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Evaluating Immunotherapy Responses in Neuro-Oncology for Glioblastoma and Brain Metastases: A Brief Review Featuring Three Cases

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Abstract

Introduction: Recent advancements in immunotherapy have offered new possibilities for treating aggressive glioblastoma (GBM) and brain metastases. However, evaluating treatment responses remains complex, prompting the development of the immunotherapy-specific Response Assessment in Neuro-Oncology (iRANO) criteria. Herein, we present case reports illustrating the intricacies of interpreting imaging changes post-immunotherapy, emphasizing the need for a comprehensive approach to assessing treatment effectiveness.

Case Reports: Case 1 discusses a 41-year-old male with GBM, highlighting the challenges of differentiating tumor progression from treatment-induced pseudoprogression. Case 2 discusses a 45-year-old female with brain metastatic malignant melanoma, presenting radiological evidence of progressive disease while undergoing nivolumab treatment. Case 3 discusses a 37-year-old male with GBM, where radiological evidence indicates progressive disease while receiving pembrolizumab treatment.

Management and Outcomes: In case 1, we discussed the challenges of distinguishing true tumor progression from treatment-induced pseudoprogression, leading to the continuation of the same treatment due to pseudoprogression. In case 2, post-surgery pathology revealed radionecrosis and treatment-related changes, guiding the continuation of nivolumab therapy. Case 3 involved a pathologically confirmed progression, and the patient received best supportive care due to his performance status.

Discussion: Despite aggressive treatment regimens, the prognosis for GBM patients remains poor, underscoring the necessity for innovative therapeutic strategies. Immunotherapy holds promise in reshaping the treatment landscape for GBM and brain metastases, but further research and refinement of assessment criteria are crucial. Throughout our cases, we discuss the iRANO criteria, developed to overcome the limitations of the RANO criteria in capturing immunotherapy responses, particularly pseudoprogression.

Keywords

glioblastoma, immunotherapy, neuro-oncology, brain metastases, pseudoprogression

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Introduction

Glioblastoma (GBM) is distinguished as the most prevalent and malignant form of glial tumor (WHO grade IV astrocytoma), with an incidence rate of approximately 3 per 100,000 individuals each year.[1] GBM is notorious for its aggressive behavior, including rapid proliferation, extensive invasion into adjacent brain tissue, molecular variability, resistance to conventional treatments, and challenges in achieving effective chemotherapeutic agent delivery to the central nervous system (CNS).[2] Despite employing aggressive therapeutic strategies such as surgical resection followed by chemotherapy and radiotherapy, the prognosis for GBM patients remains dire, with median survival times barely exceeding 15 months post-diagnosis and a 5-year survival rate falling below 10%.[3,4]

The potential of immunotherapy is promising, yet achieving enduring anti-tumor responses within the CNS presents significant challenges. Challenges such as the blood-brain barrier, which limits the penetration of therapeutic agents, and the immunosuppressive tumor microenvironment complicate the efficacy of immunotherapy in GBM. Vigilant monitoring is essential for patients with GBM receiving immunotherapy. The RANO criteria, while widely endorsed in neuro-oncology for both clinical and research applications, may not adequately capture the nuanced therapeutic responses to immunotherapy, particularly due to the distinct phenomenon of pseudoprogression.[5,6] Pseudoprogression refers to the transient worsening of radiological features on MRI after treatment of glioblastoma, especially after combined radiotherapy with alkylating agents, and is usually not associated with clinical deterioration. The concept of pseudoprogression has been updated with the use of immunotherapies in the treatment of glioblastoma and various solid tumors. Pseudoprogression is usually caused by inflammation; there is no neovascularization, and perfusion is relatively low. This underscores the critical need for specialized imaging response criteria tailored to immunotherapy in GBM scenarios.

In response to these considerations, the immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria were formulated specifically for GBM patients under immunotherapy.[6] The differences between the RANO and iRANO criteria are shown in Table 1. These criteria aim to provide a framework for interpreting early-stage imaging alterations indicative of progression. The iRANO criteria have significantly influenced clinical decision-making, enabling clinicians to avoid prematurely discontinuing effective treatments in cases where pseudoprogression is suspected. Notably, the iRANO criteria outline a pivotal six-month window post-immunotherapy for evaluating pseudoprogression, advising the continuation of immunotherapy in patients who exhibit no significant clinical symptoms and show early imaging signs of progression within this timeframe, until subsequent imaging definitively confirms tumor advancement. Emerging advanced imaging techniques, such as PET-MRI and MR spectroscopy, alongside potential biomarkers like circulating tumor DNA, hold promise in further refining treatment response evaluations.

