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A Radiologist's Guide to IDH-Wildtype Glioblastoma for Efficient Communication With Clinicians: Part I–Essential Information on Preoperative and Immediate Postoperative Imaging

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The paradigm of isocitrate dehydrogenase (IDH)-wildtype glioblastoma is rapidly evolving, reflecting clinical, pathological, and imaging advancements. Thus, it remains challenging for radiologists, even those who are dedicated to neuro-oncology imaging, to keep pace with this rapidly progressing field and provide useful and updated information to clinicians. Based on current knowledge, radiologists can play a significant role in managing patients with IDH-wildtype glioblastoma by providing accurate preoperative diagnosis as well as preoperative and postoperative treatment planning including accurate delineation of the residual tumor. Through active communication with clinicians, extending far beyond the confines of the radiology reading room, radiologists can impact clinical decision making. This Part 1 review provides an overview about the neuropathological diagnosis of glioblastoma to understand the past, present, and upcoming revisions of the World Health Organization classification. The imaging findings that are noteworthy for radiologists while communicating with clinicians on preoperative and immediate postoperative imaging of IDH-wildtype glioblastomas will be summarized.

Keywords: Central nervous system neoplasms; Glioblastoma; Magnetic resonance imaging; World Health Organization

INTRODUCTION

Isocitrate dehydrogenase (IDH)-wildtype glioblastoma, central nervous system (CNS) World Health Organization (WHO) grade 4, is the most common primary brain tumor in adults, accounting for approximately 50% of all malignant brain tumors [1]. It preferentially affects older adults (median age of 64 years), with an incidence 1.59 times higher in males compared to females and 1.99 times higher in Caucasians compared to African–Americans [2]. The standard of care includes maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide [3]. Despite these treatments, tumor recurrence and progression is inevitable, leading to a median overall

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Korean Journal of Radiology
KJR

survival of <18 months [1].

Imaging is crucial in establishing early diagnosis, optimizing postoperative treatment planning, and changing treatment regimens in case of tumor recurrence or progression on post-treatment surveillance imaging. For radiologists, acquiring up-to-date knowledge on IDH-wildtype glioblastoma is crucial for effective communication with neurosurgeons, neuro-oncologists, radiation oncologists, pathologists, and neurologists. Radiologists should recognize not only important imaging findings but also be aware of pertinent information needed by their clinical colleagues. Furthermore, acknowledging the past, present, and future of the evolving concept of IDH-wildtype glioblastoma enables radiologists to adapt more effectively to future changes – because in the near future, a WHO update will inevitably appear, and treatment strategies hopefully will be updated, leading to new demands on imaging.

Part I of the review will discuss the fundamental question of "What is a Glioblastoma?" from a pathological perspective, and it will summarize imaging findings noteworthy for radiologists for communicating with clinicians on preoperative and immediate postoperative imaging of IDH-wildtype glioblastomas. The subsequent Part II of the review will focus on information radiologists can provide to clinicians based on post-treatment imaging findings.

What is a Glioblastoma? - A Pathological Perspective

Since first used more than 100 years ago, the definition of glioblastoma has been evolving and continuously being modified for a better understanding of the disease. The definition reflects clinical and scientific advancements, differences among schools of thought (i.e., histological vs. clinical malignancy), and concepts related to cells of origin [4].

The History of Pathological Diagnosis of Glioblastoma: Past and Present

Rudolf Virchow (1821–1902), the outstanding German pathologist of the 19th century, first proposed that normal cells were the origin of cancers and suggested the term "glioma" for brain tumors resembling mature glial cells on microscopy [5]. In 1925, Bailey and Cushing [6] introduced the term "glioblastoma multiforme" to describe a high-grade malignant glioma with extraordinarily diverse histological features, even within the same tumor (hence "multiforme," now an outdated term). The histopathological hallmarks of glioblastoma include features of microvascular proliferation and necrosis. Starting from microscopic evaluation of tumors, substantial knowledge was gained about glioblastomas from the application of novel technologies. The first breakthrough of glioma characterization was available through the advent of immunohistochemistry, while the second breakthrough was triggered by novel molecular diagnostics such as next-generation sequencing (NGS) and DNA methylation profiling [7]. Thus, substantial changes have been made in the pathological diagnosis of glioblastoma to reflect updated knowledge, and what had been diagnosed and termed glioblastoma in the past may no longer be a glioblastoma in the current clinical setting.

Since 1979, five editions and one revision of the WHO classifications have been formulated, aiming for an internationally accepted, systematic approach to brain tumor classification [8-13]. In the first to fourth WHO editions, glioblastomas were classified according to their microscopic similarity to mature glial cells. However, high intra- and inter-observer variability in histopathological diagnosis was the major limitation of the early WHO classifications [14]. Advanced molecular diagnostics led to reports of IDH mutation in glioblastomas around the late 2000s, serving as a defining branch point [15,16]. Although tumors with glioblastoma-like histopathology and an IDH mutation had similar histological appearance compared to those with IDH-wildtype, they had different clinical characteristics. Tumors with IDH mutation represented approximately 10% of gliomas which have been historically denoted as "glioblastomas" based on histopathology alone, arising in younger patients who had previously been diagnosed with lower-grade glioma years before malignant transformation was taken place (coining the term "secondary glioblastoma"). Notably, tumors with IDH mutation were identified with a significantly more favorable prognosis than those with IDH-wildtype [15]. Reflecting this knowledge, the 2016 WHO revision of the 4th edition first incorporated diagnostic entities based on the integration of morphologic features with molecular markers [12], dividing glioblastoma into IDH-wildtype glioblastoma and IDH-mutant glioblastoma based on its IDH mutation status.

However, apart from their histological similarities, it became more evident over the last decade that glioblastomas with IDH mutation are biologically distinct from IDH-wildtype glioblastomas with a longer median overall survival of approximately 3.6 years [17], and the term "glioblastoma" may therefore not reflect the true

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nature of IDH-mutant tumors (even in the presence of glioblastoma-like histopathology) [13]. In turn, there was accumulating evidence that a subset of histologically grade 2 or 3 IDH-wildtype gliomas, which lack microvascular proliferation or necrosis (essential to be histologically graded as glioblastomas), showed biological aggressiveness similar to that of typical IDH-wildtype glioblastoma when a certain molecular signature, such as telomerase reverse transcriptase (*TERT*) promoter mutation, epidermal growth factor receptor (*EGFR*) gene amplification, and/or combined gain of entire chromosome 7 and loss of entire chromosome 10 (chromosome +7/-10), is present [18-21]. Thus, the subsequent 2021 WHO classification relies more on the molecular tumor profile for the classification of gliomas, reflecting the current transitional state between traditional classification system based on histopathology and the cutting-edge molecular diagnostics [13]. The term "glioblastoma" is no longer applied to CNS WHO grade 4

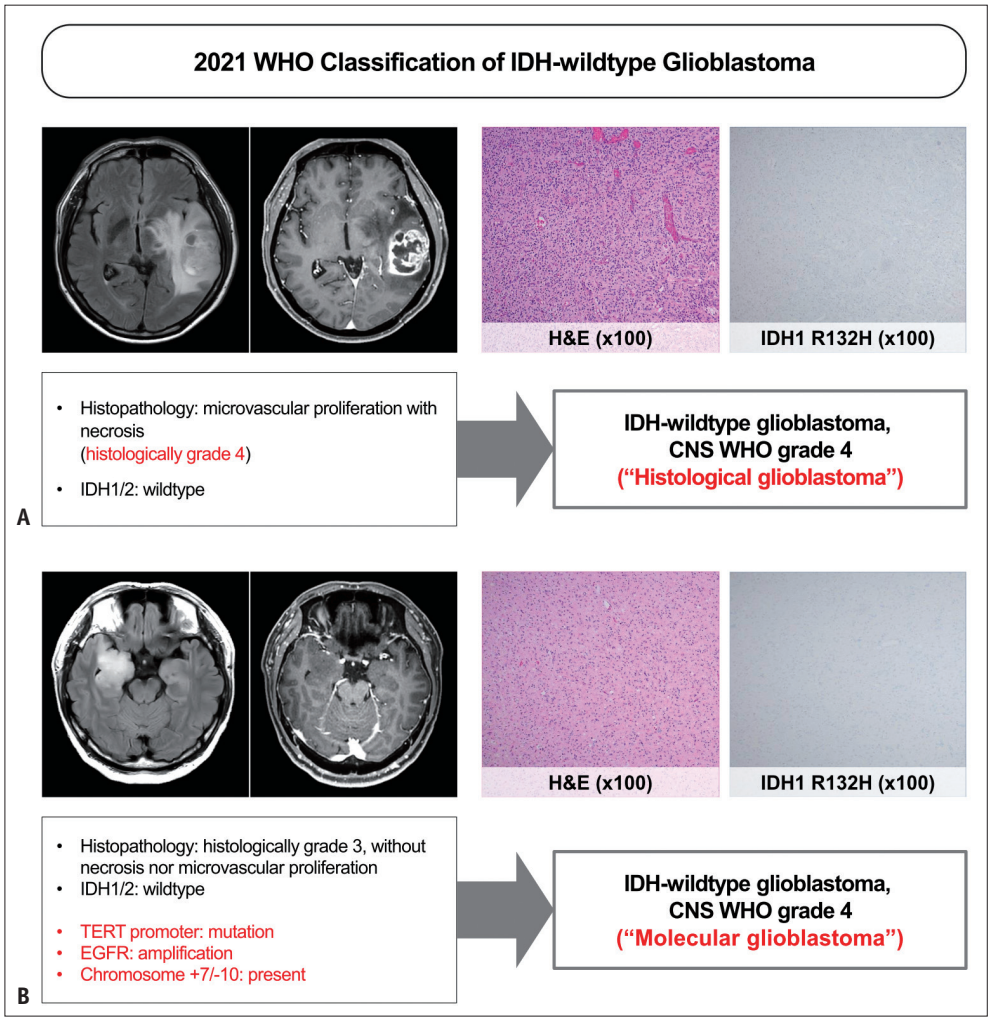

Fig. 1. Examples of the diagnosis of IDH-wildtype glioblastoma according to the 2021 WHO classification in two patients. **A:** A 72-year-old male with a contrast-enhancing tumor with central necrosis and edema at the left temporal lobe underwent surgery. On histopathology, there were microvascular proliferation and necrosis in the diffuse astrocytic glioma. IDH1/2 mutation was negative. As histological features of either microvascular proliferation or necrosis in an IDH-wildtype diffuse astrocytic glioma are sufficient for diagnosis, this patient was diagnosed as IDH-wildtype glioblastoma, CNS WHO grade 4 ("histological glioblastoma"). **B:** A 53-year-old male with a non-enhancing tumor centered at the right temporal lobe underwent surgery. On histopathology, there was no necrosis nor microvascular proliferation in the diffuse astrocytic glioma, but the mitotic activity was increased with cytological atypia, showing histologically grade 3 features. Testing for IDH1/2 mutation was negative. On NGS, there was evidence for *TERT* promoter mutation, *EGFR* amplification, and chromosome +7/-10. As the presence of any one of these genetic features is sufficient for the diagnosis of IDH-wildtype glioblastoma, the patient was diagnosed with IDH-wildtype glioblastoma, CNS WHO grade 4 ("molecular glioblastoma"). IDH = isocitrate dehydrogenase, WHO = World Health Organization, CNS = central nervous system, NGS = next-generation sequencing, *TERT* = telomerase reverse transcriptase, *EGFR* = epidermal growth factor receptor, H&E = hematoxylin and eosin

