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A Radiologist's Guide to IDH-Wildtype Glioblastoma for Efficient Communication With Clinicians: Part II–Essential Information on Post-Treatment Imaging

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Owing to recent advancements in various postoperative treatment modalities, such as radiation, chemotherapy, antiangiogenic treatment, and immunotherapy, the radiological and clinical assessment of patients with isocitrate dehydrogenase-wildtype glioblastoma using post-treatment imaging has become increasingly challenging. This review highlights the challenges in differentiating treatment-related changes such as pseudoprogression, radiation necrosis, and pseudoresponse from true tumor progression and aims to serve as a guideline for efficient communication with clinicians for optimal management of patients with post-treatment imaging.

Keywords: Glioblastoma; Magnetic resonance imaging; Pseudoprogression; Pseudoresponse; Radiation necrosis

INTRODUCTION

Isocitrate dehydrogenase (IDH)-wildtype glioblastoma, central nervous system (CNS) World Health Organization (WHO) grade 4, is a highly aggressive tumor with a median overall survival (OS) of less than 18 months despite standard treatment [1]. Notwithstanding advances in various treatment options, tumor recurrence or progression is inevitable in IDH-wildtype glioblastomas, given their aggressive biological behavior.

In clinical trials, a standardized determination of response assessment is essential for the identification of more effective therapies. Apart from clinical trials, in routine clinical practice, accurate interpretation of post-treatment imaging is crucial for assessing treatment response, changing treatment regimens in cases of tumor progression or recurrence, and predicting the prognosis in patients with IDH-wildtype glioblastoma. However, differentiating true tumor progression or recurrence and treatment response from treatment-related changes such as pseudoprogression (PsP), radiation necrosis, or pseudoresponse (PsR) presents a significant challenge. Clinical symptoms may not provide sufficient information to differentiate these conditions, as the mass effect from treatment-related changes can also cause worsening of neurological symptoms, similar to tumor

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progression or recurrence.

The prior Part I Review summarized the histopathological concept of IDH-wildtype glioblastoma, and the information radiologists can provide for preoperative and immediate postoperative imaging. This subsequent Part II Review focuses on the information that radiologists can provide to clinicians based on post-treatment imaging findings. We present an overview of the clinical pathway of patients with IDH-wildtype glioblastoma, followed by a brief guide to the updated version of the Response Assessment in Neuro-Oncology (RANO) criteria (RANO 2.0) for clinical trials. Finally, we summarize the clinical and imaging findings of treatment-related changes, as well as true tumor progression or recurrence. As immunotherapy has been more frequently applied recently, we have provided a separate section on PsP in patients undergoing immunotherapy.

Overview of Treatment Pathway for IDH-Wildtype Glioblastoma

The standard of care for newly diagnosed patients includes maximal safe resection followed by concomitant radiotherapy and chemotherapy with temozolomide plus 6–12 cycles of adjuvant temozolomide for those aged <70 years who are in good general and neurological condition [2]. Patients with unfavorable prognostic factors may undergo hypofractionated radiation therapy (RT) or chemotherapy alone according to their O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status [2,3].

At recurrence, the standard of care is not well defined [4]. Treatment is selected based on prior treatment, age, Karnofsky Performance Status, *MGMT* promoter methylation status, and patterns of disease progression [2]. A recent multicenter study showed that re-resection may lead to improved survival outcomes when maximal safe resection with minimal residual contrast-enhancing tumor is achieved [5]. The efficacy of re-irradiation remains debatable [6], whereas temozolomide rechallenge and lomustine are other options for alkylating chemotherapy. Bevacizumab, an antiangiogenic regimen, may prolong progression-free survival (PFS) but not OS in patients with recurrent tumors [7] and has been the standard salvage therapeutic option for patients with recurrent tumors in the U.S. since its approval in 2009 by the FDA. In Europe, lomustine is the most commonly used second-line chemotherapy based on clinical trials showing a similar OS between patients with recurrence receiving lomustine plus bevacizumab and those receiving lomustine alone [8]. Lomustine has never been shown to prolong post-progression survival, and other options, including regorafenib, are used depending on the individual center's preference [9]. Immunotherapy is a rapidly emerging treatment modality that includes various modalities such as vaccination therapy, oncolytic viral therapy, and immune checkpoint inhibitors such as anti-PD-1 antibody (nivolumab or pembrolizumab), anti-CTLA-4 antibody (ipilimumab), and chimeric antigen receptor (CAR) T cell therapy [10,11]. The

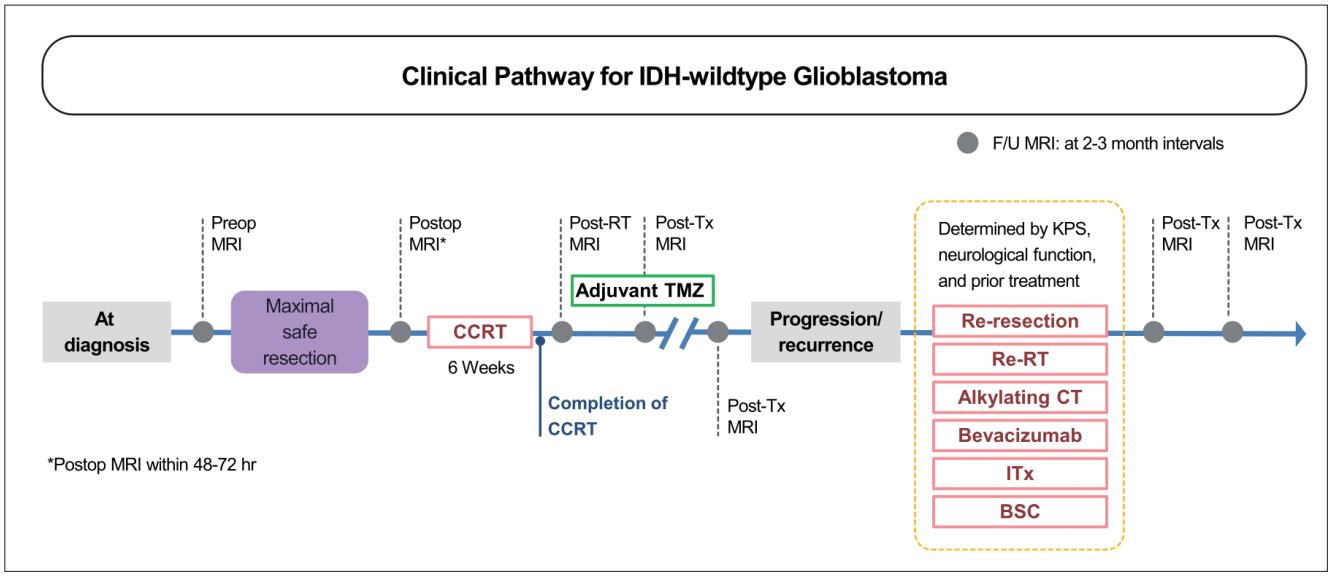

Fig. 1. The clinical pathway of IDH-wildtype glioblastoma. IDH = isocitrate dehydrogenase, F/U = follow-up, CCRT = concurrent chemoradiotherapy, Tx = treatment, TMZ = temozolomide, KPS = Karnofsky Performance Status, RT = radiation therapy, CT = chemotherapy, ITx = immunotherapy, BSC = best supportive care

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effect of immunotherapy on recurrence is currently being actively investigated, although its survival benefit has not yet been demonstrated [10]. An overview of the clinical pathway for newly diagnosed and recurrent IDH-wildtype glioblastoma, combined with the timeline and imaging period, is summarized in Figure 1.

Before Starting: Always Keep the "Big Picture" in Mind

Radiologists' key role in imaging IDH-wildtype glioblastoma in the post-treatment setting is to correctly diagnose tumor progression or recurrence from treatment-related changes, such as PsP, radiation necrosis, or PsR. Contrary to the preconceptions frequently observed by radiology trainees, the most important aspect of this process is "not" focusing solely on the current imaging findings; it also considers the underlying clinical context. In other words, radiologists should acknowledge the clinical background to provide reliable imaging interpretations, such as the incidence, time window, and risk factors of each treatment-related change. Radiologists should also realize the importance of reviewing preoperative, immediate postoperative, and serial follow-up images; checking the surgical note and RT chart; and checking the period of each treatment to provide an accurate diagnosis of the "current" post-treatment imaging. Active communication with clinicians is also crucial in difficult cases to draw a reasonable conclusion about current imaging for patient care; we advise active discussions with neurosurgeons, neurologists, radiation oncologists, and pathologists.

The Blood-Brain Barrier in IDH-Wildtype Glioblastomas

In general, brain tissue is protected by the blood-brain barrier (BBB), which prevents contrast agent molecules from passing through [12]. Contrast enhancement on MRI is a non-specific imaging finding that reflects the passage of gadolinium-based contrast agents across a disrupted BBB. While neoangiogenesis, one of the pathological hallmark of IDH-wildtype glioblastoma, is the most important cause of contrast enhancement in IDH-wildtype glioblastomas, any other cause of vascular leakage can also cause contrast enhancement. Cytotoxic therapies or immunotherapies may not only damage tumor vessels and normal brain tissue but also induce an inflammatory response in microglia, which induces pronounced BBB disruption. Therefore, a contrast-enhancing mass on post-treatment imaging may not only include tumor recurrence, but also PsP and radiation necrosis, which are notoriously difficult to differentiate from tumor recurrence on conventional imaging. In contrast, antiangiogenic therapy reduces the tumor vessel vasculature and leads to restoration of the BBB [13]. Therefore, contrast enhancement declines even in the presence of non-enhancing tumor growth, leading to PsR on MRI [13].

