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Evaluating the diagnostic ability of treatment response assessment maps (TRAMs)/contrast clearance analysis (CCA) in predicting the presence of active brain tumors

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Abstract

Introduction: Brain tumors pose significant diagnostic and therapeutic challenges due to their diverse treatment responses and complex imaging characteristics. Traditional MRI techniques often struggle to differentiate between tumor recurrence and post-treatment changes such as pseudoprogression and necrosis, highlighting the need for more accurate diagnostic tools.
Material and Methods: This retrospective study conducted at a single tertiary care center and evaluated the diagnostic efficacy of Treatment Response Assessment Maps (TRAMs), also known as Contrast Clearance Analysis (CCA), in distinguishing between tumor recurrence and post-treatment changes in patients who underwent initial treatment for brain tumors. Data from 27 patients were analyzed, including 10 who underwent surgical resection (Group 1) and 17 who had serial images and TRAMs/CCA assessment (Group 2).
Result: In Group 1, TRAMs/CCA demonstrated nine positive results, with 8 cases of tumor recurrence confirmed via biopsy. A biopsy also confirmed one negative result after a discussion with the patient. In Group 2, where patients did not undergo biopsy, TRAMs/CCA results varied but correlated with clinical outcomes, underscoring the potential utility of TRAMs/CCA in guiding treatment decisions. These findings suggest that TRAMs/CCA may have superior diagnostic performance compared to traditional MRI in differentiating between tumors.
Conclusion: TRAMs/CCA represents a promising advancement in the imaging assessment of brain tumor treatment response, offering higher sensitivity than conventional MRI methods. While implementing TRAMs/CCA could potentially improve diagnostic accuracy and optimize therapeutic strategies for patients with brain tumors, the final decision remains highly dependent on patient-centered discussions.

Keywords

Brain tumors, treatment response assessment maps, treatment response assessment maps, contrast clearance analysis, diagnostic performance, tumor recurrence

Introduction

Malignant brain and central nervous system (CNS) tumors account for only 1% of all invasive cancer cases in the United States but are associated with substantial morbidity and mortality. Despite advancements in treatment modalities, the 5-year relative survival rate for malignant brain tumors has only modestly improved, from 23% in 1975–1977 to 36% in 2009–2015.[1,2] Traditionally, T1-weighted MRI has been pivotal in imaging brain tumors, but its ability to differentiate vasogenic edema from non-enhancing tumors is limited, as this appears hyperintense on T2 FLAIR sequences. Consequently, diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and MR spectroscopy are used to discern tumors from non-tumor changes. Over the decades, various diagnostic modalities, including the McDonald Criteria, have been scrutinized for diagnosing brain cancer. However, their utility is restricted in assessing irregularly

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shaped or multifocal tumors and post-treatment lesions, particularly under the influence of temozolomide and radiotherapy.[3–7] As many systemic therapies have limited ability to cross the blood–brain barrier, radiation for CNS tumors is a cornerstone of treatment.

Despite improvements in lesion conspicuity with T1 subtraction maps in modified RANO criteria, early changes observed between post-surgical and pre-radiation exams and subsequent post-radiation exams may not accurately reflect true tumor burden changes.[3,8] MR spectroscopy, which analyzes alterations in standard brain metabolite ratios, has shown promising sensitivity (85%) and specificity (69.2%) in diagnosing brain tumor recurrences among patients with enhancing lesions.[9] A major limitation was its inability to differentiate between tumor and non-tumor tissue in mixed tumors.[10,11]

Recently introduced Treatment Response Assessment Maps (TRAMs), also known as Contrast Clearance Analysis (CCA), have emerged as a novel imaging modality for monitoring brain tumor patients.[12,13] TRAMs/CCA have been suggested to distinguish between tumor progression and post-treatment changes more effectively than traditional MRI techniques; however, existing evidence is still limited, and further validation is required.[14] Given the limitations of existing diagnostic methods, developing new strategies for diagnosing brain cancers is critical. This study aims to assess the diagnostic efficacy of TRAMs/CCA in distinguishing between tumor and post-treatment necrotic tissue in both primary and metastatic brain tumors.