https://doi.org/10.3348/kjr.2024.0982

Korean Journal of Radiology
KJR

IDH-mutant astrocytoma. In contrast, apart from the traditional definition of IDH-wildtype glioblastoma that is diagnosed based on characteristic histological presence of microvascular proliferation or necrosis ("histological glioblastoma"), IDH-wildtype diffuse gliomas previously assigned to histological grade 2 or 3 are now being defined as IDH-wildtype glioblastoma in the presence of qualifying molecular markers (including *TERT* promoter mutation, *EGFR* gene amplification, and chromosome +7/-10) ("molecular glioblastoma") [13]. The 2021 WHO classification of CNS tumor grading no longer relies exclusively on histological features; thus, CNS WHO grade 4 can be designated to all IDH-wildtype gliomas despite the histologically lower-grade appearance. Figure 1 shows examples of the diagnosis of IDH-wildtype glioblastoma, CNS WHO grade 4.

The Future of Pathological Diagnosis in IDH-Wildtype Glioblastoma

DNA methylation profiling of cytosines in CpG sites throughout the genome is an epigenetic marker that serves as a critical regulator of gene expression, accurately reflecting the cell of origin that remains constant throughout the course of the disease [22]. In the current 2021 WHO classification, DNA methylation profiling is not essential for establishing the diagnosis of IDH-wildtype glioblastoma. Currently existing subtypes, such as giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma, are diagnosed histopathologically. Notably, select tumor types or subtypes require DNA methylation profiles, such as high-grade astrocytomas with piloid features and diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, as well as tumor subtypes such as RTK1, RTK2, and MYCN subtypes within diffuse pediatric high-grade glioma, H3 wildtype, and IDH-wildtype [13]. Nevertheless, tumor subtyping in glioblastoma patients may help in prognostication but therapeutic implications remain to be established in clinical practice [23].

In the next years, new glioblastoma subtypes might be introduced into the WHO classification and DNA methylation profiling results will therefore be required for diagnosing these subtypes. The Cancer Genome Atlas (TCGA) classifier was one of the largest projects that aimed to better define subgroups of IDH-wildtype glioblastoma based on DNA methylation data [24]. Following the TCGA, the Methylation Classifier developed by DKFZ shows a glimpse of the next step of the WHO classification (https://www.molecularneuropathology.org/mnp) [25,26]. In this classifier, IDH-wildtype glioblastoma is further divided into methylation class (MC) subtypes according to its molecular features, such as RTK1, RTK2, mesenchymal, primitive neuronal component, and posterior fossa subtypes. The imaging findings and prognosis of these subtypes are only partially revealed. MC RTK1 subtype shows an enrichment of *PDGFRA* amplification (up to 30%), while MC RTK 2 subtype shows the highest frequency of *EGFR* amplification (up to 60%). MC mesenchymal subtype shows a high incidence of chromosome +7/-10, whereas MC primitive neuronal component shows a poorly differentiated histological phenotype with high rates of leptomeningeal metastases. The characteristics of MC posterior fossa subtype apart from its location in cerebellum are yet to be revealed. An update in the WHO classification incorporating DNA methylation profiling will enable further research to gain insights into imaging findings, prognosis, and possible treatment strategies according to these subtypes.

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

Radiologists' key role in imaging of IDH-wildtype glioblastoma in the preoperative and immediate postoperative setting can be summarized as follows: 1) pointing toward the diagnosis of histological glioblastoma, separate from other confounding common differential diagnoses on imaging such as brain metastases, lymphoma involvement, or abscess, guiding clinicians toward a correct treatment decision, 2) suggesting the possibility of molecular glioblastomas preoperatively, which is difficult to suspect but not impossible, 3) accurately delineating the extent of tumor on baseline imaging, with special emphasis on the non-enhancing tumor, because this information is important to neurosurgeons to plan maximum resection of non-enhancing tumor in addition to maximum resection of contrast-enhancing tumor; and 4) accurately delineating the extent of residual tumor on immediate postoperative imaging, apart from confounders such as ischemia or postoperative edema, because the extent of residual contrast-enhancing and non-enhancing tumor is important for prognostication for clinicians, as well as planning the radiation field for radiation oncologists.

Recommended Imaging Protocol

The recommended MRI protocol of adult gliomas for clinical

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trials includes 3D pre-contrast and post-contrast T1-weighted (T1), 2D post-contrast T2-weighted (T2) and pre-contrast fluid-attenuated inversion recovery (FLAIR) (3D FLAIR is an optional alternative to 2D FLAIR), and 2D diffusion-weighted imaging (DWI) [27]. Perfusion imaging, such as dynamic susceptibility contrast (DSC) imaging, provides more detailed information on the underlying tumor physiology and should be routinely used for baseline imaging as well as during follow-up in the clinical setting. Arterial spin labeling (ASL) may be an alternative technique to DSC in scenarios where contrast agent administration is not feasible; however, it is important to note that ASL only provides cerebral blood flow and has a lower spatial resolution and signal-to-noise ratio than DSC [28]. MR spectroscopy also provides more information on tumor metabolism, which is applied in some institutions in confounding cases. Post-contrast FLAIR is not a routinely recommended sequence in glioma but has been recently demonstrated useful in detection of leptomeningeal metastases [29,30]. Diffusion tensor imaging and task-based or resting state functional MRI may be helpful for surgical guidance.

In terms of PET imaging, amino acid PET may be useful at preoperative and immediate postoperative imaging [31,32] but at present is mostly approved to differentiate treatment-related change from tumor recurrence in Europe, whereas no approval is received in the U.S. [33]. The amino acid tracer ^{18}FET is most commonly used, along with ^{11}C-MET and ^{18}F-DOPA. Glucose FDG is of little use because the high physiological FDG uptake in gray matter brain structures reduces the detectability.

Information for Preoperative Communication

The current 2021 WHO classification combines histological glioblastoma and molecular glioblastoma as a singular tumor type, "IDH-wildtype glioblastoma, CNS WHO grade 4." However, there are concerns that histological glioblastomas and molecular glioblastomas may behave differently, although studies reporting on comparative outcomes remain limited [34]. Experts have expressed concerns about fully combining histological glioblastomas and molecular glioblastomas when the clinical and therapeutic implications of this broadened glioblastoma definition are not yet fully elucidated [4]. Moreover, the imaging characteristics of histological glioblastoma and molecular glioblastoma are also different. Thus, we will divide IDH-wildtype glioblastoma into histological glioblastoma and molecular glioblastoma and provide separate descriptions.

Histological Glioblastoma

Clinical Perspective

The median age of diagnosis of histological glioblastoma is 64 years [1]. The initial presentation of histological glioblastoma is frequently non-specific, including new-onset epilepsy, focal neurologic deficits, neurocognitive impairment, and signs and symptoms of raised intracranial pressure [3]. Although this clinical presentation does not greatly help in diagnosing histological glioblastoma before imaging is acquired, the onset of symptoms developing gradually over weeks to months can help it differentiate from cerebral ischemia or hemorrhage [35], which typically present with acute symptoms. Signs of systemic inflammation and a thorough discussion with the patient may aid in distinguishing between infections and a tumor, and a past medical history of known malignancy may raise concern for a brain metastasis rather than a primary brain tumor. These patients also present poorly in the Karnofsky Performance Scale compared to patients with IDH-mutant gliomas.

Approach to Differential Diagnosis

Although there are various differential diagnoses based on imaging for histological glioblastoma, because other diseases such as cerebral abscess can be relatively easily ruled out by characteristic imaging manifestations based on an adequate preoperative MRI protocol (by diffusion restriction on the central necrotic portion), we will focus on differential diagnoses including lymphoma involving the CNS and brain metastasis. IDH-wildtype glioblastoma, lymphoma involving the CNS (the previous term primary CNS lymphoma may be considered imprecise according to the 5th WHO edition's definition of hematolymphoid tumors and is no longer recommended for referring specifically to primary diffuse large B-cell lymphoma of the CNS) [36], and brain metastasis are the most common intra-axial malignant brain tumors in adults. Each of these tumors results in different clinical management and prognosis. Glioblastoma requires maximal safe surgical resection followed by concurrent chemoradiation and adjuvant temozolomide [37]. The standard treatment for lymphoma is rituximab- and methotrexate-based chemotherapy induction followed by consolidation with autologous stem cell transplantation after diagnostic biopsy. In case of brain metastasis, identification of the primary malignancy is necessary, and

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Korean Journal of Radiology
KJR

the appropriate treatment varies according to the primary tumor type, molecular type, performance status, and size/number of brain metastases. As noninvasive preoperative diagnosis serves as a crucial tool for subsequent diagnostic workup and surgical approach, radiologists should strive to provide a rational and accurate diagnosis to clinicians on the initial imaging.