Recommended Imaging Protocol

The recommended MRI protocols for adult gliomas in clinical trials include 3D pre- and post-contrast T1-weighted imaging (T1), 2D post-contrast T2-weighted (T2) and pre-contrast fluid-attenuation inversion recovery (FLAIR) imaging, and 2D diffusion-weighted imaging [14]. Perfusion imaging, such as dynamic susceptibility contrast imaging or arterial spin labeling, provides more detailed information on the underlying tumor physiology and should be routinely used for baseline imaging and follow-up in the clinical setting. MRI also provides more information on tumor metabolism and has been applied in some institutions in confounding cases. However, advanced physiological imaging methods are not included in the imaging protocols of clinical trials because of a lack of standardization and require further validation. Post-contrast FLAIR is not routinely recommended for gliomas; however, this sequence, in addition to pre-contrast FLAIR, may be useful in the detection of leptomeningeal metastases (LM) at recurrence [15]. The inherent pitfalls and limitations of each advanced imaging technique have been summarized elsewhere [16,17] and will not be discussed in detail in this review because this is the basic knowledge required for radiologists.

In terms of PET imaging, amino acid PET is mostly approved to differentiate treatment-related changes from tumor recurrence in Europe, whereas no approval has been received in the U.S. [18].

RANO 2.0 for Clinical Trials in IDH-Wildtype Glioblastomas

In 2010, RANO was developed to improve the reliability and comparability of response assessments of gliomas in clinical trials with previously released RANO statements, such as high-grade gliomas (RANO-HGG) [19] and low-grade gliomas (RANO-LGG) [20]. Over time, concerns regarding the

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challenges of differentiating PsP secondary to radiotherapy and immunotherapies from true tumor progression have led to the introduction of the Modified RANO criteria (mRANO) [21] and Immunotherapy RANO criteria (iRANO) [22].

Based on studies comparing RANO-HGG, mRANO, and iRANO [23], RANO 2.0, which provides a single unified set of response criteria for all gliomas in clinical trials [24], was recently developed. There are several distinct aspects of RANO 2.0. A single unified set of response criteria, rather than separate RANO-HGG and RANO-LGG criteria, is applied according to RANO 2.0 in all gliomas. The first post-radiotherapy (post-RT) MRI (21–35 days after RT completion), rather than the postsurgical MRI, should be used as the baseline imaging in newly diagnosed patients, whereas a pre-treatment (pre-Tx) scan (≤14 days before the start of treatment) should be used as the baseline in recurrent patients. Repeat MRI is mandatory to confirm progression within 12 weeks after radiotherapy completion to distinguish PsP from tumor progression because the incidence of PsP is high during this period. Confident diagnosis of tumor progression within 12 weeks after radiotherapy without follow-up imaging is only possible if the progression is clearly outside the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathological confirmation [24].

For IDH-wildtype glioblastomas with contrast enhancement, the non-enhancing tumor will no longer be evaluated, except when assessing the response to antiangiogenic agents. Given the limited value of evaluating non-enhancing progression in contrast-enhancing IDH-wildtype glioblastomas, the RANO group recommends removing it from the criteria for determining progression in most trials [24]. In uncommon IDH-wildtype glioblastomas without contrast enhancement, which comprise approximately 7% of IDH-wildtype glioblastomas [25], T2/FLAIR should be performed. In clinical trials, in testing agents that significantly reduce BBB permeability (i.e. antiangiogenic agents) contrast enhancement may not accurately reflect the actual tumor burden. Diameters/segmentation, as proposed for evaluating mixed contrast-enhancing and non-enhancing tumors, or a qualitative assessment can be adopted. Details of the changes in RANO 2.0 are presented elsewhere [24,26,27].

Although RANO 2.0 is useful for response assessment in clinical trials, the biggest limitation of its application in routine clinical practice is that it does not reflect advanced imaging such as diffusion, perfusion, or amino acid PET owing to validation issues [24]. Therefore, in routine practice, we advise readers to rely more on the clinical context and advanced imaging findings than sole reliance on RANO 2.0, for an accurate diagnosis in each patient.

Post-Treatment Imaging Findings

An overview of post-treatment imaging findings, such as PsP after RT, radiation necrosis, PsR, and PsP after immunotherapy, combined with the timeline and imaging period, is presented along with a checklist for interpretation in Figure 2.

Pseudoprogression After Radiotherapy

This section focuses on PsP after radiotherapy. PsP during immunotherapy will be discussed separately because of the different clinical and imaging characteristics from PsP after radiotherapy [22]. PsP after radiotherapy is defined as an enlarged or new contrast enhancement within the radiation field mimicking tumor progression that resolves spontaneously without modifying the treatment on follow-up imaging [28]. An accurate diagnosis of PsP is important because effective treatment might be erroneously terminated if PsP is misdiagnosed as tumor progression, with a potentially negative impact on survival, whereas the efficacy of subsequent therapy may be overestimated. Data on whether there is a true survival advantage for patients with PsP are controversial [29,30]. Reliable discrimination between PsP and early tumor progression can be achieved through follow-up imaging or histopathological confirmation; however, histopathological confirmation is rarely performed in cases where PsP is strongly suspected owing to its invasive approach, and a uniform pathological diagnosis of PsP is lacking [31,32]. Therefore, radiologists play a critical role in the diagnosis of PsP, as the diagnosis is primarily made by radiologic assessment with a short-term period of imaging follow-up, and rarely by histopathological confirmation.

Clinical Presentation

PsP occurs in 30%–40% of patients with IDH-wildtype glioblastoma within 12–24 weeks of completing radiotherapy [33,34]. Although the RANO 2.0 criteria restrict the time period of PsP to within 12 weeks of completing radiotherapy [24], PsP may also be seen within 24 weeks of completing radiotherapy with a lower incidence than within 12 weeks [28].

In terms of clinical findings, the literature shows discordant

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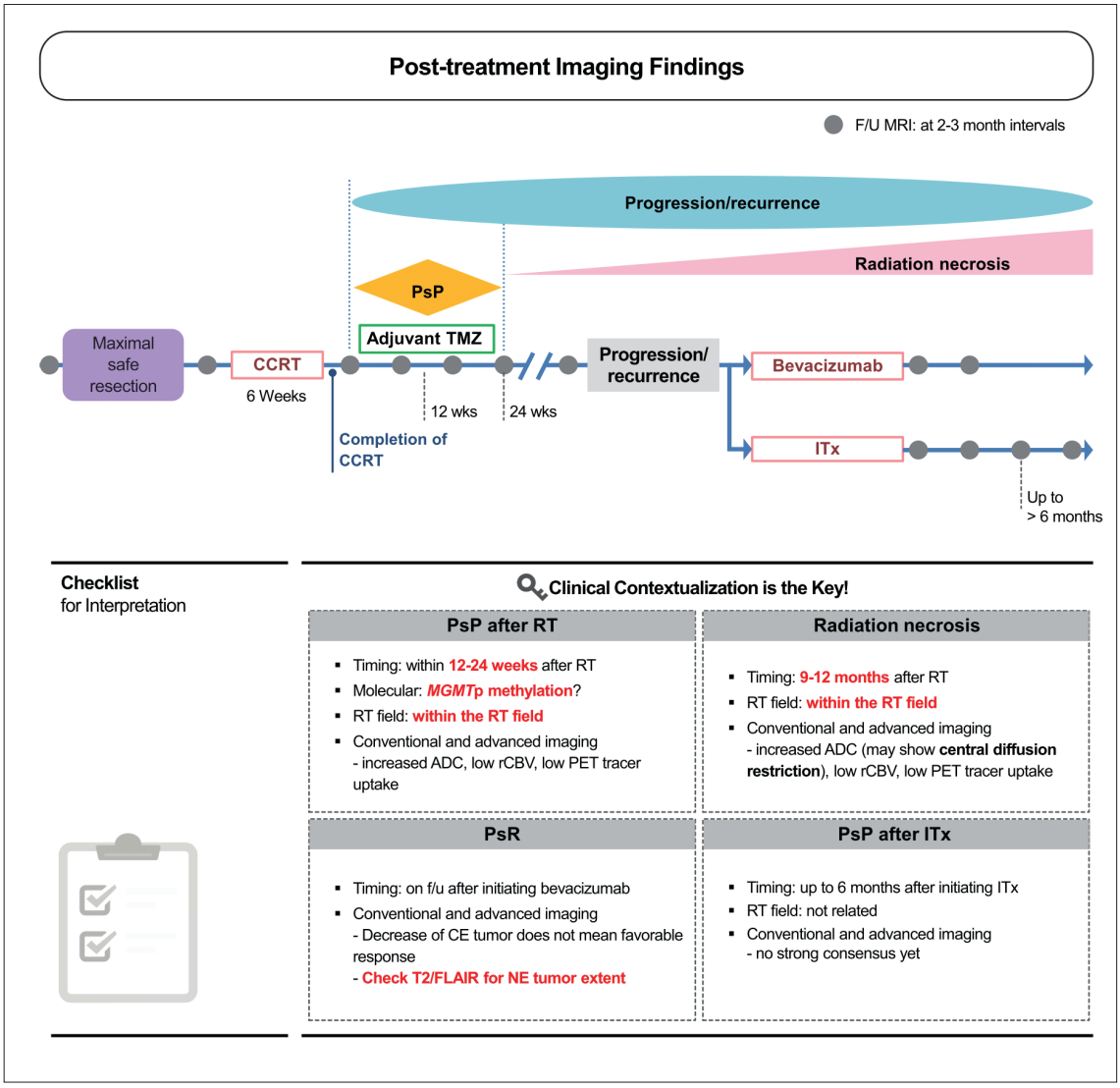

Fig. 2. Overview of post-treatment imaging findings combined with the timeline and imaging period with a checklist for interpretation.
F/U = follow-up, CCRT = concurrent chemoradiotherapy, PsP = pseudoprogression, TMZ = temozolomide, ITx = immunotherapy, RT = radiation therapy, *MGMT*p = O^6-methylguanine-DNA methyltransferse promoter, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, PsR = pseudoresponse, CE = contast-enhancing, NE = nonenhancing

results on whether neurological status is associated with PsP, whereas others suggest less neurological deterioration in PsP than in tumor progression [35,36], and some studies suggest no significant difference in neurological status between PsP and tumor progression [37,38]. PsP eventually resolves spontaneously without further treatment.