Case Reports

Case 1

A 41-year-old male underwent surgery after an intracranial mass was discovered on MRI scans, following his first-ever seizure. The diagnosis revealed glioblastoma, specifically IDH wild type, grade IV (according to WHO 2021 classification). Pathological examination indicated the absence of microsatellite instability, and the PDL1 level was negative. After concurrent chemoradiotherapy with temozolamide, the patient began adjuvant temozolamide treatment.

Due to the progression detected in the MRI scan following the second cycle of temozolamide treatment, a re-surgery was performed (Figure 1(A)), and the patient was initiated on pembrolizumab treatment. A cranial MRI performed during the third month of the patient's pembrolizumab treatment showed increased parenchymal edema around the resection cavity, dural scarring and thickening at the level of the resection cavity, and new irregular contrast enhancement at the level at the cavity (hypoperfusion could not be assessed as a definite sign of recurrence) (Figure 1(B)). Treatment continuation was decided as there was no clinical deterioration, aligning with the iRANO criteria for evaluating immunotherapy response after six months. The MRI scan taken six months after pembrolizumab initiation (Figure 1(C)) showed regression of the millimetric restricted diffusion foci, ruling out true progression. The same treatment was continued. After completing 10 cycles of treatment, a period of treatment-free monitoring commenced (Figure 1(D) and ((E))).

The patient remained under observation without any treatment until progressive disease was detected during follow-up MRI. Based on the patient's previous positive response to immunotherapy, pembrolizumab treatment was resumed. However, after four additional cycles, progressive disease was confirmed.

Case 2

A 45-year-old female underwent surgery to excise a nevus located beneath the right scapular region of her skin. Subsequent pathological examination confirmed atypical melanocytic proliferation. Later, a biopsy of the right axillary lymph node confirmed melanoma metastasis, leading to the initiation of radiotherapy following surgical excision. Since the patient tested positive for the BRAF V600 E mutation, she commenced treatment with dabrafenib and trametinib, which continued for one year.

Subsequently, the patient experienced headaches, prompting a cranial MRI scan that revealed brain metastatic disease. Following cranial surgery (Figure 2(A)), further radiotherapy was administered. The patient underwent four cycles of ipilimumab-nivolumab and continued with nivolumab maintenance treatment (Figure 2(B))

Table 1. Differences Between RANO and iRANO Criteria.

	RANO Criteria	iRANO Criteria
Progressive disease	≥25% ↑ in the sum of enhancing disease New lesions *OR* Significant worsened MRI features Significant clinical symptoms	>6 months on the current immunotherapeutic regimen: Same as RANO criteria for progressive disease. ≤6 months on the current immunotherapeutic regimen: Requires a second scan confirming further progressive disease 3 months after the initial scan indicating progressive disease
Pseudoprogression	The appearance of a new lesion or an increase in contrast-enhancing areas, which gradually fade or stabilize without any changes to the treatment regimen	The time window for pseudoprogression following immunotherapy is 6 months. Patients who exhibit no significant clinical symptoms and show evidence of early imaging progression within this 6-month period should continue immunotherapy until follow-up imaging confirms tumor progression

