECT/CT, single-photon emission computed tomography/computed tomography.

brain and reported a sensitivity of 89% and specificity of 92% for SPECT scanning.

The Response Assessment in Neuro-Oncology Working Group emphasizes the clinical value of PET imaging, particularly with amino acid radiotracers, over conventional MRI and recommends its use at every stage of management [19,20]. For example, PET can help distinguish between true and pseudoresponse to antiangiogenic agents in recurrent glioma and determine treatment failures earlier than MRI in recurrent glioma [21–23]. Though it is clear that PET has several advantages over SPECT, given its inherent quantitative nature, better resolution, and multitude of radiotracers; however, it is far more expensive and not widely available, especially in developing countries [24]. The reported diagnostic accuracy of amino acid tracers in the literature ranged from 81 to 99% [25–28].

A total of four false readings were encountered in the current work (one false-positive and three false-negative results). Intense tracer uptake was seen in the surgical wound of one patient. The uptake was continuous with an intra-axial lesion that demonstrated punctate calcification, which seemed stable on subsequent follow-up MRI. Mineralizing microangiopathy and cortical calcification have been reported after radiation therapy[29,30]. We assumed that calcification might be responsible for the false-positive uptake. Sites of active calcification/bone formation are known to show ^{99m}Tc- DMSA-V uptake [31].

The three false-negative studies in our cohort could be attributed to their small lesion size (<1.0 cm). SPECT γ-camera has limited spatial resolution, and subcentimeteric lesion could be missed, preferentially if its proliferative activity and tracer retention are low [12]. Tsiouris *et al.* [12] concluded that low-grade neoplasms and some cases of RN could have faint uptake, congruent with their low proliferation rate. It is worth noting that repeating the biopsy/surgical excision after initial surgical or irradiation therapy is challenging, and sampling scarred or gliotic foci could yield false-negative biopsies. Therefore, we used clinical course of the patient and imaging over a follow-up interval as a gold standard [32].

We employed a protocol that acquired both early and delayed SPECT images. Quantitively, both the early and delayed L/NL ratios were highly predictive of the lesion nature, which comes in agreement with previous studies [13,14]. DMSA-V bears structural similarity to phosphate ion (PO_4^{-3}) and is transported intracellularly via sodium/phosphate (NaPi) transporters and could represent a noninvasive biomarker of cancer proliferation [33]. Delayed imaging allowed better background clearance and better visualization of the suspected lesions; however, quantitatively the retention index was not associated with outcomes. While currently, we do not hold a clear explanation, we assume this could be related to the method of background correction, which involves using isocontour with voxels higher than 40% of the maximum. This method was applied to both early and delayed imaging, but the relative contribution could play differently between the two sets of images due to different noise characteristics and could attribute to the finding. Dual time-point imaging may be challenging, especially in busy departments or with severely ill patients; however, a customized imaging protocol that involves early imaging alone may be practically valuable in a subset of patients who cannot tolerate long waiting uptake times. Additional delayed imaging may be added if equivocal

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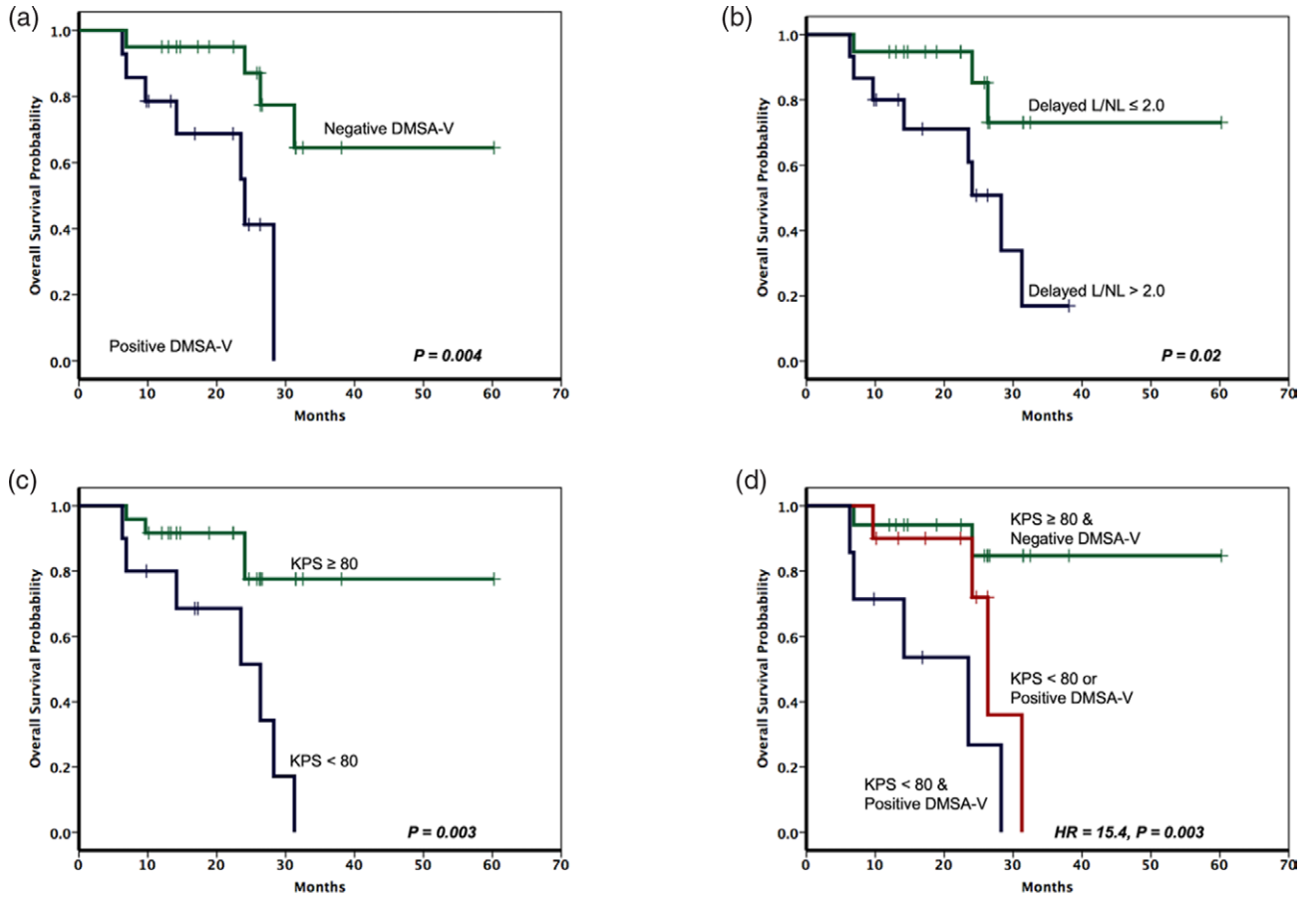
Fig. 4