Risk Factors

MGMT promoter methylation is a well-known predictive biomarker of temozolomide treatment as well as a strong prognostic biomarker in patients with IDH-wildtype glioblastoma and is observed in approximately 40% of patients [39]. *MGMT* promoter methylation is also acknowledged as a strong risk factor for PsP, with a higher likelihood of developing PsP than in patients without *MGMT* promoter methylation, although previous studies have shown variable results in terms of the incidence of PsP in *MGMT* promoter-methylated versus unmethylated tumors [33,35,36,38,40]. Nonetheless, it should be noted that patients with *MGMT* promoter methylation are more likely to develop PsP (at least twice as much as patients without *MGMT* promoter methylation), and a vast majority of early imaging changes in patients with *MGMT* promoter methylation represent PsP rather than tumor progression [41].

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Pathophysiology and Histopathology

The mechanism of PsP remains poorly understood; however, it is thought to represent edema and increased vascular permeability secondary to radiotherapy-induced tumor and endothelial cell death [42]. Transient interruption of myelin synthesis secondary to radiation injury in oligodendrocytes, leading to inflammation and increased permeability, is a possible mechanism [42]. Temozolomide, an alkylating agent, damages DNA not only in tumor cells but also in the surrounding normal tissue, amplifying the inflammatory response and contributing to PsP [43].

It should be noted that no specific histopathological classification criteria currently exist for the diagnosis of PsP or radiation necrosis; the final diagnosis depends largely on each pathologist's personal judgment and may show high interobserver variability [30,32]. Acquiring an adequate specimen is critical for effective histological analysis, which is unfortunately not always possible during reoperation [44]. Moreover, tissues may frequently contain a mixture of PsP and residual or recurrent tumors in varying proportions. Although routine pathological distinction between residual and recurrent tumors is recommended, it is not always feasible [44]. Several more problems lie in the reproducible differentiation between PsP and tumor recurrence. There is no cutoff threshold for the overall percentage of recurrent tumor tissue to diagnose tumor recurrence in a mixture of PsP and tumor recurrence, and whether this tumor tissue should include only "bona fide viable tumor" or should also include "nonviable tumor" has not been established [44].

In other words, in post-treatment diagnosis of PsP, radiologists cannot simply pass on the burden of accurate diagnosis to the pathology department, and radiological impressions should be actively communicated with clinicians and pathologists.

Imaging

Conventional imaging has low value in differentiating PsP from tumor recurrence [45,46]. Although contrast-enhancing lesions showing callosal involvement, crossing of the midline, and subependymal spread are reportedly highly associated with tumor recurrence compared to PsP, these imaging features are also commonly observed in PsP [46]. Therefore, radiologists should not rely heavily on conventional imaging for PsP diagnosis. The RT planning field should be routinely checked by a radiologist because a newly developed contrast-enhancing lesion outside the RT field strongly suggests tumor recurrence rather than PsP.

In terms of advanced imaging, PsP shows a higher apparent diffusion coefficient (ADC) value and lower relative cerebral blood volume (rCBV) than tumor recurrence because tumor tissue shows higher cellularity and vascularity, leading to low ADC and high rCBV values, respectively [47-49]. However, as there are overlapping ADC and rCBV values between PsP and tumor recurrence [50], a comparison of the ADC and rCBV values between the initial preoperative tumor and current post-treatment imaging should also be considered for accurate differentiation between PsP and tumor recurrence. The recurrent tumor on post-treatment imaging usually shows a similar trend in ADC and rCBV values as the tumor on preoperative imaging. On MR spectroscopy, relatively higher values of N-acetylaspartate (NAA) and creatinine (Cr) with lower values of choline (Cho) elevation, leading to lower Cho/NAA and lower Cho/Cr, are observed in PsP than in tumor recurrence [49,51]. In amide proton transfer imaging, lower APT signals are observed in PsP than in tumor recurrence [52]. In amino acid PET, less tracker uptake is observed in PsP than in tumor recurrence [53,54], and amino acid PET may provide useful information when perfusion imaging shows inconclusive results in differentiating PsP from tumor recurrence [54]. Figures 3, 4, and 5 show representative imaging cases of PsP, early tumor recurrence outside the RT field, and early tumor recurrence inside the RT field, respectively, all within 12 weeks of completing radiotherapy. Note that in all cases, the clinical context and advanced imaging findings were considered for the final interpretation, rather than rigorously adhering to RANO 2.0. Table 1 summarizes the clinical and imaging differences between PsP after radiotherapy and tumor progression and recurrence.

Radiation Necrosis

Radiation necrosis requires recognition because effective treatment might be erroneously terminated if it is misdiagnosed as tumor recurrence or progression [30]. Because radiation necrosis manifests as a gradually enlarging contrast-enhanced lesion on follow-up imaging, differentiating it from tumor recurrence is often difficult using conventional imaging.

Clinical Presentation

Radiation necrosis typically occurs 9–12 months after treatment and can occur up to several years later, with an incidence of up to 25% [28,55]. The clinical presentation of radiation necrosis typically mimics that of tumor progression,

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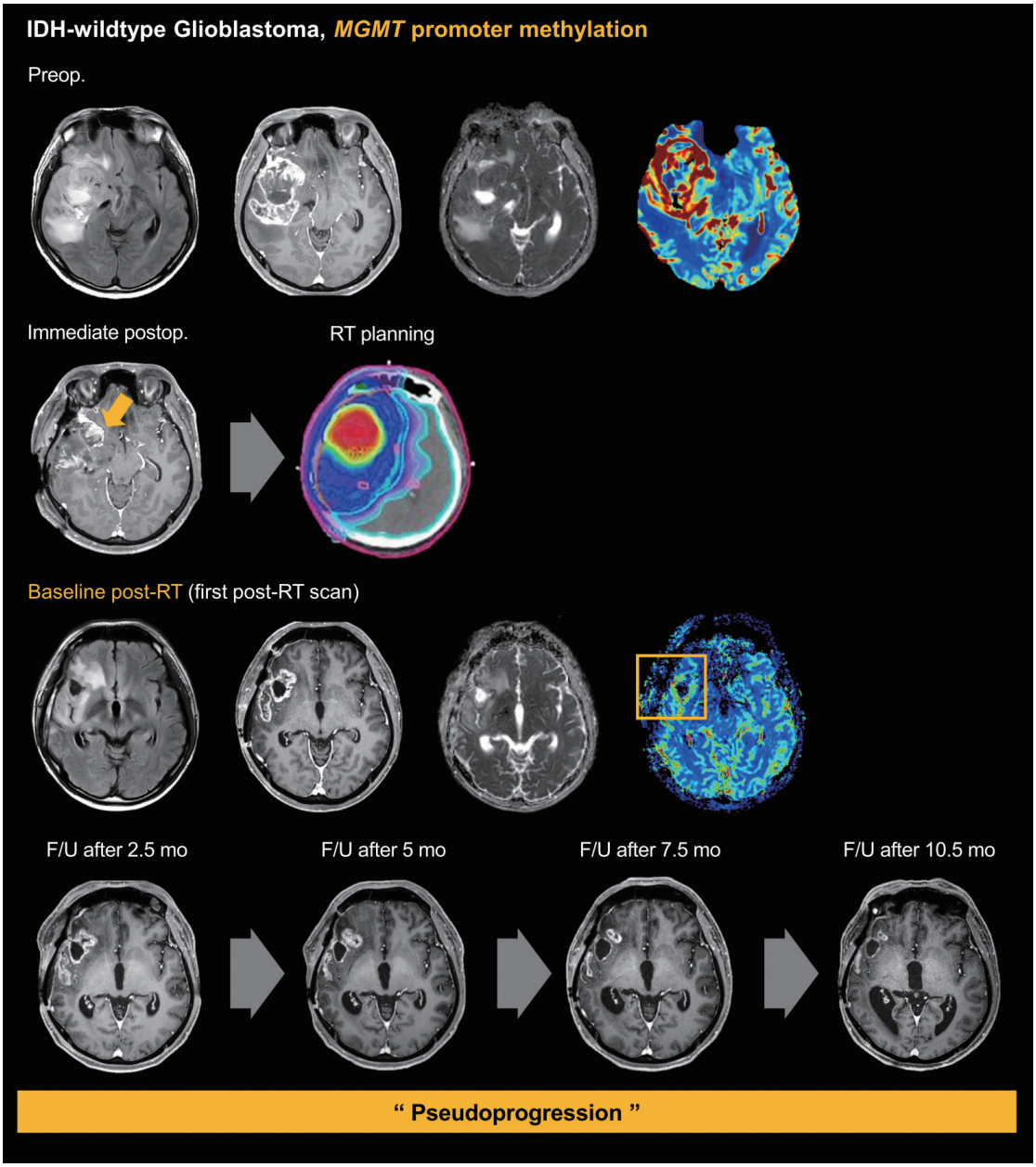

Fig. 3. A representative case of PsP after radiotherapy in a patient. A 60-year-old female presented with a ring-enhancing tumor and central necrosis involving the right frontotemporal lobe and insula on preoperative MRI. Immediate postoperative imaging shows a residual contrast-enhancing tumor at the right frontal base (arrow). The patient was diagnosed with IDH-wildtype glioblastoma with *MGMT* promoter methylation. The patient underwent standard CCRT followed by adjuvant temozolomide. On baseline post-RT imaging (the first post-RT scan performed 27 days after RT completion), there was an increase in the extent of the contrast-enhancing lesion with internal necrosis. The lesion was within the RT field. The radiology trainee interpreted this imaging finding as tumor progression because the contrast-enhancing lesion showed an increased rCBV on post-RT imaging (yellow box). However, the radiology staff interpreted this lesion as more likely of PsP than early tumor progression for several reasons: 1) the first post-RT scan typically shows radiographic changes during chemoradiation (which is considered the baseline scan in RANO 2.0) and is less likely to show early tumor progression, 2) consideration of the clinical context of the presence of *MGMT* promoter methylation with a higher possibility of PsP, and 3) the lower rCBV value of the contrast-enhancing lesion in post-RT imaging compared to the initial tumor on preoperative baseline imaging (although there was mild rCBV elevation in the post-RT imaging), while the ADC value of the contrast-enhancing lesion in the post-RT imaging was also slightly higher than that of the initial tumor on preoperative imaging. In subsequent follow-up imaging, the contrast-enhancing lesion gradually decreased over the next 10.5 months, confirming the diagnosis of PsP. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. PsP = pseudoprogression, IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, CCRT = concurrent chemoradiotherapy, RT = radiation therapy, rCBV = relative cerebral blood volume, ADC = apparent diffusion coefficient, F/U = follow-up