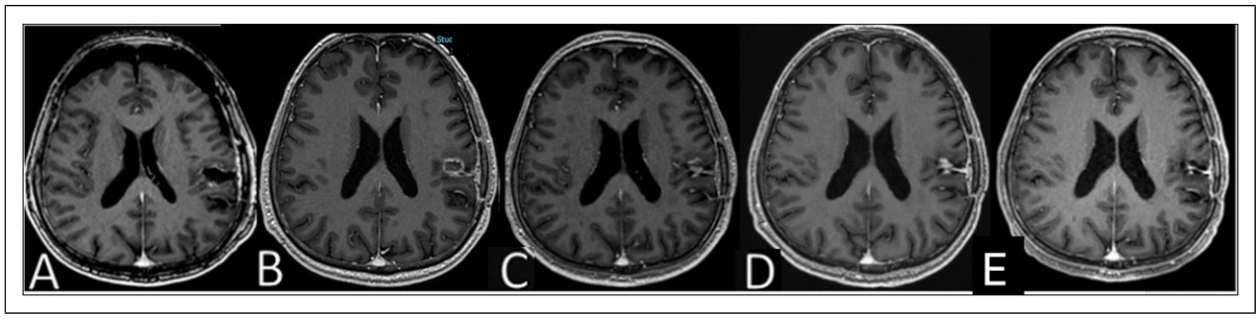

Figure 1. (a) The early postoperative axial post-contrast T1-weighted image showed a peripherally reactive enhancing resection cavity without tumor. (b) At the 3-month follow-up after starting immunotherapy, the T1-weighted image showed increased parenchymal edema around the resection cavity, new irregular contrast enhancement at the cavity level, there is no evidence of increased perfusion on the cerebral blood volume (CBV) map, indicating pseudoprogression. (Hypoperfusion could not be evaluated as a definite sign of recurrence). (c) At the 6-month follow-up, enhancement was visible within the cavity without peripheral edema. After 6 weeks, there is no difference in the findings except for the regression of the millimetric restricted diffusion foci observed in the immediate anterior-superior neighbourhood of the resection cavity. (d) At the 9-month follow-up, the enhancing part within the cavity was slightly highlighted. (e) At 24 months, there was significant regression of abnormal contrast enhancement within the central portion of the surgical bed.

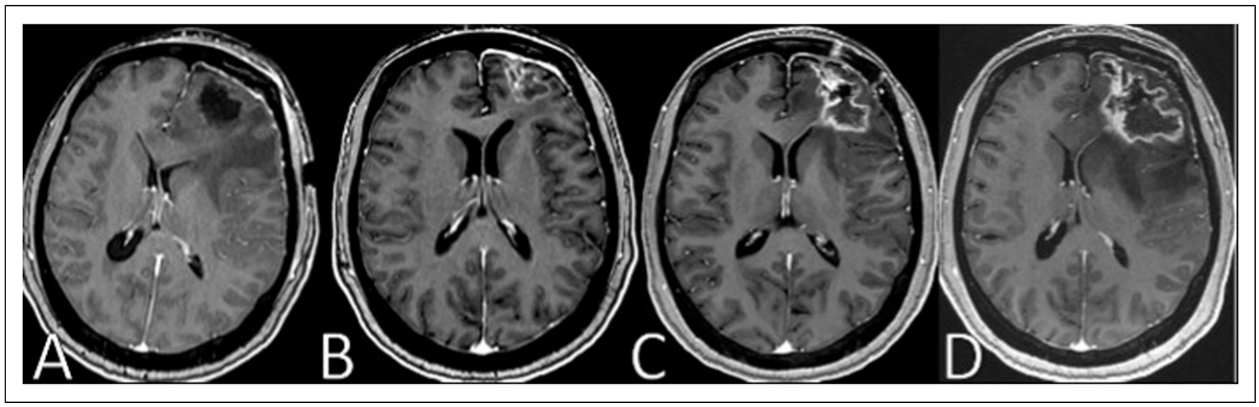

Figure 2. (a) After the first cranial surgery, the post-contrast axial T1-weighted image showed the resection cavity without tumor. (b) At the 9-month follow-up after starting immunotherapy, a prominent peripheral enhancement was observed in the resection cavity with mild peripheral oedema. (c) At the 18-month follow-up, a markedly enhancing mass-like lesion was seen in the resection cavity with peripheral edema. There is no evidence of perfusion. (d) There was a markedly increased enhancing mass-like lesion within the surgical bed with prominent peripheral edema.

Later, the patient's clinical condition worsened and was discussed at the neuro-oncology board. When re-evaluated using the iRANO criteria, progression was favored over pseudoprogression based on clinical findings and imaging (Figure 2(C) and ((D))). Increasing seizure activity also influenced the decision to proceed with further intervention. Pathological findings after surgical resection confirmed radionecrosis and treatment-related changes, leading to the continuation of nivolumab therapy.

Case 3

A 37-year-old male patient underwent surgery for subtotal mass resection within the intracranial region. Subsequently, adjuvant temozolomide treatment was initiated following concurrent chemoradiotherapy with temozolomide, as the pathology confirmed the presence of IDH wild-type glioblastoma, grade IV (according to WHO 2021 classification). However, after completing three cycles of temozolomide treatment, it had to be discontinued due to a severe allergic reaction and elevated liver function test results. Temozolomide treatment was resumed using a metronomic approach, and the patient received seven cycles of treatment. Cranial MRI revealed that in the left temporooccipital region, a residual mass with contrast enhancement in its wall had increased in size during the interim period. The shift in the midline structures had also increased significantly. Clinically, there was a noticeable increase in headache complaints, prompting the initiation of dexamethasone treatment.