The details of clinical and imaging characteristics in IDH-wildtype glioblastoma, lymphoma involving the CNS, and brain metastasis are presented in Table 1. In this paragraph, we will present several simple approaches to understand the imaging manifestations. As imaging reflects insight into the histology based on the spatial scale within the resolution of the imaging technique applied, understanding the histopathology of each tumor enables understanding of imaging manifestations of each disease. IDH-wildtype glioblastoma is histologically notorious for its infiltrative spread with invasion of neighboring brain structures and microvascular proliferation and necrosis (again, these two actually constitute the diagnostic criteria of the WHO classification) [13]. Thus, apart from the typical ring-enhancing tumor with central necrosis, IDH-wildtype glioblastomas also frequently show non-enhancing tumor areas [38]. In these cases, the possibility of lymphoma or brain metastasis can be strongly ruled out, although rare cases of non-enhancing lymphoma involvement do exist [36,39]. On the other hand, microvascular proliferation leads to increased relative cerebral blood volume (rCBV) on DSC imaging. Among three tumor types, lymphoma involving the CNS is histologically characterized by its 1) marked hypercellularity with highly proliferative tumor cells and smaller extravascular space and 2) an angiocentric growth pattern [40]. The hypercellularity is reflected on imaging as hyper-attenuation on non-contrast CT, marked hypo-intensity on T2, and marked diffusion restriction showing low apparent diffusion coefficient (ADC) value on DWI [36]. The angiocentric growth pattern of lymphoma with the absence of neoangiogenesis is reflected as low-to-intermediate rCBV. In brain metastasis, the presence of an underlying systemic malignancy is the strongest clue for diagnosis in case of metachronous (development of brain metastasis after treatment of primary cancer) or synchronous (simultaneous diagnosis of primary cancer and brain metastases) presentation, which constitute most cases [41]. Thus, seeking out for this information (with available clinical record or looking for clues in other available abdominal or chest images) is worthwhile. Multiplicity is also a strong clue, although up to 30% of brain metastasis may show a single lesion [42]. ADC values or rCBV values may be of lesser usage in differentiating between histological glioblastoma and brain metastasis. Figure 2 shows typical imaging and histological manifestations of histological glioblastoma, lymphoma involvement of CNS, and brain metastasis.

Imaging Findings

Approximately 90% of IDH-wildtype glioblastomas are located in the supratentorial compartment and usually involve the subcortical white matter. Imaging of histological glioblastomas is what we have perceived as imaging of "classical" glioblastomas for a long time. Typical conventional imaging findings of histological glioblastomas include infiltrative nature on T2 or FLAIR imaging, heterogeneous signal intensity, strong peripheral ring-enhancement with prominent central necrosis, and internal hemorrhage [43]. Calcifications are rare. Although the term "infiltrative" is used rather ambiguously and loosely among radiologists upon the basis that glioma cells extend diffusively on microscopy, for clarity, we will define "infiltrative" as the size of pre-contrast T1 abnormality much smaller than the size of FLAIR abnormality of the tumor, following the VASARI lexicon [44]. Less than 1% of histological glioblastomas show no or minimal (less than 1 cm^3) contrast enhancement, with a significantly better prognosis than those with strong contrast enhancement [45]. The presence of partial T2-FLAIR mismatch in the non-enhancing tumor portion points out toward the diagnosis of IDH-mutant astrocytoma, CNS WHO grade 4, rather than a histological glioblastoma [46].

Multifocal or multicentric location is reported in up to 10% of histological glioblastomas [45] and is a strong clue for diagnosing towards IDH-wildtype glioblastomas compared to IDH-mutant astrocytomas or IDH-mutant 1p/19q-codeleted oligodendrogliomas. "Multifocal" is often defined as having at least one region of tumor, either contrast-enhancing or non-enhancing, which is not contiguous with the dominant lesion and is outside the region of signal abnormality surrounding the dominant mass, resulting from dissemination by an established route (i.e., via commissures or cerebrospinal fluid [CSF] channels), whereas "multicentric" are widely separated lesions that cannot be attributed to any aforementioned pathway [44]. In our experience, differentiating multifocal from multicentric distribution is not always clear-cut and some gray area exists. Gliomatosis

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Table 1. Clinical and imaging characteristics in IDH-wildtype glioblastoma, lymphoma involving the CNS, and brain metastasis

	IDH-wildtype glioblastoma	Lymphoma involving the CNS	Brain metastasis
Clinical			
Incidence	m/c primary malignant tumor	Less common, 7% of all malignant tumors	m/c CNS neoplasm (up to 50%)
History	NA	NA	History of an underlying primary malignancy is a strong clue for diagnosis
Median age	64	66	57–63
Male:female	1.6:1	1.1–1.5:1	Ratio differs by the underlying primary malignancy
Imaging			
Noncontrast CT	Usually hypoattenuating	Frequently hyperattenuating	Usually hypoattenuating
Conventional MRI			
Location	Usually located supratentorially (>90%), involves subcortical white matter	Usually located supratentorially (>80%), frequently involves corpus callosum	m/c at gray-white matter junctions, up to 15% localize at the cerebellum
Multiplicity	Rare (less than 10%)	Single (65%–70%) or multiple (30%–35%) lesions	Multiple lesions are common but up to 25% can be single brain metastasis
Corpus callosum involvement	Common	Common	Rare
T2 signal	Typically hyperintense	Typically markedly hypointense	Typically hyperintense
Ring-enhancement with necrosis	m/c	Less common, seen in immunocompromised patients	Possible
Homogeneous enhancement	Rare	Common	Common
Shape of CE tumor	Non-spherical (d/t anisotropic growth along the white matter)	Non-spherical	Spherical
Presence of NE tumor component	If visible, strongly assists toward diagnosis	No	No
Calcification	Rare if untreated	Rare if untreated	Rare if untreated
Hemorrhage	Common	Less common, but up to 50% when evaluated with SWI	Less common
Leptomeningeal involvement	Possible	Possible but rare	Possible
Advanced MRI findings			
ADC	Similar to normal white matter in solid component, may show areas of slightly low ADC	Markedly low ADC	Variable
rCBV	High rCBV, intermediate PSR	Low-to-intermediate rCBV, high PSR [49]	Variable rCBV, low-to-intermediate PSR [49]
MR spectroscopy	Higher Cho/Cr ratio than brain metastasis	Higher Cho/Cr ratio than brain metastasis Higher lipid and acetate levels [101]	Lower Cho/Cr ratio than histological glioblastoma or lymphoma involvement [102]
APT	Higher APT signal in CE tumor than lymphoma	Lower APT signal in CE tumor [102]	Similar or lower APT signal in CE tumor, lower APT signal in peritumoral edema than NE tumor in histological glioblastoma [103]
Clinical course			
Treatment	Maximal safe resection followed by concurrent chemoradiation therapy and adjuvant temozolomide	High-dose chemotherapy-based induction and consolidation with autologous stem cell transplantation	Variable according to underlying histology, molecular type, performance status, and size/number of brain metastases
Prognosis	Median OS less than 18 months	Median OS less than 37 months	Median OS less than 19 months, differs according to underlying malignancy stage, performance status, etc

IDH = isocitrate dehydrogenase, CNS = central nervous system, m/c = most common, NA = not available, T2 = T2-weighted, CE = contrast-enhancing, d/t = due to, NE = non-enhancing, SWI = susceptibility weighted imaging, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, PSR = pecrertage signal recovery, Cho/Cr = choline-to-creatine ratio, APT = amide proton transfer, OS = overall survival

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Korean Journal of Radiology
KJR