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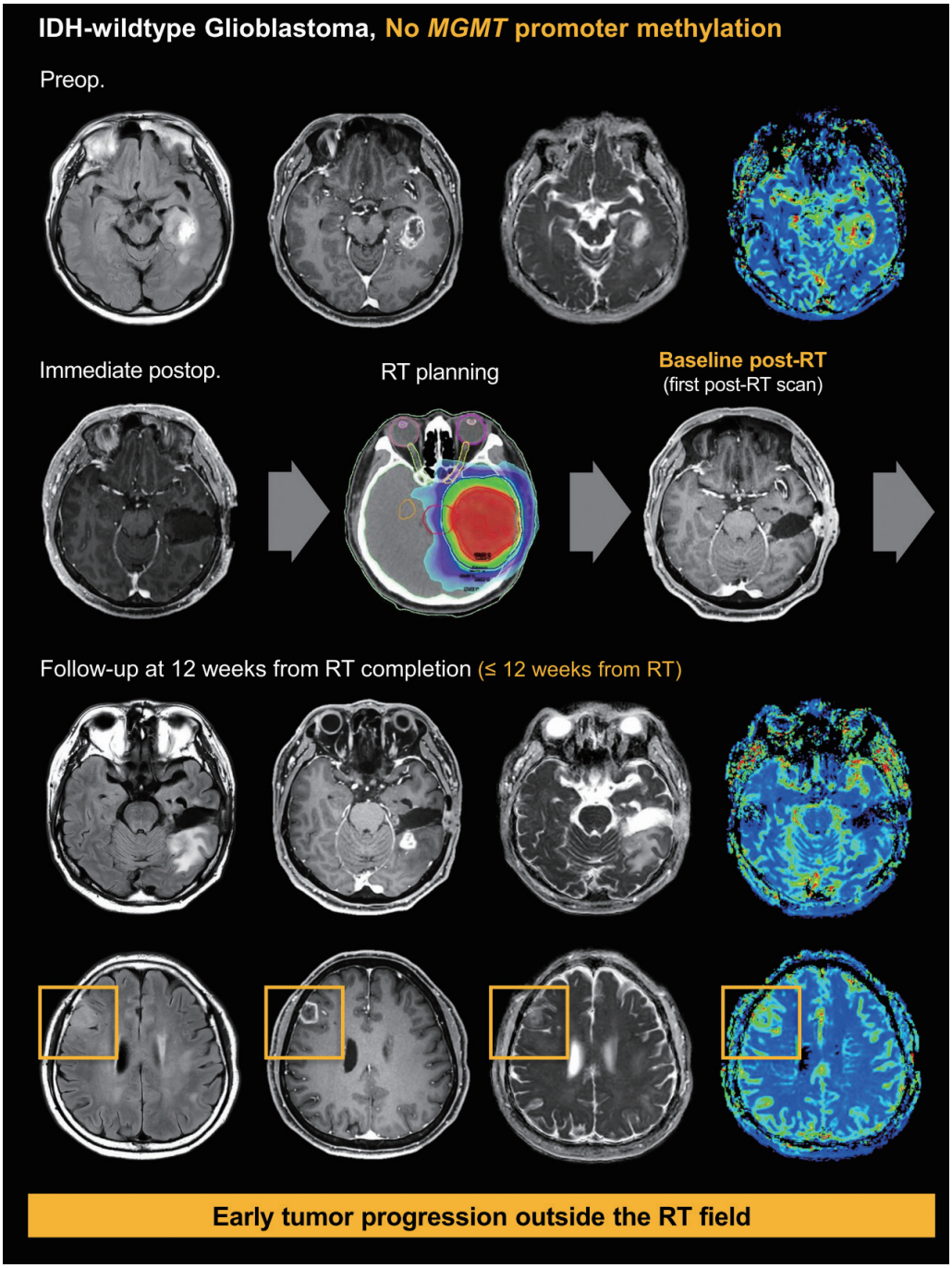

Fig. 4. Representative case of early tumor progression outside the RT field after radiotherapy. A 61-year-old male presented with a ring-enhancing tumor and central necrosis involving the left temporal lobe on preoperative MRI. On immediate postoperative imaging, there is no residual tumor, and supramaximal resection was performed. The patient was diagnosed with IDH-wildtype glioblastoma without *MGMT* promoter methylation. The patient underwent standard CCRT followed by adjuvant temozolomide. On baseline post-RT imaging (the first post-RT scan performed 27 days after RT completion), there is only minimal enhancement along the surgical margin. On follow-up imaging at 12 weeks from RT completion (≤12 weeks from RT), there were two newly developed contrast-enhancing lesions with internal necrosis in the left temporal lobe and right frontal lobe. As the left temporal lobe lesion is within the RT field and shows only mild rCBV elevation, differentiation of PsP from tumor progression was not possible for this lesion. However, the right frontal lobe lesion is clearly outside the RT field (yellow box), allowing for a confident diagnosis of tumor recurrence without follow-up imaging. This lesion also shows increased rCBV, similar to that of the preoperative tumor. Therefore, the patient was diagnosed with early tumor recurrence based on imaging. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. RT = radiation therapy, IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, CCRT = concurrent chemoradiotherapy, rCBV = relative cerebral blood volume, PsP = pseudoprogression, ADC = apparent diffusion coefficient

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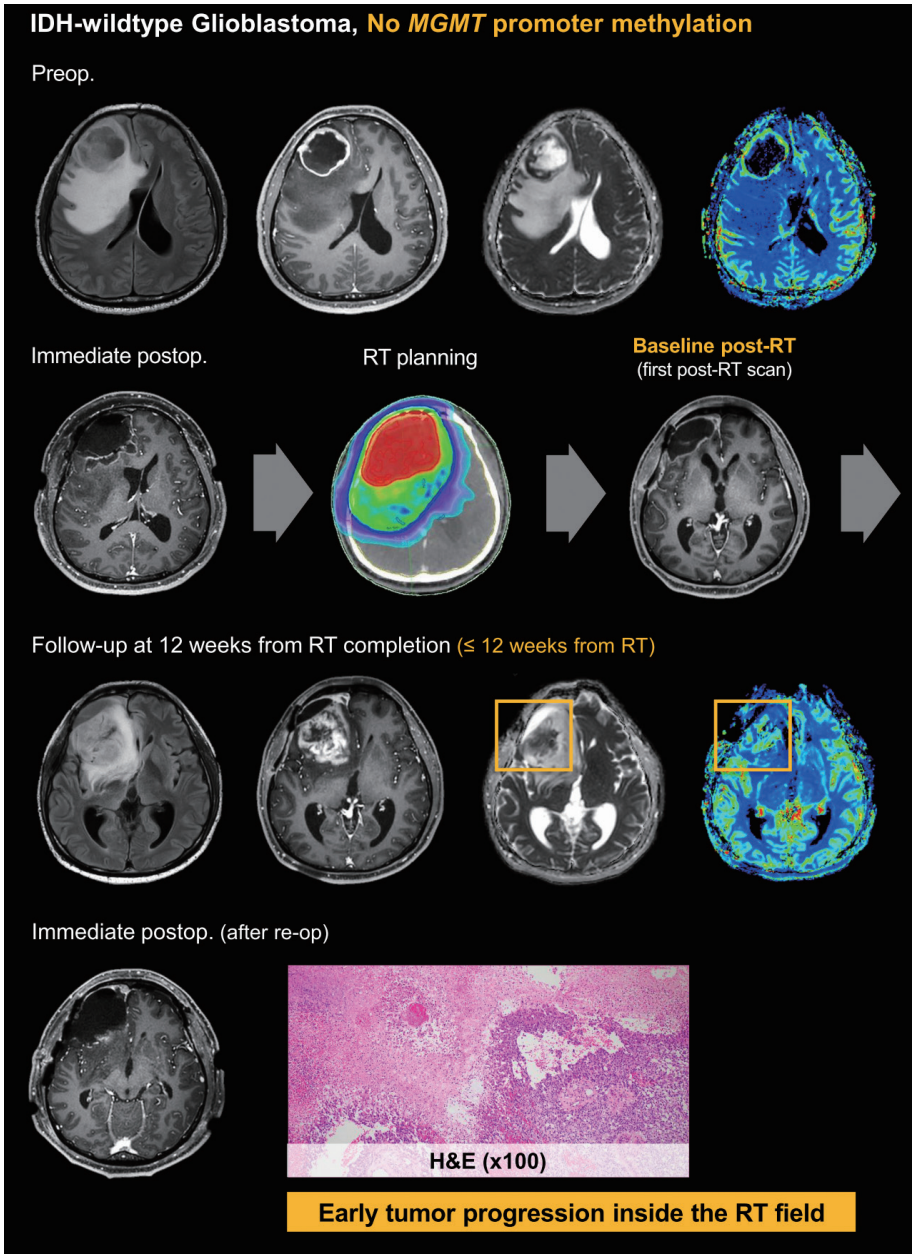