The patient underwent a second cranial surgical procedure due to progressive disease (Figure 3(A)), and pembrolizumab treatment was initiated. During the 6-month follow-up after starting immunotherapy, postoperative MRI showed an increase in the size of the expansile enhancing lesion in the left temporal region (Figure 3(B)). However, there was regression in areas of increased perfusion adjacent to the left lateral ventricular wall compared to the previous examination, along with a stable peripheral FLAIR signal. When interpreted alongside a slight increase in the size of the lateral peripheral enhancing nodular focus, the stability of the FLAIR signal, and the decrease in areas of high perfusion adjacent to the ventricle, these findings suggested possible treatment-related fibrotic changes in the patient under immunotherapy. Close follow-up of this area was recommended. The patient was able to continue immunotherapy treatment until this point because he could afford the cost of the medication. Subsequently, he was monitored with intermittent dexamethasone treatment and stable clinical findings.

After six months of follow-up, the patient underwent surgery due to increased intracranial pressure (Figure 3(C)). The pathology confirmed the presence of IDH wild-type glioblastoma. Due to an extended hospitalization period caused by a wound infection, the patient is currently receiving best supportive care considering his performance status.

Discussion

The advent of immunotherapy has revolutionized the treatment landscape for various solid tumors primarily through the employment of immune-checkpoint inhibitors (ICIs) targeting

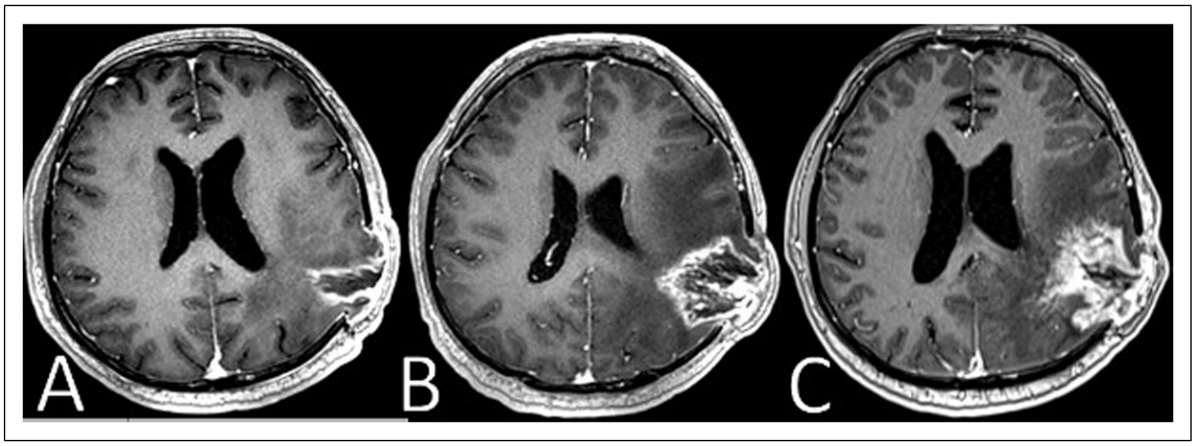

Figure 3. (a) Immediately after the second cranial surgery, the post-contrast axial T1-weighted image showed a peripherally reactive enhancing resection cavity. (b) At the 6-month follow-up after the start of immunotherapy, compared with the postoperative MRI, there is an increase in the size of the expansile enhancing lesion in the left temporal follow-up, regression in the interval process in the areas of increased perfusion adjacent to the left lateral ventricular wall compared with the previous examination, and a stable peripheral FLAIR signal. Taken together with the slight increase in size of the lateral peripheral enhancing nodular focus, the stability of the FLAIR signal, and the decrease in areas of high perfusion adjacent to the ventricle at the previous examination, this may be due to possible treatment-related fibrotic changes in the patient undergoing immunotherapy treatment, and close follow-up of this area will be useful. (c) In the left posterior temporal lobe, contrast enhancement increased and the lesion grew in the interim period, and there was growth of the mass component extending under the scalp on the left. The findings were evaluated in favor of tumor progression.