Kaplan–Meier analysis of overall survival, in patients with (a) negative and positive technetium-99m pentavalent dimercaptosuccinic acid (^{99m}Tc-DMSA-V) SPECT/CT findings, (b) delayed lesion-to-nonlesion ratio (L/NL) ≤2 and >2, (c) Karnofsky performance score (KPS) ≥80 and <80, and (d) in patients stratified according to KPS and ^{99m}Tc-DMSA-V SPECT/CT findings into three subgroups. The hazard ratio (HR) for death in the subgroup with both KPS < 80 and positive ^{99m}Tc-DMSA-V SPECT/CT findings is 15.4 times that of the first subgroup (KPS ≥ 80 and negative ^{99m}Tc-DMSA-V SPECT/CT findings). SPECT/CT, single-photon emission computed tomography/computed tomography.

lesions are encountered. It is worth noting that we have not performed the same qualitative reading on the early images and further work is needed to specify the utility of each phase.

Both qualitative and quantitative parameters showed association with OS. Patients with positive ^{99m}Tc-DMSA-V visual findings or higher L/NL ratio at the early or delayed phases had shorter OS compared with the negative cases or those with lower L/NL ratios. Amin *et al.* [34] assessed the prognostic role of ^{99m}Tc-DMSA-V in 40 patients with GBM and concluded that higher degrees of tracer uptake were associated with worse survival that concurs with our results.

The association between lesion uptake in DMSA-V and performance status may reflect the fact that rapidly proliferating tumors are more aggressive and associated with the worse general condition. The two factors together have the potential to further stratify the risk in patients with glioma beyond each of them separately. Compared with patients with good performance status and negative DMSA-V findings, the hazard for death was 15.4 times higher in patients with poor performance status and positive DMSA-V findings. It is worth mentioning that our final results come in agreement with prior initial pilot works [11,35–37]. These findings are indicative of potential prognostic utility that could be utilized towards selecting patients for novel therapies or clinical trials.

Finally, our study has multiple limitations. First, the study has a small sample size, with different grades of glioma, which limits any systematic subgroup analysis. Also, data were collected from a single center, which may limit any solid generalizable conclusions. Second, patients were referred to perform SPECT/CT, at the discretion of their treating physicians, at variable durations after therapy. Third, most of the patients had their MRI performed out-of-the-institution, which limited any systematic

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comparison with conventional imaging or multiparametric MRI. On the other hand, the current work has the advantages of prospective design, standardized acquisition and interpretation protocol, studying the inter- and intrareader reproducibility, and correlation with OS.

In conclusion, we demonstrated that posttherapy brain SPECT/CT with ^{99m}Tc- DMSA-V SPECT/CT is a reproducible technique that can yield specific findings for detecting residual/recurrent disease in patients with brain glioma after their definitive therapy. Positive scan findings are linked to worse OS, and lesion uptake intensity is associated with worse general performance status and adverse survival outcomes.

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Parts of this work were presented as abstracts at the SNMMI 2017 and EANM 2019 [35–37]. A manuscript with a subgroup of the current cohort (glioblastoma multiforme) was previously published [11].

Availability of data and material: available.

Ethics approval: local ethics committee approval.

Consent for participation: obtained from each patient.

Consent for publication: obtained.

Conflicts of interest

There are no conflicts of interest.

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