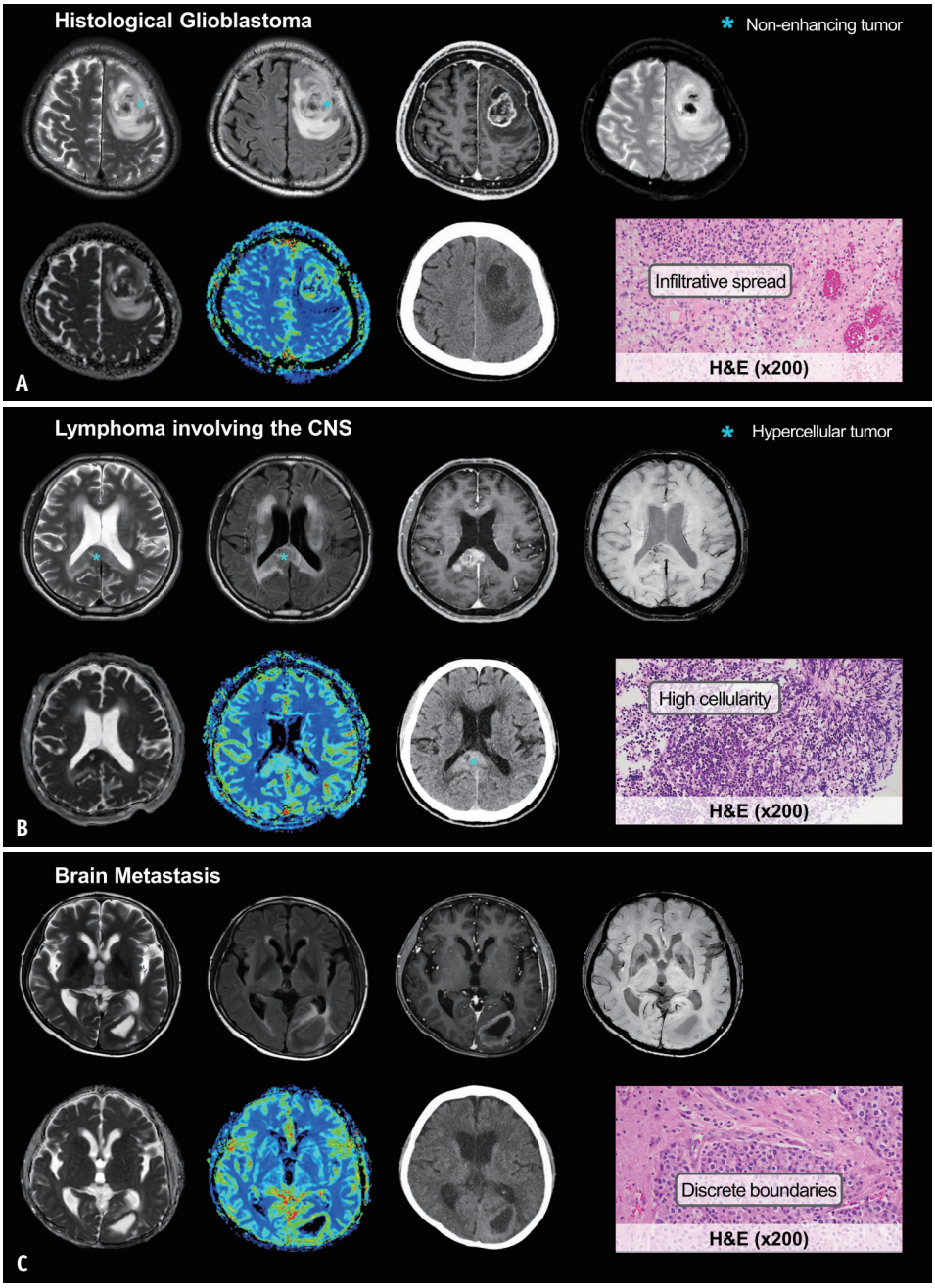

Fig. 2. Typical imaging and histological manifestations of histological glioblastoma, lymphoma involving the CNS, and brain metastasis. **A:** A 63-year-old male with histological glioblastoma, showing a ring-enhancing tumor with central necrosis at the left frontal lobe. A non-enhancing tumor is noted laterally to the contrast-enhancing tumor (asterisks), increasing the confidence of preoperative diagnosis of histological glioblastoma. The tumor shows marked hemorrhage on the T2* GRE image, some areas of increased cellularity of ADC map, and markedly increased rCBV. On non-contrast CT, a predominantly hypoattenuating mass with peritumoral edema is noted. **B:** A 66-year-old male with lymphoma involving the CNS, showing a relatively homogeneously contrast-enhancing mass involving the corpus callosum splenium. The hypercellularity of lymphoma involvement translates into marked T2/FLAIR hypo-intensity (asterisk), low ADC value, and a hyperattenuating mass on non-contrast CT (asterisk). Minimal hemorrhage is seen in this lesion on SWI, which is common in lymphoma involvement. Relatively mild rCBV elevation is noted because there is no neoangiogenesis. **C:** A 66-year-old female with single brain metastasis, showing a ring-enhancing tumor with central necrosis at the left occipital lobe. The tumor shows minimal hemorrhage on SWI, increased cellularity of ADC map, and markedly increased rCBV. On non-contrast CT, a slightly hyperattenuating mass with peritumoral edema is noted. The patient was diagnosed with breast cancer 6 years ago, and also had lung and bone metastases, which increased the confidence in the diagnosis of single brain metastasis. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. CNS = central nervous system, GRE = gradient echo, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, SWI = susceptibility weighted imaging, H&E = hematoxylin and eosin

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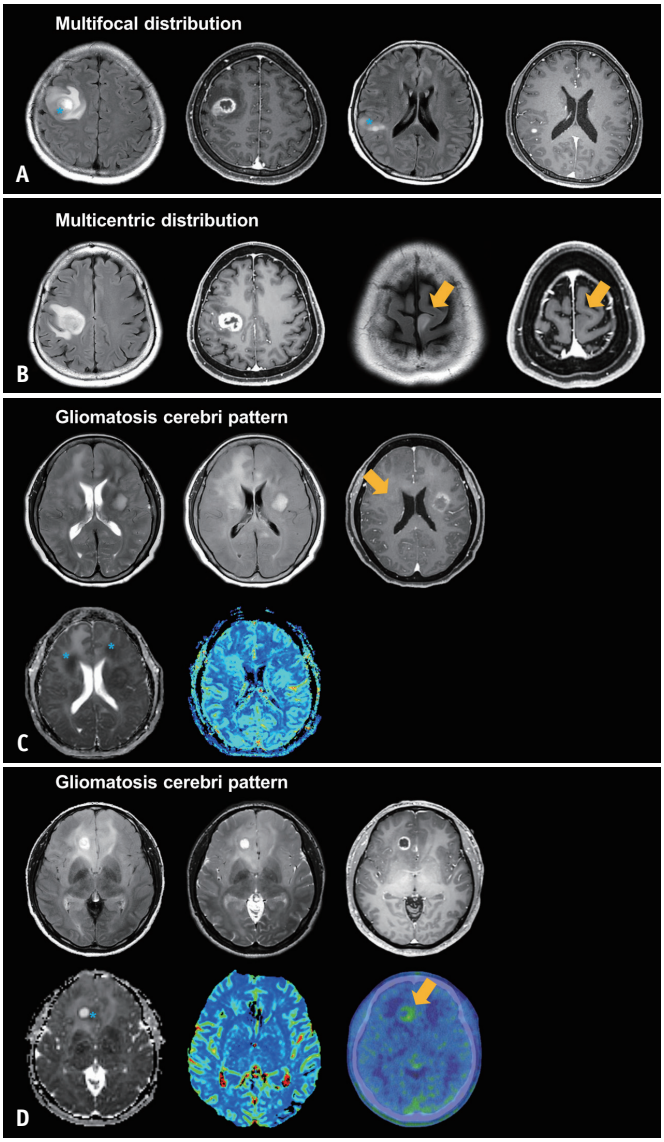

Fig. 3. Examples of histological glioblastoma showing multifocal or multicentric distribution, or gliomatosis cerebri in four patients. **A:** A 60-year-old female with a ring-enhancing tumor and central necrosis at the right frontal lobe. Another separate small contrast-enhancing tumor is noted in the right parietal lobe. As both contrast-enhancing tumors had adjacent non-enhancing tumors (asterisks), the possibility of brain metastases was not considered in this multifocal imaging manifestation and IDH-wildtype glioblastoma was the preoperative impression. **B:** A 61-year-old female with a ring-enhancing tumor and central necrosis at the right frontal lobe. The radiology resident missed the non-enhancing tumor located separately at the left superior frontal gyrus (arrows), and this lesion was detected by a senior neuroradiologist. In clinical practice, non-enhancing tumors with multifocal or multicentric distribution can be frequently missed due to the satisfaction of search error. **C:** A 62-year-old female with a ring-enhancing tumor and central necrosis at the left frontal lobe. Minimal faint enhancement is also noted at the right corona radiata without any discernable mass (arrow). On the underlying background, there is diffuse non-enhancing infiltrative tumor involving the bilateral cerebral hemispheres with relative preservation of the anatomic architecture. Apart from the contrast-enhancing portion of the tumor showing decreased ADC and slightly increased rCBV, decreased ADC and slightly elevated rCBV are also noted at some portions of the infiltrative non-enhancing tumor (asterisks). **D:** A 33-year-old male with a ring-enhancing tumor and central necrosis at the right frontal lobe. The patient also shows a diffuse non-enhancing infiltrative tumor involving the bilateral cerebral hemispheres, suggesting gliomatosis cerebri pattern. A focal area of non-enhancing tumor medial to the enhancing tumor shows decreased cellularity without definite rCBV elevation (asterisk). On amino acid PET (^{11}C-methionine PET), there is only increased tracer uptake in the contrast-enhancing tumor but not in the non-enhancing tumor except for the spill-out partial volume effect (arrow). Most of the infiltrative non-enhancing tumor with gliomatosis cerebri does not show decreased ADC, increased rCBV, nor increased amino acid tracer uptake. It should be noted that amino acid PET does not always delineate the full extent of non-enhancing tumors, as seen in this case. 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, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume

https://doi.org/10.3348/kjr.2024.0982

Korean Journal of Radiology
KJR

cerebri appearance, which refers to diffuse infiltration of a tumor involving three or more consecutive lobes with relative preservation of the underlying anatomical architecture on T2 or FLAIR, is seen in up to 8% of histological glioblastomas [47]. This appearance is associated with a poor prognosis [47]. Figure 3 shows representative cases of multifocal/multicentric distribution and gliomatosis cerebri pattern.

Leptomeningeal metastases may be seen in up to 11% of histological glioblastomas on initial diagnosis, especially when using CSF-sensitive post-contrast FLAIR [30], although this early detection of leptomeningeal metastases is probably much less with standard-of-care postcontrast T1 imaging alone. This information may be of importance because the presence of leptomeningeal metastases on initial diagnosis is an independent prognostic factor in patients with IDH-wildtype glioblastoma [30] and may change the treatment strategy (i.e., radiation field) in some institutions according to the extent of involvement [30,48]. Figure 4 shows representative cases of leptomeningeal metastases on baseline preoperative imaging.

On advanced imaging, regions of intermediate-to-low ADC and high rCBV within the solid component is observed. The percentage signal recovery, which reflects the complex interplay of capillary permeability and contrast agent extravasation from tumor capillaries, is lower than that of lymphoma involvement of CNS [49]. On MR spectroscopy, choline, lactate, and lipids are increased, whereas the N-acetylaspartate (NAA) and myoinositol are decreased [50].

Differentiation of Non-Enhancing Tumor and Peritumoral Edema

Differentiation between non-enhancing tumor and peritumoral edema on preoperative imaging in histological glioblastoma is difficult and has been relatively neglected