Methods

Patient data collection and statistics analysis

This retrospective chart review study, authorized by the Institutional Review Board (IRB Number: E−23-923), was conducted at Englewood Hospital and Medical Center, a single tertiary care facility in New Jersey, USA, spanning from 2020 to 2022. Informed consent was waived by the IRB due to the retrospective nature of the study. The study included all patients who were diagnosed with confirmed brain lesions either by biopsy or brain imaging, received treatment, and underwent follow-up imaging of TRAMs/CCA to assess treatment response. Exclusion criteria encompassed patients who did not undergo treatments before TRAMs/CCA, those lacking any follow-up repeat imaging or surgical biopsy post-initial TRAMs/CCA, and patients not followed at the center.

Patient data were extracted from the hospital's electronic medical record system (Epic). Basic characteristics such as gender, age, tumor type, initial TRAMs/CCA results, and treatment types were recorded. Outcomes were meticulously documented, including TRAMs/CCA reports, biopsy results, and follow-up duration.

A total of 27 patients were identified who received initial treatment, which included surgical excision, chemotherapy, or radiotherapy, followed by post-treatment TRAMs/CCA assessment. Among these, 10 patients underwent surgical pathology (Group 1). In comparison, the remaining 17 patients (Group 2) underwent repeat brain MRI imaging with and without contrast, alongside TRAMs/CCA evaluation for those not undergoing surgical interventions.

MRI data acquisition and analysis

The TRAMs/CCA MRI data were acquired using the Brain Lab protocol, which involved acquiring two series of 3D-T1 images: one at 5 minutes and another at 60-105 minutes post-contrast injection. These images were then processed using Brainlab Elements software suite, Contrast Clearance Analysis, version 4.0.2.8 (Brainlab AG, Olof-Palme-Str. 9, D-81,829 Munich, Germany), where early images were subtracted from late images to highlight areas of contrast enhancement over time.

In the analysis, red areas indicated post-treatment effects or necrosis, while blue areas indicated active tumor tissue. The timing from initial treatment to image acquisition was not explicitly calculated. A consensus approach was used in cases where lesions exhibited both blue (suggestive of active tumor) and red (suggestive of post-treatment effects) components and based on the expertise of the radiologists. Importantly, the interpretation of results was conducted independently by three radiologists who were blinded to the patient's clinical conditions.

Patient outcomes were classified as positive for cancer (blue areas) or negative for tumor recurrence (red areas suggestive of necrosis/post-treatment changes). These findings were subsequently validated by surgical pathology reports or repeat imaging studies.

Histology

For patients who underwent brain biopsy with tissue collection, pathologist reports were documented. These tissue samples were meticulously examined in the pathology laboratory. Individual pathologists inspected the slides and reported their findings based on their expertise. In cases requiring further multidisciplinary input, the cases were presented at the brain cancer tumor board for oncologists and other specialists to review and discuss optimal diagnostic and treatment strategies.

Results

Table 1 demonstrated the characteristics of the patients included in this study. Group 1 consisted of 10 patients who underwent biopsy confirmation after positive TRAMs/CCA results. The group included six males (60.0%) and four females (40.0%), with a mean age of 58 years (interquartile range (IQR): 16). The most common tumor type was primary brain tumor, identified in seven patients (70.0%). All patients had received radiotherapy before TRAMs/CCA. In Group 1, initial TRAMs/CCA results were positive in nine patients (90%) and negative in one patient (10%). All 10 patients proceeded to surgery following TRAMs/CCA. Among patients with positive TRAMs/CCA findings, eight (80%) had a positive biopsy, and one (10%) had a negative biopsy result. The positive result of TRAMs/CCA confirmed by biopsy was demonstrated in Figure 1. Additionally, the one negative TRAMs/CCA result was confirmed by biopsy.

Group 2 consisted of 17 patients who did not undergo biopsy. The gender distribution was slightly skewed towards females, with seven males (41.2%) and 10 females (58.8%). The median age for this group was 71 years (IQR 18).