Fig. 5. Representative case of early tumor progression inside the RT field after radiotherapy. A 26-year-old male presented with a ring-enhancing tumor and central necrosis involving the right frontal lobe on preoperative MRI. On immediate postoperative imaging, there is no residual tumor, and supramaximal resection was performed. The patient was diagnosed with IDH-wildtype glioblastoma without *MGMT* promoter methylation. This patient underwent standard CCRT followed by adjuvant temozolomide. On baseline post-RT imaging (the first post-RT scan performed 28 days after RT completion), there is only minimal enhancement along the surgical margin. On follow-up imaging at 12 weeks from RT completion (≤12 weeks from RT), there is a newly developed contrast-enhancing lesion with internal necrosis at the right frontal base. As the imaging is within 12 weeks from RT completion, and the contrast-enhancing lesion is within the RT field, according to RANO 2.0, this lesion can only be diagnosed as "preliminary progressive disease" at this stage by imaging and "progressive disease" can only be confirmed if the subsequent follow-up image shows additional size increase. However, the radiology staff interpreted this lesion as more likely early tumor recurrence than PsP for several reasons: 1) consideration of the clinical context of patients having no *MGMT* promoter methylation leading to a lower possibility of PsP and 2) manifestation of markedly low ADC and high rCBV values of the contrast-enhancing lesion in post-RT imaging, similar to those of the initial tumor on preoperative imaging. On reoperation, the patient underwent supramaximal resection. On histopathology (H&E, x100), the patient was confirmed as recurrent IDH-wildtype glioblastoma, showing densely cellular tumor cells with robust microvascular proliferation. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. RT = radiation therapy, IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, CCRT = concurrent chemoradiotherapy, PsP = pseudoprogression, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, H&E = hematoxylin and eosin

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Table 1. Summary of the clinical and imaging differences between PsP after radiotherapy and tumor progression/recurrence

	PsP	Tumor recurrence/progression
Time period	Within 12–24 weeks of completing RT (higher incidence within the first 12 weeks)	Can occur at any time after treatment; early recurrence occurs less frequently than PsP
Incidence	30%–40%	Inevitable process
Risk factor	Associated with *MGMT* promoter methylation (patients with *MGMT* promoter methylation have at least twice the occurrence of PsP than those without methylation)	NA
Pathophysiology	Edema and increased vascular permeability secondary to radiotherapy-induced cell death and inflammation	Actual tumor cell proliferation
Imaging		
Conventional MRI	Similar imaging features to tumor recurrence/progression: contrast-enhancing lesion with necrosis within the RT field (a new lesion outside RT field strongly suggest recurrence rather than PsP)	Callosal involvement, midline crossing, and subependymal spread may be more common, but frequently overlap with PsP
Advanced MRI	Higher ADC value	Lower ADC value
	Lower rCBV value	Higher rCBV value
	Low Cho, high NAA, high Cr in MR spectroscopy: Low Cho/NAA, low Cho/Cr	High Cho, low NAA, low Cr in MR spectroscopy: High Cho/NAA, high Cho/Cr
	Lower APT value	Higher APT value
Amino acid PET	Lower tracer uptake	Higher tracer uptake
Outcome	Resolves spontaneously without further treatment	Requires a change of treatment regimen

PsP = pseudoprogression, *MGMT* = O^6-methylguanine-DNA methyltransferase, NA = not available, RT = radiation therapy, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, Cho = choline, NAA = N-acetylaspartate, Cr = creatinine, APT = amide proton transfer

showing neurological decline. Compared with PsP, which usually shows transient clinical symptoms, radiation necrosis may persist for a longer period with a worse prognosis [55].

The treatment of radiation necrosis includes corticosteroids to relieve cerebral edema and surgical decompression in cases of severe mass effects. Bevacizumab has also shown efficacy in radiation necrosis in terms of improved neurological symptoms [56], although the dose is usually lower compared to treatment in recurrent tumors (median dose of 7.5 mg/kg in radiation necrosis compared to a standard dose of 10 mg/kg in recurrent tumors) [56,57].

Risk Factors

Re-irradiation, particularly at high doses and large treatment volumes, increases the risk of radiation necrosis [6,58]. As these risk factors are widely acknowledged, re-irradiation is now carefully planned in patients with recurrent IDH-wildtype glioblastoma to conform to the cumulative biologically equivalent radiation dose that avoids radiation necrosis [6].

Pathophysiology and Histopathology

Compared to PsP, radiation necrosis shows more severe tissue reactions. Radiation-induced vascular insult leads to endothelial cell damage, vascular hyalinization, cellular swelling, and necrosis [55]. Oligodendrocyte and white matter damage is also induced by DNA-damaging free radicals. Upregulated vascular endothelial growth factor (VEGF) expression is associated with the magnitude of edema and BBB breakdown [59].

Histologically, radiation necrosis is characterized by coagulative necrosis accompanied by gemistocytic astrocytes, indicating gliosis with atypia. Collections of abnormally dilated and thin-walled telangiectasias can also be observed [55].

As explained in detail in the Pathophysiology and Histopathology section of PsP, there are currently no specific guidelines for the histopathological characterization of radiation necrosis. Pathological differentiation from tumor recurrence is not always easy in tissues with mixed radiation necrosis and tumor recurrence; details are presented in the previous section (Pathophysiology and Histopathology section of PsP).

Imaging

In conventional imaging, radiation necrosis usually

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occurs in the white matter within the radiation field. Internal enhancement patterns such as "Swiss cheese" or "soap bubble" patterns have been shown to be more typical of radiation necrosis than true tumor recurrence [60]. However, the evaluation of these imaging patterns remains subjective and inaccurate [60]. Contrast-enhancing lesions showing multiplicity, callosal involvement, crossing of the midline, and subependymal spread are reportedly more highly associated with tumor recurrence than with radiation necrosis [61]. However, these imaging findings commonly overlap between radiation necrosis and tumor recurrence, and relying on conventional imaging alone to differentiate between radiation necrosis and tumor recurrence may not be optimal.

On advanced imaging, radiation necrosis shows a higher ADC value and lower rCBV than tumor recurrence [62-64]. The presence of centrally restricted diffusion in the necrotic portion of the ring-enhancing lesion may indicate radiation necrosis rather than tumor recurrence; this area is thought to represent coagulative necrosis during radiation necrosis [65,66]. The rCBV value may be more helpful than the ADC value in distinguishing radiation necrosis from tumor recurrence [62]. On MR spectroscopy, relatively higher values of NAA and lower values of Cho favor radiation necrosis over tumor recurrence, leading to lower Cho/NAA and Cho/Cr ratios, whereas an elevated lipid-lactate peak may also suggest radiation necrosis [67]. In amide proton transfer imaging, lower APT signals are observed in radiation necrosis than in tumor recurrence [68]. In amino acid PET, less tracker uptake is observed in radiation necrosis than in tumor recurrence [16,64,69,70]; however, false-positive uptake was reported in a patient who underwent re-irradiation with a high cumulative radiation dose, in which strong tracer uptake can be related to strong reactive astrogliosis [16].

Figure 6 shows a representative case of pathologically confirmed radiation-induced necrosis. According to RANO 2.0, this case could have been defined as progressive disease because of an increased tumor burden based on conventional imaging; however, careful interpretation based on the clinical context and advanced imaging may lead to a more accurate and plausible diagnosis of radiation necrosis. Table 2 summarizes the clinical and imaging differences between radiation necrosis and tumor recurrence or progression.

Pseudoresponse in Antiangiogenic Therapy

PsR occurs during bevacizumab treatment, an antiangiogenic therapy that targets VEGF. Bevacizumab may prolong PFS, but not OS, in patients with recurrent tumors [7]. PsR is characterized by a decrease in contrast enhancement without a true antitumor effect, whereas the lesion remains stable or has progressed on T2/FLAIR images [33,71].

The term PsR has historically been used to describe the phenomenon in which a seemingly rapid response to bevacizumab is observed (for example, a markedly decreased size of contrast-enhancing tumor on post-contrast T1-weighted images) without any difference in OS in clinical trials of patients with recurrent tumors [71]. This term is not used as commonly as PsP or radiation necrosis nowadays because it is important to determine whether the patient has progressive or stable disease in either contrast-enhancing or non-enhancing tumors rather than specifically determining PsR, which may include both progressive and stable disease (visualized as non-enhancing tumors on T2/FLAIR images) by its definition. However, understanding the concept of PsR is important for correctly interpreting post-treatment imaging results during bevacizumab treatment.

Clinical Presentation

PsR is usually observed shortly after the initiation of bevacizumab treatment during follow-up imaging [33]. Owing to the rapid decrease in vasogenic edema and mass effect, neurological symptoms may improve.

Approximately 30% of patients undergoing bevacizumab treatment may show PsR [72]. In terms of tumor progression patterns, the proportion of predominantly non-enhancing tumor recurrence patterns, which may be considered a form of PsR, was reported to be 34.2% in a meta-analysis of recurrent high-grade gliomas [73].

Pathophysiology and Histopathology

By targeting VEGF, bevacizumab not only reduces tumor vascularity but also normalizes tumor vasculature, improving the distribution of blood supply while also reducing tumor-associated edema and tissue hypoxia [74]. When angiogenesis is blocked with bevacizumab, the growth pattern of IDH-wildtype glioblastoma may change, leading to the utilization of mature vasculature after infiltrating normal host tissue (called "vessel co-option") [75,76].

The histopathology of PsR is not well described in the literature because reoperation with pathological confirmation is usually not performed in this state of imaging manifestation.