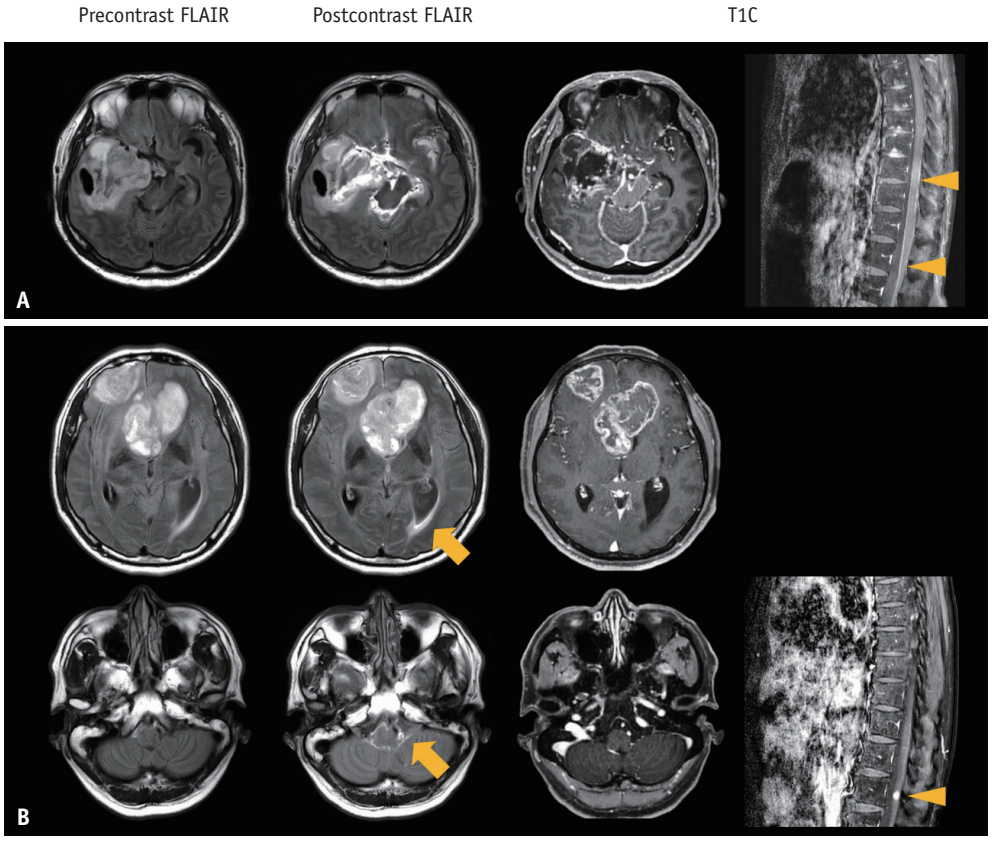

Fig. 4. Representative cases of histological glioblastomas with leptomeningeal metastases on preoperative imaging. **A:** A 66-year-old male with a ring-enhancing tumor and central necrosis at the right temporal lobe. Diffuse leptomeningeal metastases are well delineated on both postcontrast FLAIR and T1C imaging. Diffuse leptomeningeal metastases also extended throughout the entire spinal cord surface on whole spine MRI (arrowheads). **B:** A 57-year-old male presenting with ring-enhancing tumors and central necrosis at bifrontal lobes and corpus callosum genu. Leptomeningeal metastases are best delineated on postcontrast FLAIR as enhancements along the ependymal lining of left lateral ventricle and lower brainstem surface (arrows), but it is difficult to delineate these areas on postcontrast T1C imaging. The patient showed nodular leptomeningeal metastases on whole spine MRI at the L-spinal cord level (arrowhead). T1C = postcontrast T1-weighted

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by radiologists for a long time. This could have been due to several reasons: 1) accurately delineating non-enhancing tumor was presumed to have to have no real impact on the next clinical step in treatment of IDH-wildtype glioblastoma and was only speculated to have impact on the initial step of differential diagnosis (i.e., differentiation of histological glioblastoma from lymphoma involvement or brain metastasis), and 2) radiologists were nihilistic about differentiating non-enhancing tumor from peritumoral edema on imaging because it is well known that glioma cells infiltrative much beyond lesion margins visible on imaging. Thus, delineating non-enhancing tumor based on MRI seemed futile and inaccurate.

However, clinical studies based on MRI delineation of non-enhancing tumor have brought game-changing concepts. Currently, the earlier controversy regarding whether a reduction in non-enhancing tumor can improve survival in IDH-wildtype glioblastoma [51] has been resolved in recent large studies showing that a reduction in non-enhancing tumors has independent prognostic significance [52,53]. Based on a multi-national study, the RANO resect group has validated that a resection beyond the contrast-enhancing tumor margin and into the non-enhancing tumor region of the FLAIR abnormality (termed "supramaximal" resection) has a significant impact for improved overall survival [53]. As peritumoral edema is usually more extensive than non-enhancing tumor, resecting the entire T2 high area containing both non-enhancing tumor and peritumoral edema is not a feasible approach. Thus, radiologists should strive to preoperatively point out the non-enhancing tumor area on MRI, separate from peritumoral edema, to guide surgical strategy.

Table 2 shows imaging characteristics to differentiate between non-enhancing tumor and peritumoral edema. On conventional MRI, non-enhancing tumors usually show a slightly lower T2 signal than peritumoral edema, with gray matter involvement and eccentric location around the contrast-enhancing tumor, whereas the adjacent anatomical tissue architecture is usually destroyed [38,54]. On advanced MRI, some areas of non-enhancing tumors may show lower ADC value, higher rCBV value, or increased choline and decreased NAA on MR spectroscopy [38,55]. On amino acid PET, there may be areas of metabolically active tumor areas by increased tracer uptake [56,57]. However, in literature as well as in our experience, non-enhancing tumors do not always show change on advanced MRI nor amino acid PET [32,38,57,58]. Thus, although apparent changes on advanced MRI sequences or amino acid PET may raise the confidence of delineating non-enhancing tumors, absence of these changes does not ensure that this is not a non-enhancing tumor. Figure 5 shows representative cases to differentiate between non-enhancing tumor and peritumoral edema.

Imaging Correlates of Molecular Markers

Among various molecular markers, O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation, which is present in approximately 40%–50% of IDH-wildtype glioblastomas, is undoubtedly one of the most important clinically relevant markers. The presence of *MGMT* promoter methylation is not only a predictive biomarker of temozolomide response but also a strong prognostic factor [59,60]. On the other hand, the prognostic impact of molecular markers such as *EGFR* amplification or *TERT* promoter mutation status in IDH-wildtype glioblastomas are debatable [61-63]. The study of radiogenomics, which

Table 2. Imaging features for differentiating NE tumor and peritumoral edema in IDH-wildtype glioblastoma

	NE tumor	Peritumoral edema
Conventional MRI	Hypointense to isointense compared with CSF on T2/FLAIR	Isointense to hyperintense compared with CSF on T2/FLAIR
	Gray matter involvement	Spares the gray matter
	Eccentric around CE tumor	Relatively concentric around CE tumor
	Destruction of anatomical tissue architecture	Unaffected anatomical tissue architecture
Advanced MRI	Possible lower ADC value, but not always	Higher ADC value
	Possible higher rCBV, but not always	No rCBV elevation
	MR spectroscopy may show increased Cho/Cr or Cho/NAA ratios	No increase in Cho/Cr or Cho/NAA
Amino acid PET	May show areas of metabolically active tumor areas by increased tracer uptake, but not always	No increase in tracer uptake

NE = non-enhancing, IDH = isocitrate dehydrogenase, CSF = cerebrospinal fluid, T2 = T2-weighted, CE = contrast-enhancing, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood volume, Cho/Cr = choline-to-creatine ratio, NAA = N-acetylaspartate

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Korean Journal of Radiology
KJR

denotes the relationship between the imaging features of a particular disease and various genetic or molecular features, has been previously studied in glioblastomas. However, we believe that current results are inconclusive and there are no validated imaging findings to predict molecular markers such as *MGMT* promoter methylation, *EGFR* amplification, or *TERT* promoter mutation status in histological glioblastomas. Previous studies based on the 2016 WHO classification

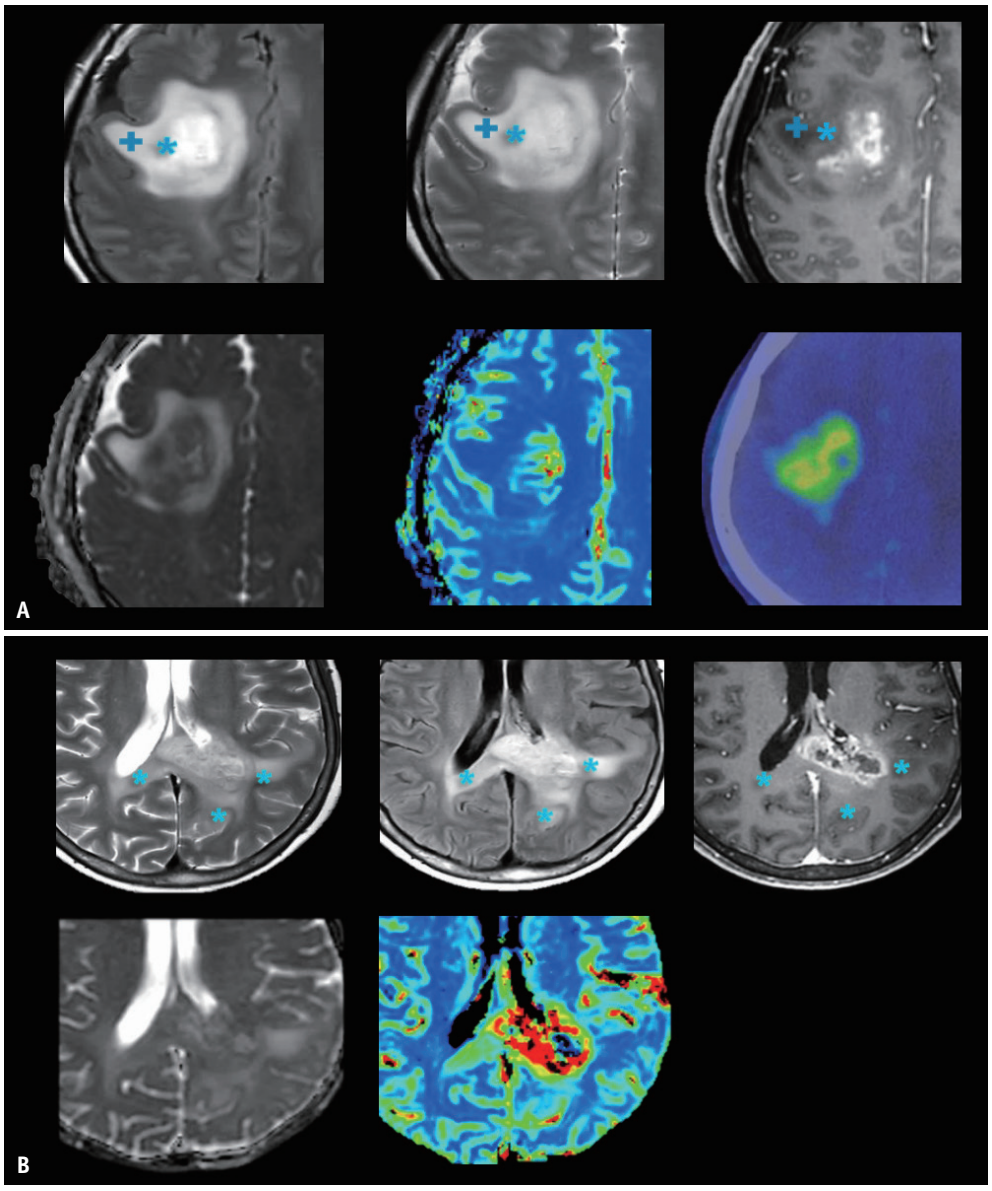

Fig. 5. Examples of differentiation between non-enhancing tumor and peritumoral edema. **A:** A 66-year-old female presenting with a heterogeneously enhancing tumor at the left frontal lobe. On T2 and FLAIR, the peritumoral edema (cross sign) spares the cortex and shows higher signal intensity than non-enhancing tumor (asterisks), and high ADC signal on peritumoral edema is observed, whereas the non-enhancing tumors shows low ADC value. The rCBV is only elevated in the contrast-enhancing tumor but not in the non-enhancing tumor. On ^{11}C-acetate PET, increased tracer uptake is also seen in the non-enhancing tumor in addition to enhancing-tumor, but not in the peritumoral edema. **B:** A 58-year-old female with a ring-enhancing tumor and central necrosis involving the corpus callosum splenium and left parietal lobe. In this image, there are slightly expansile non-enhancing tumors (asterisks) eccentric to the enhancing tumor, involving the right side of corpus callosum splenium, left occipital lobe, and left parietal lobe. The ADC shows a minimal decrease in the non-enhancing tumor involving the right side of corpus callosum splenium, and the rCBVs of the non-enhancing tumors involving the right side of the corpus callosum splenium and right occipital lobe are also mildly increased, although less than that of the contrast-enhancing tumor. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. T2 = T2-weighted, ADC = apparent diffusion coefficient, rCBV = relative cerebral blood value

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incorporated both histological glioblastomas and IDH-mutant astrocytomas, CNS WHO grade 4, to discover imaging correlates of molecular features [64-66], and may be inherently biased because *MGMT* promoter methylation, *EGFR* amplification, and *TERT* promoter mutation status are significantly correlated with IDH mutation status; IDH-mutant astrocytomas, WHO grade 4, show a significantly higher rate of *MGMT* promoter methylation and a lower rate of *EGFR* amplification and *TERT* promoter mutation than IDH-wildtype glioblastomas [4]. Further studies are warranted to discover an imaging correlate with molecular markers; these studies should be performed exclusively in IDH-wildtype glioblastomas.