Regarding tumor types, eight patients (47.1%) had primary brain tumors, three (17.6%) had lung cancer, two (11.8%) had breast cancer, and four (23.5%) had other types of tumors, such as neuroendocrine tumor, adenocarcinoma, and melanoma. Initial TRAMs/CCA results for Group 2 showed seven patients (41.2%) testing positive and 10 patients (58.8%) testing negative. Notably, none of the patients in Group 2 underwent surgery after TRAMs/CCA. For patients with repeated positive TRAMs/CCA results, clinical decisions were influenced by factors such as patient comorbidities, poor prognosis, or patient preference for less invasive management. This approach reflects a patient-centered strategy, particularly in elderly patients or those with limited life expectancy.

Table 1. Patient characteristics.

Patient group		Group 1	Group 2
Total number		10 (100.0)	17 (100.0)
Gender			
	Male	6 (60.0)	7 (41.2)
	Female	4 (40.0)	10 (58.8)
Age (years)		58 (16)	71 (18)
Tumor type			
	Primary brain tumor	7 (70.0)	8 (47.1)
	Lung	2 (20.0)	3 (17.6)
	Breast	1 (10.0)	2 (11.8)
	Other	0 (0.0)	4 (23.5)
Initial TRAMs/CCA results			
	Positive	9 (90.0)	7 (41.2)
	Negative	1 (10.0)	10 (58.8)
Surgery after TRAMs/CCA			
	Yes	10 (100.0)	0 (0)
	No	0 (0)	17 (100.0)
Biopsy results			
	Positive	8 (80.0)	Non done
	Negative	2 (20.0)	Non done
Radiotherapy prior TRAMs/CCA			
	Yes	10 (100.0)	17 (100.0)
	No	0 (0)	0 (0)
Positive follow-up (n = 9) TRAMs/CCA			
	With positive biopsy	8 (80.0)	Non done
	With negative biopsy	1 (10.0)	Non done
Negative follow-up (n = 1) TRAMs/CCA			
	With positive biopsy	1 (10.0)	Non done
	With negative biopsy	0 (0)	Non done

Categorical variables were presented as n (%). Continuous variables were presented as median (IQR)

Detailed TRAMs/CCA and biopsy results were demonstrated in Table 2 and Table 3 for Group 1 and Group 2, respectively. Patient 1, diagnosed with Anaplastic Astrocytoma, showed a positive TRAMs/CCA result but negative pathology after surgical biopsy. The TRAMs/CCA result indicated radiation necrosis/red associated with the right frontal surgical cavity, potentially influenced by Avastin treatment. Biopsy specimens from the right frontal site revealed extensive necrotic glial tissue without evidence of tumor recurrence (Figure 2). Patient 2, with Large Cell Neuroendocrine Carcinoma of the Lung, had negative TRAMs/CCA, but the decision was still made to pursue a biopsy after being discussed with the patient. TRAMs/CCA revealed an enlarged right frontal lobe peripherally enhanced hypointense signal abnormality measuring 5.1 × 4.3 cm (previously 5.0 × 3.8 cm), extending into the anterior corpus callosum (Figure 3). The biopsy result revealed extensive necrosis with negative findings of the cancer.

Table 3 presents the TRAMs/CCA results for 16 patients with TRAMs/CCA follow-up but no biopsy proof, detailing their primary cancer types and outcomes of first and second TRAMs/CCA assessments. In this group, patients with negative results typically did not have surgery. They continued follow-up with multiple TRAMs/CCA, where subsequent negative TRAMs/CCA suggested the absence of disease progression. Conversely, patients with positive TRAMs/CCA results sometimes discontinued follow-up due to poor prognosis, leading to patient mortality. For instance,