CTLA-4 and PD-1 pathways. These therapies have significantly improved overall survival rates in several cancers.[7] Nevertheless, utilizing immunotherapy for GBM poses distinct challenges due to the diversity of immunotherapeutic methods, choice of molecular targets, and combination therapy approaches, leading to uncertainties regarding their effectiveness and safety in this setting.[8,9] The complexity of treating GBM stems largely from the small subset of therapy-resistant glioblastoma stem cells and the intricate network of inter- and intra-tumor heterogeneity, encompassing different GBM subtypes and stromal cells within the tumor microenvironment.[10]

Clinical trials evaluating immunotherapy in recurrent GBM patients have yielded mixed results. A phase I study for recurrent GBM comparing nivolumab monotherapy to combination with ipilimumab showed superior median overall survival with nivolumab alone.[11] Phase III of this trial in recurrent GBM patients, comparing nivolumab to bevacizumab, revealed comparable overall survival and side effects, but a shorter radiologic duration of response in bevacizumab-treated patients.[12] Ongoing phase III trials aim to further evaluate nivolumab's potential in GBM treatment, particularly in MGMT-unmethylated tumors, comparing it to standard of care or TMZ in combination with radiation therapy.[13,14] Although these findings highlight the potential of ICIs like nivolumab, the limited efficacy underscores the need for additional strategies to enhance their effectiveness. For instance, combination regimens that incorporate ICIs with tumor-targeted agents or radiotherapy might help overcome resistance in GBM. Pembrolizumab monotherapy in phase I recurrent GBM trial demonstrated durable antitumor activity in a subset of patients with manageable toxicity.[15] Future studies evaluating pembrolizumab combination regimens may improve outcomes in patients with recurrent GBM. Clinical trials are underway to evaluate the efficacy of ICIs targeting CTLA-4, LAG-3, and TIM-3 in recurrent GBM patients.

Understanding the immunosuppressive mechanisms of GBM is crucial for the development of effective immunotherapy. GBM exerts negative effects on both local and systemic immune responses, potentially through the activation of signaling pathways that induce immunosuppression.[16,17] Factors such as the overexpression of STAT3 signaling and the secretion of IL-10 and TGFβ contribute to the creation of an immunosuppressive microenvironment within the tumor.[17-19] Additionally, GBM patients often exhibit reduced T cell expression, resulting in decreased responsiveness to immune checkpoint blockade therapies.[20,21] The tumor microenvironment also contains abundant myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells that reinforce immune suppression. GBM's ability to suppress the immune response, both locally and systemically, warrants a deeper investigation into its underlying mechanisms. Successful immunotherapy for GBM must overcome the obstacles posed by tumor-induced immunosuppression.

Assessing treatment response in primary and metastatic brain tumors post-immunotherapy presents challenges. Differentiating true progression from pseudoprogression is essential, necessitating the development of specific criteria like iRANO. These criteria provide guidelines for interpreting imaging findings post-immunotherapy, aiding in treatment decision-making and patient management. Our cases demonstrated the complexities associated with evaluating treatment responses in both primary brain tumors and metastatic brain tumors following immunotherapy. They emphasize the critical need to differentiate between true progression and pseudoprogression, a challenge addressed by the iRANO criteria, which provide guidelines for ongoing treatment and follow-up in cases of unconfirmed progression. In the first case, gliosis-like changes were observed after receiving immunotherapy and were subsequently monitored without any indication of disease recurrence. Close adherence to the iRANO criteria facilitated continued treatment without premature discontinuation. MRI findings in this case provided clearer insights for decision-making. In the second case, the patient developed cranial metastatic disease following a melanoma diagnosis. The iRANO criteria guided the differentiation between suspected progression and treatment-related changes in this metastatic melanoma patient, ultimately informing a surgical decision. Although MRI findings and clinical progression were consistent with the diagnosis, post-surgery pathology revealed changes related to treatment. In the final case, clinical and MRI findings indicated progression, with progressive MRI findings consistent with iRANO recommendations supporting the decision for reoperation. Subsequent surgical pathology confirmed the presence of GBM. The iRANO criteria, while consistent with the RANO criteria for stable disease, partial response, and complete response, introduce nuanced criteria for progressive disease, particularly within the initial 6-month period post-immunotherapy. The iRANO criteria ensures that therapeutic decisions are not solely based on early radiologic findings but are instead informed by a combination of imaging, clinical, and pathological data.