Molecular Glioblastoma

Clinical Presentation

Molecular glioblastomas constitute less than 10% of IDH-wildtype glioblastomas [67], and this rate is likely much lower in Asians [68]). Whether the clinical manifestation and prognosis of molecular glioblastomas are identical or discordant to histological glioblastomas is highly debatable. Although the 2021 WHO classification does not separate the terminology between molecular glioblastomas and histological glioblastomas and most studies show a similar overall survival between these two [18-20,69,70], some other reports showed that molecular glioblastomas have a slightly favorable prognosis than histological glioblastomas [34,68,71]. A slightly younger age of molecular glioblastomas compared to histological glioblastomas has been also reported [72].

Are They Simply Histological Glioblastomas Detected at an Earlier Stage?

Prior to the acknowledgement of molecular glioblastomas, there were cases reporting that patients with initial MRI findings of non-enhancing tumors rapidly developed ring enhancement and central necrosis within a short period of follow-up and were pathologically confirmed as histological glioblastomas [73,74]. Such cases are rare but can be encountered to radiologists in clinical practice (representative cases presented in Fig. 6). Thus, several studies have suggested that molecular glioblastomas showing little or no contrast enhancement may represent an early or evolving clinical presentation of histological glioblastomas [75,76]. However, not all reports support the notion that molecular glioblastomas and histological glioblastomas are biologically similar; several studies showed that histologically grade 2 molecular glioblastoma patients with "isolated *TERT* promoter mutation" (*TERT* promoter mutation without accompanying *EGFR* amplification or chromosome +7/-10) demonstrated better prognosis than other molecular glioblastomas and histological glioblastomas [34,71].

On the other hand, a small proportion of molecular glioblastomas that underwent limited surgical sampling of a mass may show imaging features similar to that of histological glioblastoma (i.e., ring enhancement with central necrosis), and the UCSF group suggests that these may be "undersampled histological glioblastomas" rather than true molecular glioblastomas [76]. We agree with this suggestion and will omit the description of imaging features of possible "undersampled histological glioblastomas" in this section.

Imaging Findings

Preoperative prediction of molecular glioblastoma may assist postoperative therapeutic decisions because NGS results may take some time. In addition, as the extent of resection is still important in molecular glioblastomas [45], radiologists should accurately delineate the non-enhancing tumor portion, although this is much easier in molecular glioblastoma compared to histological glioblastomas. In our experience, it is difficult to suggest the possibility of molecular glioblastoma on preoperative imaging. Nonetheless, there are several clinical and imaging characteristics that strongly point out toward increased possibility. An older patient age points out toward the possibility of a molecular glioblastoma even in tumors without contrast enhancement compared to younger patients with IDH-mutant astrocytomas or oligodendrogliomas, which also frequently show no contrast enhancement, but there may be overlap in age [77].

Many molecular glioblastomas may be misdiagnosed as stroke on initial imaging work-up due to non-enhancing cortical involvement [78]. Approximately 55%–65% of molecular glioblastomas do not show contrast enhancement and are composed of entirely non-enhancing portions. Even those with contrast enhancement usually exhibit a much larger proportion of non-enhancing tumors [79]; the contrast-enhancing tumor portion may be faint or nodular and usually constitutes a small portion of the entire tumor volume [80]. Cortical involvement is common, whereas necrosis, cystic change, calcification, or hemorrhage is rare

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Korean Journal of Radiology
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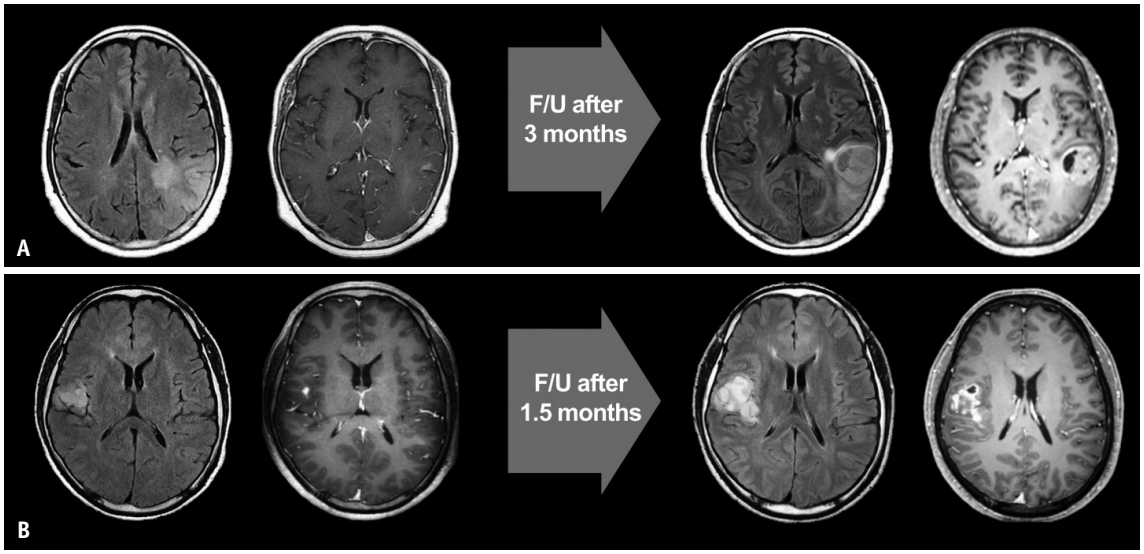

Fig. 6. Representative cases showing the imaging evolution of pathologically confirmed histological glioblastomas. These cases were diagnosed more than 10 years ago, when the superiority of early surgery compared to the "wait and see" approach was debatable in so-called low-grade gliomas without contrast enhancement (the term "low-grade gliomas" is now outdated because non-enhancing tumors can also be high-grade). As molecular glioblastomas usually show no or minimal contrast enhancement, these cases may support the notion that molecular glioblastomas are histological glioblastomas detected at an early stage. **A:** A 63-year-old female presenting with an infiltrative non-enhancing tumor involving the left temporooccipital lobe. Follow-up imaging obtained 3 months later shows a typical histological glioblastoma with ring enhancement and central necrosis in the background of infiltrative non-enhancing tumor. **B:** A 49-year-old male presenting with an infiltrative non-enhancing tumor with focal contrast-enhancing area involving the right temporal lobe. Follow-up imaging obtained 1.5 months later shows a typical histological glioblastoma with ring enhancement and central necrosis in the background of the infiltrative non-enhancing tumor. F/U = follow-up

[81,82]. Infiltrative appearance is common in molecular glioblastoma [34,83]. One characteristic imaging finding of molecular glioblastoma is the high incidence of gliomatosis cerebri pattern [79,83]; one study shows that approximately 35% of molecular glioblastomas show this diffuse infiltrative pattern extending to more than three contiguous lobes [79], which is a significantly higher proportion compared to histological glioblastoma (8.4%) as well as oligodendrogliomas (8.9%) or IDH-mutant astrocytomas (3.2%) [84]. Thus, gliomatosis cerebri appearance with little or no contrast enhancement may serve as a useful imaging finding and raise suspicion for diagnosis of molecular glioblastoma.

Advanced MRI findings, such as areas of low ADC value and high rCBV in a non-enhancing or minimally contrast-enhancing tumor, may also support the possibility of molecular glioblastoma reflecting an underlying biological aggressiveness [82,85,86]; however, based on prior research, it should be noted that there is a small proportion of molecular glioblastoma patients who may not show low ADC value or high rCBV. Figure 7 shows representative cases of molecular glioblastoma patients without and with gliomatosis cerebri. Amino acid PET imaging features have not yet been reported in molecular glioblastomas.

Immediate Postoperative Imaging Features

Immediate postoperative MRI should be obtained within 48 hours after surgery (at latest within 72 hours) to reduce the risk of mistakenly considering postoperative contrast enhancement as residual contrast-enhancing tumor [87]. As acute infarct lesions evolve into contrast-enhancing lesions that may mimic contrast-enhancing tumor on follow-up, these lesions should be detected on immediate postoperative MRI [87], typically showing restricted diffusion on DWI along the surgical cavity margins. Postoperative hemorrhage can obscure residual contrast-enhancing tumor, requiring careful imaging examination. Minimal thin linear contrast enhancement resulting from local impairment of the blood-brain barrier at the surgical resection margin can mimic residual contrast-enhancing tumor on immediate postoperative MRI [88]. Postoperative edema and acute infarction can mimic residual non-enhancing tumor, and preoperative and postoperative imaging including DWI should be carefully reviewed to differentiate these lesions [89].