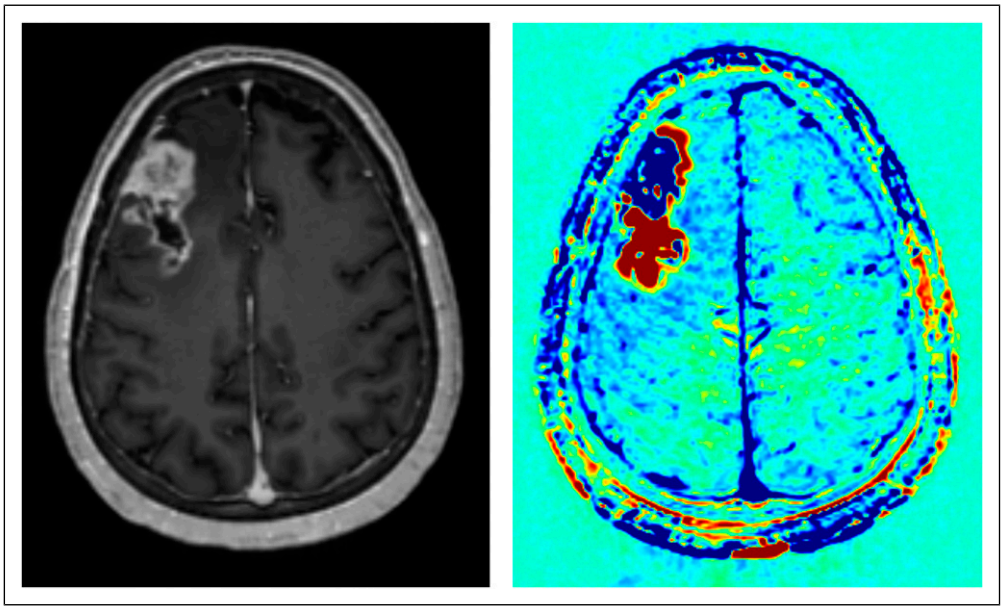

Figure 1. Corresponding MRI image of the positive TRAMs/CCA imaging. Positive TRAMs/CCA image (The blue/positive area with surrounding red/negative area).

Table 2. Detailed results of patients in Group 1.

Patient number	Primary cancer	TRAMs results with evidence of tumor	Pathology with evidence of tumor	Note
1	Anaplastic astrocytoma	Yes	No	
2	Large cell adenocarcinoma with neuroendocrine tumors of lung	No	No	Patient had negative TRAMs/CCA but decision was made to still do the biopsy. Biopsy result revealed negative with necrosis findings
3	Glioblastoma multiforme	Yes	Yes	
4	Breast cancer	Yes	Yes	Patient had 2 TRAMs/CCA positive before the biopsy
5	High-grade spindle cell sarcoma	Yes	Yes	
6	Glioblastoma multiforme	Yes	Yes	Patient had 2 TRAMs/CCA positive before the biopsy
7	Glioblastoma multiforme	Yes	Yes	
8	Astrocytoma	Yes	Yes	
9	Glioblastoma multiforme	Yes	Yes	
10	Adenocarcinoma of the lung	Yes	Yes	

Table 3. Detailed results of patients in Group 2.

Patient number	Primary cancer	First TRAMs results with evidence of tumor	Second TRAMs results with evidence of tumor	Comments
11	Endometrial neuroendocrine tumor	No	No	
12	Glioblastoma multiforme	No	No	
13	Glioblastoma multiforme	No	No	With third TRAMs/CCA also negative
14	Adenocarcinoma of the lung	No	No	With following 3 TRAMs/CCA revealed either negative or post-treatment necrosis
15	Adenocarcinoma of unknown primary	Yes	Yes	Patient with total 4 TRAMs/CCA positive
16	Glioblastoma multiforme	Yes	Yes	
17	NSCLC	No	No	
18	Metastatic neuroendocrine tumor	No	No	Patient with all the following TRAMs/CCA negative
19	Adenocarcinoma of the lung	Yes	Yes	Patient had in total 3 TRAMs/CCA positive but surgery was not pursued. Patient had passed away
20	Melanoma	No	Nil	No further follow up was documented in the chart
21	Central neurocytoma	No	No	Patient with all the following TRAMs/CCA negative
22	Breast cancer	Yes	Nil	Patient has passed away, so no repeat TRAMs/CCA
23	Breast cancer	Yes	Yes	Patient had 3 positive TRAMs/CCA.
24	Atypical meningioma	No	No	
25	Glioblastoma multiforme	Yes	Yes	Patient had 3 positive TRAMs/CCA. Patient has passed away
26	Glioblastoma multiforme	Yes	Nil	Patient has passed away, so no repeat TRAMs/CCA
27	Glioblastoma multiforme	Yes	Nil	Repeat MRI revealed no progression

Nil: No repeated TRAMs/CCA.

patients 22 and 26 had positive initial TRAMs/CCA but passed away before further evaluations could be conducted. This table highlighted the necessity for personalized follow-up strategies tailored to individual patient responses and prognoses.