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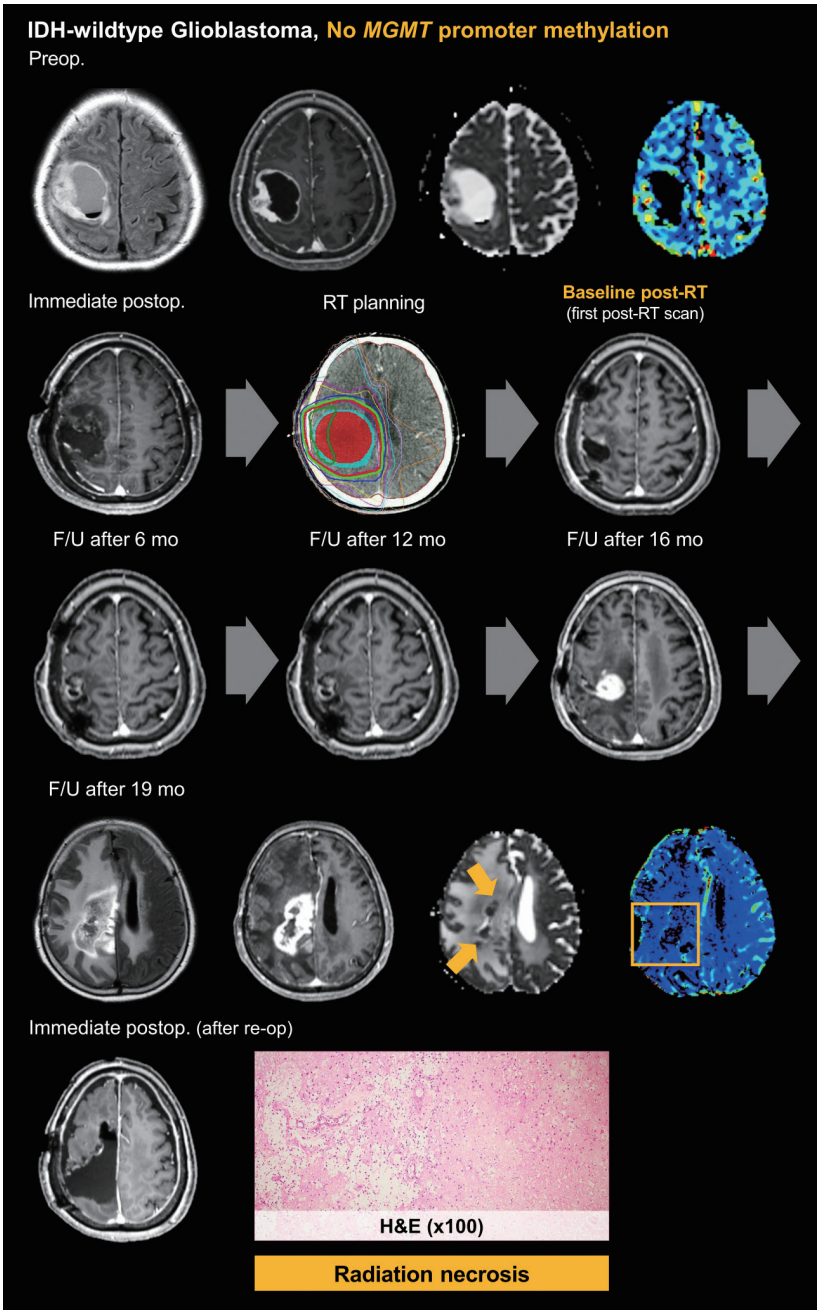

Fig. 6. Representative case of radiation necrosis showing central diffusion restriction. A 65-year-old female presented with a ring-enhancing tumor and central necrosis involving the right parietal lobe on preoperative MRI. On immediate postoperative imaging, there is no residual tumor, and supramaximal resection was performed. The patient was diagnosed with IDH-wildtype glioblastoma without *MGMT* promoter methylation and underwent standard CCRT followed by adjuvant temozolomide. On baseline post-RT imaging, there is only minimal linear enhancement along the surgical margin. On follow-up imaging at 6 months after RT completion, there is a newly developed small contrast-enhancing lesion along the surgical margin within the RT field. Over a follow-up period of over a year, the contrast-enhancing lesion gradually increase in size with the development of internal necrosis. The radiology staff interpreted this lesion as more likely radiation necrosis than true tumor progression for several reasons: 1) consideration of the clinical context of the timing, RT field, and slow, gradual increase in size over a year, 2) the markedly high ADC and low rCBV values of the contrast-enhancing lesion, which were discordant from those of the initial tumor on preoperative imaging, and 3) the central diffusion restriction in the necrotic portion of the lesion (arrows on the ADC map), which suggests a higher possibility of radiation necrosis. After total resection of this lesion, the patient was diagnosed with radiation necrosis without any residual tumor on histopathology (H&E, x100). ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, CCRT = concurrent chemoradiotherapy, RT = radiation therapy, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, H&E = hematoxylin and eosin, F/U = follow-up

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Table 2. Summary of the clinical and imaging differences between radiation necrosis and tumor recurrence/progression

	Radiation necrosis	Tumor recurrence/progression
Time period	Typically occurs 9 to 12 months after treatment but can occur several years later	Can occur at any time after treatment
Incidence	Up to 25%	Inevitable process
Risk factor	High doses of re-irradiation and large treatment volumes increase risk	NA
Pathophysiology	Radiation-induced vascular insult, endothelial cell damage, vascular hyalinization, cellular swelling, and necrosis	Actual tumor cell proliferation
Imaging		
Conventional MRI	Contrast-enhancing lesion with necrosis: "Swiss cheese" or "soap bubble" may be typical imaging features but not very helpful within the RT field	Callosal involvement, midline crossing, and subependymal spread may be more common, but frequently overlap with radiation necrosis
Advanced MRI	Higher ADC value (may show central diffusion restriction at the necrotic portion)	Lower ADC value
	Lower rCBV value	Higher rCBV value
	Low Cho, high NAA, high Cr in MR spectroscopy, elevated lipid/lactate peak: Low Cho/NAA, low Cho/Cr	High Cho, low NAA, low Cr in MR spectroscopy: High Cho/NAA, high Cho/Cr
	Lower APT value	Higher APT value
Amino acid PET	Lower tracer uptake	Higher tracer uptake
Outcome	May cause gradual neurological deterioration	Requires a change of treatment regimen

NA = not available, RT = radiation therapy, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, Cho = choline, NAA = N-acetylaspartate, Cr = creatinine, APT = amide proton transfer

Imaging

On imaging, PsR shows a rapid decrease in contrast-enhancing tumor and peritumoral edema, usually at the first follow-up imaging after bevacizumab treatment initiation, whereas the non-enhancing tumor remains stable or has increased in size [28,33,77]. Therefore, careful examination of the T2/FLAIR sequence is required for follow-up imaging after antiangiogenic therapy to delineate the extent of non-enhancing tumors, even when contrast-enhancing tumors decrease or nearly disappear on post-contrast T1-weighted imaging. The non-enhancing tumor must be differentiated from peritumoral edema, because the effect of bevacizumab may result in a decrease in peritumoral edema, whereas the extent of the non-enhancing tumor may actually increase in PsR. A detailed explanation of the imaging differentiation of non-enhancing tumors from peritumoral edema has been provided in Part I Review and elsewhere [78-80].

Few studies have evaluated the advanced imaging of PsR. One study reported a trend of normalization of ADC values in previous contrast-enhancing tumors and FLAIR hyperintense areas in patients with PsR, which may be attributed to decreased edema [72]. However, this study included both peritumoral edema and non-enhancing tumors as FLAIR hyperintense areas. In our experience, non-enhancing tumors (apart from peritumoral edema) may not show normalization of ADC values. Figure 7 shows a representative case of PsR tumor progression.

Pseudoprogression During Immunotherapy

During immunotherapy, PsP may manifest as enlarged or newly developed contrast-enhancing lesions with increased perilesional edema, which may decrease in size during follow-up without further treatment. PsP during immunotherapy is discussed separately from PsP after radiotherapy because of the different clinical and imaging characteristics of these two conditions: 1) As concurrent chemoradiotherapy is the standard of care in initially diagnosed patients, whereas immunotherapy is mostly performed in recurrent patients with IDH-wildtype glioblastoma, the clinical course in which PsP after radiotherapy and PsP during immunotherapy appear is different, 2) The underlying mechanism for PsP during immunotherapy is probably distinct from the mechanism associated with radiotherapy and may lead to different time windows and imaging manifestations, 3) Unlike PsP after radiotherapy, PsP during immunotherapy is not limited within the RT field, and a completely new contrast-enhancing lesion appearing at a distant site could also be PsP in patients treated with immunotherapy, whereas a new

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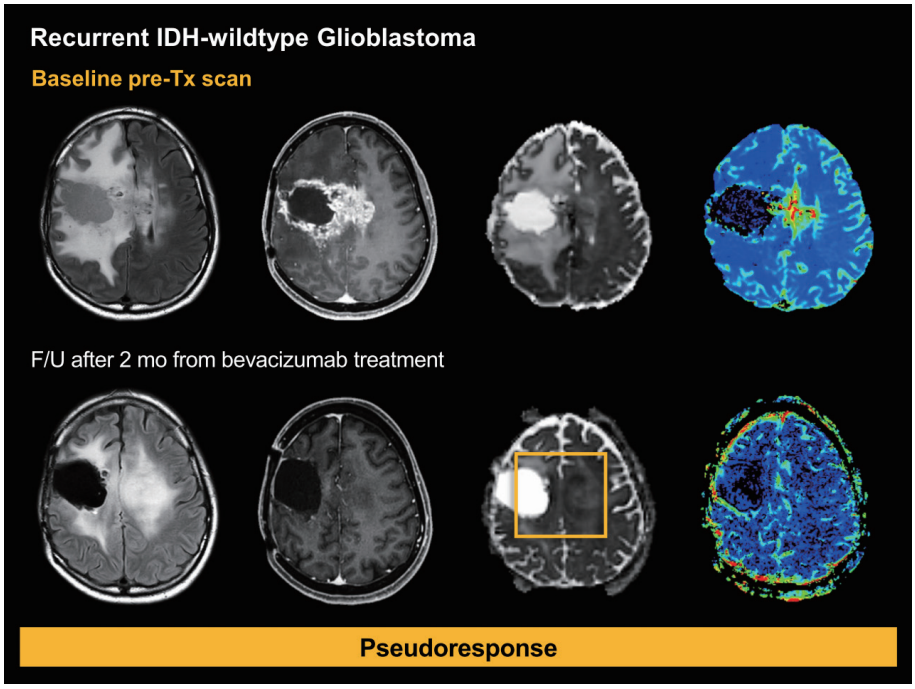

Fig. 7. Representative case of PsR after bevacizumab treatment. A 36-year-old female with IDH-wildtype glioblastoma showed tumor recurrence and underwent bevacizumab treatment. The baseline pre-treatment scan (performed 2 days before the start of treatment) shows a recurrent tumor with ring-enhancement and central necrosis involving bifrontal lobes and corpus callosum with marked peritumoral edema, showing markedly increased rCBV at the contrast-enhancing tumor. On follow-up imaging at 2 months after the initiation of bevacizumab treatment, the contrast-enhancing tumor has nearly disappeared, and the extent of peritumoral edema has markedly decreased. However, there is expansion of the non-enhancing tumor to the left frontoparietal white matter apart from peritumoral edema observed in the FLAIR sequence, which is consistent with PsR with non-enhancing tumor progression. Although this non-enhancing tumor does not show an rCBV increase, there are some areas of decreased ADC (box), indicating increased cellularity. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. PsR = pseudoresponse, IDH = isocitrate dehydrogenase, rCBV = relative cerebral blood volume, ADC = apparent diffusion coefficient, Tx = treatment, F/U = follow-up

contrast-enhancing lesion appearing outside the RT field after radiation treatment is tumor progression but not PsP after radiotherapy [22].