In terms of extent of resection, the residual tumor

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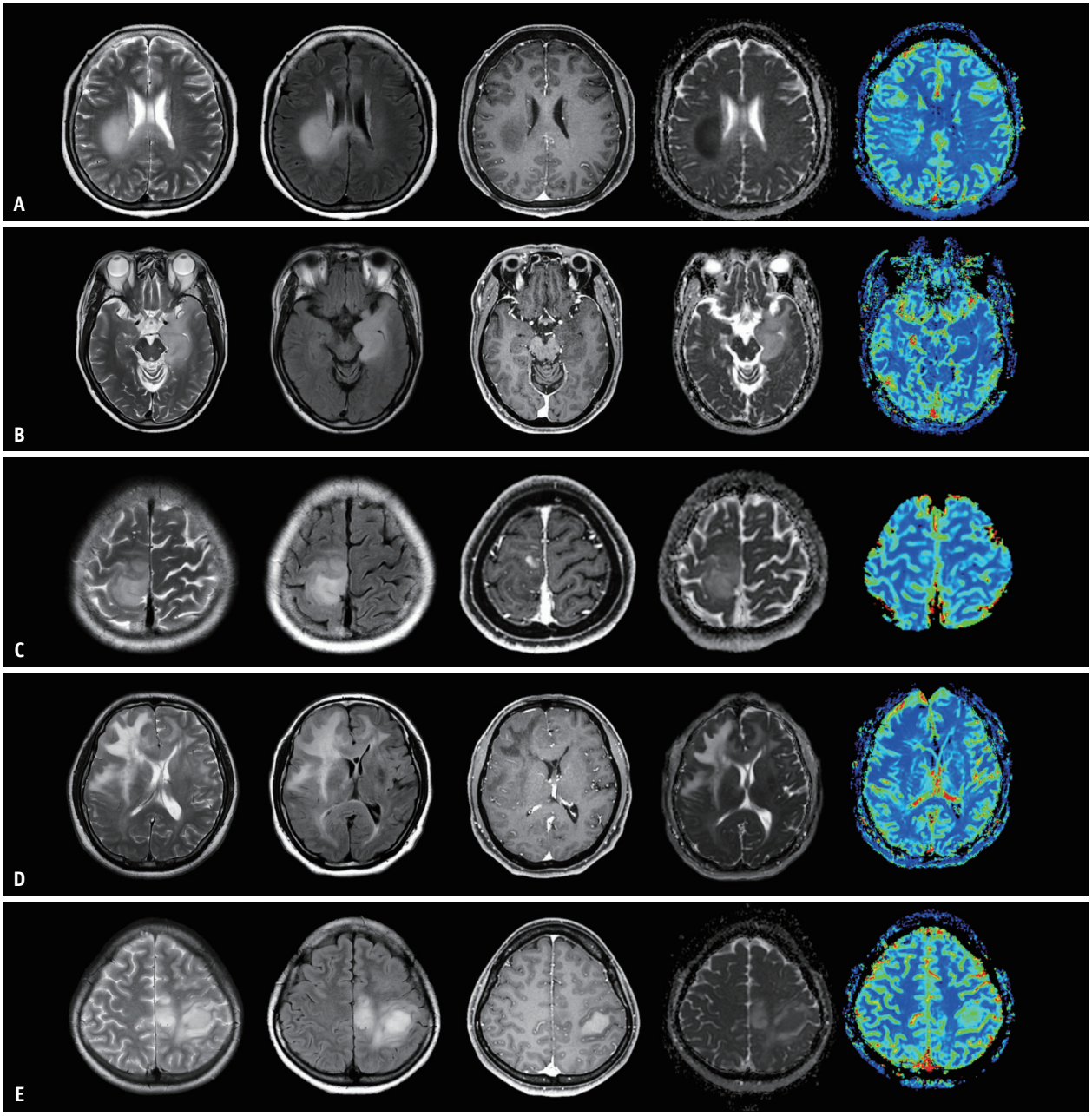

Fig. 7. Representative cases of molecular glioblastomas, without or with the gliomatosis cerebri pattern, showing various features on advanced imaging. **A:** A 66-year-old female presenting with a non-enhancing infiltrative tumor involving the right frontoparietal lobe and corpus callosum splenium. There is a markedly low ADC signal, while the rCBV is minimally elevated. The infiltrative appearance and markedly low ADC signal suggest the possibility of molecular glioblastoma. **B:** A 70-year-old male presenting with a non-enhancing tumor involving the left frontotemporal lobe and insula (full extent not shown in this image). There is no decrease in ADC signal nor increase in rCBV. However, the old age of the patient suggests a higher possibility of molecular glioblastoma than IDH-mutant astrocytoma or oligodendroglioma. **C:** A 75-year-old female presenting with a non-enhancing tumor with focal enhancing area at the right frontoparietal lobe. There is no decrease in ADC signal nor increase in rCBV. The slightly infiltrative appearance and old age of the patient suggests a higher possibility of molecular glioblastoma rather than IDH-mutant astrocytoma or oligodendroglioma. **D:** A 69-year-old male presenting with a non-enhancing tumor with gliomatosis cerebri involving bilateral cerebral hemispheres and corpus callosum genu. There is no hemorrhage on SWI. There is no decrease in ADC signal nor increase in rCBV. **E:** A 23-year-old female presenting with a non-enhancing tumor with gliomatosis cerebri and a contrast-enhancing tumor at the left parietal lobe (the full extent of the tumor involving the corpus callosum splenium and contralateral parietotemporal lobe is not shown). There is no hemorrhage on SWI. There is low ADC signal and high rCBV at the contrast-enhancing tumor. ADC map created from b = 0 and b = 1000 (s/mm^2) and uncorrected rCBV map estimated by integrating the relaxivity-time curve. ADC = apparent diffusion coefficient, rCBV = relative cerebral blood value, IDH = isocitrate dehydrogenase, SWI = susceptibility weighted imaging

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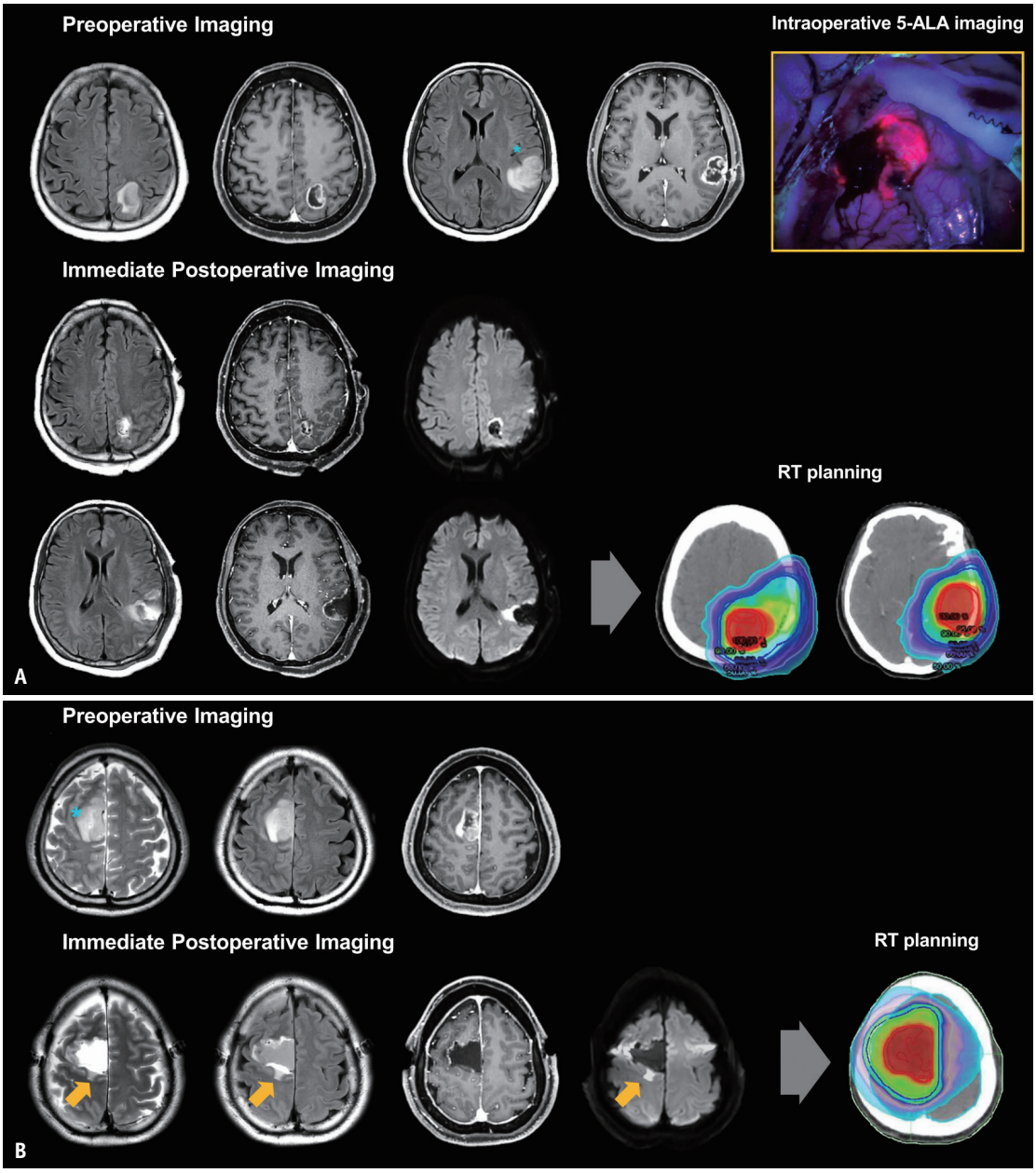

Fig. 8. Representative cases of IDH-wildtype glioblastomas that have undergone supramaximal resection without residual contrast-enhancing or non-enhancing tumor. **A:** A 59-year-old female showed multicentric distribution of tumors on left parietal and temporal lobes (non-enhancing tumor marked in asterisk). Multicentric tumors were both removed. On surgical note, there were strongly fluorescent tumor tissues with 5-ALA guidance, and there was no residual fluorescent tumor tissue after tumor removal, suggesting total removal of the high-grade tumor portion. The T2 hyperintensities on preoperative and immediate postoperative imaging indicate postoperative edema and acute infarction (on diffusion-weighed imaging at b = 1000 s/mm^2). Note that the surgical note can provide additional information when interpreting immediate postoperative imaging. In supramaximal resection without residual contrast-enhancing or non-enhancing tumor, the GTV (red contour) includes the resection cavity in RT planning. In supramaximal resection without residual contrast-enhancing or non-enhancing tumor, the GTV includes the resection cavities in RT planning. The red contour demonstrates the radiation isodose line encompassing the high-dose PTV, delineated with an additional margin from the GTV. **B:** A 53-year-old male underwent total resection of contrast-enhancing tumor as well as non-enhancing tumor (asterisk). On immediate postoperative imaging, postoperative edema is noted around the operative margin, while there is a newly seen T2 high, diffusion-restricted lesion posterior to the surgical cavity indicating postoperative infarction (arrows). Imaging confounders of residual non-enhancing tumor, such as residual peritumoral edema and surgically induced edema as well as ischemia, should be carefully examined. The GTV in this patient also included the resection cavity in RT planning. The red contour demonstrates the radiation isodose line encompassing the high-dose PTV, delineated with an additional margin from the GTV. IDH = isocitrate dehydrogenase, 5-ALA = 5-aminolevulinic acid, T2 = T2-weighted, GTV = gross tumor volume, RT = radiation therapy, PTV = planning target volume