Discussion

In this study, we evaluated the diagnostic performance of TRAMs/CCA in distinguishing between tumor recurrence and post-treatment changes in patients with brain tumors who underwent initial treatment (surgery and radiotherapy) at a single center. Notably, we did not calculate the sensitivity and specificity because there were no biopsy results to confirm true positives or negatives in Group 2. Also, patients with negative TRAMs/CCA may opt to continue follow-up with TRAMs/CCA, with awareness of the possibility of false negatives. However, for patients with positive results, the decision to pursue surgical biopsy or resection should be based on individual patient-centered considerations.

According to a previous meta-analysis, anatomical MRI demonstrates a pooled sensitivity of 68% (95% CI 51–81) and

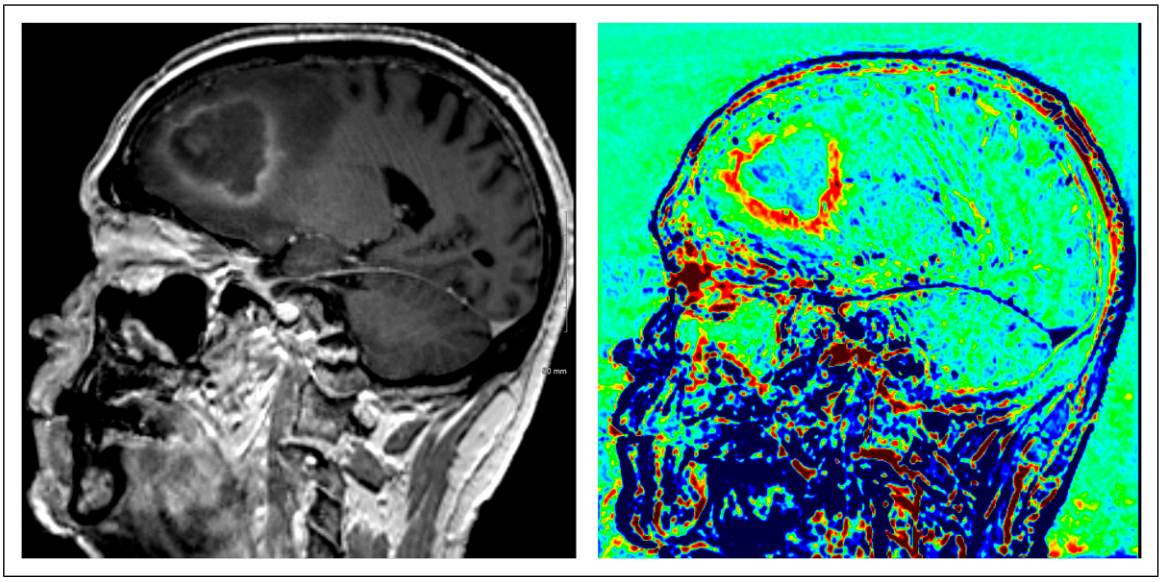

Figure 2. The corresponding MRI image of negative TRAMs/CCA. Negative TRAMs/CCA study result.