Immunotherapy is a rapidly emerging treatment modality for patients with recurrent IDH-wildtype glioblastoma, although its survival benefit has not been demonstrated [10,11,81]. This includes various modalities such as vaccination therapy, oncolytic viral therapy, immune checkpoint inhibitors, and CAR T cell therapy. Vaccination therapy relies on dendritic cell-mediated presentation of peptide vaccines, whereas oncolytic viral therapy creates viruses that selectively infect or replicate in tumor cells. Immune checkpoint inhibitors such as anti-PD-1 antibody (nivolumab or pembrolizumab) and anti-CTLA-4 antibody (ipilimumab), enable cytotoxic T cell activation, whereas CAR T cell therapy uses genetically modified T cells to target the tumor.

Clinical Presentation

The timeframe for PsP during immunotherapy is usually several months longer than that for PsP after radiotherapy (within 12–24 weeks after completing RT) and remains to be defined. The previous Immunotherapy RANO criteria defined the period up to 6 months after initiating immunotherapy [22]. Furthermore, the timeframe may differ depending on the class of immunotherapy administered. Patients may present with worsening neurological symptoms during immunotherapy owing to the increased mass effect.

Pathophysiology and Histopathology

In PsP during immunotherapy, intratumoral immune cell infiltrates, including macrophage cytotoxic T cells, are associated with geographic necrosis and vascular wall hyalinization [82,83]. Increased cellularity can be observed because of reactive astrocytosis with occasional atypical cells [82,83].

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Imaging

Little information is available regarding the differentiation of PsPs during immunotherapy from tumor progression in terms of both conventional and advanced imaging in IDH-wildtype glioblastoma. It is generally presumed that advanced imaging may play a much larger role in the accurate diagnosis of PsP. However, as previous studies evaluating the role of advanced imaging were mostly single-institution studies with a limited number of patients, with different immunotherapy modalities, and different imaging sequences [81,84-87], we speculate that there is no strong conclusion yet. These studies showed discordant results regarding the significance of each imaging parameter in predicting PsP during immunotherapy [84], and some new MRI contrast agents (such as ultrasmall superparamagnetic iron oxide) or PET radiotracers are not widely available [88]. Future research directions include a multicenter study with a comprehensive evaluation of both MRI and PET imaging parameters to identify imaging biomarkers that predict PsP in immunotherapy [88].

Tumor Recurrence/Progression

The long journey of explaining various treatment-related changes has been to correctly diagnose tumor recurrence or progression. Tumor recurrence/progression is an inevitable and formidable process in IDH-wildtype glioblastomas, indicating the failure of the current treatment regimen. The median OS after the first tumor recurrence or progression is approximately 9 months [5,8,89]. Although there is no standard of care for recurrent tumors, various treatment options can be selected according to the patient's age, performance status, *MGMT* promoter methylation status, and patterns of tumor recurrence/progression [2]. Therefore, accurate diagnosis of tumor recurrence/progression and accurate description of the pattern are important for treatment decisions.

There is no unified classification for the pattern of tumor recurrence, and the definition varies in the literature depending on whether the criteria are based on the distance from the resection cavity or the isodose surface of the radiation field [90-94]. The pattern can be roughly divided into local recurrence, distant recurrence, and mixed recurrence (showing both local and distant recurrences) (schematic illustrations are shown in Fig. 8). Local recurrence occurs adjacent to the resection cavity (≤2 cm) or within the clinical target volume of the radiation field and is the most commonly observed recurrence/progression pattern, whereas distant recurrence occurs distant (>2 cm) to the resection cavity or beyond the radiation field and is less frequently observed than local recurrence (usually less than 20% among tumor recurrence patterns) [90-93,95]. The clinical and molecular characteristics of local and distant recurrences require further investigation. Distant recurrence was previously regarded as reflecting the capability of tumor cells to migrate throughout the brain, with a longer period of manifestation leading to a longer PFS [90,91]. However, caution should be taken when interpreting these results, as these included CNS WHO grade 4 IDH-mutant astrocytomas along with IDH-wildtype glioblastomas before the 2021 WHO classification, which confounded the results. A recent multicenter study suggested that distant recurrence patterns were associated with better survival outcomes in cases of re-resection, which can be attributed to the distinct accessibility of extensive resection compared to local recurrence [93].

In terms of imaging, tumor recurrence/progression is mostly observed as a contrast-enhancing tumor, typically

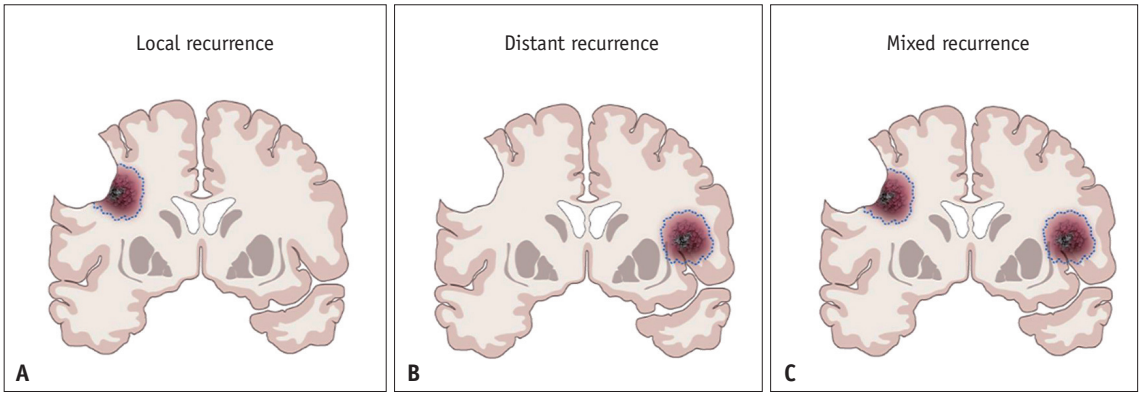

Fig. 8. Schematic illustrations of tumor recurrence patterns categorized into local **(A)**, distal **(B)**, and mixed **(C)** recurrence.

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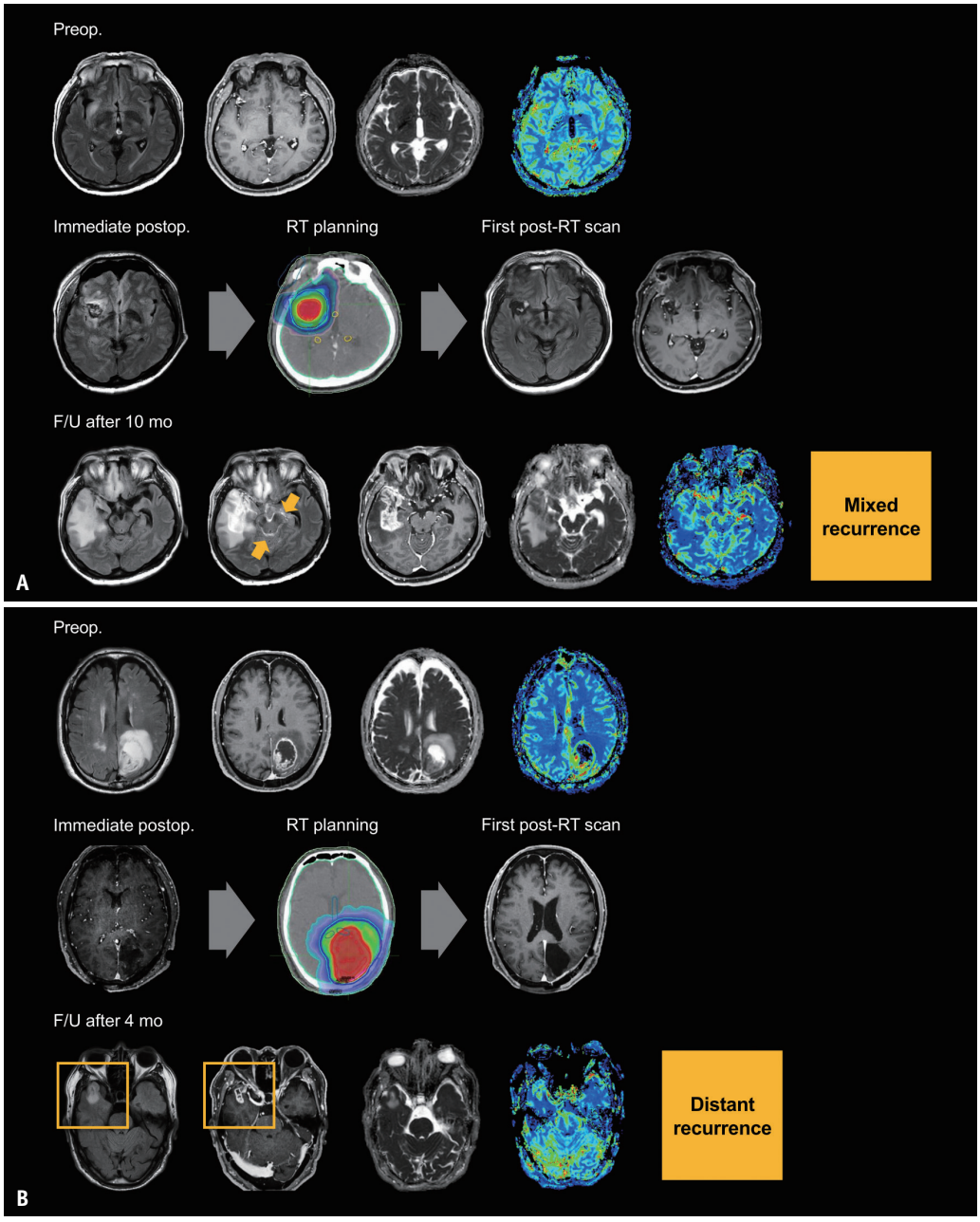