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volume has a larger survival impact than the relative tumor reduction volume; in other words, what matters is what is "left behind," not what has been taken out [53]. Thus, accurate delineation of residual contrast-enhancing and non-enhancing tumor is important for patient prognostication [53,90]. Accurate delineation of residual contrast-enhancing and non-enhancing tumor is also important in radiation target delineation; usually, the gross tumor volume (GTV) encompasses visible tumor area on imaging, while clinical target volume (CTV) includes both the GTV and surrounding tissue areas at risk for microscopic tumor spread. According to the updated ESTRO-EANO guidelines, a new MRI is recommended for all patients within 2 weeks prior to starting the radiation therapy due to the high risk of tumor increase or changes in resection cavity volumes, especially in patients who underwent subtotal or partial resection [91]. This

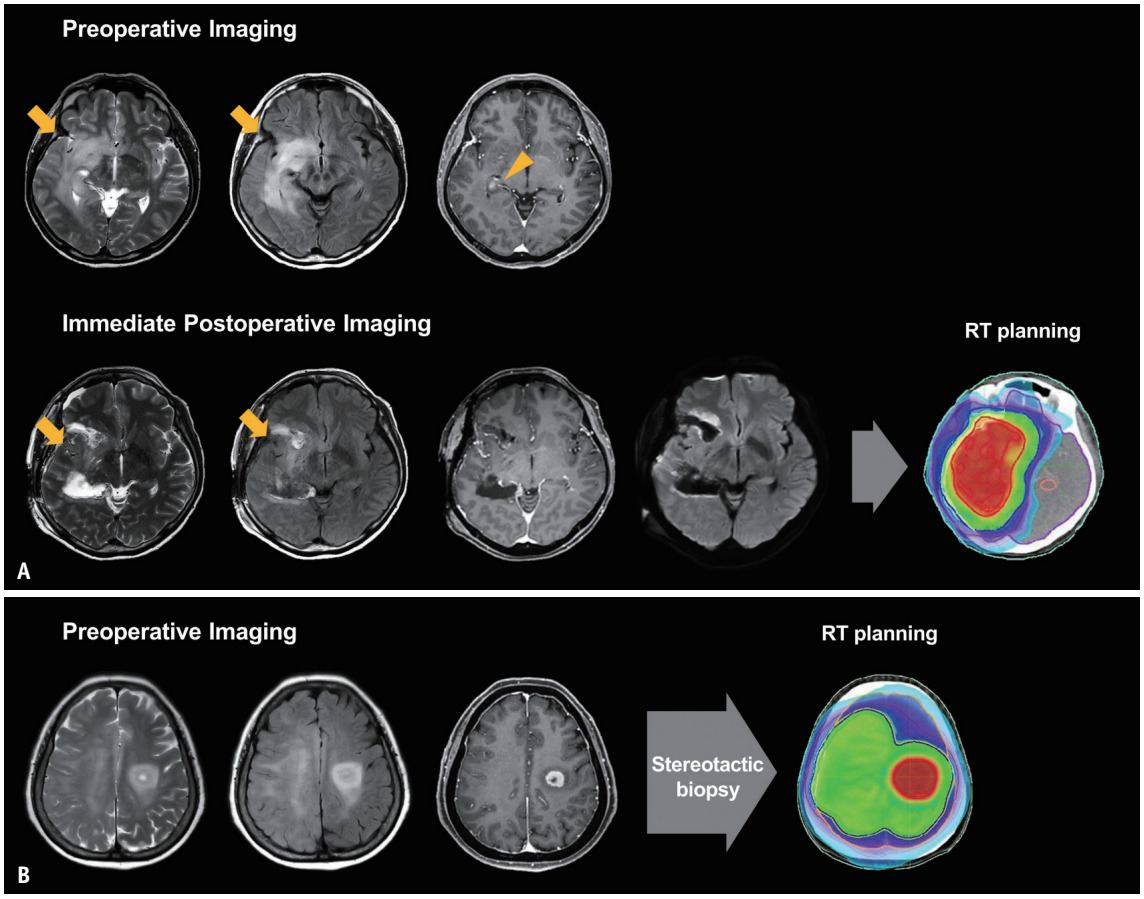

Fig. 9. Representative cases of IDH-wildtype glioblastomas that have undergone complete resection of contrast-enhancing tumor with residual non-enhancing tumor. **A:** A 55-year-old female with molecular glioblastoma shows diffuse non-enhancing tumor involving the right frontotemporal lobe and insula (arrows) as well as a focal contrast-enhancing tumor at the right temporal lobe (arrowhead) on preoperative imaging. This patient underwent total resection of contrast-enhancing tumor, but residual non-enhancing tumor is noted at the right insula on immediate postoperative imaging (arrow). There is minimal acute infarction at the surgical margin (on diffusion-weighed imaging at b = 1000 s/mm^2). Due to the insula's proximity to critical arteries such as the middle cerebral and lenticulostriate arteries, total resection of tumor in this area remains challenging. Note that comparison of immediate postoperative imaging with preoperative imaging enables confident diagnosis of residual non-enhancing tumor. The surgical cavity as well as the residual non-enhancing tumor was included in the GTV in RT planning. The red contour demonstrates the radiation isodose line encompassing the high-dose PTV, delineated with an additional margin from the GTV. **B:** A 73-year-old female with a gliomatosis cerebri pattern of non-enhancing tumor involving the bilateral cerebral hemispheres as well as a ring-enhancing tumor with central necrosis at the left precentral gyrus on preoperative imaging. Stereotactic biopsy was performed in this patient. The contrast-enhancing tumor was included in the GTV, while the non-enhancing tumor with gliomatosis cerebri pattern was included in the PTV. Due to the extremely large extent of gliomatosis cerebri pattern, this area was not included in the GTV in RT planning. The red contour demonstrates the radiation isodose line encompassing the high-dose PTV, delineated with an additional margin from the GTV, whereas the green contour demonstrates radiation isodose line encompassing the low-dose PTV, delineated with an additional margin from the non-enhancing infiltrative tumor. IDH = isocitrate dehydrogenase, GTV = gross tumor volume, RT = radiation therapy, PTV = planning target volume

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Korean Journal of Radiology
KJR

recommendation shows that a recent MRI rather than an immediate postoperative MRI or CT simulation has become mandatory in radiation therapy planning for appropriate determination of residual tumor. Furthermore, in addition to the commonly applied GTV delineation based on residual contrast-enhancing tumor, non-enhancing tumor (apart from peritumoral edema) should also be considered to be included within the GTV [91], based on prior reports that most tumor recurrences occur within proximity of the primary tumor support the ESTRO-EANO guidelines [92,93]. Peritumoral edema is not included in GTV or CTV in the ESTRO-EANO guidelines. The imaging approach for differentiation between non-enhancing tumor and peritumoral edema is detailed in the section describing the "Differentiation of Non-enhancing Tumor and Peritumoral Edema," and it remains crucial in postoperative imaging as well. However, variability exists in target volume margin size and extent among different guidelines [91,94,95].

The surgical note should "always" be routinely reviewed by radiologists after a first read of the images to assist in identifying areas with intraoperatively suspected residual tumor. Fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) is commonly used, which may provide useful information on residual tumor. 5-ALA is a biochemical precursor that tumor cells convert into protoporphyrin IX, which fluoresces under blue-violet light, allowing tumor visualization during surgery [96]. 5-ALA's fluorescence is due to intratumoral synthesis rather than crossing a disrupted blood-brain barrier. Although 5-ALA fluorescence is most commonly associated with CE tumors in IDH-wildtype glioblastomas (which represent areas of active tumor growth), there are occasional reports of fluorescence in non-enhancing tumors [97,98]. In some patients there is no gross residual tumor visible on immediate postoperative MRI, but there may be residual fluorescent tumor based on 5-ALA that may require attention on follow-up [99]. In turn, the neurosurgeon's judgement of a "complete" resection has previously been shown as inaccurate and requires a high level of caution [100]. Figures 8 and 9 show several representative cases from immediate postoperative MRI to delineate residual contrast-enhancing and non-enhancing tumors. The key considerations and imaging features in immediate postoperative imaging are shown in Table 3.

CONCLUSION

Excitingly, neuro-oncology is a constantly evolving field. Radiologists should strive to see the forest from the trees to stay focused in this ever-changing field. In order for radiologists to provide relevant information to clinicians in management of patients with IDH-wildtype glioblastoma, neuroradiologists must quickly evolve to match the rate at which molecular and clinical knowledge are evolving. We hope that this review series may serve as a guide for current practice and preparation for the next step.

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.

Table 3. Key considerations and imaging features in immediate postoperative assessment of IDH-wildtype glioblastoma

	Details	Importance
Immediate postoperative MRI	• Should be taken within 48–72 hours • Acute infarct showing restriction diffusion on DWI • Minimal thin linear contrast enhancement on surgical margin: usually postoperative change rather than residual CE tumor	• To reduce misinterpretation of postoperative enhancement or edema as residual CE or NE tumor
Residual tumor volume	• Accurate delineation of residual CE and NE tumors (separate from pertiumoral edema)	• Larger impact on survival than relative tumor reduction; accurate delineation necessary for RT planning of GTV and CTV
Review of surgical note	• Residual 5-ALA fluorescence may indicate residual tumor • Neurosurgeon's judgement of "complete" resection: may be helpful but requires caution	• Aids in correlating imaging findings with intraoperative assessments

IDH = isocitrate dehydrogenase, DWI = diffusion-weighted imaging, CE = contrast-enhancing, NE = non-enhancing, RT = radiation therapy, GTV = gross target volume, CTV = clinical target volume, 5-ALA = 5-aminolevulinic acid

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