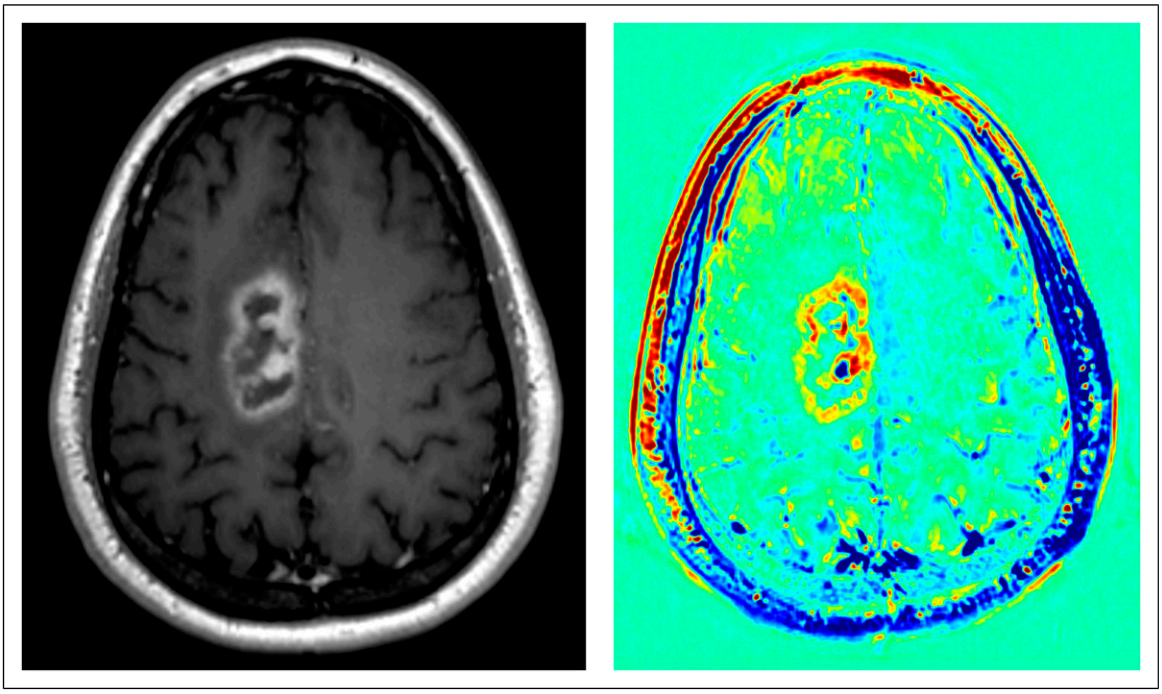

Figure 3. The corresponding MRI imaging of false positive TRAMs/CCA. The image of false positive TRAMs/CCA (Blue nodule).

specificity of 77% (95% CI 45–93) in distinguishing between tumor recurrence and post-treatment changes.[15] Patients undergoing surgical intervention, radiation therapy, or chemotherapy for brain tumors often present with residual MRI-enhancing lesions, posing challenges for conventional methods in differentiating tumor recurrence from pseudoprogression or necrosis.[16] Our study suggests that TRAMs/CCA might offer a promising alternative in the imaging assessment of brain tumors; however, the decision ultimately remains highly dependent on patient-centered discussions.

Brain post-radiation treatment effects, such as pseudoprogression and radiation necrosis, are common aftereffects observed in the management of brain tumors and are significant clinical concerns. Pseudoprogression involves an increase in lesion size due to treatment, manifesting as enlarged contrast-enhancing areas on MRI that mimic progressive disease despite the absence of true tumor growth. These phenomena can complicate treatment decisions and impact patient care. Approximately 15% of treated patients experience pseudoprogression post-radiation, with this rate doubling to 30% when radiation is combined with chemotherapy. Accurately distinguishing pseudoprogression from true tumor progression is crucial for determining appropriate therapeutic strategies.[1,17]

Previous study has shown that TRAMs/CCA exhibit high sensitivity (96.06%) and a positive predictive value of 99.2% but lower sensitivity (66.7%) in diagnosing radiation effects among patients with metastatic brain tumors treated with Gamma Knife radiosurgery.[17] In another study focusing on TRAMs/CCA' ability to differentiate pseudoprogression and

radiation necrosis from progressive disease, the sensitivity and specificity of CCA were reported as 0.93 and 0.78, respectively.[18] Furthermore, a recent study validated TRAMs/CCA's efficacy in distinguishing recurrent glioblastoma from radiation necrosis.[19] Pseudoprogression remains a significant challenge in differentiating true tumor recurrence from post-treatment effects. Moreover, changes induced by therapies like bevacizumab can alter imaging characteristics, potentially leading to false positive TRAMs/CCA results. Future studies should explore advanced imaging techniques or biomarkers to differentiate these complex cases.