Fig. 9. Representative cases of tumor recurrence/progression showing mixed recurrence (local recurrence with leptomeningeal metastases) and distant recurrence. **A:** A 58-year-old female presented with a non-enhancing tumor in the right insula on preoperative MRI. On immediate postoperative imaging, there is no residual tumor and supramaximal resection was performed. The patient was diagnosed as histologically grade 3 astrocytic glioma with isolated *TERT* promoter mutation, which is now defined as molecular glioblastoma, and underwent RT followed by adjuvant temozolomide. On baseline post-RT imaging, there is only minimal linear enhancement along the surgical margin. On follow-up imaging at 10 months after RT completion, there is a newly developed large contrast-enhancing lesion along the right frontotemporal lobe with diffuse leptomeningeal metastases (arrows on post-contrast FLAIR image). The patient showed a mixed recurrence pattern consisting of local recurrence and leptomeningeal metastases. **B:** A 75-year-old male presented with a ring-enhancing tumor and central necrosis at the left occipitotemporal lobe on preoperative MRI. On immediate postoperative imaging, there is no residual tumor and supramaximal resection was performed. The patient was diagnosed with IDH-wildtype glioblastoma without *MGMT* promoter methylation and underwent hypofractionated RT. On baseline post-RT imaging, there is only faint minimal linear enhancement along the surgical margin. On follow-up imaging at 4 months after RT completion there is a newly developed ring-enhancing lesion with central necrosis along the right temporal lobe, showing an rCBV increase. The patient showed distant recurrence, distant from the surgical field and outside the radiation field. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. RT = radiation therapy, IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, rCBV = relative cerebral blood volume, ADC = apparent diffusion coefficient, F/U = follow-up

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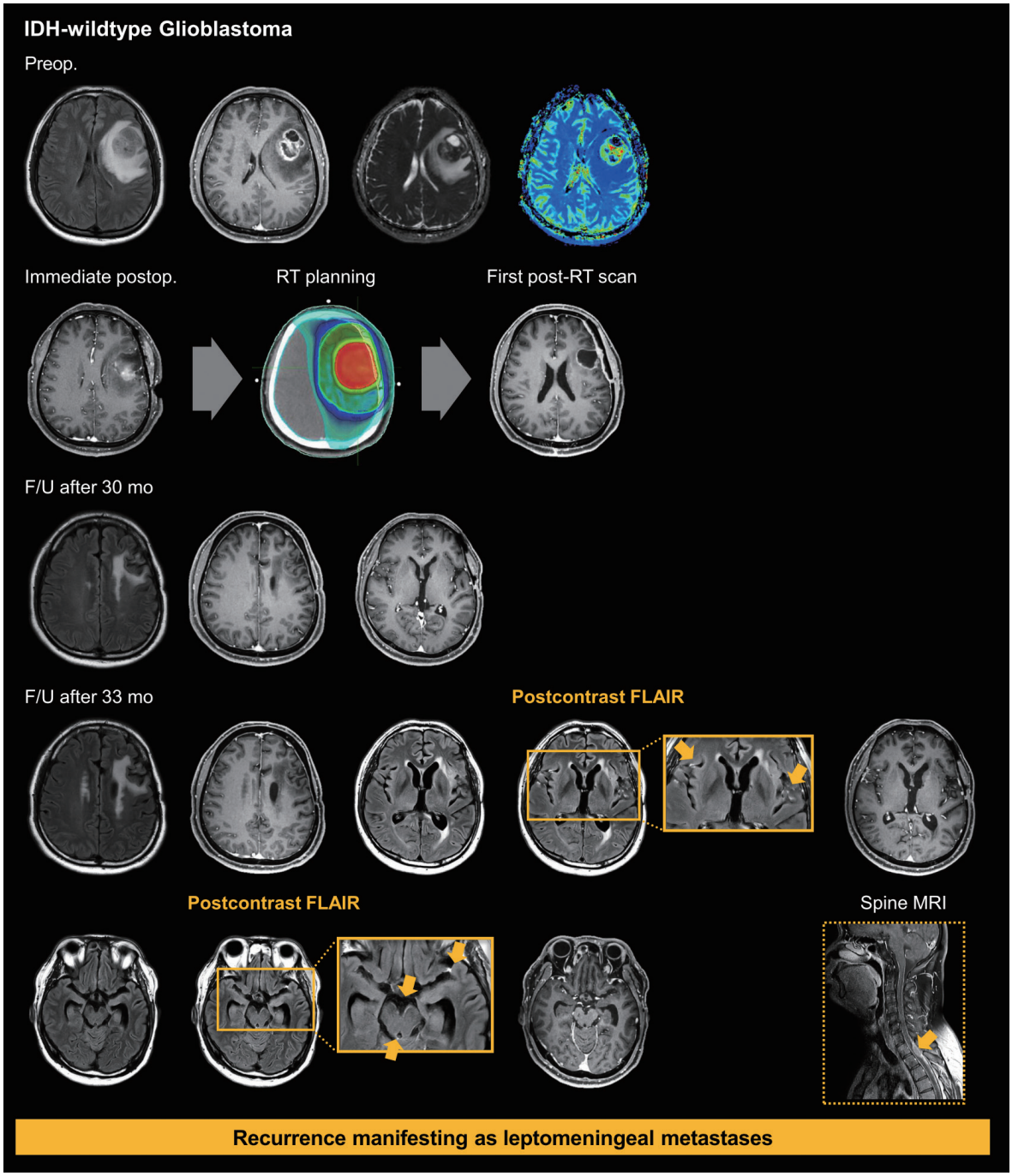

Fig. 10. Representative case of tumor recurrence/progression showing isolated LM. A 45-year-old male presented with a ring-enhancing tumor and central necrosis in the left frontal lobe on preoperative MRI. On immediate postoperative imaging, there is no residual tumor (only subacute stage hemorrhage), and supramaximal resection was performed. The patient was diagnosed with IDH-wildtype glioblastoma with *MGMT* promoter methylation and underwent CCRT followed by adjuvant temozolomide. On baseline post-RT imaging, there is only minimal linear enhancement along the surgical margin. On follow-up imaging until 30 months after RT completion, there was no evidence of tumor recurrence (note the ventricle size in this scan). On follow-up imaging at 33 months from RT completion, the size of the ventricles slightly increased. On post-contrast FLAIR, compared to pre-contrast FLAIR imaging, there are multifocal leptomeningeal enhancements along the cerebral sulci and cisternal surface (in arrows), suggestive of LM. Note that LM is only faintly delineated on post-contrast T1-weighted imaging, whereas it is more sensitively seen on post-contrast FLAIR imaging. On spine MRI, the patient also showed diffuse LM along the spinal cord, with mass formation at the T1 spinal cord level. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. LM = leptomeningeal metastases, IDH = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA methyltransferase, CCRT = concurrent chemoradiotherapy, RT = radiation therapy, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, F/U = follow-up

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with necrosis, low ADC, and high rCBV values. Non-enhancing tumor recurrence may also be observed, especially after bevacizumab treatment [73]. In MR spectroscopy, higher values of Cho and lower values of NAA and Cr were observed, indicating high Cho/NAA and Cho/Cr ratios [67]. In amide proton transfer imaging, high APT signals are observed during tumor recurrence [68]. In amino acid PET, increased tracker uptake has been observed during tumor recurrence [16,64,69,70].

LM usually occur concurrently with local or distant recurrence; however, there is often a solitary manifestation of LM as the tumor progresses, which can easily be overlooked or missed. The detection of ventricular enlargement, compared to the previous study, is an important imaging finding that can be easily detected and leads to suspicion of LM [96]. Post-contrast FLAIR, in addition to routinely acquired pre-contrast FLAIR, greatly increases the sensitivity of LM diagnosis at recurrence [15]. Figure 9 shows representative cases of tumor recurrence/progression with mixed recurrence (local recurrence with LM) and distant recurrence, whereas Figure 10 shows a representative case of tumor recurrence manifesting as a solitary LM.

CONCLUSION

Interpretation of post-treatment imaging in IDH-wildtype glioblastoma is complicated and challenging; a deep understanding of both the imaging information and clinical background is essential to provide an accurate diagnosis to clinicians. It is essential to note that radiologists are an integral part of the multidisciplinary neuro-oncology team struggling to achieve optimal care for patients with IDH-wildtype glioblastoma. Therefore, an accurate diagnosis of true tumor progression, apart from confounding treatment-related changes such as PsP or radiation necrosis, is essential. Effective communication between neurosurgeons, neurologists, radiation oncologists, and pathologists regarding post-treatment imaging will ultimately lead to an enhanced understanding of the disease and significant advancement toward a successful fight against IDH-wildtype glioblastoma.

Availability of Data and Material

The data in this study are available on request from the corresponding author.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Philipp Vollmuth, Yae Won Park. Data curation: Yae Won Park, Philipp Vollmuth, Sung Soo Ahn, Rajan Jain. Funding acquisition: Philipp Vollmuth, Yae Won Park. Project administration: Philipp Vollmuth, Yae Won Park. Resources: Yae Won Park. Supervision: Rajan Jain. Validation: Yae Won Park, Philipp Vollmuth, Rajan Jain. Visualization: Yae Won Park. Writing—original draft: Yae Won Park, Philipp Vollmuth, Philipp Karschnia, Felix Sahm, Sung Soo Ahn. Writing—review & editing: Philipp Vollmuth, Yae Won Park, Rajan Jain.

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