Advanced imaging techniques are pivotal in distinguishing true progression from pseudoprogression in GBM patients undergoing immunotherapy. Diffusion-weighted imaging and advanced diffusion models, such as intravoxel incoherent motion (IVIM) MRI and restriction spectrum imaging (RSI) MRI, assess cellular density and microvascular perfusion, providing insights into tumor physiology.[22-24] IVIM MRI differentiates diffusion from perfusion-related changes, aiding in distinguishing treatment-related effects from tumor progression. RSI MRI enhances specificity in identifying tumor boundaries by quantifying restricted water diffusion. Amide proton transfer (APT) imaging, a molecular imaging technique, detects mobile amide protons within proteins and peptides, showing promise in identifying treatment-related changes in gliomas by capturing metabolic alterations. Magnetic resonance spectroscopy (MRS) evaluates metabolic

profiles, such as elevated choline-to-creatine ratios and decreased N-acetylaspartate, helping distinguish active tumor from necrosis.[22,25,26] Positron emission tomography-computed tomography (PET-CT) and PET-MRI enhance diagnostic accuracy by combining functional and anatomical imaging.[22,27-29] PET tracers like [18F]FDG, [18F]FET, and [18F]FLT are studied for their ability to assess metabolic activity, amino acid transport, and proliferation, respectively. PET-MRI allows simultaneous acquisition of PET and high-resolution MRI data, enabling comprehensive evaluation of tumor metabolism, structure, and treatment response.

Emerging biomarkers complement these imaging modalities. Biomarkers like circulating cell-free DNA, chromosomal instability quantification of cfDNA, interleukin-8 levels, p53, small extracellular vesicles, O6-methylguanine-DNA methyltransferase, interferon regulatory factor 9, X-ray repair cross-complementing gene 1, isocitrate dehydrogenase 1, Ki67 expression and CDH2 protein alone or in combination with ELAVL1 protein can be used to differentiate pseudoprogression from true progression.[30-37]

The integration of advanced imaging techniques and biomarker research into glioblastoma management holds significant promise but requires further exploration. Combination therapies, particularly those integrating ICIs with advanced molecular targets, such as angiogenesis inhibitors or tumor vaccine therapies, may help overcome resistance mechanisms in GBM.[38] Radiotherapy combined with ICIs has shown synergistic effects in preclinical studies, potentially enhancing tumor immunogenicity and disrupting the immunosuppressive microenvironment.[38,39] Prospective studies should evaluate the utility of novel imaging techniques like RSI MRI, PET-MRI, and APT imaging, in conjunction with biomarker panels, to improve the differentiation of pseudoprogression from true progression.[22] Longitudinal studies employing serial imaging and biomarker monitoring could provide deeper insights into the dynamics of tumor evolution and treatment responses. Understanding the mechanisms of immune escape within the GBM microenvironment remains critical. Preclinical studies focusing on myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells could uncover novel targets for immune modulation. Exploring the role of exosomal cargo, such as microRNAs and proteins secreted by GBM cells, could yield innovative therapeutic targets and diagnostic tools.[38]

Multidisciplinary collaboration among neuro-oncologists, radiologists, immunologists, and computational scientists is essential for optimizing imaging protocols, validating biomarkers, and establishing standardized treatment pathways. Future research should also focus on the development of artificial intelligence-driven imaging analyses and biomarker interpretation to streamline diagnostics and therapeutic decision-making in GBM. This comprehensive methodology has the potential to improve immunotherapeutic strategies and improve the prognosis for patients with GBM.

Conclusion

GBM remains a challenging malignancy with limited treatment options and poor prognosis despite aggressive therapeutic approaches. Immunotherapy holds promise as a potential treatment avenue for GBM; however, its application comes with unique complexities and challenges, including the need for vigilant monitoring and specialized assessment criteria like the iRANO criteria. Our case studies highlight the intricacies of evaluating treatment responses post-immunotherapy, emphasizing the importance of distinguishing between true progression and pseudoprogression. While making this distinction, it is also very important to monitor changes in the patient's clinical findings. A clinical and radiological correlation, combined with a multidisciplinary approach to the patient, ensures the most accurate decision-making. Moving forward, further research and clinical trials are necessary to optimize immunotherapeutic approaches and improve outcomes for GBM patients.

Author Contributions

Conception and design of the work: NK, GY. Data collection: NK, GK. Data analysis and interpretation: NK, SA, GC. Drafting the article: GK, AII, Critical revision of the article: NK, GK, GY. Other (study supervision, fundings, materials, etc): AII. All authors reviewed the results and approved the final version of the manuscript.

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