Upon further review of Patient 1 with a primary tumor of anaplastic astrocytoma Grade III, following craniotomy, a TRAMs/CCA scan conducted 2 years later suggested tumor recurrence, in which the surgical pathology revealed only necrotic and gliosis tissue. The patient was initiated on Bevacizumab therapy, and previous studies have highlighted challenges associated with interpreting traditional imaging signatures for tumor presence and treatment response in patients receiving angiogenic agents like bevacizumab.[20] In this case, further tools might need to be developed while encountering the patient with angiogenic agents, such as Bevacizumab, to facilitate a more accurate diagnostic process.

Regarding Patient 2 who had true negative results, the primary tumor was identified as lung adenocarcinoma with neuroendocrine tumor (NET). The patient underwent two TRAMs/CCA imaging sessions 4 months and 1 month prior to a repeat craniotomy, both of which indicated findings suggestive of necrosis. However, the patient still decided to pursue a biopsy to confirm the diagnosis. Only extensive necrosis was observed upon surgical pathology examination, with no viable tumor cells detected. This provided valuable insight into the validity of TRAMs/CCA's specificity, underscoring the importance of TRAMs/CCA in accurately identifying necrosis and highlighting its reliability as a non-invasive diagnostic tool.

Notably, our sensitivity and specificity analysis was not done due to the absence of biopsy results in some of the patients. Among those with negative TRAMs/CCA results, most patients did not undergo surgery, suggesting that the specificity of TRAMs/CCA could potentially be higher if these patients' biopsies had been negative, indicating no evidence of disease progression. Conversely, for patients with positive TRAMs/CCA results who did not undergo further invasive surgery, many experienced deterioration of their underlying conditions, with several patients succumbing to disease progression. In our study, patients in Group 2 were older, which may have influenced their preference for less invasive management. This finding highlights the importance of patient-centered discussions. It suggests that further studies are needed to determine which patients would benefit most from TRAMs/CCA and whether its use can improve survival outcomes. The lack of surgical confirmation in patients in Group 2 with repeated positive TRAMs/CCA results raises concerns about the potential for false positives and the impact on clinical decision-making. This highlights the need for future studies to establish clearer guidelines on when to pursue invasive diagnostic confirmation following positive TRAMs/CCA findings.

Our study has several limitations that warrant consideration despite our effort to make the study as comprehensive as possible. First, variability in imaging intervals and treatment regimens among patients may potentially influence the accuracy of TRAMs/CCA results. Additionally, the inclusion of patients receiving immunotherapy introduces a confounding factor that may affect imaging outcomes. A larger sample size and standardized follow-up protocols would enhance the robustness of future studies exploring TRAMs/CCA efficacy. There is a potential selection bias in the surgical cohort, as patients chosen for biopsy or resection were more likely to have clinical and radiological evidence suggestive of tumor progression. This may lead to overestimating the diagnostic performance of TRAMs/CCA in detecting recurrent tumors. Our study cohort included both infiltrative primary brain tumors and well-demarcated brain metastases, which may have different imaging characteristics and responses to treatment. This heterogeneity could influence the diagnostic performance of TRAMs/CCA, potentially limiting the generalizability of our findings.

The retrospective design and small sample size further limit the statistical power of our study, reducing the generalizability of the findings, particularly in diverse clinical settings involving varying tumor types and treatment modalities. Moreover, the lack of systematic comparison between TRAMs/CCA and conventional MRI techniques in all cases limits our ability to fully assess its incremental diagnostic value.

Future studies should incorporate stratified analyses based on tumor type to better understand the diagnostic accuracy of TRAMs/CCA across different tumor characteristics. Additionally, prospective studies with larger and more diverse cohorts are necessary to validate these findings, include direct comparisons with conventional radiological practices, and establish standardized follow-up protocols. Such efforts would significantly enhance the robustness, applicability, and generalizability of TRAMs/CCA as a reliable diagnostic tool in diverse clinical settings.

In conclusion, TRAMs/CCA represents a promising advancement in the imaging assessment of brain tumor treatment response. Future research should focus on refining imaging protocols, validating findings across larger patient cohorts, and integrating TRAMs/CCA into routine clinical practice to improve outcomes for patients with brain tumors.

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Ethical statement

Ethical approval

This research is conducted according to the principles expressed in the Declaration of Helsinki. It was reviewed and approved by our Institutional Review Board (IRB, Title: Retrospective Analysis of

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